Quantitative Biliary Dynamics: Introduction of a New Noninvasive Scintigraphic Technique

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We used a Tc-99m-labeled hepatobiliary agent to measure the partition of hepatic bile between gallbladder and intestine in sixteen normal patients and nine patients with cholelithiasis. In normal subjects, the fractions of the hepatic bile that flow into the gallbladder and the small intestine were widely variable, with mean values of 69 ± 7% (s.e.) and 31 ± 7% respectively. Bile reflux into the common hepatic duct was rare, occurring during the first 2/3 of the gallbladder ejection period and only when the ejection fraction was greater than 59%. The gallbladder's mean latent period, ejection period, ejection fraction, and ejection rate were 2 ± 1 min, 11 ± 1 min, 59 ± 4%, and 5.9%/min respectively. In patients with cholelithiasis, the fraction of hepatic bile flowing into the gallbladder was normal, but the ejection fraction was significantly reduced ($p < 0.005$). For an equivalent dose of cholecystokinin, the gallbladder in cholelithiasis is less responsive than in normal subjects.

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The daily secretion of one–two liters of bile by the liver is continuous, but its entry into the intestine is either continuous or periodic depending upon the time of need (*1*). After its secretion, the hepatic bile drains in two directions; one fraction enters the small intestine directly through the common bile duct (continuous flow) and the other fraction drains into the gallbladder through the cystic duct. The entry of hepatic bile into the gallbladder is controlled primarily by the sphincter of Oddi, whose increased tone raises the pressure in the common bile duct, diverting the hepatic bile into the relaxed gallbladder during fast. When the gallbladder contracts, either because of ingestion of meal or upon injection of cholecystokinin, it empties its contents first into the common bile duct and then into the intestine (periodic flow). The entire mechanism is under both nervous and hormonal control and normally is carried out in a well-coordinated fashion. None of the current diagnostic tests allow the measurement of these biliary motor functions noninvasively and quantitatively (*2*). Some of the important questions that require answers are: 1. How much of hepatic bile flows into gallbladder and intestine after an overnight fast? 2. How soon and how long does the gallbladder contract following a single injection of cholecystokinin? 3. How much does it empty? 4. How much delay is there between gallbladder emptying and common bile duct emptying? 5. Is there bile reflux into common hepatic duct from the common bile duct during gallbladder emptying? 6. What type of changes in biliary dynamics occur in patients with gallstones? To answer these questions in patients, it is essential to establish the values in normal subjects. Ideally, a test should be simple, noninvasive, accurate, quantitative, short in duration, and widely available with minimum cost. In this communication we report the results of a scintigraphic test for biliary dynamics that fulfills all of the above criteria. The reproducibility of gallbladder emptying results obtained with pinhole and parallel-hole collimators was established in rabbits in a comparison study

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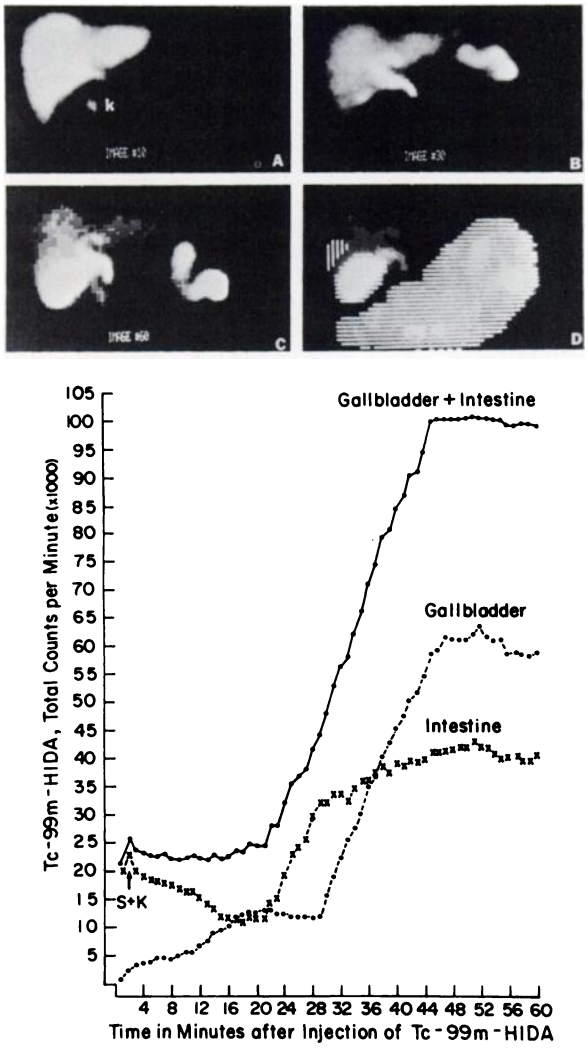


FIG. 1. First-phase study. Hepatobiliary image at 10 min (A) shows good liver uptake and slight kidney (K) excretion of Tc-99m HIDA. Common bile duct, gallbladder, and intestine are seen, with kidneys invisible beyond 30 min (B). By 60 min (C) most of radioactivity enters gallbladder and intestine. Regions of interest are marked over entire gallbladder, intestine, and liver (background) as shown (D), and time-activity curves are generated for entire 60 min (E). Sum of total counts in 60th frame over gallbladder and intestine are used to calculate differential hepatic bile flow.

MATERIAL AND METHODS

Control subjects. Sixteen normal volunteers (10 male and 6 female) ranging in age from 27 to 55 yr (mean age 40), were chosen as controls. Women were not on oral contraceptives. Gray-scale ultrasound studies showed normal bile ducts, with no stones in the gallbladder (*3*,*4*).

Patients. Nine patients with gallstones (7 men and 2 women), ranging in age from 38 to 88 (mean 65) were studied. The presence of stones in the gallbladder was documented in all nine by ultrasound, and additional confirmation was obtained in four by oral cholecystography and also at surgery.

Data collection. This was carried out in two phases.

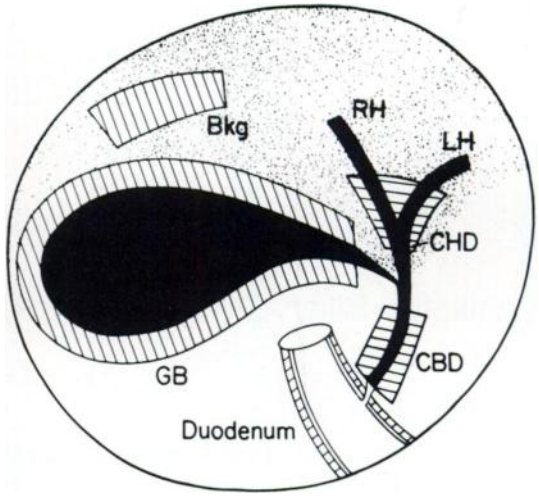


FIG. 2. Second-phase study. Selection of four regions of interest: one over entire gallbladder (GB); one over proximal common hepatic duct (CHD), including distal right and left hepatic ducts (RH & LH); one over common bile duct (CBD); and one over liver to provide a background (Bkg).

The first, lasting 60 min, permitted the measurement of relative hepatic bile flow, and the second phase, lasting 30 min, monitored the biliary dynamics.

First phase. After an overnight fast, each subject was given 5 mCi of Tc-99m HIDA (*5*) intravenously while lying supine under a large-field gamma camera fitted with low-energy, all-purpose, parallel-hole collimator. Serial, hepatobiliary analog images 2 min each, were obtained for 60 min (Fig. 1). The information was simultaneously recorded in word mode on 64 × 64 computer matrices at 1 frame per min, and stored on magnetic disk for later analysis.

Second phase. Immediately after completion of the first phase of data collection, the gamma camera was refitted with a pinhole collimator (5 mm diameter) and focused to include the gallbladder, common bile duct, and common hepatic duct as shown in Fig. 2. At 2-min intervals the analog images were recorded for 30 min and the data were simultaneously collected in 64 × 64 matrix in the computer at 1 frame/min. At 5 min, 2 ml of saline placebo was infused. At 10 min, either 10 ng/kg (n = 15) or 40 ng/kg (n = 10) of octapeptide of cholecystokinin (OP-CCK) was infused intravenously over 3 min through a Harvard infusion pump. The symptoms felt by the patient during the latent and ejection periods of the gallbladder were considered as biliary and symptoms at other times as non-biliary in origin.

First-phase data analysis. On a composite image that included 5 early and 5 late frames, three regions of interest (ROI) were chosen: one over the entire gallbladder, a second over the abdomen (excluding the liver, gallbladder, and urinary bladder), and a third (background) over the liver, superior and lateral to the gallbladder (Fig. 1A,B,C,D). The gallbladder and liver

ROIs were of approximately equal size. The time-activity curves, for the entire 60 min, were generated for three regions and the counts were corrected for physical decay. The liver counts (background), from pixels equal in number to the total gallbladder pixels, were subtracted from the gallbladder to obtain the net gallbladder counts. The intestinal and gallbladder counts in the 60th frame (between 59 and 60 min) were summed and considered to represent total hepatic bile counts. The counts in the gallbladder and small intestine were used to calculate the fractions of hepatic bile flowing into gallbladder and intestine (Fig. 1E).

Second-phase data analysis. Four regions of interest on a composite Phase 2 image, consisting of five early and five late frames, were chosen (Fig. 2): the first over the entire gallbladder (GB), the second over the common hepatic duct (CHD) including the distal right and left hepatic ducts (RH and LH), the third over the common bile duct (CBD), and the fourth (background) over the superolateral aspect of the liver. The time-activity curves were generated for each region, the background counts were subtracted, and the net counts decay-corrected and normalized. The time from beginning of OP-CCK infusion to the beginning of emptying (latent period), and the time from beginning to end of gallbladder emptying (ejection period), were noted (Fig. 3). The gallbladder ejection fraction (EF) was calculated as described earlier (*6*). The ejection rate was calculated by dividing the percent ejection fraction by total ejection period, expressed as percent ejection fraction per minute (Table 1).

From the CBD curve, (Fig. 3), the time from beginning of OP-CCK infusion to the peak (T_1) and the time from the peak to new baseline (T_2) were noted. In the absence of a CBD peak, the time from OP-CCK infusion to the new baseline was considered entirely as the T_2 time (Fig. 4).

Since the specific activity of hepatic bile after 60 min is very low, usually no rise in CHD counts is noticed beyond 60 min. A rise in CHD curve counts (during gallbladder emptying), if any, over the baseline (before OP-CCK) was considered as bile reflux from the CBD. The reflux usually lasts during the gallbladder ejection period and can be calculated for any period of time. We have chosen to calculate the reflux at its peak as shown on CHD curve. A reflux index for the common hepatic duct was calculated from the following formula:

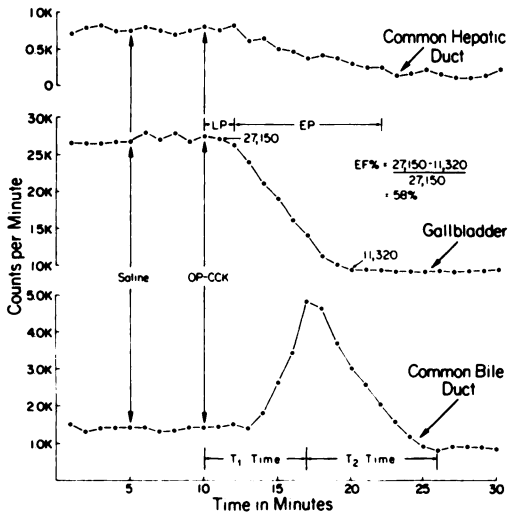


FIG. 3. Normal Biliary dynamics. Note no response to saline, and prompt emptying response to OP-CCK infusion. Usually no reflux is seen into common hepatic duct. Gallbladder starts to eject after latent period (LP) of 2 min. Ejection fraction (EF) of 58% is seen during ejection period (EP) of 9 min. Note peak in curve for common bile duct during last ⅓ of gallbladder ejection period. T_1 and T_2 times are measured as shown.

Comparison of pinhole with parallel-hole collimator. Four New Zealand white male rabbits (3–5 kg) with a mean weight of 4 kg were studied twice within a period of two weeks to test whether the pinhole and parallel-hole collimator studies would give comparable results. Except for the change in collimators, the rest of the procedure remained identical in both studies, including the dose of OP-CCK.

After an overnight fast, each rabbit was anesthesized with 50 mg/kg of ketamine and 5 mg/kg of Xylazine and was injected i.v. with 0.3 to 0.5 mCi of Tc-99m HIDA. Sixty minutes later, the animal was positioned supine under the gamma camera. In the parallel-hole study, the detector was positioned to include the entire abdomen; in the pinhole study it was placed to view the gallbladder, which was clearly visible in all rabbits by 60 min after injection of Tc-99m HIDA. The data were recorded in a computer at 1 frame/30 sec for 30 min in 64 × 64 matrix. At 10 min, 10 ng/kg of octapeptide of cholecystokinin was infused over a 3-min period through a Harvard infusion pump. The gallbladder ejection fraction was calculated as described above for humans. The results were tested by paired Student's t-test for any statistical difference between the two means (Table 2). P values of less than 0.05 were considered significant.

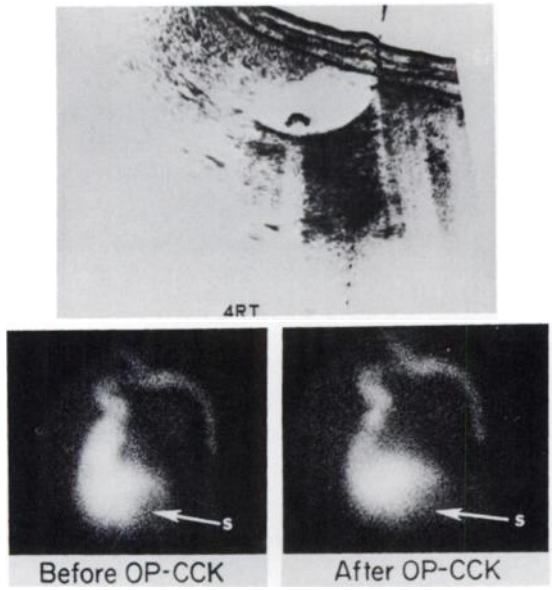
$$\text{Peak hepatic duct reflux index} = \frac{\text{CHD counts at peak time } (T_p) - \text{CHD baseline counts}}{\text{CBD counts at time } T_p - \text{Baseline CBD counts} + \text{GB baseline counts} - \text{GB counts at time } T_p}$$

The difference between the mean values was tested for any statistical significance by two-tailed unpaired Student's t-test.

TABLE 1. QUANTITATIVE BILIARY DYNAMICS

Subject	Age	Sex	Weight	Hepatic bile flow GB %	Hepatic bile flow Int %	Hepatic duct reflux	Common bile duct T_1 time (min)	Common bile duct T_2 time (min)	Gallbladder Latent period (min)	Gallbladder Ejection period EP (min)	Gallbladder Ejection fraction EF (%)	Gallbladder Ejection rate (EF/EP)
Normal control subjects n = 16												
DPa	49	M	165	62	38	Reflux 45%	6	5	3	8	65	8.1
KW	41	M	185	72	28	No reflux	2	6	1	7	78	11.1
MG	37	F	145	86	14	No reflux	5	14	2	10	35	3.5
AbH	41	M	133	ND*		No reflux	8	17	5	9	42	4.7
MW	47	F	184	64	36	No reflux	9	5	2	13	57	4.4
SJ	36	M	240	ND		No reflux	9	6	3	11	89	8.1
DC	40	M	174	ND		No reflux	2	6	4	11	48	4.4
RN	45	M	194	ND		Reflux 41%	2	6	3	7	73	10.0
LK	35	F	135	ND		No reflux	7	12	2	12	70	5.8
AH	27	M	120	83	17	No reflux	3	20	1	10	49	4.9
PB	28	F	150	62	38	No reflux	8	5	1	11	46	4.2
FH	46	F	150	93	7	Reflux 41%	8	5	1	20	59	2.8
EL	50	M	145	ND		No reflux	15	3	1	9	76	8.4
RW	55	F	116	ND		No reflux	6	13	1	10	64	6.4
RH	32	M	175	ND		No reflux	13	6	2	14	35	2.5
DH	35	M	205	31	69	No reflux	5	10	1	11	63	5.7
Mean	40		164	69	31		7	9	2	11	59	5.9
SD	8		33	19	19		4	5	1	3	16	2.5
SE	2		8	7	7		1	1	0.3	1	4	0.6
Cholelithiasis n = 9												
LD	56	M	184	75	25	No reflux	13	4	0	11	31	2.8
VM	63	F	142	39	61	No reflux	5	3	2	10	67	6.7
ER	85	M	122	ND		No reflux	0	12	2	8	47	5.9
JD	58	F	173	41	59	No reflux	4	20	1	13	56	4.3
LK	61	M	126	ND		No reflux	11	7	9	11	20	1.8
LH	77	M	170	ND		No reflux	0	12	5	7	37	5.3
CL	59	M	207	ND		No reflux	0	13	5	7	42	6.0
SG	88	M	136	86	14	Reflux 41%	0	8	2	9	28	3.1
JJ	38	M	290	ND		No reflux	9	8	3	12	12	1.0
Mean	65		172	60	40		5	10	3	9.8	38	4.1
SD	16		52	24	24		5	5	3	2.2	17.4	2.0
SE	5		17	12	12		2	2	1	0.7	6	0.7
P Value				NS	NS		NS	NS	NS	NS	<0.005	NS

* ND = not done.
† NS = not significant.



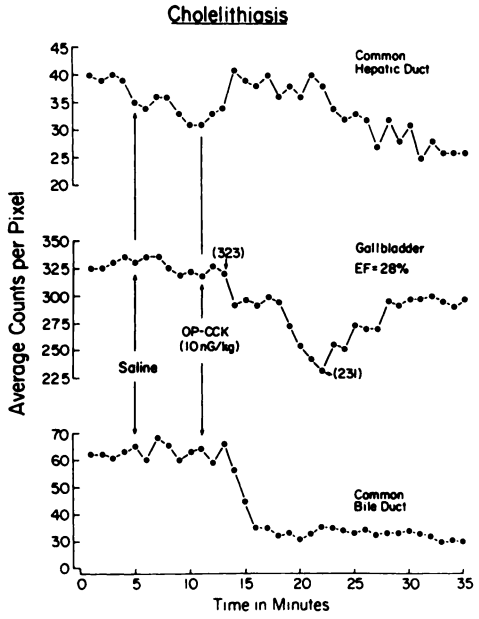


FIG. 4. Biliary dynamics in cholelithiasis. Ultrasound study (top), shows large gallstone with prominent acoustic shadow. Biliary Tc-99m HIDA images (middle) show uniform caliber of common bile duct, twisted neck, and a filling defect (S) due to stone (left) at fundus of gallbladder, defect becoming less clear after OP-CCK (right). Bile reflux into common hepatic duct is seen throughout gallbladder ejection period, and curve for common bile duct shows no peak. Gallbladder ejection fraction is 28% and ejection rate 3.1%/min. Note rapid gallbladder refilling to ¾ of its original volume, probably with bile that had refluxed into common hepatic duct (bottom).

RESULTS

Normal subjects (n = 16). The fractional mean (±s.e.) hepatic bile flow into the gallbladder was 69 ± 7%, and directly into the small intestine 31 ±7% (Fig. 1E and Table 1). Following OP-CCK infusion, the mean latent period and the ejection period of the gallbladder were 2 ± 0.3 min and 11 ± 1 min respectively. The mean ejection fraction was 59 ± 4%, with a mean ejection rate of 5.9 ± 0.6%/min. No reflux into the hepatic duct was found during gallbladder emptying in 13 of 16 subjects, and in the remaining three subjects a reflux index varying from (41 to 45)% was found, either corresponding to or just before the onset of CBD curve peak. The CHD reflux did not last beyond the peak of the CBD curve (Fig. 3). The CBD curve T_1 and T_2 times were 7 ± 1 min and 9 ± 1 min respectively. No untoward symptoms were experienced by the subjects following OP-CCK infusion.

TABLE 2. COMPARISON OF PINHOLE WITH PARALLEL-HOLE COLLIMATORS FOR MEASURING GALLBLADDER EMPTYING FOLLOWING A CONSTANT DOSE OF OP-CCK IN RABBITS

		Gallbladder ejection fraction (%)	
Rabbit (all male) No.	Wt.	Study 1 (pinhole)	Study 2 (parallel-hole)
1	5.0	70	60
2	5.0	42	52
3	3.0	79	87
4	3.0	83	86
Mean		68.5	71.2
		P > 0.05	

Eleven normal subjects, in the initial stages, were given 40 ng/kg of OP-CCK; this was reduced to 10 ng/kg in the last five subjects. The mean (±s.d.) ejection fraction of (59.3 ± 17)% obtained with 40 ng/kg, was not significantly different from that of (59.4 ± 15)% obtained with 10 ng/kg dose (P<0.05). There were no differences in any of the other parameters between 10- and 40-ng/kg dose. Therefore, the two subgroups are combined into one normal control group of sixteen.

Cholelithiasis. The mean fractional hepatic bile flow into the gallbladder in patients with cholelithiasis was 60 ± 12% and was not different from that for normal subjects (P>0.05). Following 10 ng/kg of OP-CCK, the mean gallbladder latent period was 3 ± 1 min and the ejection period 9.8 ± 0.7 min; these were similar to the values found in normal subject (P>0.05). The mean gallbladder ejection fraction (38 ± 6)% was significantly lower than that of the normal subjects (P<0.005), but the ejection rate (4.1 ± 0.7)%/min was normal (P>0.05). The shape of CBD curve was like the normal (Fig. 3) in five patients, and the peak was absent in the remaining four (Fig. 4). No symptoms were felt by patients following OP-CCK infusion.

In four rabbits the mean ejection fractions were 68.5% and 71.2% by pinhole and parallel collimators respectively (Table 2), these not being significantly different from each other (P>0.05).

DISCUSSION

Hepatic bile flow. Tc-99m HIDA serves as the most reliable bile marker for the evaluation of biliary physiology under basal conditions (*7–10*). The large-field gamma camera (40 cm diam) permits the inclusion of all of the areas between the left ventricle and the lower abdomen to the level of the urinary bladder (Fig. 1). The relationship between counts and volume is close to linear under parallel-hole collimator geometry (*11*). The fractions of hepatic bile that partition between the gallbladder and intestine in normal people are widely variable. Our findings agree with those of others (*12,13*) in showing that—granted a patent cystic duct—the fraction of hepatic bile flowing into the gallbladder in cholelithiasis is entirely within normal limits.

Pressure differences are known to exist at various levels of the biliary tree. In humans the resting mean (and range) pressures in the sphincter of Oddi common bile duct, and in the gallbladder are 15 (*9–23*), 12 (*10–15*), and 10 (*8–12*) cm of water respectively (*14–17*). Pressures as high as 100 mm of mercury have been recorded across the sphincter of Oddi (*18–23*). The sphincter normally shows alternate contraction and relaxation at a frequency of 7.5 per min. The pressure falls to the CBD level during relaxation, allowing the bile to pass from CBD to duodenum, whose pressure normally is zero (*22*).

Normal gallbladder dynamics. Since the typical pressure rise between the gallbladder and the common bile duct is normally less than 2 cm of water, the gallbladder can contract and overcome the CBD pressure easily, starting ejection as early as 2 min, usually during OP-CCK infusion. The gallbladder discharge lasts 11 min, with a mean ejection fraction of 59% (range 35 to 89%); the mean ejection rate is thus $\propto$6%/min. In only two control subjects was the ejection rate less than 3.5%/min (Table 1).

The sphincter of Oddi can withstand a mean pressure of 15 cm of water (range 9–23 cm) in CBD (*24*). This means that the contracting gallbladder should generate pressures exceeding 15 cm of water to empty its contents. The results of our study show that the gallbladder accomplishes this in about 11 min following OP-CCK infusion.

The method described here does not require any assumption of a particular shape for the gallbladder, and thus it overcomes the major limitation of those tests that are geometry dependent. Ultrasound, for example, incurs a mean error of 17% for gallbladder volumes less than ~17 cc (*25*).

Pinhole collimators limit the field of view to the primary region of interest and provide the clear separation of gallbladder, common bile duct, common hepatic duct, and upper small intestine. On some occasions, the gamma images of these structures at 60 min are not separable by any angulation tricks with the parallel collimator, whereas they are easily separable by the pinhole.

Normal dynamics of the common bile duct. When the gallbladder ejects its bile into the common bile duct, the CBD curve shows a rapid peak occurring in the last third of the gallbladder ejection period (Fig. 3). We measure a time, T_1, from the beginning of OP-CCK infusion to the CBD peak, but we are still not sure what T_1 and T_2 (the falloff time) really measure.

Normal dynamics of the common hepatic duct. In three of 16 normal controls there was 41% to 45% bile reflux into common hepatic duct during gallbladder ejection. The peak reflux lasted only during the first and middle third of the gallbladder ejection period. The ejection fraction in these three was >58%, suggesting that the reflux index results from a recalcitrant sphincter of Oddi. No normal controls with ejection fractions <50% showed hepatic duct reflux.

Dynamics in cholelithiasis (n = 9). One of nine patients with cholelithiasis had a CHD reflux of 41%, with ejection fraction only 28%; the reflux continued through the last third of GB ejection (Fig. 4).

The cholelithiasis patients in general showed significantly lower GB ejection fractions than the controls ($P<0.005$), and only two exceeded 50%. Their gallbladders were evidently less responsive to intravenous cholecystokinin. The mean ejection rate of 4.1 ± 0.7 did not differ significantly from that in the normal controls ($P>0.05$). Four of nine patients showed no rise in CBD counts during gallbladder ejection (Fig. 4), and had much lower ejection fractions (Table 1).

OP-CCK stimulation. The serum half-life of cholecystokinin is only 2.5 min (*26*), so it is critical to maintain the uniform dose rate of OP-CCK throughout the 3-min infusion period. We found it rather difficult to achieve uniform dose rate by hand injection, and prefer the infusion pump for a predetermined dose rate.

The 30-min data collection is adequate (20 min after OP-CCK) for the dynamic phase of the study if OP-CCK is used as the stimulus. The 13-min sum of latent period (2 min) and ejection period (11 min) still leaves another 7 min for delayed gallbladder contraction in disease. With the short serum half-life of OP-CCK, there is little chance of further ejection after the 20 min.

Our recommended dose of OP-CCK (10 ng/kg over 3 min) is based on another study involving a large number of subjects (*27,28*), but some normal gallbladders may not discharge even with a larger dose, so each laboratory should establish its own standard technique and dose rate for OP-CCK.

Potential application of current method. The current technique is unique in several ways: (a) it is nongeometric; (b) does not require the use of contrast agents, catheters, or drugs in pharmacologic dose; (c) provides simultaneous anatomic and physiologic information; (d)

allows precise identification of time of filling, emptying, and refilling of the gallbladder (Fig. 4C); and (e) the results are quantitative. All the components required for the study (gamma camera, computer, and radiopharmaceuticals) are already available in most nuclear medicine departments, and the radiation dose is within safe limits (*29*). The entire data collection takes about 90 min, and this can be reduced to 30 min if only dynamic data are of interest. The prime areas where this technique is applicable are: (a) in the study of the effect of drugs on biliary function; (b) to furnish indications for, or monitor the effects of, endoscopic or surgical sphincterotomy; (c) in biliary dyskinesia; (d) for the quantitation of partial CBD obstruction based on gallbladder ejection rate; and (e) in the study of nervous and hormonal effects on biliary dynamics. We hope that this approach will enable the physician to unravel the unknown of biliary pathophysiology noninvasively.

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