

Gallbladder Dynamics Induced by a Fatty Meal in Normal Subjects and Patients with Gallstones: Concise Communication

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A study was undertaken to establish the pattern of gallbladder emptying in normal subjects and in patients with gallstones, using a fatty meal as stimulus to release endogenous cholecystokinin. The time from meal ingestion to beginning of gallbladder emptying (latent period), the total duration of emptying (ejection period), degree of emptying (ejection fraction), and the rate of emptying (ejection fraction/ejection period) were measured noninvasively by a nongeometric scintigraphic technique. The mean latent period and ejection rate were similar in normal subjects and patients with gallstones, but the mean ejection period and ejection fraction were significantly reduced in the patients. This study suggests that for an identical stimulus, the gallbladder in cholelithiasis begins to empty at the normal time but empties for a shorter duration; the result is a reduction of ejection fraction but not of ejection rate.

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There are 15-20 million people with gallstones in the United States (1). The incidence of gallstones increases with age and in patients with diabetes and celiac disease (1-3). The gallbladder's motor function plays a role in the pathogenesis of gallstones (4-6). Gallbladder emptying has been studied by oral cholecystography and ultrasonography (7,8), which are geometry-dependent and imply the fulfillment of many assumptions. The recent introduction of Tc-99m-labeled iminodiacetic acid derivatives (9) made it possible to study the hepatobiliary system nongeometrically using the gamma camera and an on-line computer. With this new technique, the gallbladder's motor function has been described for normal subjects and patients with gallstones, using cholecystokinin as the stimulus (10). The current study was undertaken to assess the following physiological parameters in normal subjects and in patients with gallstones, using a fatty meal as the stimulus: (1) How soon after a test meal does gallbladder emptying

begin, which would indirectly suggest the time of release of endogenous cholecystokinin into the circulation? (2) How long and how much does the gallbladder empty? and (3) Is there any difference in the rate of emptying between normal subjects and patients with gallstones? Endogenous serum CCK levels were not measured, since the technique for measurement is neither routinely available nor standardized.

MATERIALS AND METHODS

Subjects chosen for the study were seven normal adult males (control) with a mean age of 36 yr (range 26-53) and seven male patients with gallstones, mean age of 67 yr (range 37-79). The good health of the normal subjects was verified as described elsewhere (11). The patients were found to have incidental gallstones by ultrasound or radiological examination during the evaluation of their primary medical problems. They had normal liver function tests. Informed consent was obtained from each subject as approved by the hospital's committee for human studies.

After an overnight fast, each subject received an intravenous injection of 5 mCi (185 MBq) of one of the

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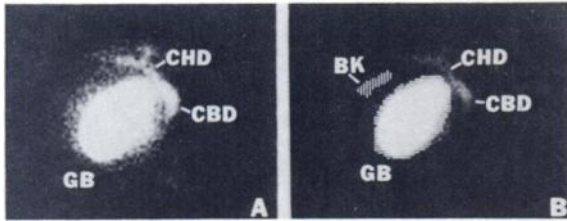


FIG. 1. Digital pinhole images of gallbladder without (A) and with (B) regions of interest marked. BK = background (liver); CBD = common bile duct; CHD = common hepatic duct; GB = gallbladder.

Tc-99m IDA derivatives: seven normal subjects and three patients received Tc-99m dimethyl-IDA (Tc-99m HIDA) and the other four patients received Tc-99m di-isopropyl-IDA (Tc-99m DISIDA). Sixty minutes later the subject was placed under a gamma camera fitted with a 5-mm pinhole collimator, as described elsewhere (11). Serial analog images were obtained every 2 min for 70 min. The data were concurrently stored in the computer, using a 64 × 64 byte-mode matrix, at a rate of 1 frame/min. At 10 min the subject ingested 8 oz/70 kg of half cream and half milk through a straw. Each 8 oz of this fatty meal contains 11 g of carbohydrate, 28 g of fat, 8 g of protein, and 325 cal. The subject's position was not disturbed during the entire study. Any nausea, abdominal pain, or any other symptom experienced by the subject was recorded. Symptoms experienced by the subject during the latent and ejection periods are considered to be biliary in origin.

Computer data analysis. Two regions of interest (ROI) were chosen on the composite computer image, one over the entire gallbladder and the second (background) over the right hepatic lobe lateral and superior to the gallbladder. The duct system was carefully excluded (Fig. 1). The counts from both ROIs were normalized to an

equal number of pixels and corrected for radioactive decay. Background subtraction provided the net gallbladder time-activity curve for the entire 70 min (Fig. 2).

The following four parameters were determined from the net time-activity curve: (a) latent period (LP), the time between the ingestion of the fatty meal to the onset of gallbladder emptying, (b) ejection period (EP), the time between the beginning and end of gallbladder emptying; (c) ejection fraction (EF), the bile emptied from the gallbladder by its contraction, expressed as a percent obtained by dividing the counts emptied by baseline counts before the fatty meal (11); (d) ejection rate (ER), obtained by dividing EF by EP.

Statistical analysis. The four parameters in both groups were subjected to an independent t-test to check for significant differences between means at the 95% confidence limit.

RESULTS

The mean (\pm s.e.m.) and range of LP, EP, EF, and ER in both groups are presented in Table 1.

In patients with gallstones, the mean LP and ER do not differ significantly from the normal means ($p > 0.05$). On the other hand, the mean EP and EF for the patients are significantly different from normal, EP being shorter ($p < 0.01$) and EF being lower ($p < 0.005$). No symptoms of any kind were experienced after fatty meals, either by normal subjects or by patients with gallstones.

DISCUSSION

Technetium-99m IDA hepatobiliary imaging is a sensitive test for the diagnosis of acute cholecystitis (12,13), in which the most common pattern is nonvisu-

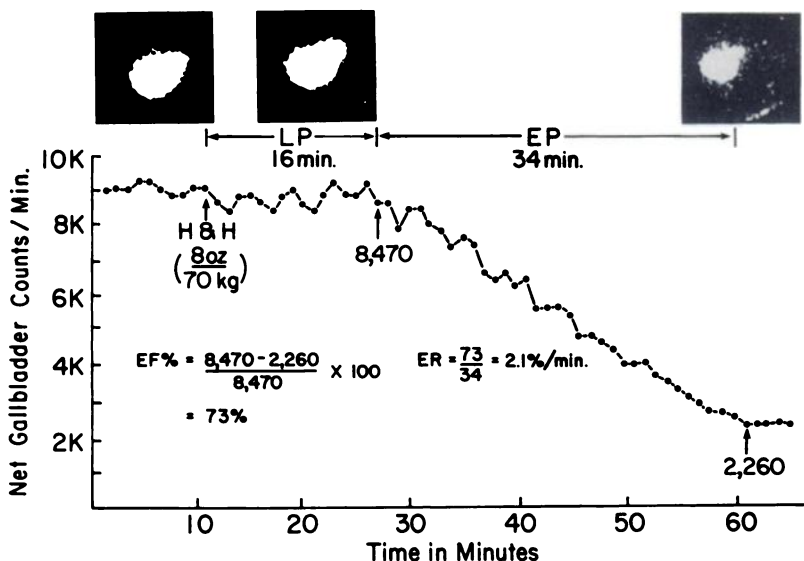


FIG. 2. Typical net gallbladder time-activity curve from normal subject. Initial part of curve represents steady state of gallbladder. Subject ingested half and half milk at 10 min, but gallbladder did not begin to empty for another 16 min. Once emptying started, it proceeded smoothly with no fluctuations for 34 min, at which time gallbladder reached a new base line. Corresponding images of gallbladder before, during, and after emptying are shown. EF = ejection fraction, EP = ejection period, ER = ejection rate, H&H = half cream and half milk, LP = latent period. See text for details.

TABLE 1. GALLBLADDER DYNAMICS INDUCED BY FATTY MEAL IN NORMAL SUBJECTS AND PATIENTS WITH GALLSTONES

	Latent period LP (min)	Ejection period EP (min)	Ejection fraction EF (%)	Ejection rate (EF/EP %/min)
Normal subjects N = 7				
1	24	33	40	1.21
2	13	37	82	2.21
3	6	31	53	1.7
4	26	30	56	1.87
5	15	16	88	5.51
6	11	27	77	2.87
7	14	32	55	1.71
Mean	15.6	29.4	64.4	2.4
s.d.	7.1	6.7	17.8	1.4
s.e.m.	2.7	2.5	6.7	0.5
Patients with gallstones G = 7				
1	18	14	25	1.79
2	7	7	34	4.86
3	11	4	35	8.75
4	12	18	25	1.38
5	8	26	34	1.3
6	8	17	36	2.14
7	9	27	55	2.03
Mean	10.4	16.1	34.9	3.1
s.d.	3.8	8.7	10.0	2.7
s.e.m.	1.4	3.3	3.8	1.0
p value (G vs. N)	>0.05	<0.01	<0.005	>0.05

alization of the gallbladder. In patients with chronic cholecystitis, gallbladder visualization is either delayed (14) or the emptying response to cholecystokinin infusion is decreased (15,16). None of our patients had acute or chronic symptoms, which suggests that theirs are asymptomatic gallstones. In the fasting state, the gallbladder contains nonradioactive bile. The visualization of the gallbladder with Tc-99m IDA is due to the entrance of radioactive bile, which will mix with nonradioactive bile.

Biokinetic differences do exist among various IDA agents, especially during the first 60 min (17). Since our gallbladder-emptying study begins after 60 min, these biokinetic differences should not have any major impact on gallbladder emptying (17,18). Since the counts before and after the emptying are used in the calculation of emptying parameters, the absolute radioactivity in the gallbladder in any patient is not important. The change from Tc-99m HIDA to Tc-99m DISIDA in our study should not have any effect on gallbladder emptying. In 115 normal subjects, we have shown that the filling and

emptying of the gallbladder are independent of the chemical nature of IDA compounds (18).

The gallbladder's motor function in gallstone patients is variable and the results are often conflicting. One study showed increased gallbladder emptying in response to a test meal (19), whereas another study found no divergence from the normal (20). The gallbladder requires CCK for contraction and emptying, and we believe that the latent period indirectly indicates the time for release of endogenous cholecystokinin. The gallbladder begins to empty when the endogenous cholecystokinin level rises above the baseline, and maximum emptying is noticed when the endogenous cholecystokinin reaches its peak (3,7). The similar latent period between controls and patients suggests that the time for release of endogenous cholecystokinin is the same in both groups (Table 1). The similar ER in both groups also suggests that once the gallbladder begins to empty, it expels the same fractional amount of bile volume per minute. However, a significant difference is noted in the gallbladder ejection period and ejection fraction between the two groups. The mean EP and EF in patients with gallstones are each about one half of normal (Table 1). These reductions cannot be attributed to either decreased duration or decrease in level of endogenous CCK, since we have shown previously that for an identical dose of exogenous CCK, the gallbladder's ejection fraction is again significantly reduced in patients with gallstones (10). The reasons for decreased EP and EF in patients with gallstones may include the following: (a) high levels of "anti-cholecystokinin peptide" in the serum, which may inactivate cholecystokinin rapidly in gallstone patients (21); (b) decrease in duration and degree of gallbladder contraction due to fibrosis of its wall; or (c) decrease in the number of gallbladder wall receptors for cholecystokinin. The last explanation appears the most attractive, since similar results were obtained on gallstone patients with exogenous OP-CCK (16). In older men the gallbladder emptying has been found decreased in one report (22) but increased in another (23). A more recent study, using a technique similar to ours, found that age and sex have no influence on gallbladder emptying (24). The age difference may account for some but not for all the difference between our control and gallstone patients.

Fatty-meal stimulation for a study of gallbladder motor function has certain advantages over CCK infusion. The ingestion of a test meal more closely simulates the normal physiological changes that accompany food ingestion. The test meal releases not only endogenous cholecystokinin but also other gastrointestinal hormones such as gastrins (25) that affect gallbladder contraction and emptying. Also, the fatty meal releases cholecystogogues for a longer time. The occasional side effects such as bradycardia, hypotension, nausea, and abdominal pain observed in subjects receiving high doses of exogenous cholecystokinin infusion (26) are not seen after a test

meal. Shafer et al. have shown that in normal subjects the fatty meal produced a consistent and more predictable effect on gallbladder emptying, compared with cholecystokinin (27). The two disadvantages of the fatty-meal stimulation are: (a) it cannot be given to patients who are advised to take nothing by mouth, and (b) the gallbladder emptying has to be monitored for a minimum of 60 min. In patients who are permitted nothing orally, exogenous OP-CCK infusion is the alternative method for evaluating gallbladder emptying. Functional abnormalities of the gallbladder are detected in symptomatic patients who may have an otherwise normal image pattern (15).

In summary, we find that the gallbladder in patients with gallstones shows a significantly reduced ejection period and ejection fraction in response to a fatty meal. Whether these functional changes are the cause or effect of gallstones is not clear at this stage.

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