# Effect of Sequential Administration of an Opioid and Cholecystokinin on Gallbladder Ejection Fraction: Brief Communication

Shakuntala Krishnamurthy and Gerbail T. Krishnamurthy

*Nuclear Medicine Department, Tuality Community Hospital, Hillsboro, Oregon*

This study was undertaken to test the effect of sequential administration of an opioid and intravenous cholecystokinin (CCK) on gallbladder ejection fraction. **Methods:** Forty-nine patients who had received an opioid underwent quantitative cholescintigraphy with octapeptide of CCK (CCK-8). Gallbladder ejection fraction and CCK-8–induced paradoxical filling were calculated. **Results:** In the basal state, more of the hepatic bile entered the gallbladder (67%) than the small intestine (33%). After CCK-8 infusion, gallbladder ejection fraction was low in 37 (76%) of 49 patients and normal in 12 (24%). All 5 types of opioids lowered ejection fraction. CCK-induced paradoxical filling of the gallbladder was noted in 7 patients, but only one showed paradoxical filling of greater than 20% and none had a normal gallbladder ejection fraction. The lowering effect of opioids on gallbladder ejection fraction may last as long as 18 h after intake. **Conclusion:** CCK-8 produced a normal gallbladder ejection fraction in 24% of patients who had received an opioid and thus could exclude both acute and chronic cholecystitis during a single hepatobiliary study.

**Key Words:** opioid; cholecystokinin; gallbladder; ejection fraction; cholecystitis

**J Nucl Med 2006; 47:1463–1466**

In the assessment of gallbladder disease, cholescintigraphy plays a major role because of its high sensitivity (96%) and specificity (94%) and is unchallenged by other diagnostic modalities (*1*). When a patient with suspected gallbladder disease comes to the emergency department, the diagnosis has to be established immediately to enable the physician to decide whether to admit the patient to the hospital if acute cholecystitis is confirmed or to discharge the patient for outpatient follow-up if acute cholecystitis is excluded. During cholescintigraphy, visualization of a normal gallbladder usually occurs within 60 min and excludes acute cholecystitis reliably (*2*). When the gallbladder does not become visible within 60 min, 2 options are available for further evaluation: an option to obtain delayed images at 3–4 h and an option to administer morphine intravenously after 60 min. Delayed imaging enables evaluation of both acute and chronic cholecystitis during a single study. Acute cholecystitis is confirmed when the gallbladder does not become visible on the delayed images, and chronic cholecystitis is confirmed when the gallbladder is visualized but shows a low ejection fraction in response to cholecystokinin (CCK). Acute cholecystitis is confirmed when the gallbladder does not become visible within 30 min after morphine administration. Because acute cholecystitis is confirmed much sooner with morphine (within 90 min) than with delayed imaging (3−4 h), some physicians prefer morphine intervention for early diagnosis (*3*).

Physicians often prescribe an opioid for pain control before performing cholescintigraphy. Many times, an opioid is administered in the nuclear medicine department when the gallbladder does not appear by 60 min (*4*). The question often arises of whether one should assess for chronic cholecystitis with CCK when the gallbladder is seen after an opioid. Some patients may show a normal ejection fraction despite morphine (*5*). In such patients, both acute cholecystitis and chronic cholecystitis are excluded by means of a single hepatic iminodiacetic acid (HIDA) study, thus avoiding the need to repeat the study without opioid to confirm chronic cholecystitis. The frequency, dose, duration, and temporal relationship between opioid intake and CCK administration have not been analyzed critically to check the rationale for this type of approach. For example, for how long after administration of an opioid does it affect gallbladder ejection fraction? Do different opioids exert varied effects on gallbladder ejection fraction? Because CCK is known to induce gallbladder emptying, filling after CCK administration is a paradoxical phenomenon. CCK-induced paradoxical filling of the gallbladder has been shown to be a unique feature of patients with sphincter-of-Oddi spasm (*6,7*). Does prior opioid administration cause paradoxical filling of the gallbladder with CCK, mimicking sphincter-of-Oddi spasm? We undertook this study to critically analyze the effects of opioid intake on gallbladder response to CCK, and we discuss the results and rationale for such an approach.

Received Apr. 11, 2006; revision accepted Jun. 8, 2006.
For correspondence or reprints contact: Gerbail T. Krishnamurthy, MD, Tuality Community Hospital, 335 SE 8th Ave., Hillsboro, OR 97123.
E-mail: gtkrishna@aol.com

## MATERIALS AND METHODS

This report is based on 49 patients (33 women and 16 men) ranging in age from 20 to 84 y, with a mean (±SD) age of 52 ± 17 y and a mean weight of 83 ± 26 kg, who had received an opioid followed by CCK (Table 1). Ultrasound examination showed gallstones in 10, polyps in 1, and a normal gallbladder in 38. The types of opioids are shown in Table 1. The time from opioid intake to CCK infusion during cholescintigraphy was less than 0.5 h in 8 patients, 0.5–3 h in 13, 4–6 h in 15, 7–12 h in 10, and 13–18 h in 3. Liver function was normal in 45 and abnormal in 4. Total leukocyte count was elevated (>11,000) in 19 and normal in the remaining 30 (Table 1).

After a minimum 4 h of fasting, cholescintigraphic images were obtained with 111−296 MBq of $^{99m}$Tc-mebrofenin (adjusted for serum bilirubin level) using a large-field-of-view dual-head γ-camera fitted with a low-energy parallel-hole collimator. Images were collected at 2 s per frame during the first minute (perfusion) and at 1 min per frame for the next 59 min (function) during the hepatic phase and were recorded on a 128 × 128 × 16 matrix. Gallbladder-phase images were collected at 1 min per frame for 30 min with octapeptide of CCK (CCK-8). Bile flow into the gallbladder versus the small intestine was calculated as previously described (*1*). When the gallbladder had not become visible by 60 min, 0.04 mg of morphine per kilogram of body weight (maximum, 4 mg total) was given intravenously at 61 min and images obtained for an additional 30 min before the beginning of gallbladder-phase imaging with CCK-8. CCK-8 was infused through an infusion pump at a dose rate of 3 ng/kg/min for 3 min in the first 12 patients and for 10 min in the last 37 patients. When the gallbladder was seen, CCK-8 was given irrespective of the presence or absence of gallstones. With a 3-min infusion of CCK-8, a gallbladder ejection fraction of at least 35% was considered normal, and with a 10-min infusion, an ejection fraction of at least 50% was considered normal. Decay-corrected geometric mean counts were used to calculate gallbladder ejection fraction using custom-designed hepatobiliary software, as previously described (*1*). CCK-8 was not given to patients whose gallbladder did not become visible after morphine. Patients with acute cholecystitis underwent urgent cholecystectomy, and those with chronic cholecystitis underwent elective cholecystectomy.

**TABLE 1**
Patient Demography and Types of Opioid Intake

| Characteristic | No. of patients |
|---|---|
| Age (y) | |
| Mean | 52 |
| SD | 17 |
| Sex | |
| Female | 33 |
| Male | 16 |
| Liver function test result | |
| Normal | 45 |
| Abnormal | 4 |
| Total white blood cell count | |
| Normal (<11,000) | 30 |
| Elevated (>11,000) | 19 |
| Opioid received | |
| Morphine | 17 |
| Hydrocodone bitartrate and acetaminophen | 5 |
| Hydrocodone | 4 |
| Meperidine | 2 |
| Not known | 21 |
| Time from opioid intake to CCK-8 administration (h) | |
| <0.5 | 8 |
| 0.5–3 | 13 |
| 4–6 | 15 |
| 7–12 | 10 |
| 13–18 | 3 |

## RESULTS

The gallbladder was visualized within 60 min of hepatic-phase imaging in 44 of 49 patients. The mean hepatic bile flow into the gallbladder was 67% ± 30%. In the remaining 5 patients, the gallbladder became visible only after intravenous administration of morphine in the nuclear medicine department. Gallbladder ejection fraction was low in 37 (76%) of 49 patients and normal in the remaining 12 patients (24%) (Table 2). One patient with a normal ejection fraction (53%) was receiving a continuous infusion of morphine sulphate while being studied in the department. Seven patients showed CCK-induced paradoxical filling of the gallbladder. Paradoxical filling was less than 20% of basal gallbladder volume in 6 patients and was up to 40% in the seventh patient. All opioids lowered ejection fraction for as long as 12–18 h after intake.

## DISCUSSION

Our study confirmed some of the known effects of opioids on biliary dynamics and also showed some interesting new findings. In general, opioids decrease gastrointestinal and biliary tract motility and increase the tonus of sphincters (pyloric and Oddi sphincters). An increase in the tonus of the sphincter of Oddi diverted more of the hepatic bile to the gallbladder (67%) than to the small intestine (27%). The amount of bile entering the gallbladder after opioid administration (67%) is similar to that in subjects fasting longer than 4 h (64%) (*8*), suggesting that prolonged fasting has the same effect as opioids in facilitating gallbladder filling. Despite prior opioid intake, 12 (24%) of 49 patients had a normal ejection fraction, indicating that the force of CCK-induced gallbladder contraction can overcome the effects of opioid-induced increased tonus of the

**TABLE 2**
Effect of Cholecystokinin on Gallbladder Emptying in 49 Patients Who Had Received an Opioid

| Characteristic | No. of patients |
|---|---|
| Low gallbladder ejection fraction | 37 |
| Normal gallbladder ejection fraction | 12 |
| No paradoxical filling | 42 |
| Paradoxical filling | 7 |
| Filling < 20% | 6 |
| Filling > 20% | 1 |

sphincter of Oddi. These results confirm the findings of Achong and Oates (*5*), who reported a normal ejection fraction in 58% of their patients receiving morphine. Preemptying of the gallbladder with CCK in some may have contributed to their higher incidence of normal ejection fraction after morphine. Interestingly, one of our patients had an ejection fraction of 53% while receiving a continuous infusion of morphine during the study. Compared with our normal gallbladder ejection fractions for both a 3-min and a 10-min CCK-8 infusion, all 5 types of opioids reduced the gallbladder ejection fraction, irrespective of their structural differences (Table 1).

Opioids are metabolized in the liver into diglucoronide forms (morphine-3-glucuronide and morphine-6-glucuronide) and excreted in urine. Metabolized forms retain some of the actions of the parent molecule and have biologic effects lasting much longer than the serum half-life of the parent molecule. The effect of opioids on lowering of the gallbladder ejection fraction was evident for as long as 12–18 h after their intake.

A low ejection fraction in both calculus and acalculus chronic cholecystitis is attributed to spasm of the cystic duct (*8*). The low ejection fraction in 37 of our 49 patients could have been due to either cystic duct spasm or increased sphincter tonus induced by opioids. A low ejection fraction secondary to opioid intake is probably due to an increase in the tonus of the sphincter of Oddi and to a decrease in contraction of the gallbladder smooth muscle. We reported earlier that a low ejection fraction due to opioid intake is reversible but that a low ejection fraction due to cystic duct spasm is irreversible, when the study is repeated (*9*).

CCK-induced paradoxical filling of the gallbladder is unique to sphincter-of-Oddi spasm (*6,7*). The results of this study now show that CCK-induced paradoxical filling may also occur in some patients who have received an opioid. However, paradoxical filling is much less with opioid intake than with sphincter-of-Oddi spasm. Most patients with sphincter-of-Oddi spasm show a CCK-8–induced paradoxical filling of greater than 20% (*6,7*). In contrast, 6 of 7 patients with prior opioid intake showed CCK-induced paradoxical filling of less than 20%. Other features that distinguish sphincter-of-Oddi spasm from prior opioid intake include basal bile filling and CCK-stimulated gallbladder emptying. Mean bile flow into the gallbladder tends to be much lower in sphincter-of-Oddi spasm (28% ± 24%) than after opioid intake (67% ± 30%). Gallbladder emptying with CCK-8 remains normal in most patients with sphincter-of-Oddi spasm (6, 7) but is low in most patients after opioid intake. Six of 7 patients with paradoxical filling had a low gallbladder ejection fraction (Table 2). One patient with the largest paradoxical filling (40%) had an ejection fraction of 0%. CCK-induced paradoxical filling after intake of opioids is due to their constrictive effect on the sphincter, but paradoxical filling in sphincter-of-Oddi spasm is attributed to abnormal CCK receptor response (*6*). These filling and emptying differences should help to differentiate paradoxical filling due to opioids from that due to true sphincter-of-Oddi spasm.

Twelve (24%) of 49 patients had normal emptying with CCK-8 despite prior opioid intake (Table 2), and complete information about gallbladder function was obtained from a single HIDA study merely by extending it for an additional 30 min, thus avoided the need to repeat the entire study without an opioid. This approach saves the cost of the second study, which may vary from $2,100 to $2,400. It also spared patients the inconvenience of having to take time off from work for the second study. One may raise the question of the safety of giving CCK-8 to a patient with known gallstones. The answer to this question is self-evident if one recognizes the fact that endogenous CCK acts on the gallstone-containing gallbladder at least 3 times daily, once after each meal. The total endogenous CCK release after a meal is much higher and lasts longer than the total CCK infused over 3 or 10 min (3 ng/kg/min) during a HIDA study. Of the 805 HIDA studies done from January 2002 to December 2005 at our hospital, we gave CCK-8 to 63 patients with gallstones and saw no adverse effects, including acute obstruction of the common bile duct because of dislodgement of the gallstone. Giving exogenous CCK-8 within the physiologic dose range to a patient with gallstones is safe and merely mimics normal postmeal biliary dynamics.

Because opioids are used frequently for pain control, it is essential to obtain a detailed history before interpreting the results of the HIDA study, especially when the ejection fraction is low. For elective studies on patients with chronic cholecystitis, we ask the patients not to take opioids for a minimum of 24 h before the study (48 h is preferred). This requirement is waived for those who come to the emergency department and receive an opioid for relief of acute abdominal pain. We usually do not give CCK-8 to patients with amylase or lipase levels greater than 3 times normal. Because as many as 24% of patients may show a normal ejection fraction, it appears reasonable to give CCK-8 to those patients with prior opioid intake.

## CONCLUSION

Routine measurement of gallbladder ejection fraction with CCK-8 in patients with prior opioid intake enables early diagnosis of both acute and chronic cholecystitis, is convenient for the patient, and reduces the overall cost of diagnosing cystic duct spasm.

## REFERENCES

1. Krishnamurthy GT, Krishnamurthy S. *Nuclear Hepatology: A Textbook of Hepatobiliary Diseases*. New York, NY: Springer-Verlag; 2000.
2. Eikman EA, Cameron JE, Colman L, Natarajan TK, Dugal P, Wagner HN Jr. A test for patency of the cystic duct in acute cholecystitis. *Ann Intern Med.* 1975; 82:318–322.

3. Kim CK, Kevin KM, Juweid M, Mozley D, Woda A, Alavi A. Cholescintigraphy in the diagnosis of acute cholecystitis: morphine augmentation is superior to delayed imaging. *J Nucl Med.* 1993;34:1866–1870.
4. Choy D, Shi EC, McLean RG, Hoschi R, Murray IP, Ham JM. Cholescintigraphy in acute cholecystitis: use of intravenous morphine. *Radiology.* 1984;151: 203–207.
5. Achong DM, Oates E. Normal gallbladder ejection fraction after morphine augmentation. *Clin Nucl Med.* 1999;24:837–841.
6. Krishnamurthy GT, Krishnamurthy S, Watson RD. Characterization of basal hepatic bile flow and the effects of intravenous cholecystokinin on the liver, sphincter, and gallbladder in patients with sphincter of Oddi spasm. *Eur J Nucl Med Mol Imaging.* 2004;31:85–93.
7. Krishnamurthy GT, Krishnamurthy S. Diagnosis of sphincter of Oddi spasm with quantitative cholescintigraphy. *Indian J Nucl Med.* 2004;19:23–29.
8. Krishnamurthy GT, Krishnnamurthy S, Pinkert TC. Impact of cholescintigraphy and ultrasound in the management of gallbladder disease. *World J Nucl Med.* 2004;3:271–278.
9. Krishnamurthy GT, Krishnamurthy S, Brown PH. Constancy and variability of gallbladder ejection fraction: impact on diagnosis and therapy. *J Nucl Med.* 2004; 45:1872–1877.

JNM The Journal of NUCLEAR MEDICINE

# Effect of Sequential Administration of an Opioid and Cholecystokinin on Gallbladder Ejection Fraction: Brief Communication

Shakuntala Krishnamurthy and Gerbail T. Krishnamurthy

*J Nucl Med.* 2006;47:1463-1466.



*The Journal of Nuclear Medicine* is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)



SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING