EDITORIAL

Gallbladder Ejection Fraction: A Decade of Progress and Future Promise

The year 1991 marked the 10th anniversary of the description of gallbladder ejection fraction (GBEF) measurement scintigraphically (*1*). During the decade, GBEF measurement has become clinically valuable in the diagnosis and management of patients with acalculous chronic cholecystitis (*2,3*), cystic duct syndrome (*4*), common bile duct obstruction (*5*), and varieties of congenital and acquired biliary diseases (*6–8*). An accurate measurement and appropriate interpretation of GBEF values calls for clear understanding of two closely related fundamental principles. The first is the understanding of the physical principle behind the method used to image the gallbladder, and second is the understanding of the physiology associated with the stimulus (cholecystokinin) chosen to induce gallbladder emptying.

Imaging of the gallbladder began with the introduction of radiocontrast cholecystography by Graham and Cole in 1924 (*9*). A geometric method to compute gallbladder volume by a technique called the sum of the cylinder method was described in 1949 by de Silva (*10*). In this method, the gallbladder is assumed to be a pear-shaped organ cut into series of cylinders which are then stacked one above the other. Gallbladder volume is computed for a series of stacked cylinders by using the formula for the volume of a cylinder. By applying a slight modification of de Silva's geometric method, resting gallbladder volume has been measured using ultrasound images (*11*).

For organs such as the gallbladder or the urinary bladder which possess enormous capacity for receptive relaxation and change volume from moment to moment, the measurement of volume at any particular point in time does not have much pathologic significance except when the organ is enormously dilated. Gallbladder diseases are related more to an empyting abnormality than to resting volume changes. A decrease in emptying results in bile supersaturation, leading to sludge formation, crystallization, and ultimate stone formation (*12*).

Cholescintigraphy is a powerful technique for measuring gallbladder emptying nongeometrically by monitoring the change in ^{99m}Tc-IDA counts which represent bile volume. The gallbladder bile volume-count relationship is perfectly linear, between 0 and 50 ml range ($r = 0.998$). In addition, scintigraphy enables the measurement of minute-to-minute changes in bile volume (*1*), since bile emptying is a complex physiologic process requiring hormonal and neuromuscular coordination. The resting mean pressure inside the gallbladder is 10 cm of water, 12 cm in the common bile duct (CBD), and 15 cm in the sphincter of Oddi. A tensed gallbladder may appear small in size by changing its shape from one form to another without emptying its contents if it does not generate enough pressure inside to overcome the sphincter or the CBD pressure. In the presence of partial distal CBD obstruction, gallbladder bile often refluxes into the hepatic duct and reenters the gallbladder immediately (*5*). When calculating GBEF, it is essential to identify the exact time of onset, the end of gallbladder emptying and the beginning of refilling. A technique that does not enable precise identification of these points is likely to suffer from technical errors. The geometric volume measurement at rest is accurate as long as the assigned shape is maintained. Problems arise when the geometric method is extended to measure bile emptying. It is well recognized that the gallbladder changes its axis and shape when it contracts (*13*). The assumptions made for volume measurement at rest are not necessarily satisfied during contraction and emptying. In a recent study comparing simultaneous measurement of gallbladder emptying with cholescintigraphy and ultrasound, a good correlation was found in the mid range of GBEF (20%–50%). In five instances where GBEF by scintigraphy was between 0% and 20%, ultrasound overestimated EF as between 20% and 40%. In three other instances when scintigraphic EF was between 55%–80%, ultrasound underestimated EF to be at 45% and 60% (*14*).

The second important component of GBEF is understanding the role of cholecystokinin (CCK) in the regulation of gallbladder emptying. In 1928, only 4 yr after the description of cholecystography, cholecystokinin, the hormone responsible for gallbladder emptying, was identified by Ivy and Oldberg (*15*). Although several other hormones as well as the vagus nerve influence gallbladder emptying, the primary regulator is CCK (serum half-life, 2.5 min). Following intravenous CCK infusion, the gallbladder begins to empty within 2–3 min and continues to empty during infusion and for an additional 8–12 min after the cessation of infusion. The gallbladder ceases emptying when serum CCK levels drop below the threshold and it resumes emptying upon CCK reinfusion (*16*). The time for gallbladder refilling following cessation of CCK infusion varies widely, depending upon the dose and duration of CCK infusion. In some patients, the gallbladder may begin to refill within 8–10 min; in others it may take 40–60 min (*17*).

Because of short study times, many

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clinicians prefer intravenous CCK or CCK-8 to induce gallbladder emptying. When CCK-8 (Sincalide) was made available in 1973, the human dose was established by using an oral cholecystogram and applying a geometric method to measure gallbladder size (*18*). The package insert accompanying the kit recommends a CCK-8 dose of 0.02 μg/kg (20 ng/kg) infused over 30 or 60 sec, resulting in a dose rate of 20 or 40 ng/kg/min, respectively. During a study on a large number of normal subjects to evaluate new ^{99m}Tc-IDA agents, we first noted that 20 or 40 ng/kg produced intense abdominal pain in subjects who had never before experienced pain. This prompted us to re-evaluate CCK dose response with the then newly described scintigraphic technique. In 59 healthy adult volunteers (29 men and 30 women), CCK-8 doses (ranging from 1 to 40 ng/kg) were infused over a 3-min period. We found that 10 ng/kg for 3 min (3.3 ng/kg/min) was the optimal physiologic dose. Eleven of 42 subjects (26%) who received 20 ng/kg for 3 min (6.6 ng/kg/min) or 40 ng/kg for 3 min (13.3 ng/kg/min) doses experienced intense abdominal pain, nausea, transient bradycardia and hypotension and showed no gallbladder emptying (*19*). In the this issue of the *Journal*, Ziessman et al. point out the problem one may encounter by choosing the dose suggested in the package insert (*20*). Ziessman et al. found that a 3-min infusion of 20 ng/kg in normal subjects produced GBEFs ranging from 0% to 100%, but many of their subjects experienced untoward reactions. They obtained better GBEFs with 20 ng/kg infused over 30 min (0.6 ng/kg/min); the results improved further when they reduced the dose to 10 ng/kg over 30 min (0.03 ng/kg/min).

Why is a bigger CCK-8 dose not better? It has been shown in dogs that the thin, smooth muscle layer in the cystic duct is continuous with that of the gallbladder wall smooth muscle. The cystic duct smooth muscle displays a relatively higher threshold for CCK than the gallbladder wall muscle (*21*). An explanation for nonemptying of the gallbladder in normal subjects given 20 or 40 ng/kg of CCK could be that this high CCK-8 dose exceeds the cystic duct smooth muscle threshold, resulting in its contraction earlier than the fundus with subsequent nonemptying of the gallbladder.

In light of this information, one could ask: Why didn't the manufacturer of Sincalide (Bristol-Meyer—Squibb) change the package insert? Understandably, the manufacturer wants to avoid the requisite FDA paperwork, so they seem to rely on published literature (*19*), wall charts, and audiovisual tapes (available through Squibb Diagnostic, Montreal, Canada), all of which describe the more recent information on CCK-8 doses, for educational purposes. However when a dose of CCK-8 is needed, the physician or the technologist tends to choose the dose recommended in the package insert. This problem can be easily solved by incorporating correct CCK-8 dose rates into the nuclear medicine procedure manual for gallbladder imaging.

When measuring GBEF, it is better to not preset the time of the ejection period, but to individually identify the exact time of the beginning and end of emptying and the period of refilling. A preset time will alter the GBEF if the actual emptying period is longer than the preset time or when there is refilling within the preset interval. Also, the ejection rate will be inaccurate. A preset ejection period is satisfactory only when it equals the CCK-8 infusion time. Once the appropriate CCK-8 dose rate is chosen, one must determine how long to infuse it? The degree of GBEF is controllable to any desired level simply by changing the duration of CCK infusion. A 3-min infusion works well as long as the dose rate is physiologic. Ziessman et al's claim that the 30 min infusion is superior to the 3-min infusion may be true, but it does not set the record straight. A better conclusion based on their results would be that a 30-min infusion of a physiologic Sincalide dose rate is superior to a 3-min infusion of a nonphysiologic dose rate.

The appropriate clinical application of GBEF results requires standardization of the technique by avoiding some of the potential problems mentioned previously. GBEF is a relatively new measurement, and the method is based on sound physiologic and physical principles. The test, when correctly performed, should provide accurate answers to questions related to biliary dynamics posed by the referring clinician. GBEF measurements will have a major impact on studying the pharmacological effects of drugs that act due to nerve stimulation or due to stimulation or blockage of CCK receptor sites in the gallbladder wall.

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SELF-STUDY TEST

Pulmonary Nuclear Medicine

Questions are taken from the *Nuclear Medicine Self-Study Program I*, published by The Society of Nuclear Medicine

DIRECTIONS

The following items consist of a question followed by five lettered answers. Select the one lettered answer that is best in each case. Answers may be found on page 580.

1. The ^{81m}Kr ventilation and ^{99m}Tc MAA perfusion images shown in Figure 1 were obtained from a 23-yr-old man with shortness of breath. Which *one* of the following is the most likely diagnosis?

A. bronchial adenoma
B. pulmonary embolism
C. fibrosing mediastinitis
D. asthma
E. Swyer-James syndrome

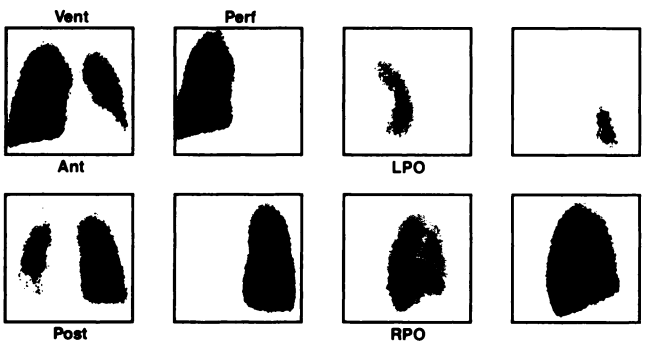

Figure 1

2. The same patient underwent a repeat ventilation–perfusion study (Fig. 2) 10 days later. Considering both of this patient's studies, which *one* of the following is the most likely diagnosis?

A. emphysema
B. anxiety reaction
C. pneumonia
D. asthma
E. pulmonary embolism

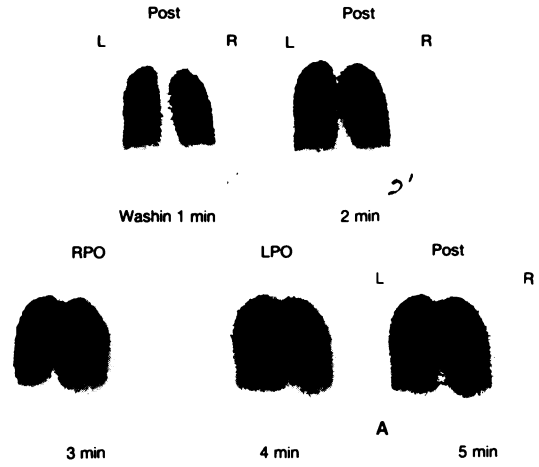

Figure 2A

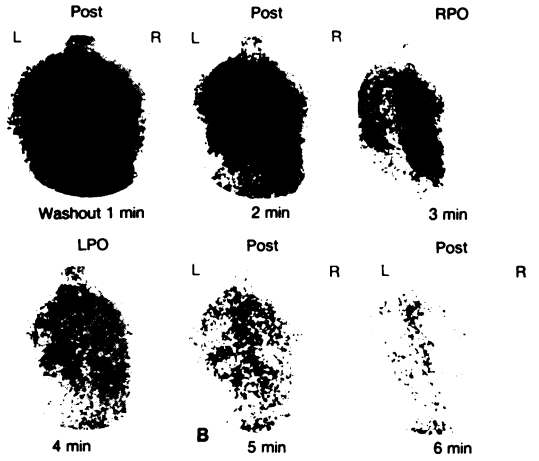

Figure 2B

(continued on p. 569)