

## Quantitative Gallbladder Imaging Following Cholecystokinin

Thomas E. Topper, Thomas W. Ryerson, and Paul F. Nora

*Columbus-Cuneo-Cabrini Medical Center and Northwestern University Medical School, Chicago, Illinois*

**Quantitative gallbladder imaging with Tc-99m paraisopropylimidodiacetic acid (PIPIDA) was performed and time-activity curves over the gallbladder were obtained following i.v. injection of cholecystokinin (CCK). The gallbladders that failed to contract after CCK were found to be abnormal at surgery. This test appears to be helpful in evaluating patients who have normal oral cholecystograms but have persistent symptoms of gallbladder disease.**

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A frustrating clinical problem is presented by the patient who has symptoms strongly suggestive of gallbladder disease yet has had multiple oral cholecystograms interpreted as normal. At present there is no safe, simple, and reliable test that evaluates gallbladder function in such patients, and the need for cholecystectomy is, therefore, difficult to determine. Often both the patient and the surgeon are less than satisfied with the uncertainty of the indications for operative intervention. A new test using the biliary agent Tc-99m PIPIDA, followed by quantitative gallbladder imaging after stimulation with cholecystokinin (CCK), has been devised, and it may be of significant value in predicting which of these patients may benefit from cholecystectomy.

### MATERIAL AND METHODS

Imaging was performed on 34 patients (ages 23-79 yr) who had histories suggestive of biliary tract disease, and on four normal volunteers to serve as controls. The patients were kept on a fat-free diet the morning before the examination. An i.v. dose of Tc-99m PIPIDA (1-5 mCi) was given and the gallbladder region was scintigraphed at about 30-min intervals for 3 hr. If the gallbladder were identified, 0.2 mg/kg of Sincalide (a biologically active synthetic fragment of CCK) was given

intravenously. Scintigraphic recording was then performed continuously with a digital computer over the right upper quadrant and gallbladder for approximately 10 min. Areas of interest were then drawn around the gallbladder and surrounding background (Fig. 1). The stored data provided a background-corrected time-activity curve for the gallbladder. Note that with the background correction the activity in the gallbladder is directly proportional to gallbladder volume. The half-time ( $t_{1/2}$ ) of any CCK-generated contraction of the gallbladder was then measured.

### RESULTS

From January through October 1979 38 patients were studied with this method. The results fell into three categories.

**Normal gallbladder visualization with Tc-99m PIPIDA, with normal contraction after cholecystokinin.** (Fig. 1). Ten subjects had normal time-activity data. Four were normal volunteers with no symptoms. The other six had normal oral cholecystograms and vague upper-abdominal symptoms; none has come to surgery, so all are presumed to be free of gallbladder disease. Of these normal patients the time required for the gallbladder to contract to one-half its pre-CCK volume was measured from the corrected activity curves. Mean half-time for emptying was 140 sec ( $\pm 47$  s.d.).

**Normal oral cholecystograms, normal visualization with Tc-99m PIPIDA, but no contraction with cholecystokinin.** (Fig. 2). Eighteen patients were in this cat-

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For reprints contact: Thomas Ryerson, MD, Columbus Hospital, Dept. of Nuclear Medicine, 2520 N. Lakeview, Chicago, IL 60614.

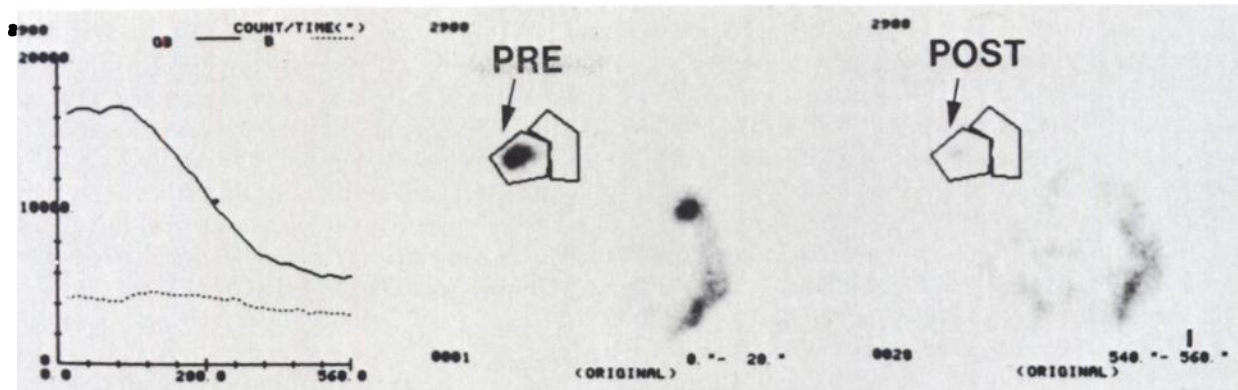


FIG. 1. Normal study with Tc-99m PIPIDA: Time-activity curves for gallbladder and background (left) show half-time for emptying to be 110 sec. Image of right upper quadrant is shown before (PRE) and 10 min after (POST) CCK injection. Arrow indicates gallbladder.

egory and eight have come to surgery. Seven underwent cholecystectomy, had histologic findings of low-grade cholecystitis, and have since improved clinically. Two of these patients had cholelithiasis proven by oral cholecystogram. One patient with failure of gallbladder contraction was operated on for chronic peptic ulcer. At surgery, a tense gallbladder was found and it did not empty significantly with manipulation. Because of the presence of ulcer, the surgeon elected not to perform a cholecystectomy in addition to the gastric resection. The postoperative course of the sixth patient has been unremarkable. Of the remaining ten patients, five have been lost to follow-up and five are not free of symptoms and are being treated medically with dietary restrictions and/or anticholinergic medications. Repeat studies are planned to reevaluate them for gallbladder surgery.

**Nonvisualization of the gallbladder with Tc-99m PIPIDA.** Ten patients had failure of gallbladder visualization. They also failed to visualize by oral cholecystogram, and were considered to have gallbladder disease.

DISCUSSION AND CONCLUSIONS

Gallbladder disease is a common problem, accounting

for a large percentage of hospital admissions annually. Acute and chronic calculous cholecystitis comprise about 90-95% of this large group of patients. With the introduction of oral cholecystography by Graham and Cole in 1924 (1), the diagnosis of gallbladder disease became simpler and the indications for cholecystectomy seemed better defined. The accuracy of modern oral cholecystography is generally accepted to be 90-95%. More recently ultrasonography of the gallbladder and biliary tree has added a new dimension to the diagnosis of calculous disease. Thus, the majority of patients with gallbladder disease present no major diagnostic problem, and the indication for cholecystectomy is almost universally accepted for patients with abnormal oral cholecystograms and/or ultrasonic studies.

However, the patient who is suspected of having acalculous gallbladder disease presents a much more challenging and often frustrating diagnostic and therapeutic problem. The plight of the patient is well documented in the medical literature. Acalculous cholecystitis as a pathological entity is well recognized among clinicians as gallbladder dysfunction secondary to disturbances of the autonomic nervous system that result in abnormal gallbladder emptying. This term describes a functional state rather than an anatomical or patho-

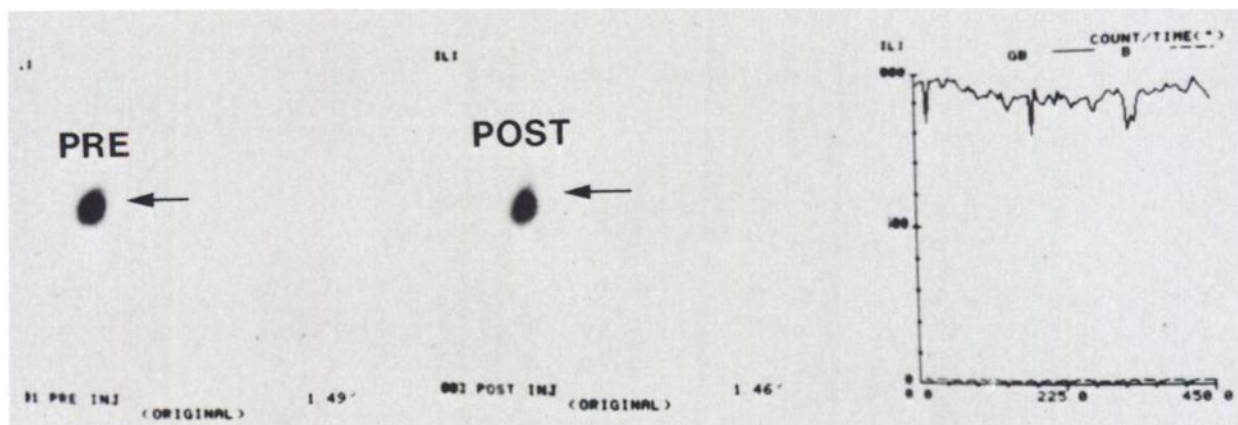


FIG. 2. Normal gallbladder visualization, but no contraction after CCK.

logical finding, and therefore has not been useful in the clinical evaluation of such patients. Many other terms have been applied to a condition where partial cystic-duct obstruction exists, resulting in delayed or abnormal emptying of the gallbladder associated with gallbladder colic. The most popular of these terms is "cystic-duct syndrome" (2). Another set of pathological entities affecting the gallbladder has been extensively studied and described by Arianoff (3) and collectively called the "cholecystoses." He defines cholecystosis as a pathological state of the gallbladder, independent of cholelithiasis, and different from cholecystitis. He subdivided this condition into cholesterolosis, polyposis, and intramural diverticulosis.

Of these acalculous disease states the last three have enjoyed wider recognition and more extensive study in Europe and South America than they have in the United States. Clinicians in this country have therefore been reluctant to recognize these clinical entities, and patients suffering from them often go untreated.

The purification of cholecystokinin (CCK) by Jorpes and Mutt (4) in 1959, and the subsequent availability of its synthetic, biologically active fragment, Sincalide, made possible the dynamic study of the gallbladder. Several series based upon such observations have been reported (5,6). The test involves the administration of CCK after the visualization of the gallbladder by routine radiographic methods. A test is judged to be positive if the following criteria are met:

1. A duplication of the patient's symptoms occurs following injection of CCK.

2. Failure of the gallbladder to empty properly, that is, less than a 50% reduction in its estimated volume.

3. The presence of abnormal contractions of the gallbladder, giving it a globular shape.

Due to the subjective criteria by which this examination is evaluated, however, cholecystokinin cholecystography does not appear to be as useful and reliable as was initially proposed (7).

Various Tc-99m-labeled compounds for scintigraphy of the hepatobiliary tree have been developed within the past 5 yr. Of these compounds, the iminodiacetic acid derivatives appear to be the most effective and useful. Two such agents, 2-6 methyliminodiacetic acid (HIDA)

and PIPIDA, are commercially available in standard kits, and are currently being used to demonstrate cystic-duct patency in the diagnosis of acute and chronic cholecystitis (8-10). The ability to measure quantitatively the emptying of the gallbladder scintigraphically following a well-defined physiological stimulant opens an avenue of investigation in these difficult groups of patients. Considering the results in the small number of patients reported in this paper, we believe that the dynamic function of the gallbladder can be assessed by the injection of CCK following gamma imaging of the gallbladder. The graphic analysis of the radionuclide imaging quantified this function and, we hope, will provide the clinician with an objective means of evaluating patients who have normal oral cholecystograms along with recurrent symptoms suggestive of gallbladder disease.

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