



Functional Hepatobiliary Disease: Chronic Acalculous Gallbladder and Chronic Acalculous Biliary Disease

Harvey A. Ziessman, MD

Chronic acalculous gallbladder and chronic acalculous biliary disease are considered functional hepatobiliary diseases. Cholescintigraphy provides physiologic imaging of biliary drainage, making it ideally suited for their noninvasive diagnosis. For chronic acalculous gallbladder disease, calculation of a gallbladder ejection fraction during sincalide cholescintigraphy can confirm the clinical diagnosis and has become a common routine procedure in many nuclear medicine clinics. Published data generally confirm a high overall accuracy for predicting relief of symptoms with cholecystectomy. However, data also exist suggesting it is not useful. The discrepant results probably are caused by the various different methodologies that have been used for sincalide infusion. Proper methodology of sincalide infusion is critical for providing accurate reproducible results, minimizing false positive studies, and preventing adverse side effects. The most common causes for the postcholecystectomy pain syndrome are partial biliary obstruction secondary to stones or tumor and sphincter of Oddi dysfunction. The latter is a partial biliary obstruction at the level of the sphincter. This has long been considered a functional hepatobiliary disease because of the lack of anatomical abnormalities. Sphincterotomy is the present treatment; however, diagnosis requires invasive procedures, such as endoscopic retrograde cholangiopancreatography and sphincter of Oddi manometry, which has a high complication rate and is not widely available. The unique ability of cholescintigraphy to image biliary drainage allows noninvasive diagnosis. Different methodologies have been reported, many with good overall accuracy. Various pharmacologic interventions and quantitative methodologies have been used in conjunction with cholescintigraphy to enhance its diagnostic capability. Further investigations are needed determine the optimal methodology; however, cholescintigraphic methods have already a clinical role in the diagnosis of sphincter of Oddi dysfunction and will be used increasingly in the future.

Semin Nucl Med 36:119-132 © 2006 Elsevier Inc. All rights reserved.

The ^{99m}Tc -iminodiacetic acid (^{99m}Tc -IDA) radiopharmaceuticals were first introduced 30 years ago, in 1976. Their potential applicability to clinical practice was quickly appreciated, and many publications in the 1980s confirmed the diagnostic value of cholescintigraphy. Unlike some radiopharmaceuticals that have fallen into disuse with time or their indications severely reduced, ^{99m}Tc -IDA imaging has shown remarkable staying power and, in fact, clinical indications have increased over the years.

Two ^{99m}Tc -IDA radiopharmaceuticals are commercially available in the United States: (1) ^{99m}Tc -diosopropyl-IDA

(DISIDA), or disofenin (Hepatolite; Cis Inc, Bedford, MA), and (2) ^{99m}Tc -bromotriethyl-IDA, or mebrofenin (Choletec; Squibb, New Brunswick, NJ). Of the 2, mebrofenin has higher hepatic extraction (98% versus 88%) and more rapid washout from the liver ($T_{1/2}$ of 17 minutes versus 19 minutes). Other ^{99m}Tc -IDA radiotracers used in various parts of the world, include ^{99m}Tc -EIDA (diethyl-IDA), ^{99m}Tc -DIDA (diisopropyl-IDA), and ^{99m}Tc -IODIDA (diethyl-iodo-IDA). Although similar in mechanism, they have different pharmacokinetics. This takes on importance when trying to compare the results of quantitative cholescintigraphy from various investigators around the world.

The most common clinical indications for cholescintigraphy have been for the diagnosis of various acute biliary diseases, eg, acute cholecystitis, biliary obstruction, and biliary leaks.¹ Specific clinical situations include differentiating bil-

Division of Nuclear Medicine, The Russell H. Morgan Department of Radiology, Johns Hopkins Medical Institutions, Baltimore, MD.

Address reprint requests to Harvey A. Ziessman, MD, 601 N. Caroline Street, JHOC 3231, Baltimore, MD 21278-0817. E-mail: hziessm1@jhmi.edu

Table 1 Terminologies Used for Chronic Acalculous Gallbladder and Biliary Disease

Chronic acalculous biliary disease	Chronic acalculous gallbladder disease
Sphincter of Oddi dysfunction	Gallbladder dyskinesia
Papillary spasm	Gallbladder spasm
Biliary dyskinesia	Cystic duct syndrome
Papillitis	Chronic acalculous cholecystitis
Tachyoddia	
Ampullary stenosis	
Papillary stenosis	

iliary atresia from neonatal hepatitis, the postoperative complications of cholecystectomy, liver transplantation, biliary and gastric diversion procedures, and biliary stent patency.

Cholescintigraphy is playing an increasingly important role in the diagnosis of chronic hepatobiliary diseases, for example, partial biliary obstruction, the postcholecystectomy syndrome, and chronic gallbladder disease. Many of these diseases will be the subject of this review. The use of quantitative cholescintigraphy will be emphasized.

Chronic Acalculous Gallbladder and Acalculous Biliary Disease

The chronic acalculous diseases of the gallbladder and biliary system often are referred to as functional hepatobiliary diseases. To some extent, the term functional refers to the fact that patients have symptoms of recurrent biliary colic-like pain; however, repeated medical workups reveal no morphologic or anatomic cause, such as gallstones, cholelithiasis, common duct stricture, or tumor. The term functional may say more about our limited understanding of the pathophysiologic processes involved rather than clarifying their etiology. In fact, some of these diseases do have anatomical or histopathological abnormalities by invasive methodologies; however, the diagnosis can be made by noninvasive functional imaging. The names for various the chronic acalculous gallbladder and biliary diseases have been a source of confusion. Different names have been for the same entity and the same name has been used for distinct entities (Table 1).

Chronic Acalculous Gallbladder Disease

To understand acalculous gallbladder disease, it is useful to first discuss chronic calculous gallbladder disease. Gallstones are common; however, most patients with cholelithiasis are asymptomatic. Fewer than 15% of patients with gallstones who are followed for 20 years develop biliary colic.

Patients with symptomatic chronic calculous cholecystitis not only have gallstones but also histopathological evidence of chronic inflammation of the gallbladder wall. In addition, they have a functional abnormality, ie, poor contractility.^{2,3} In contrast, patients with asymptomatic cholelithiasis have normal gallbladder contractility.⁴ Current practice dictates

that the presence of gallstones detected by anatomical methods in patients with typical symptoms of recurrent biliary colic is sufficient evidence to recommend cholecystectomy. However, on occasion, when a patient's symptoms are not characteristic of cholecystitis, cholecystokinin (CCK) cholescintigraphy can help determine if the pain and stones are related.

Approximately 5% to 10% of patients of patients with symptomatic chronic cholecystitis do not have stones (chronic acalculous cholecystitis).⁵ They have the same chronic inflammatory changes within the gallbladder wall, but no cholelithiasis. Recent reports from the laparoscopic literature suggest that the incidence may be even higher than previously reported, perhaps as high as 25%.⁶ The diagnostic dilemma is that the workup is negative because the patients do not have imaging evidence of stones. There are many diseases that can cause recurrent abdominal pain and some of them do not have diagnostic imaging or endoscopic findings, eg, the irritable bowel syndrome. Thus, in the past, medical workups were often repeatedly performed without resulting diagnosis and sometimes even misdiagnosis. Chronic acalculous cholecystitis (CAC) was a diagnosis of exclusion. Even when strongly suspected, surgeons were hesitant to operate without objective confirmation.

Approximately 90% of patients with chronic acalculous gallbladder disease have histopathologic evidence of chronic cholecystitis.^{7,8} However, other diseases may present identically, eg, the cystic duct syndrome, defined by cystic duct narrowing caused by chronic inflammation and fibrosis, or occasionally due to ductal kinking.⁹ Many of these patients have concomitant histopathologic evidence of chronic cholecystitis.

There are some patients with similar symptoms, poor gallbladder contractility, and relief of their symptoms postcholecystectomy that do not have postoperative histopathological evidence of inflammation. Thus, terms such as gallbladder spasm, cystic duct spasm, or gallbladder dyskinesia have been used. The pathophysiology is uncertain. Various hypotheses have been proposed, including abnormalities of CCK release, reduced gallbladder CCK receptor sensitivity/density, increased cystic duct receptor CCK sensitivity, and impaired smooth muscle contractility.¹⁰ Because all of these patients have similar presentation, poor gallbladder contractility, and good response to cholecystectomy, they are discussed together.

Finally, there are a number of chronic diseases that have been associated with impaired gallbladder emptying. These include diabetes mellitus, cirrhosis, myotonic dystrophy, irritable bowel syndrome, celiac disease (deficiency of CCK), and obesity.

Attempts to preoperatively diagnose chronic acalculous gallbladder disease by noninvasive methods date back to the late 1970s and early 1980s. Investigators used fatty meal or CCK stimulated oral cholecystography to evaluate gallbladder contractility. Some reported that poor gallbladder contraction predicted relief of biliary colic symptoms by cholecystectomy.¹¹ However, other investigators did not find the technique useful.^{12,13} In retrospect, the discrepant results

may likely have been due to the subjective nonquantitative nature of the procedure and the different methodologies of sincalide infusion.

When ^{99m}Tc -IDA radiopharmaceuticals and cholescintigraphy became available in the early 1980s, investigators soon saw their potential use for investigation of gallbladder contractility and the diagnosis of chronic acalculous gallbladder disease. The radionuclide methodology had the advantages of being objective, reproducible, and quantitative.¹⁴ Initial investigations suggested that CCK cholescintigraphy could have an important role in the noninvasive diagnosis of chronic acalculous gallbladder disease.¹⁵⁻¹⁷

Numerous investigations subsequently were published confirming the utility of CCK cholescintigraphy for making the diagnosis of chronic acalculous gallbladder disease.^{6-8,18-33} Two studies published in 1991 were pivotal in convincing gastroenterologists, surgeons, and nuclear medicine physicians that CCK cholescintigraphy was an accurate diagnostic test that could noninvasively confirm the clinical diagnosis. One was a large retrospective study by Fink-Bennett and coworkers published in the *Journal of Nuclear Medicine*.⁸ The other was a prospective and randomized study published by Yap and coworkers in *Gastroenterology* that same month and year.⁷ Both investigations reported that a low gallbladder ejection fraction (GBEF) had a positive predictive value of greater than 90% that the patient had the disease, cholecystectomy would relieve their symptoms, and the gallbladder would show histopathologic evidence of chronic cholecystitis.

The study of Yap and coworkers was particularly convincing because it was prospective and randomized. Patients in this study who had a low GBEF were assigned randomly to either surgical or nonsurgical therapy.⁷ More than 91% of patients who had cholecystectomy had resolution of their symptoms and 92% had histopathological evidence of chronic cholecystitis. Patients who did not go to surgery continued to be symptomatic and many ultimately demanded surgery, which cured their symptoms. In this study, sincalide (Kinevac; Bracco Diagnostics, Inc, New Brunswick, NJ) was infused at a dose rate of $0.02 \mu\text{g}/\text{kg}/\text{min}$ for 45 minutes and the GBEF calculated at 60 minutes. The investigators established their own normal values for GBEF by studying 40 normal subjects. The GBEF lower limits of normal were 40% (mean \pm 3 SD). This high-quality study convinced many of the clinical utility of CCK cholescintigraphy.

Most other published studies have been retrospective (Table 2). The publication of Fink-Bennett and coworkers is one of the largest.⁸ Of 374 patients studied, 113 had a low GBEF followed by cholecystectomy. Of these, 110 of 113 (97%) became asymptomatic and 94% had histopathologic evidence of chronic cholecystitis. In addition to its high positive predictive value, the negative predictive value was 91%. For various reasons, 221 patients were followed medically. Of those with a low GBEF, 84% continued to be symptomatic. Of those with a normal GBEF, most clinically improved with therapy for nongallbladder disease.

Although the results of the 2 described studies were similar, the methodologies for CCK infusion differed. Fink-Ben-

nett and coworkers infused $0.02 \mu\text{g}/\text{kg}$ sincalide over the course of 3 minutes. Abnormal was defined in the study as a GBEF of less than 35%. They also studied 27 normal subjects. Of interest and puzzling was that 59% (16/27) had a GBEF of less than 35%. Thus, these subjects did not serve as the basis of the normal values used in this study. A subsequent review of the literature showed that no data existed at that time regarding normal values based on a 3-minute infusion³⁴

At most recent count, at least 22 investigations have now been published data that confirm the utility of CCK cholescintigraphy for the diagnosis chronic acalculous gallbladder disease (Table 2). The sum of the evidence is that CCK cholescintigraphy is a clinically important noninvasive diagnostic methodology for confirming the diagnosis of CAC. On the other hand, there are approximately 6 publications that have not found CCK cholescintigraphy helpful for predicting response to cholecystectomy (Table 2).^{13,35-39} There are various possible explanations for this discrepancy between studies, including the limited number of subjects in many studies, referral biases, and the retrospective nature of most investigations. Few of the published studies would rate high on an evidence-based medicine analysis. However, the study of Yap and coworkers is one that would.⁴⁰ Another possible explanation for the different results relates to the many different methods of infusing CCK. The total dose of sincalide administered (0.01, 0.015, 0.02, 0.03, 0.04, 0.05 $\mu\text{g}/\text{kg}$), the length time over which sincalide was infused (bolus, 1, 2, 3, 5, 15, 20, 30, 45, and 60 minutes), the time from infusion of sincalide to calculation of the GBEF (15, 20, 30, and 60 minutes), and the GBEF lower limits of normal (<30%, <35%, <40%, <50%, and <65%) all vary remarkably from study to study (Table 2).^{6-8,13,15-17,19-32,35-39}

The fact that both Yap and coworkers and Fink-Bennett and coworkers had similar results might suggest that the method of sincalide infusion is not critical. However, there is substantial evidence to the contrary, that is, the method of infusion does matter. Published data reveal considerable variability in the GBEF between normal subjects administered 1- to 3-minute infusions of sincalide. Drane and Johnson,⁴¹ studying 31 normal subjects, found GBEFs to vary between 7% and 85% when using a 1 to 2-minute infusion of $1.5 \mu\text{g}$ of sincalide. Sarva and coworkers,⁴² studying patients without gallbladder or hepatobiliary disease, found that the GBEFs varied between 12% and 92% when using a 1-minute infusion method but had a much narrower range of 65% to 96% with a 45-minute infusion of the same total dose. Limitations of this study were that the 2 different infusion methods were given to 2 different subject groups, the subjects were not truly normals but patients with symptoms but without gallbladder disease, and that GBEF normal values were not determined.

In 1992 and 2001, Ziessman and coworkers published^{43,44} investigations that directly compared different sincalide infusion methods in the same normal subjects and established normal values based on the method of infusion. In the first study, a 3-minute infusion of $0.02 \mu\text{g}/\text{kg}$ was compared with a 30-minute infusion of the same total dose performed on different days. The second study compared a 3-minute infu-

Table 2 Accuracy of CCK Cholescintigraphy for Chronic Acalculous Gallbladder Disease

	First author	Ref no.	Date	No. pts	Preop Dx of CAC*	Sincalide dose ($\mu\text{g}/\text{kg}$)	Infusion time (min)	Time of GBEF calculation (min)	Abnormal GBEF	Symptoms resolved (%)‡	CAC* histopathology (%)†
Confirmatory											
1	Topper	15	1980	38	7	0.2	NA	10	<50	100	100
2	Pickelman	16	1985	36	14	0.02-0.04	2	15	<50	93	53
3	Fink-Bennett	17	1985	14	14	0.02	3	20	<35	97	86
4	Brugge	18	1986	36	15	0.01 $\mu\text{g}/\text{kg}/\text{min}$	20	20	<40	91	73
5	Fink-Bennett	8	1991	374	124	0.02	3	20	<35	97	96
6	Yap	7	1991	103	21	0.02 $\mu\text{g}/\text{kg}/\text{min}$	45	60	<40	91	92
7	Misra	19	1991	187	69	0.02	3	20	<35	84	48
8	Zech	20	1991	83	60	0.04	2 to 3	60	<50	95	92
9	Halverson	21	1992	12	12	0.02-0.04	3	30	<35	100	92
10	Middleton	22	1992	89	34	CCK-33	2	NA	<35	100	88
11	Sorenson	23	1993	18	11	0.01	3	30	<35	100	100
12	Reed	24	1993	30	30	0.02	4	20	<35	97	90
13	Watson	25	1994	56	9	0.015	45	65	<50	100	100
14	Barron	26	1995	38	38	0.02	3	30	<35	100	95
15	Jones	33	1996	36	29	0.02	3	30	<35	93	83
16	Khosla	27	1997	35	30	0.02	2 to 3	30	<35	94	83
17	Klieger	28	1998	52	28	0.02	3 to 5	30	<35	96	93
18	Yost	29	1999	72	27	0.03	NA	30	<35	89	57
19	Middleton	30	2001	244	141	CCK-33	3	20	<35	100	82
20	Chen	6	2001	152	32	NA	NA	NA	<35	87	NA
21	Poynter	31	2002	26	26	0.02	15	15	<35	92	100
22	Majeski	32	2003	56	56	0.02	30	30	<35	100	96
Non confirmatory											
1	Davis	13	1982	10	9	0.02	3	30	<35	70	78
2	Raptopoulos	38	1986	26	17	0.01 to 0.03	2	15	<40	38	NA
3	Westlake	39	1990	26	23	0.02 $\mu\text{g}/\text{kg}/\text{min}$	30	30	<65	69	NA
4	Miskind	37	1997	58	27	0.04	2 to 3	20	<35	56	67
5	Adams	35	1998	50	50	0.02	3 to 5	30	<35	78	NA
6	Goncalves	36	1998	111	44	0.01	3	30	<35	75	95

NA, not available from publication.

Note: Same investigators in articles 2, 5, and 7; same investigators in articles 10 and 19.

*Preoperative diagnosis of CAC based at least on biliary colic, lack of stones, and low GBEF.

†Pathologic criteria varied.

‡Clinical criteria of response varied to some degree.

sion of 0.01 $\mu\text{g}/\text{kg}$ with a 60-minute infusion of the same total dose. Both investigations showed similar results in that the 3-minute infusions of either 0.02 $\mu\text{g}/\text{kg}$ or 0.01 $\mu\text{g}/\text{kg}$ were not reliable for quantifying gallbladder contractibility and calculating a GBEF. The response to a 3-minute infusion was extremely variable in these normal subjects (GBEF of 0 to 100%) and, as a result, normal GBEF values could not be established. However, when the same subjects received longer infusions of 30 or 60 minutes, the variability was much less and normal values could be determined (>30% for the 30-minute infusion and > 40% for the 60-minute infusion). The 60-minute infusion normal values were nearly identical to those of Yap and coworkers,⁷ who had used a 45-minute infusion of sincalide and calculated the GBEF at 60 minutes. The GBEFs were higher (70 ± 20 versus 52 ± 26) with the longer infusions compared with the 3-minute infusion. With the 3 minute infusions, 30% to 35% of normal subjects had a GBEF less than 35%; however, when sincalide was infused for 30 or 60 minutes, few subjects had a GBEF of less than 35%. Thus, methodology does make a difference.

To understand why the slower infusion gives superior results, it is helpful to review the physiology of gallbladder contraction. With oral ingestion of a fatty meal, endogenous production of CCK is stimulated, producing a slow rise in the serum CCK, gradually reaching equilibrium and a plateau. The serum CCK level begins to decrease after the meal has emptied from the stomach and proximal bowel.⁴⁵ The gallbladder begins to contract as the serum CCK increases and stays contracted until CCK decreases below the contraction threshold. A very similar pattern of response is seen with a slow sincalide infusion method, ie, a slow rise, plateau, and slow fall-off after discontinuation of infusion. However, a short infusion of sincalide results in rapid supraphysiological peaking of serum CCK, followed by a rapid fall off.⁴⁶

An explanation for the superiority of slower infusion method is that the high peak serum CCK levels produced by more rapid infusions stimulates low-density CCK receptors in the neck of the gallbladder and cystic duct, which do not normally contract at physiological serum levels of CCK. The increased back-pressure prevents normal gallbladder contraction. This phenomenon was observed in the 1970s during CCK-stimulated oral cholecystography. Bolus infusions of CCK up to 30 seconds in length caused spasm of the neck of the gallbladder and ineffective contraction in some patients. For this reason, the sincalide package insert subsequently recommended infusions of at least 30 to 60 seconds. Evidence presented suggests that a similar effect is seen with 1- to 3-minute infusions.

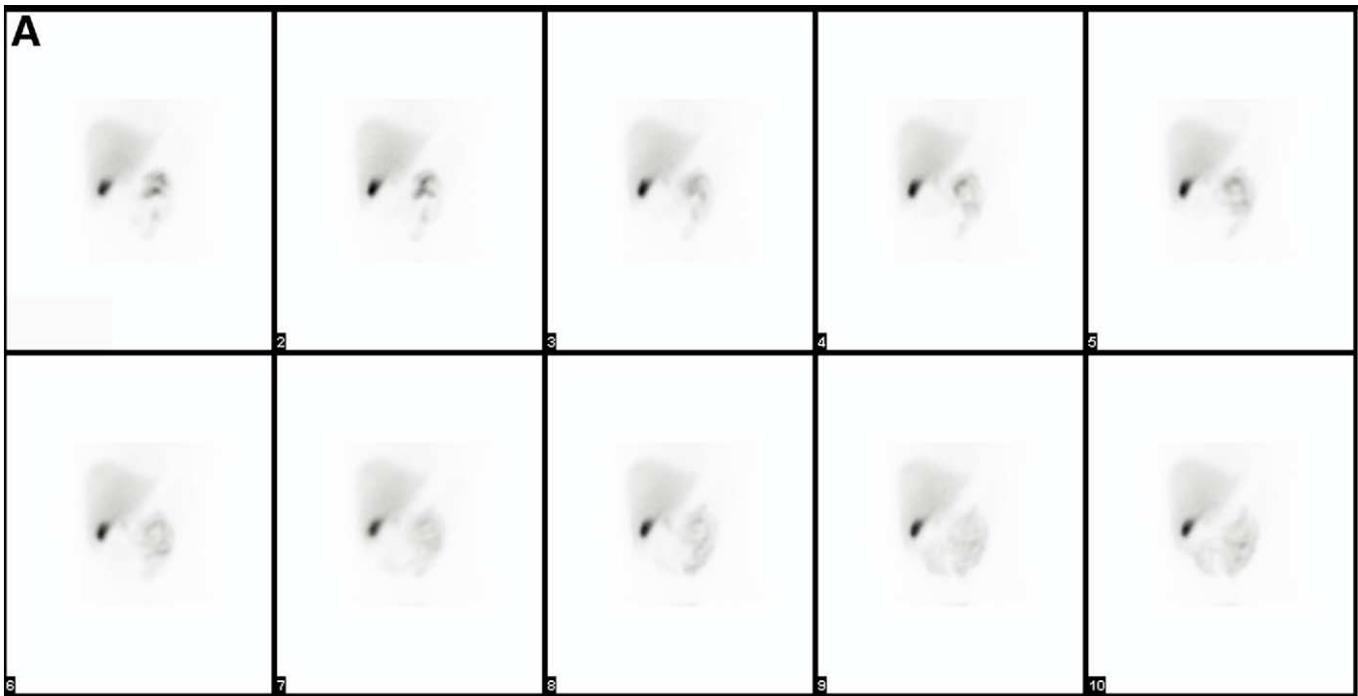
So what is the reason that many investigations have not reported a high number of false-positive studies in clinical investigations? It could be attributable to the limited numbers of subjects studied, to the retrospective nature of most studies, and or to a referral bias. A false positive rate of 30% to 35% in normal subjects does not necessarily indicate that it would be that high in clinical patients referred for suspected chronic cholecystitis. Normal subjects have a low pretest probability for disease. In published investigations, patients had a moderately high pre-

test probability. They had been worked up extensively to exclude other causes for their symptoms and had been followed for months or years, allowing sufficient time for other diseases to present. Thus, they had a moderately high pretest probability of disease. According to Bayes' theorem, a positive test would likely be a true positive. However, in a group of normal subjects with a low pretest probability, a positive test is more likely to be a false positive. In any case, any false positive is unacceptable and a methodology should be used that minimizes them.

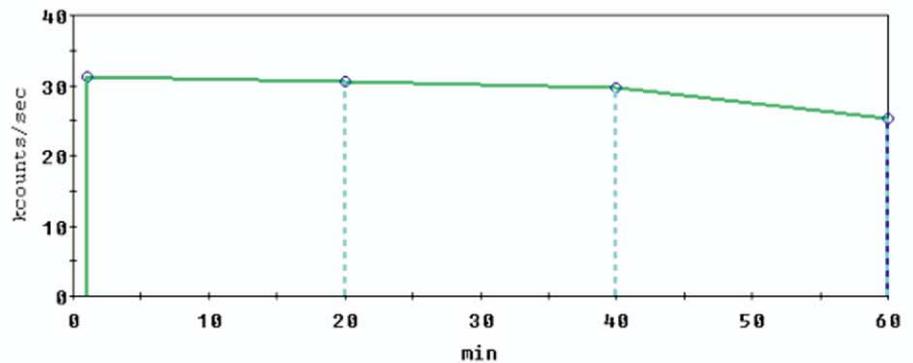
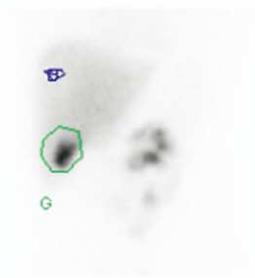
Because CCK cholescintigraphy has become more widely used to confirm the diagnosis of symptomatic chronic acalculous gallbladder disease, many patients are being referred with less-extensive workups than those in published investigations and often referred a single or limited number of episodes of pain. One group of investigators has even proposed a new algorithm that shortens the workup so that patients with negative gallbladder ultrasonography and a low GBEF go directly to cholecystectomy.²⁹ The new referral population is not the same as the one that was originally investigated, but rather one with a lower likelihood of disease. Thus, minimizing the false positive rate by using proper methodology becomes increasingly important.

Another important factor to consider is that the incidence of abdominal cramping and nausea with a 1- to 3-minute sincalide infusion approaches 50%.^{43,47} In contrast, those receiving an infusion of 30 or 60 minutes almost never experience adverse symptoms. CCK increases intestinal motility, a likely cause of abdominal cramping. CCK is reported to exacerbate the symptoms of patients with the irritable colon syndrome.⁴⁸ Provoking biliary colic with short infusions of CCK has been used over the years as a diagnostic test. However, repeated studies have shown that the results are not predictive of symptomatic benefit from cholecystectomy.⁴⁹ Pain production with CCK is the result of the method of infusion and not the underlying disease.

Fatty meals can be used as an alternative to CCK to evaluate gallbladder contraction. A fatty meal is considered by some to be more physiological and the lower cost is preferred. Furthermore, CCK formulations are not available for clinical use in some countries. In the recent past, sincalide was commercially unavailable in the United States for more than a year because of production problems. The disadvantage of fatty meal cholescintigraphy is that gallbladder emptying is dependent on good gastric emptying that ensures prompt and sufficient endogenous stimulation of CCK. Before performing CCK cholescintigraphy, one does not usually know whether the patient's gastric emptying is normal. Furthermore, all fatty meals are not the same. At least 10 g of fat is necessary to contract the gallbladder. And similar to CCK, the resulting normal GBEF range depends on the composition of the meal and the methodology. Because of the time required for gastric emptying, a study of at least 60 minutes is required. A variety of fatty meals have been used. Milk has been most studied and normal values determined.^{50,51} However, many persons have lactose-intolerance and cannot tolerate milk products. EnsurePlus, a commercial product, has



B



EF between 1.0 min and 60.0 min = 19 %

EF (@20 min)= 2 %

EF (@40 min)= 4 %

EF (@60 min)= 19 %

Figure 1 Sincalide cholecystigraphy. The patient was suspected of having chronic acalculous gallbladder disease. Other workup including sonography was negative. (A) Sincalide, $0.02 \mu\text{g}/\text{kg}$, was infused for 60 minutes. Poor gallbladder contraction is seen on the sequential 3-minute summed images. (B) Quantification determined the GBEF to be 19% at 60 minutes (abnormal $<40\%$).

been investigated, found satisfactory, and normal values established.⁵² Lipomul, a soybean oil, has also been used successfully over the years.^{53,54}

It is important to consider the patient's clinical situation when interpreting CCK cholecystigraphy. The investigations that have confirmed the use of CCK cholecystigraphy generally were performed on outpatients who were not acutely ill or having pain at the time of the test. There are no data on the predictive value of this test in sick and hospitalized patients. Acute viral illness has been reported to cause a gastroparesis in some patients that resolves with the illness.⁵⁵ It would not be surprising if other visceral

organs like the gallbladder could become dysfunctional during acute illnesses unrelated to gallbladder disease.

A large number of commonly used therapeutic drugs cause reduced gallbladder contraction. These include opiates, atropine, nifedipine, indomethacin, progesterone, octreotide, theophylline, and benzodiazepine.³⁴ Hospitalized patients are invariably on multiple medications.

Thus, interpretation of CCK cholecystigraphy should take into consideration the clinical context. The study should be confirmatory in outpatients with recurrent biliary-colic like pain of several months duration, with otherwise negative medical workups that have excluded other diseases, and are

not taking drugs known to inhibit gallbladder contraction (Fig. 1).

Chronic Acalculous Biliary Disease (Sphincter of Oddi Dysfunction)

The sphincter of oddi is a smooth muscle structure surrounding the distal common bile duct, pancreatic duct, and their common channel, the ampulla of Vater. During fasting, the sphincter prevents bile to flow through the common duct into the small bowel, facilitates gallbladder filling, and prevents duodenal bile reflux. After meal ingestion, endogenous CCK relaxes the sphincter of Oddi, permitting bile to transit into the small bowel. Secretin has a similar function for the pancreatic sphincter.

After cholecystectomy, approximately 10% to 20% of patients have recurrent biliary colic-like pain (postcholecystectomy syndrome).⁵⁶ Although in many patients, the pain is of nonbiliary origin, the most common biliary cause is attributable to residual or recurrent biliary duct stones. Less common causes include ductal inflammatory stenosis or, rarely, inflammation or obstruction of a cystic duct remnant. Sphincter of Oddi dysfunction (SOD) occurs in approximately 10% of patients with the postcholecystectomy syndrome, although there are reports of greater than a 50% incidence from some specialized referral centers.⁵⁷ The recurrent biliary colic pain of SOD often cannot be distinguished from the pain of stone disease or a diseased pancreatic sphincter. This review will emphasize biliary sphincter disease.

SOD is a partial biliary obstruction at the level of the sphincter of Oddi, in which no morphologic or anatomical cause (stones or tumor) can be found. At sphincterotomy, approximately 60% of patients have histopathologic evidence of inflammation, muscular hypertrophy, fibrosis, or adenomyosis within the papillary zone. These findings may be caused by inflammation and scarring from repeated passage of microlithiasis, intraoperative trauma, or infection. The other 40% of patients have normal histology.

The explanation for why sphincter pain occurs after cholecystectomy is that the gallbladder normally acts as a reservoir and pressure release valve, decompressing the biliary ducts when the pressure increases, thus preventing pain. After cholecystectomy this effect is lost and pain ensues in patients predisposed to obstruction. It is not clear what precipitates the intermittent obstruction and pain. However, it is known that acute symptoms of sphincter obstruction can be provoked by various drugs, such as prostigmin (neostigmine) and morphine, and can be reversed by other drugs and hormones, eg, cholecystokinin, glucagons, amyl nitrite, and nitroglycerine. Although it is postulated that some patients with SOD have symptoms before cholecystectomy, no objective test can reliably make this diagnosis before cholecystectomy.

In the past patients with suspected SOD were classified either as having a fixed stenosis (papillary stenosis) or a functional obstruction caused by sphincter hypertonicity (dyskinesia). To standardize the workup, diagnosis, and therapy,

the Hogan or Milwaukee classification is now used, which categorizes patients into 3 types.⁵⁸ All 3 have episodic pain. In addition to pain, type I patients have liver enzyme elevations with the episodic pain and dilated biliary ducts. Type II patients have either enzyme elevations or dilated biliary ducts. Type III patients have only pain. It is uncertain whether these groups represent varying stages or degrees of a single entity or similar presentations of a heterogenous group of disorders.⁵⁹

Type I patients are the most straight-forward from a diagnostic standpoint. After excluding anatomical causes, eg, stones and tumor, with imaging and endoscopy, sphincterotomy is performed. Sphincter of Oddi manometry (SOM), generally considered the diagnostic gold standard (described below), is abnormal in as many as 90% of type I patients and thus not thought necessary before definitive therapy.⁶⁰ Most patients respond to sphincterotomy with relief of symptoms.

In type II patients, the diagnosis is less certain and documentation of abnormal sphincter pressure with manometry is recommended before proceeding to sphincterotomy. SOM is abnormal in approximately 50% of patients. Those patients with elevated pressure, from 65% to 90%, are more likely to respond to sphincterotomy.⁶¹

Type III patients are more problematic. Only 7% to 30% have abnormal SOM. Documentation of abnormal sphincter pressure is strongly recommended before sphincterotomy. It also is suggested that these patients be evaluated extensively for other causes of pain. In some, the pain may be a component of a more generalized functional intestinal motor disorder, eg, irritable bowel syndrome or duodenal hyperalgesia.

The diagnosis of SOD is challenging. In the past, endoscopic retrograde cholangiopancreatography (ERCP) was required to exclude stones, common duct strictures, and tumor and used to confirm ductal dilation and delayed clearance of contrast media. However, the findings were not specific and the incidence of serious complications high, eg, pancreatitis. Magnetic resonance cholangiopancreatography (MRCP) has now replaced ERCP for exclusion of tumor and confirmation of ductal dilation.

SOM is considered by gastroenterologists to be the gold standard for diagnosis of SOD. In the absence of stones, common duct stricture, or tumor, an elevated basal sphincter pressure (>40 mm Hg above duodenal pressure) is diagnostic. Other manometric findings have been described in SOD, including an increased frequency and amplitude of phasic contractions, rapid phasic contractions (tachyoddia), increased retrograde contractions, and the so-called "paradoxical response to CCK," ie, an increase rather than decrease in sphincter.^{62,63} However, these findings are poorly reproducible⁶⁴ and none, except for basal sphincter pressure, is predictive of therapeutic response.

SOM is a complex procedure available only at specialized biliary centers. During duodenoscopy, a triple-lumen pressure manometry gauge is positioned within the sphincter of Oddi and pressure readings obtained. The procedure is technically demanding with a failure rate of 20% to 25%, has poor reproducibility, and an incidence of pancreatitis reported to be 5% to 30%.^{63,65}

Table 3 Accuracy of Quantitative Cholescintigraphy for Diagnosis of Chronic acalculous Biliary Disease

Publication	Date	Reference	No. patients	Controls	Quantitative parameters	Sens. (%)	Spec. (%)
Darweesh	1988	67	28	28		67	85
Kloiber	1988	76	50	22	T_{peak}	93	64
					CBD $T_{1/2}$	88	68
Peng	1944	77	34	26	CBD dynamics	69	90
					CBD 45% clearance	88	80
Corazziari	1994	78	19	11	HDTT	100	83
Madacsy	2000	74	20	20	HDTT	79	71
Sostre	1992	82	26		CBD	100	100
Thomas	2000	89	34		T_{max} , 45, 60 min % clearance	83	81

T_{peak} , time to peak; CBD, common bile duct; HDTT, hilar-to-duodenal transit time; T_{max} , time to maximum activity.

Noninvasive methods of making the diagnosis would be preferable and a number of different methods have been investigated and clinically used. One of the earliest, a non-imaging method, was the Nardi test, a provocative pharmacologic test using morphine and prostigmin (neostigmine). Morphine produces contraction of the sphincter of Oddi and neostigmine stimulates bile secretion. A positive test for SOD included reproduction of the patient's pain and an increase in serum liver enzymes or amylase. Although specific, the test has low sensitivity for predicting the presence of SOD and poor correlation with outcome after sphincterotomy.⁶⁶

Ultrasonography is routinely used to detect common bile duct dilation. However, dilation is nonspecific and not diagnostic of SOD. Fatty meal or CCK simulated sonography has been investigated. CCK normally increases bile flow and relaxes of the sphincter. However, in the setting of obstruction and SOD, the increased flow and pressure may produce ductal dilation. However, the finding has a low sensitivity (70%) for biliary obstruction and SOD.⁶⁷ MRCP has a high accuracy for detection of ductal dilation and tumor. However, MRCP often does not detect small stones and it demonstrates anatomy and not bile flow physiology.

Because cholescintigraphy provides visualization of biliary drainage, it has long been expected to be valuable in the noninvasive diagnostic workup of biliary obstruction and SOD. Investigations in the mid-1980s suggested that cholescintigraphic image analysis could be used to make this diagnosis.^{68,69} Accuracy was reported to be high; however, the number of patient studied was not large, patient populations were highly selected, and the studies retrospective. The most reliable diagnostic criteria were found to be that of (1) delayed biliary duct clearance and (2) abnormal ductal dynamics, ie, prominent retained common duct activity at 60 minutes and no decrease in ductal activity, or even an increase, on delayed imaging at 2 hours. Delayed biliary-to-bowel transit was a considerably less sensitive diagnostic criteria. This is a postcholecystectomy pattern of partial biliary obstruction and cannot be expected to differentiate SOD from other causes, eg, cholelithiasis.

Quantitative cholescintigraphic methods subsequently were investigated with the expectation that they might be more sensitive than qualitative image analysis.⁷⁰ Pace and coworkers⁷⁰ were the first to investigate this methodology.

Twenty-six patients suspected of having "papillary stenosis" were studied. Normal values for hepatobiliary clearance were established with 10 asymptomatic postcholecystectomy subjects. Regions of interest (ROI) were drawn around the liver and biliary ducts, time-activity curves (TACs) generated, and a time to maximal activity (T_{max}) and half-time of emptying ($T_{1/2}$) were calculated. With this quantitative method, 25 of 26 subjects, with either normal or impaired biliary drainage were confirmed by ERCP.

Investigations from various other institutions also reported on the utility of quantitative analysis for cholescintigraphy.⁷¹⁻⁷⁵ Many of these studies demonstrated significant differences in quantitative scintigraphic parameters between patient groups with proven SOD and asymptomatic postcholecystectomy controls. In subsets of patients, follow-up quantitative hepatobiliary scintigraphy (QHBS) after successful sphincterotomy showed improvement in TACs and quantitative parameters.

Different methodologies were used by the various investigators, ie, in the choice of ROIs and the parameters quantified. ROIs included the liver, common bile duct, liver hilum, liver with biliary ducts, and duodenum. Quantitative parameters included T_{peak} , $T_{1/2}$, percent emptying at 45 and 60 minutes, duodenal appearance time, and hilar to duodenal transit time.

In 1988, 2 publications addressed the predictive accuracy of QHBS to diagnose biliary obstruction and SOD. Darweesh and coworkers⁶⁷ compared quantitative cholescintigraphy with fatty meal sonography in 34 patients and 22 asymptomatic controls. ERCP was the primary gold standard, although some patients had SOM. The most sensitive quantitative parameter was the 45-minute percent clearance derived from a hilar TAC. The diagnostic sensitivity was low, 67%, and the specificity, 85% (Table 3). Fatty meal sonography had similar sensitivity but a higher specificity of 100%. Combining both tests, sensitivity increased to 80%.

Also in 1988, Kloiber and coworkers published their investigation of 50 consecutive patients suspected of having biliary obstruction or SOD, using QHBS.⁷⁶ ERCP was the gold standard. Six patients had cholelithiasis, 10 had stricture, and 12 SOD. T_{peak} was the best quantitative discriminator, although the common bile duct $T_{1/2}$ and percent retention at 60 minutes were not very different. Sensitivity was 95%, specificity 68% (Table 3).

In 1994, Peng and coworkers reported on 34 patients suspected of having SOD and 26 asymptomatic controls.⁷⁷ Cholescintigraphic results were correlated ERCP and SOM. This was an unusual population consisting exclusively of men at a veteran's hospital (most patients with SOD are women). First, image analysis was analyzed, using the criteria of Zeman and coworkers described previously.⁶⁸ Sensitivity and specificity were 69% and 90%, respectively (Table 3). Using common duct TACs to determine the T_{\max} , $T_{1/2}$, percent clearance at 45 and 60 minutes, sensitivity and specificity were similar. Combining the 2 methods, sensitivity was 88% and specificity was 80%.

In 1994, Corazziari and coworkers investigated 19 symptomatic subjects with suspected SOD and 11 asymptomatic controls.⁷⁸ All had ERCP and SOM. A hilar-to-duodenal transit time (HDTT) was calculated. Normal values for HDTT were determined to be between 2 to 9 minutes. A prior study from these investigators found HDTT to be a more reproducible quantitative parameter than numerous others studied.⁷⁹ The HHDT and sphincter basal pressure had a strong correlation. Sensitivity for SOD was 100% and specificity, 83%. Improvement in the HHDT was seen after sphincterotomy.

In 2002, Cicala and coworkers, a study by the same investigative group, investigated 30 patients with clinical type I and type II SOD.⁸⁰ All had QHBS, and the following day, SOM. HDTT was delayed in all patients with increased basal pressure, in 100% of biliary Type I patients and 64% of Type II patients. Sphincterotomy was offered to patients with abnormal HHDT exceeding 9 minutes. All patients who had sphincterotomy became symptom free and HDTT either normalized or improved. A favorable postsphincterotomy outcome was predicted in 93% of cases by QHBS, but in only 57% of cases based on SOM.

However, Sand and coworkers, using the methodology of Corazziari and coworkers, found considerably more variability in the HDTT.⁸¹ Thirty-seven postcholecystectomy asymptomatic volunteers were studied. The mean HHDT was 12 ± 11 minute (range, 1 to 48 minutes), a considerably wider normal range than had previously been reported by Corazziari (5 ± 2 minute, range 2-8 minutes). Sand and coworkers used ^{99m}Tc-iodida and Corazziari, ^{99m}Tc-EIDA, both of which normally have slower liver clearance than ^{99m}Tc-mebrofenin but also are different from each other. Whether this explains the discrepancy is uncertain. However, it emphasizes the point that normal quantitative values must be established for the both the radiopharmaceutical and the specific methodology used.

In 2000, Madacsy and coworkers studied 20 symptomatic patients and 20 asymptomatic postcholecystectomy controls, using SOM as the gold standard.⁷⁴ A good correlation was found between SOM pressure and quantitative parameters, including HDTT, T_{\max} , and common duct $T_{1/2}$. Sensitivity was reported to be 79%, specificity 71% (Table 3), positive and negative predictive value, 88%, and 55%, respectively.

A different approach was taken by Sostre and Kaloo and coworkers, in 1992 at Johns Hopkins.⁸² First, sinalide was administered to increase bile flow. They sought to maximize the sensitivity of the test by increasing intrabiliary duct pres-

sure, similar to what had been done with ultrasonography. Sinalide 0.02 $\mu\text{g}/\text{kg}$ was infused over 3 minutes beginning 15 minutes before radiopharmaceutical injection. Second, they combined qualitative image analysis with quantitative analysis. Third, they used a scoring system consisting of 6 different parameters, scored 1 to 3 in severity, derived from image analysis and common bile duct time-activity curves. The six scored parameters included T_{peak} liver activity, time of first biliary visualization, degree of the biliary tree visualization, first bowel visualization, degree of common bile duct emptying, and a CBD-to-liver ratio. The 6 category scores were summed. Truth was determined in most cases by ERCP and SOM. SOD was diagnosed in 12 of 26 patients, all of whom had scores of 6 and greater. Of those that did not have SOD, all had scores equal of 4 or less, giving a sensitivity and specificity of 100% (Table 3; Fig 2). Although 100% should always be taken with a grain of salt, the results were impressive.

However, Pineau and coworkers, using the Sostre methodology in 20 asymptomatic postcholecystectomy patients, found a poor correlation between two scans performed on separate days in the same patient.⁸³ They found an overall specificity of 78%, which was reduced to 60% when a true negative was defined as two negative studies. ^{99m}Tc-mebrofenin was used by Pineau and coworkers and ^{99m}Tc-disofenin by Sostre and coworkers, but that probably does not by itself explain the discrepant findings.

The results of Corazziari and Sostre had stimulated considerable enthusiasm that quantitative cholescintigraphy would play an important role in the workup of patients suspected of having SOD. However, these good results were obtained at single institutions and included relatively small numbers of subjects. Furthermore, as noted, concerns have been raised about the specificity of both methodologies.

In 2003, Craig and coworkers reported on a prospective trial of 32 patients, 15 type II and 17 type III.⁸⁴ Type II and III are the more relevant clinical groups, since Type I is easily diagnosed. They directly compared the methods of Corazziari and Sostre. SOM was performed within one month of QHBS. Sinalide 0.02 $\mu\text{g}/\text{kg}$ was infused for 45 minutes, starting 15 minutes before ^{99m}Tc-diethyl IDA (DIDA) injection. Quantitative analysis was performed using a common duct ROI and the derived HDTT of Corazziari and the scoring system of Sostre.

Using the Sostre scoring system and a score of ≥ 6 for positive a positive test the sensitivity was only 38% and the specificity, 81%. Altering the positive criteria to ≥ 5 or ≥ 4 improved the sensitivity modestly to 38% and 46%, respectively, but reduced specificity to 63% and 50%, respectively. The results for HDTT were equally poor, with a sensitivity of 8% (HDTT ≥ 9) and specificity of 94%. Liberalizing the HDTT from ≥ 8 to ≥ 5 improved the sensitivity from 15% to 54% but at the cost of specificity, which decreased from 88% to 56% respectively. The HDTT and Sostre score correlated poorly with SO basal sphincter pressure.

The results of Craig and coworkers were disappointing to those that hoped that one or both of these methods would be a noninvasive alternative to SOM. The paper was strongly

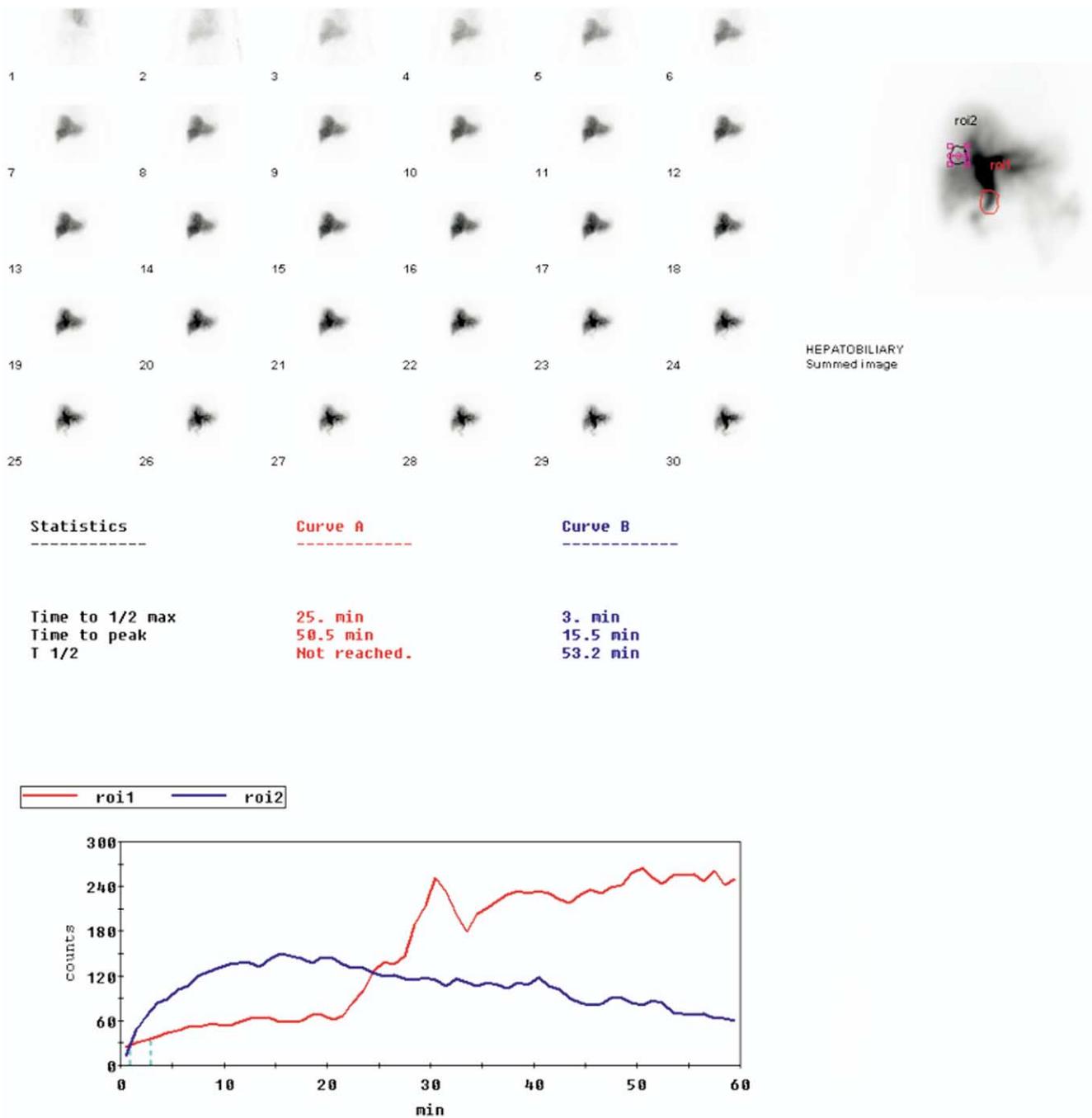


Figure 2 Quantitative cholescintigraphy in a patient with symptoms of the postcholecystectomy syndrome. Sincalide at $0.02 \mu\text{g}/\text{kg}$ was infused over the course of 10 minutes starting 15 minutes before the study. The sequential 2-minute summed images for 60 minutes show prominent retention in the common duct and little biliary-to-bowel transit. ROIs were drawn for the common duct and liver, time-activity curves generated, and quantitative parameters determined. Image analysis in conjunction with the quantitative parameters was used along with the Sostre scoring system. The score was 9, consistent with a partial biliary obstruction, eg, sphincter of Oddi dysfunction.

criticized, in regard to the specific methodologies used, because in fact, they differed from those of Corazziari and Sostre. First, the method of sincalide infusion differed. The rationale of Craig and coworkers, for the long 45-minute sincalide infusion was that a three-minute infusion was not physiological, had a higher incidence of side effects, and that its pharmacologic effect would dissipate before the start of

the study, due to its short half-life in serum (2.5 minutes). That rationale made sense in terms of gallbladder contraction as discussed in the prior section of this review, however, as was pointed out by Madacsy and coworkers the longer sincalide infusion may have masked delayed bile flow by counteracting hypertonicity of the sphincter, thus lowering the sensitivity for detection of SOD.⁸⁵

Madacsy and coworkers⁸⁵ had found that many patients with elevated sphincter pressure and abnormal bile drainage by QHBS will have a decrease in sphincter pressure and increase in transpapillary bile flow when sincalide is administered between 60 and 90 minutes after radiopharmaceutical injection. Thus, the 3-min infusion given by Sostre⁸² and coworkers may have been essentially homeopathic because its physiological effect was dissipated by the time of radio-tracer injection and thus had no adverse effect on the results, but by chance avoided the error of a longer infusion which relaxes a hypertonic sphincter.

Other methodological problems were criticized. Craig and coworkers⁸⁴ did not use the somewhat complicated background subtraction method of Corazziari and coworkers for generating common duct TACs. The original method “subtracted the liver TAC from the hilar TAC after normalizing the two curves taking into consideration the ratio of the two ROIs and their geometrical differences. The entire blood curve was multiplied by an appropriate factor to obtain a zero value in the subtraction of the activity of the heart from the liver at the first flexus”.^{78-80,86} The rationale for this method was that it corrected for variability of hepatic uptake and clearance between subjects. The method used by Craig and coworkers did not correct for background. Although Corazziari and coworkers had previously shown that the HHDT was the only reproducible quantitative variable of several they investigated, the subtraction technique was used with all their variables and no data were presented showing that the subtraction technique per se was necessary.

Finally, the Craig and coworkers study had no control subjects to validate their methodology, while Corazziari and Cicala had shown their method to be reproducible in asymptomatic controls and in patients with SO dysfunction and demonstrated that it discriminated asymptomatic controls from SOD patients.^{79,80}

A potential source of error for QHBS is drawing an appropriate ROI. This can occasionally be quite problematic due to overlying bowel and common bile duct. Image analysis in conjunction with ROI and quantitative analysis is thus quite important. In some patients an appropriate ROI is impossible to draw that will exclude bowel activity. In those patients, ingestion of fluids and delayed images may be helpful.

In addition to CCK, other provocative diagnostic tests have been used in conjunction with QHBS. In 1994, Madacsy and coworkers combined the Nardi test (morphine and neostigmine) with QHBS.⁸⁷ They compared Nardi positive patients (increased liver enzymes and pain) (#12) with the Nardi negative patients (#10) and found the QHBS results (hilar and common bile duct T_{max} , $T_{1/2}$, hilar, duodenal arrival time) to be significantly delayed ($P > 0.05$) only in the Nardi positive patients. Pain alone had four false positives. In another study, Bertalan and coworkers reported that they could differentiate patients with fixed stenosis from those with dyskinesia by the administration of nitrous oxide.⁸⁸ Continuous inhalation between 60 and 90 minutes reversed the obstructive bile flow pattern in patients with dyskinesia, but not in patients with stenosis. Similar results were shown by this investigative group using nitroglycerin and sincalide.^{74,88}

In 2000, Thomas and coworkers published an investigation of morphine provocation in conjunction with QHBS to diagnose SOD, on the same premise, that the drug might provoke functional abnormalities in patients with SOD.⁸⁹ Thirty-four patients had a clinical diagnosis of type II²¹ or III SOD,¹³ again the most diagnostically pertinent group of patients. SOM was the gold standard. The study was performed twice, with and without morphine provocation. Morphine 0.04 mg/kg was infused over 5 minutes immediately after ^{99m}Tc-IDA injection. The 2 studies were performed at least 48 hours apart. Without morphine, there was no difference in T_{max} or percent excretion at 45 or 60 minutes between those with normal pressure and those with abnormal sphincter pressure. With morphine, there was a significant difference ($P < 0.002$). The median percent excretion at 60 minutes was 4.9% in those with abnormal SOM and 28% in those with normal SOM. The sensitivity and specificity for detecting elevated sphincter of Oddi basal pressure by morphine augmented QHBS were 83% and 81%, respectively (Table 3). Further investigation of this method is indicated.

The so-called “paradoxical response to CCK” is repeatedly mentioned in the medical literature as being characteristic of SOD. It was reported by Toouli and coworkers and others that at SOM, CCK normally abolishes SO phasic contractions and decreases basal SO pressure.^{62,63} They further showed that in some patients with SOD, CCK had a “paradoxical effect,” ie, sphincter pressure increased, or did not decrease.

There is reason to question the whole concept of a paradoxical response. The total number of SOD patients studied with SOM reported to have a paradoxical response to CCK is not large. Of patients with proven SOD, overall only about 20% have been reported to have this finding. No normal subjects have been studied with SOM to establish the specificity of this finding, only small numbers of symptomatic patients without other evidence of the hepatobiliary disease. Unlike elevated sphincter pressure, a paradoxical response to CCK is not predictive of a response to sphincterotomy.⁶³ CCK is no longer used in conjunction with SOM. It is not clear if these short-term observations (2-10 minute recordings per pull-through) reflect the 24-hour pathophysiology of the sphincter.⁹⁰

During SOM, CCK was administered as a bolus infusion of 10 to 30 seconds. As discussed, this is not a physiological method of infusing CCK.⁴⁶ Unlike the gallbladder, little is known about the effect of different infusion methods on the sphincter of Oddi. As discussed in the prior section, some normal subjects (one-third) may have ineffective contraction of the gallbladder due to spasm of the cystic duct and neck of the gallbladder when administered a rapid infusion of sincalide, a different “paradoxical response”.⁴⁴ Whether the sphincter is similarly supersensitive to CCK is not certain, but that would not be surprising. When this paradoxical response has been looked for during cholescintigraphy in SOD patients receiving a slow infusion of CCK cholescintigraphy, no paradoxical response has been noted.^{72,74}

Although SOD generally is considered a functional disease, for the most part, therapy is anatomic, that is, endoscopic sphincterotomy. Multiple studies indicate that patients un-

dergoing sphincterotomy for SOD have complication rates 2 to 5 times higher than patients undergoing sphincterotomy for ductal stones. Pancreatitis occurs in as many as 20% of patients.⁶⁵ The current Hogan categorization of patients, type I-III, categorizes patients in a way that determines further workup and therapy, specifically, whether SOM and sphincterotomy are indicated. However, this approach has limitations, particularly in patients with type II and III disease, since many patients do not have abnormal sphincter pressure. In reality, many of these patients ultimately receive sphincterotomy. Now that MRCP has replaced ERCP in the workup, more attention should be paid to the functional aspects of this disease or diseases. The use of QHBS in conjunction with pharmacologic intervention allows noninvasive investigation of pathophysiology and may give better insight into the mechanism, diagnosis, and proper treatment of sphincter of Oddi disease.

One could also question whether SOM should truly be the gold standard for diagnosis. Relief of symptoms is the most important indicator of outcome, however, most published investigations have either not looked at this or evaluated therapeutic response over a relatively short time course. Pre- and post-therapy QHBS is an objective method for evaluating response to therapy that has uncommonly been used and could be easily correlated with clinical outcome. Pharmacologic interventions might predict response to various different nonsurgical therapies.

Because the Sphincter of Oddi is a smooth muscle structure, one would assume that muscle relaxants could have a therapeutic role. Sublingual nitrates and nifedipine have been shown to reduce basal Sphincter of Oddi pressure. Clinical benefit with nifedipine has been shown in 75% of patients with a reduction in pain during short-term follow-up. However, therapeutic drugs to date have had side-effects in up to one-third of patients and have been only partially effective. Antidepressants have been found useful in many type III patients. Transcutaneous electrical nerve stimulation and electro-acupuncture have all been shown to relax the Sphincter of Oddi.^{91,92} Further study on nonsurgical methodologies is indicated. QHBS can play an important role in evaluating these methodologies.

In an era of rapidly improving anatomical imaging methods, cholescintigraphy can perform a unique and need role in the evaluation of functional hepatobiliary disease. There is likely to be increasing need for QHBS for diagnosis and evaluation of therapeutic effectiveness in acalculous biliary disease. Although further investigation of the different methodologies is indicated, QHBS is already a clinically useful method for noninvasively making the diagnosis of chronic acalculous biliary disease.

References

- Ziessman HA: Acute cholecystitis, biliary obstruction, and biliary leakage. *Semin Nucl Med* 33:279-296, 2003
- Fisher RS, Stelzer F, Rock E, et al: Abnormal gallbladder emptying in patients with gallstones. *Dig Dis Sci* 27:1019-1024, 1982
- Raymond F, Lepanto L, Rosenthal L, et al: Tc-99m-IDA gallbladder kinetics and response to CCK in chronic cholecystitis. *Eur J Nucl Med* 14:378-381, 1988
- Thompson JC, Fried GM, Ogden WD, et al: Correlation between release of cholecystokinin and contraction of the gallbladder in patients with gallstones. *Ann Surg* 195:670-676, 1982
- Gracie WA, Ransohoff DF: The natural history of silent gallstones: The innocent gallstone is not a myth. *N Engl J Med* 307:798-800, 1982
- Chen PF, Nimeri A, Pham QH, et al: The clinical diagnosis of chronic acalculous cholecystitis. *Surgery* 130:578-581, 2001
- Yap L, Wycherley AG, Morphett AD, et al: Acalculous biliary pain: Cholecystectomy alleviates symptoms in patients with abnormal cholescintigraphy. *Gastroenterology* 101:786-793, 1991
- Fink-Bennett D, DeRidder P, Kolozsi WZ, et al: Cholecystokinin cholescintigraphy: detection of abnormal gallbladder motor function in patients with chronic acalculous gallbladder disease. *J Nucl Med* 32:1695-1699, 1991
- Cozzolino H, Goldstien F, Greening RR, et al: The Cystic Duct Syndrome. *JAMA* 185:920-924, 1963.
- Merg AR, Kalinowski SE, Hinkhouse MM, et al: Mechanisms of impaired gallbladder contractile response in chronic acalculous cholecystitis. *J Gastrointest Surg* 6:432-437, 2002
- Goldberg HI: Cholecystokinin cholescintigraphy. *Semin Roentgenol* 11:175-179, 1976
- Dunn FH, Christensen ED, Reynolds J, et al: Cholecystokinin cholescintigraphy. Controlled evaluation in the diagnosis and management of patients with possible acalculous gallbladder disease. *JAMA* 228:997-1003, 1974
- Davis GB, Berk RN, Scheible FW, et al: Cholecystokinin cholescintigraphy, sonography, and scintigraphy: Detection of chronic acalculous cholecystitis. *AJR Am J Roentgenol* 139:1117-1121, 1982
- Krishnamurthy GT, Bobba VR, Kingston E: Radionuclide ejection fraction: a technique for quantitative analysis of motor function of the human gallbladder. *Gastroenterology* 80:482-490, 1981
- Topper TE, Ryerson TW, Nora PF: Quantitative gallbladder imaging following cholecystokinin. *J Nucl Med* 21:694-696, 1980
- Pickleman J, Peiss RL, Henkin R, et al: The role of sincalide cholescintigraphy in the evaluation of patients with acalculus gallbladder disease. *Arch Surg* 120:693-697, 1985
- Fink-Bennett D, DeRidder P, Kolozsi W, et al: Cholecystokinin cholescintigraphic findings in the cystic duct syndrome. *J Nucl Med* 26:1123-1128, 1985
- Brugge WR, Brand DL, Atkins HL, et al: Gallbladder dyskinesia in chronic acalculous cholecystitis. *Dig Dis Sci* 31:461-467, 1986
- Misra DC Jr, Blossom GB, Fink-Bennett D, et al: Results of surgical therapy for biliary dyskinesia. *Arch Surg* 126:957-960, 1991
- Zech ER, Simmons LB, Kendrick RR, et al: Cholecystokinin enhanced hepatobiliary scanning with ejection fraction calculation as an indicator of disease of the gallbladder. *Surg Gynecol Obstet* 172:21-24, 1991
- Halverson JD, Garner BA, Siegel BA, et al: The use of hepatobiliary scintigraphy in patients with acalculous biliary colic. *Arch Intern Med* 152:1305-1307, 1992
- Middleton GW, Williams JH: Is gall bladder ejection fraction a reliable predictor of acalculous gall bladder disease? *Nucl Med Commun* 13:894-896, 1992
- Sorenson MK, Fancher S, Lang NP, et al: Abnormal gallbladder nuclear ejection fraction predicts success of cholecystectomy in patients with biliary dyskinesia. *Am J Surg* 166:672-674, 1993
- Reed DN Jr, Fernandez M, Hicks RD: Kinevac-assisted cholescintigraphy as an accurate predictor of chronic acalculus gallbladder disease and the likelihood of symptom relief with cholecystectomy. *Am Surg* 59:273-277, 1993
- Watson A, Better N, Kalf V, et al: Cholecystokinin (CCK)-HIDA scintigraphy in patients with suspected gall-bladder dysfunction. *Australas Radiol* 38:30-33, 1994
- Barron LG, Rubio PA: Importance of accurate preoperative diagnosis and role of advanced laparoscopic cholecystectomy in relieving chronic acalculous cholecystitis. *J Laparoendosc Surg* 5:357-361, 1995
- Khosla R, Singh A, Miedema BW, et al: Cholecystectomy alleviates acalculous biliary pain in patients with a reduced gallbladder ejection fraction. *South Med J* 90:1087-1090, 1997
- Klieger PS, O'Mara RE: The clinical utility of quantitative cholescintig-

- raphy: The significance of gallbladder dysfunction. *Clin Nucl Med* 23:278-282, 1998
29. Yost F, Margenthaler J, Presti M, et al: Cholecystectomy is an effective treatment for biliary dyskinesia. *Am J Surg* 178:462-465, 1999
 30. Middleton GW, Williams JH: Diagnostic accuracy of 99Tcm-HIDA with cholecystokinin and gallbladder ejection fraction in acalculous gallbladder disease. *Nucl Med Commun* 22:657-661, 2001
 31. Poynter MT, Saba AK, Evans RA, et al: Chronic acalculous biliary disease: cholecystokinin cholescintigraphy is useful in formulating treatment strategy and predicting success after cholecystectomy. *Am Surg* 68:382-384, 2002
 32. Majeski J: Gallbladder ejection fraction: an accurate evaluation of symptomatic acalculous gallbladder disease. *Int Surg* 88:95-99, 2003
 33. Jones DB, Soper NJ, Brewer JD, et al: Chronic acalculous cholecystitis: Laparoscopic treatment. *Surg Laparosc Endosc* 6:114-122, 1996
 34. Ziessman HA: Cholecystokinin cholescintigraphy: Clinical indications and proper methodology. *Radiol Clin North Am* 39:997-1006, 2001
 35. Adams DB, Tarnasky PR, Hawes RH, et al: Outcome after laparoscopic cholecystectomy for chronic acalculous cholecystitis. *Am Surg* 64:1-5, 1998
 36. Goncalves RM, Harris JA, Rivera DE: Biliary dyskinesia: natural history and surgical results. *Am Surg* 64:493-497, 1998
 37. Mishkind MT, Pruitt RF, Bambini DA, et al: Effectiveness of cholecystokinin-stimulated cholescintigraphy in the diagnosis and treatment of acalculous gallbladder disease. *Am Surg* 63:769-774, 1997
 38. Raptopoulos V, Compton CC, Doherty P, et al: Chronic acalculous gallbladder disease: multiimaging evaluation with clinical-pathologic correlation. *AJR Am J Roentgenol* 147:721-724, 1986
 39. Westlake PJ, Hershfield NB, Kelly JK, et al: Chronic right upper quadrant pain without gallstones: does HIDA scan predict outcome after cholecystectomy? *Am J Gastroenterol* 85:986-990, 1990
 40. DiBaise JK, Oleynikov D: Does gallbladder ejection fraction predict outcome after cholecystectomy for suspected chronic acalculous gallbladder dysfunction? A systematic review. *Am J Gastroenterol* 98:2605-2611, 2003
 41. Drane WE, Johnson DA: Sincalide-augmented quantitative hepatobiliary scintigraphy (QHBS): Definition of normal parameters and preliminary relationship between QHBS and sphincter of Oddi (SO) manometry in patients suspected of having SO dysfunction. *J Nucl Med* 31:1462-1468, 1990
 42. Sarva RP, Shreiner DP, Van Thiel D, et al: Gallbladder function: Methods for measuring filling and emptying. *J Nucl Med* 26:140-144, 1985
 43. Ziessman HA, Fahey FH, Hixson DJ: Calculation of a gallbladder ejection fraction: Advantage of continuous sincalide infusion over the three-minute infusion method. *J Nucl Med* 33:537-541, 1992
 44. Ziessman HA, Muenz LR, Agarwal AK, et al: Normal values for sincalide cholescintigraphy: Comparison of two methods. *Radiology* 221:404-410, 2001
 45. Wiener I, Inoue K, Fagan CJ, et al: Release of cholecystokinin in man: correlation of blood levels with gallbladder contraction. *Ann Surg* 194:321-327, 1981
 46. Hopman WP, Jansen JB, Rosenbusch G, et al: Gall bladder contraction induced by cholecystokinin: Bolus injection or infusion? *Br Med J (Clin Res Ed)* 292:375-376, 1986
 47. Nathan MH, Newman A, Murray DJ, et al: Cholecystokinin cholescintigraphy. A four year evaluation. *Am J Roentgenol Radium Ther Nucl Med* 110:240-251, 1970
 48. Harvey RF, Read AE: Effect of cholecystokinin on colonic motility and symptoms in patients with the irritable-bowel syndrome. *Lancet* 1:1-3, 1973
 49. Smythe A, Majeed AW, Fitzhenry M, et al: A requiem for the cholecystokinin provocation test? *Gut* 43:571-574, 1998
 50. Mackie CR, Baxter JN, Grime JS, et al: Gall bladder emptying in normal subjects—a data base for clinical cholescintigraphy. *Gut* 28:137-141, 1987
 51. Xynos E, Pechlivanides G, Zoras OJ, et al: Reproducibility of gallbladder emptying scintigraphic studies. *J Nucl Med* 35:835-839, 1994
 52. Ziessman HA, Jones DA, Muenz LR, et al: Cholecystokinin cholescintigraphy: methodology and normal values using a lactose-free fatty-meal food supplement. *J Nucl Med* 44:1263-1266, 2003
 53. Shafer RB, Marlette JM, Morley JE: The effects of Lipomul, CCK, and TRH on gallbladder emptying. *Clin Nucl Med* 8:66-69, 1983
 54. Hadigan C, Fishman SJ, Connolly LP, et al: Stimulation with fatty meal (Lipomul) to assess gallbladder emptying in children with chronic acalculous cholecystitis. *J Pediatr Gastroenterol Nutr* 37:178-182, 2003
 55. Oh JJ, Kim CH: Gastroparesis after a presumed viral illness: Clinical and laboratory features and natural history. *Mayo Clin Proc* 65:636-642, 1990
 56. Black NA, Thompson E, Sanderson CF: Symptoms and health status before and six weeks after open cholecystectomy: a European cohort study. ECHSS Group. European Collaborative Health Services Study Group. *Gut* 35:1301-1305, 1994
 57. Linder JD, Geels W, Wilcox CM: Prevalence of sphincter of Oddi dysfunction: Can results from specialized centers be generalized? *Dig Dis Sci* 47:2411-2415, 2002
 58. Hogan W: The post-cholecystectomy syndrome: The role of sphincter-of-Oddi dysfunction. *Bildgebung* 59:42-50, 1992 (suppl 1)
 59. Petersen BT: An evidence-based review of sphincter of Oddi dysfunction: Part I, presentations with “objective” biliary findings (types I and II). *Gastrointest Endosc* 59:525-534, 2004
 60. NIH state-of-the-science statement on endoscopic retrograde cholangiopancreatography (ERCP) for diagnosis and therapy. *NIH Consens State Sci Statements* 19:1-26, 2002
 61. Corazziari E, Shaffer EA, Hogan WJ, et al: Functional disorders of the biliary tract and pancreas. *Gut* 45:II48-II54, 1999 (suppl 2)
 62. Toouli J, Hogan WJ, Geenen JE, et al: Action of cholecystokinin-octapeptide on sphincter of Oddi basal pressure and phasic wave activity in humans. *Surgery* 92:497-503, 1982
 63. Rolny P, Arleback A, Funchjensen P, et al: Paradoxical response of sphincter of Oddi to intravenous-injection of cholecystokinin or ceruletide—manometric findings and results of treatment in biliary dyskinesia. *Gut* 27:1507-1511, 1986
 64. Thune A, Scicchitano J, Roberts-Thomson I, et al: Reproducibility of endoscopic sphincter of Oddi manometry. *Dig Dis Sci* 36:1401-1405, 1991
 65. Freeman ML, Nelson DB, Sherman S, et al: Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 335:909-918, 1996
 66. Steinberg WM, Salvato RF, Toskes PP: The morphine-prostigmin provocative test—is it useful for making clinical decisions? *Gastroenterology* 78:728-731, 1980
 67. Darweesh RM, Dodds WJ, Hogan WJ, et al: Efficacy of quantitative hepatobiliary scintigraphy and fatty-meal sonography for evaluating patients with suspected partial common duct obstruction. *Gastroenterology* 94:779-786, 1988.
 68. Zeman RK, Burrell MI, Dobbins J, et al: Postcholecystectomy syndrome: evaluation using biliary scintigraphy and endoscopic retrograde cholangiopancreatography. *Radiology* 156:787-792, 1985
 69. Lee RG, Gregg JA, Koroshetz AM, et al: Sphincter of Oddi stenosis: Diagnosis using hepatobiliary scintigraphy and endoscopic manometry. *Radiology* 156:793-796, 1985
 70. Pace RF, Chamberlain MJ, Passi RB: Diagnosing papillary stenosis by technetium-99m HIDA scanning. *Can J Surg* 26:191-193, 1983
 71. Varro V, Dobronte Z, Hajnal F, et al: The diagnosis of hypertonic Oddi's sphincter dyskinesia. *Am J Gastroenterol* 78:736-739, 1983
 72. Shaffer EA, Hershfield NB, Logan K, et al: Cholescintigraphic detection of functional obstruction of the sphincter of Oddi. Effect of papillectomy. *Gastroenterology* 90:728-733, 1986
 73. Roberts-Thomson IC, Toouli J, Blanchett W, et al: Assessment of bile flow by radioscintigraphy in patients with biliary-type pain after cholecystectomy. *Aust N Z J Med* 16:788-793, 1986
 74. Madacsy L, Middelfart HV, Matzen P, et al: Quantitative hepatobiliary scintigraphy and endoscopic sphincter of Oddi manometry in patients with suspected sphincter of Oddi dysfunction: Assessment of flow-pressure relationship in the biliary tract. *Eur J Gastroenterol Hepatol* 12:777-786, 2000
 75. Fullarton GM, Allan A, Hilditch T, et al: Quantitative 99mTc-DISIDA

- scanning and endoscopic biliary manometry in sphincter of Oddi dysfunction. *Gut* 29:1397-1401, 1988
76. Kloiber R, AuCoin R, Hershfield NB, et al: Biliary obstruction after cholecystectomy: diagnosis with quantitative cholescintigraphy. *Radiology* 169:643-647, 1988
 77. Peng NJ, Lai KH, Tsay DG, et al: Efficacy of quantitative cholescintigraphy in the diagnosis of sphincter of Oddi dysfunction. *Nucl Med Commun* 15:899-904, 1994
 78. Corazziari E, Cicala M, Habib FI, et al: Hepatoduodenal bile transit in cholecystectomized subjects. Relationship with sphincter of Oddi function and diagnostic value. *Dig Dis Sci* 39:1985-1993, 1994
 79. Cicala M, Scopinaro F, Corazziari E, et al: Quantitative cholescintigraphy in the assessment of choledochoduodenal bile flow. *Gastroenterology* 100:1106-1113, 1991
 80. Cicala M, Habib FI, Vavassori P, et al: Outcome of endoscopic sphincterotomy in post cholecystectomy patients with sphincter of Oddi dysfunction as predicted by manometry and quantitative choledochoscintigraphy. *Gut* 50:665-668, 2002
 81. Sand JA, Turjanmaa VM, Koskinen MO, et al: Variables affecting quantitative biliary scintigraphy in asymptomatic cholecystectomized volunteers. *Hepatogastroenterology* 46:130-135, 1999
 82. Sostre S, Kalloo AN, Spiegler EJ, et al: A noninvasive test of sphincter of Oddi dysfunction in postcholecystectomy patients: The scintigraphic score. *J Nucl Med* 33:1216-1222, 1992
 83. Pineau BC, Knapple WL, Spicer KM, et al: Cholecystokinin-Stimulated mebrofenin (^{99m}Tc-Choletec) hepatobiliary scintigraphy in asymptomatic postcholecystectomy individuals: Assessment of specificity, interobserver reliability, and reproducibility. *Am J Gastroenterol* 96:3106-3109, 2001
 84. Craig AG, Peter D, Saccone GT, et al: Scintigraphy versus manometry in patients with suspected biliary sphincter of Oddi dysfunction. *Gut* 52:352-357, 2003
 85. Madacsy L, Szepes A, Bertalan V, et al: Is hepatobiliary scintigraphy insensitive for the diagnosis of sphincter of Oddi dysfunction? *Gut* 52:1385-1386, 2003
 86. Corazziari E, Cicala M, Scopinaro F, et al: Scintigraphic assessment of SO dysfunction. *Gut* 52:1655-1656, 2003
 87. Madacsy L, Velosy B, Lonovics J, et al: Evaluation of results of the prostigmine-morphine test with quantitative hepatobiliary scintigraphy: A new method for the diagnosis of sphincter of Oddi dyskinesia. *Eur J Nucl Med* 22:227-232, 1995
 88. Bertalan V, Madacsy L, Pavics L, et al: Scintigraphic sign of functional biliary obstruction is pathognomic for sphincter of Oddi dysfunction. *Hepatogastroenterology* 51:76-81, 2004
 89. Thomas PD, Turner JG, Dobbs BR, et al: Use of (^{99m}Tc)-DISIDA biliary scanning with morphine provocation for the detection of elevated sphincter of Oddi basal pressure. *Gut* 46:838-841, 2000
 90. Sherman S, Lehman GA: Sphincter of Oddi dysfunction: Diagnosis and treatment. *JOP* 2:382-400, 2001
 91. Lee SK, Kim MH, Kim HJ, et al: Electroacupuncture may relax the sphincter of Oddi in humans. *Gastrointest Endosc* 53:211-216, 2001
 92. Guelrud M, Rossiter A, Souney PF, et al: The effect of transcutaneous nerve stimulation on sphincter of Oddi pressure in patients with biliary dyskinesia. *Am J Gastroenterol* 86:581-585, 1991