Gallbladder Function During Gallstone Dissolution

Effect of Bile Acid Therapy in Patients With Gallstones

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Impaired gallbladder emptying has been associated with gallstone disease but any effect on or from bile acid therapy for gallstone dissolution is unknown. We evaluated gallbladder filling and emptying with low-dose cholecystokinin infusion (0.02 U/kg · h) by computer-assisted cholescintigraphy in 52 controls versus 31 gallstone patients: 17 treated with 12–15 mg/kg · day of chenodeoxycholic acid and 14 with 8–10 mg/kg · day of ursodeoxycholic acid. Thirteen of 31 patients with complete dissolution had four scans: before, after 3 mo of therapy, after stone dissolution, and after discontinuation of bile acids. The 18 failures had three scans: before and after 3 and 15–18 mo of therapy. Before therapy, the 31 gallstone patients had significantly impaired gallbladder emptying compared with controls, but filling was not decreased. Bile acids significantly decreased emptying in both treatment groups after 3 mo of therapy. In the dissolution group, emptying improved once the stones had dissolved and increased further upon discontinuing the bile acids. In the failures, impaired emptying persisted for up to 15–18 mo. Gallbladder filling in the 31 gallstone patients was also significantly decreased after 3 mo of bile acid therapy, particularly in the failure patients, 5 of whom exhibited zero filling. No differences were detected between ursodeoxycholic acid and chenodeoxycholic acid for either gallbladder function or efficiency of dissolution. Thus, bile acid therapy impairs gallbladder filling and emptying in gallstone patients. Gallstone dissolution improves emptying, which is further enhanced when bile acids are discontinued.

There is growing evidence that gallbladder emptying is abnormal in patients with cholelithiasis (1–4). This altered gallbladder motor function may be a consequence of the physical presence of the stones, result from the chronic inflammatory process affecting the gallbladder, or relate to the etiology of stone formation. It may also influence the outcome of bile acid therapy to dissolve gallstones. Moreover, some patients with cholelithiasis have normal gallbladder evacuation (4,5). Ursodeoxycholic acid (UDCA), despite its proven efficacy in cholesterol gallstone dissolution (6–8), has also been reported to reduce gallbladder contractility (3). As no information is available on gallbladder filling and emptying during or after gallstone dissolution, we now report results from a group of patients with cholelithiasis treated with bile acids and followed from 1979 to 1987.

Materials and Methods

Patients

Thirty-seven patients with cholelithiasis treated with bile acids were included in the study (Table 1). All were within 20% of their ideal body weight and had radiolucent gallstones in a radiologically functioning gallbladder. The final analysis was conducted in 31 patients. Six patients were excluded because of loss from follow-up (3), cholecystectomy early in the course of the study (2), and death unrelated to biliary tract disease (1). The remaining 31 patients consisted of 16 women aged 21–83 yr (mean 45.4 yr) and 15 men aged 31–65 yr (mean 45.1 yr). Ten had contraindications to surgical treatment (5 ischemic heart disease, 2 congenital heart defect, 2 old age, and 1 severe chronic lung disease). The remaining 21 patients

Table 1. *Comparison of Features Between the Groups of Gallstone Patients Who Received Medical Therapy*

Features	Dissolution	Failure	Exclusions
Clinical			
Number	13	18	6
Female	8	8	2
Male	5	10	4
Age (yr)	48.5 (21–70)	51.1 (31–83)	43.0 (31–55)
CDCA treatment	8	9	4
UDCA treatment	5	9	2
Episodes of biliary colic			
None	6	9	2
1–3	3	5	3
>3	4	4	1
Radiologic			
Gallstones			
Floating	3	1	—
Size			
<1 cm	9	7	3
1–2 cm	1	10	3
Number of stones			
Single	—	3	2
1–5	7	6	1
>6	6	9	3

CDCA, chenodeoxycholic acid; UDCA, ursodeoxycholic acid.

refused surgery. Patients were classified according to clinical presentation and frequency of biliary colic as previously described (4). Sixteen of the 31 patients included in the study had episodes of biliary colic 1–16 mo before entry into the study without fever or jaundice. The other 15 had a history of nonspecific right upper quadrant discomfort or poorly defined postprandial "dyspepsia," or both, cholelithiasis being discovered during the course of investigation. None had a history suggestive of previous attacks of acute cholecystitis or biliary obstruction. There was no evidence of gallbladder wall thickening on ultrasound. Routine liver function tests were normal at the time of each hepatobiliary nuclear medicine scan. The clinical and radiologic findings are provided in Table 1. All gave written informed consent for these investigations, which had been approved by the Ethics Committee of the University of Calgary in 1982. Radiation dosimetry for technetium 99m-labeled diisopropyliminodiacetic acid (^{99m}Tc-DISIDA) cholescintigraphy has been assessed at 0.1 rad to the whole body and liver and 1.5 rad to the small intestine, which is the main excretory target.

Upon entry all patients had oral cholecystography and quantitative DISIDA cholescintigraphy (scan 1). Seventeen of the 31 patients were treated with 12–15 mg/kg body wt of chenodeoxycholic acid (CDCA) (9,10) and 14 with 8–10 mg/kg body wt of UDCA (7,11) (both bile acids supplied by InterFalk). When complete gallstone dissolution was first detected by ultrasound, bile acid therapy was continued for another 3 mo after which a second ultrasound examination was performed to confirm that dissolution had been accomplished.

Dissolution group. This group consisted of 13 patients for whom bile acid therapy was completely success-

ful. Treatment was required for 1 yr in 9, 2 yr in 3, and 3 yr in 1 patient. Progress of dissolution was followed by ultrasonography done every 6 mo and by a second cholescintigraphy after the initial 3 mo of therapy (scan 2). Two further DISIDA scans were done: one while still on bile acid therapy when complete dissolution was first demonstrated by ultrasound (scan 3) and the last, 4 mo later, 1 mo after discontinuing bile acids (scan 4). For 2 patients in this dissolution group, only scans 1 and 4 could be performed. Another 3 patients missed scan 3 and 2 patients missed scan 4.

Failure group. This group consisted of 18 patients in whom dissolution therapy was unsuccessful according to the serial ultrasound examinations. In this group, 9 patients were treated for 1 yr and the other 9 for 2 yr. Failure was declared in 10 patients due to no change, in 1 patient when stones (<1 cm) became calcified after 18 mo of UDCA, in 3 patients because of an increase in size, and in 4 patients due to no further progress after an initial decrease in size or number of gallstones, or both. In 1 patient with small floating gallstones, failure occurred after 12 mo when cholecystectomy was performed because of an episode of severe biliary colic; stones were still present at surgery and by appearance at least could be classified as cholesterol gallstones.

All 18 patients in the failure group had follow-up DISIDA scans after the initial 3 mo of bile acid therapy (scan 2). Eight patients also had a DISIDA scan repeated after 15–18 mo (scan 3). Of these 8 patients, 2 had ultrasound evidence of a slight decrease in gallstone size, 1 an increase in size, and 5 no change in size. The other 10 patients refused to have cholescintigraphy repeated after 15–18 mo. None agreed to have a repeat study when off bile acids.

Control group. This group consisted of 52 subjects who had gallstones excluded by history and a normal ultrasound examination or oral cholecystogram. Ten were paid volunteers; the other 42 had functional gastrointestinal complaints (23 had mild reflux esophagitis, 18 chronic constipation, and 1 pruritus ani). None had upper abdominal pain or clinical features of biliary tract disease, nor required surgery or developed a significant gastrointestinal illness.

Safety of bile acid therapy was monitored clinically and biochemically on a monthly basis in the 31 compliant patients. Thirteen of 17 patients treated with CDCA and 1 of 14 on UDCA developed diarrhea at the onset of treatment, which in 7 patients required a transient reduction in dose. None developed any evidence of hepatotoxicity (12,13).

Quantitative Cholescintigraphy Protocol

The method of gallbladder scanning has been previously described (4). All potentially interfering medications other than bile acids were withheld for 5–7 days before cholescintigraphy. After an overnight fast, a 5-mCi bolus of ^{99m}Tc-DISIDA was injected intravenously. Changes in activity were recorded on a computer interfaced to a γ-scintillation camera during a 60-min basal period and throughout a 30-min infusion of cholecystoki-

nin (CCK) at 0.02 Ivy dog units/kg · min (GIH Research Unit, Karolinska Institute, Stockholm, Sweden). This dose was chosen, as originally described (1), to be just above the threshold necessary to initiate gallbladder emptying in most healthy individuals (14). The response is comparable to that measured after a standard liquid meal (2,15) and would be expected to yield serum levels comparable to those observed postprandially, as noted previously (4). The areas of interest, the gallbladder and the intestine, were outlined according to the distribution of activity. The computer program normalized these regions for background subtraction and radioactive decay, and excluded the liver and bile duct areas (1). The maximum counts attained over the gallbladder served as the reference point for determining the rate of gallbladder filling and emptying. No subject experienced pain during the CCK infusion. The first 30 min of the basal period were ignored, so as to be well beyond the initial appearance of the radionuclide in the duodenum.

Gallbladder filling during the basal period from 30 to 60 min after the injection of ^{99m}Tc-DISIDA was expressed as percentage of filling, that portion of counts transferred into the gallbladder rather than the duodenum.

Gallbladder emptying in response to the CCK infusion from 60 to 90 min was described in terms of (a) t_{lag}, the refractory period from the start of CCK infusion until gallbladder emptying became obvious, as manifest by a loss of >2% of counts per minute; (b) $t_{1/2}$, the subsequent time necessary to empty 50% of gallbladder contents, and (c) ejection fraction, the portion of the radionuclide ejected from the gallbladder in response to the 30-min CCK infusion. These three measurements were determined directly from the computer record. Gallbladder emptying assessed by cholescintigraphy has been shown to be reproducible in our early studies (1), in work by others (2,15), and in animal studies (16).

Interpretations of oral cholecystograms, ultrasound examinations, and DISIDA scans were done independently by members of the Departments of Radiology and Nuclear Medicine at the Foothills Hospital and by one of the investigators (E.A.S.). No important discrepancies were evident; we used the radiologic interpretation in the analysis described here.

Results were expressed as mean ± SE. Analysis of variance with repeated measures (17) and paired t-test were used for statistical analysis where appropriate. The Fisher exact probability test was used to compare clinical and radiologic features between patients. Differences were considered significant when p < 0.05. For cases where no filling was evident, emptying was assessed. In instances when <50% emptied during CCK infusion, 30 min was arbitrarily chosen as the $t_{1/2}$.

Results

Clinical and Radiologic Features

Thirteen patients exhibited complete gallstone dissolution and were compared with 17 treatment failures (Table 1). No differences were detected between the patients on CDCA and those who re-

ceived UDCA, either in terms of clinical or radiologic features on entry, or in response to therapy. There also was no difference between the dissolution and failure groups with respect to clinical features (sex, age, or episodes of biliary colic). Frequency of biliary colic decreased on bile acid therapy compared with the pretreatment period; biliary pain occurred in 3 dissolution and 6 failure patients, each having more than two attacks while on therapy. None of the patients had a biliary colic attack within 2 mo before the DISIDA scan. In the dissolution group, 3 patients had floating stones, 9 had small (<1 cm) stones, and only 1 had a large stone, whereas 10 of 18 patients in the failure group had large gallstones (>1 cm) (Table 1). These differences in gallstone size were significant (p < 0.05). The total number of gallstones did not correlate either with pretreatment parameters of gallbladder function or with the outcome of bile acid therapy.

Treatment with bile acids caused marked changes in both gallbladder filling and emptying.

Gallbladder Filling

Before bile acid therapy there was no overall difference in the percentage of gallbladder filling between the two treatment groups with cholelithiasis. Together these 31 gallstone patients exhibited an insignificant 8% decrease in gallbladder filling compared with the control group. The 6 excluded patients also had normal filling (Table 2). In the control subjects, the lower limit (mean − 2 SD) of filling was defined at 42%. No difference was evident in any measurement of gallbladder function between the 10 volunteer subjects in the control group and the 42 patients in this group with functional gastrointestinal complaints. Pretreatment filling of the gallbladder using 42% as the lower limit was abnormal in 3 patients who went on to dissolution and in 2 failure patients (Figure 1).

Treatment with bile acids caused changes in gallbladder filling (Table 2). After 3 mo on bile acids, gallbladder filling decreased 31% in the two combined treatment groups, falling from 67.0% ± 5.2% to 46.2% ± 5.1% (p < 0.005). When the two treatment groups were separately analyzed, the effect of bile acids differed in each. In the dissolution group, bile acid therapy was associated with a modest 17% decline in mean gallbladder filling. Analysis of individual cases, however, revealed that 10 patients in the dissolution group entered the study with normal values (>42%), and their gallbladder filling decreased significantly after 3 mo of treatment (p < 0.02) (Figure 1). In the other 3 patients, filling increased. No one in this successfully treated group

Table 2. *Gallbladder Filling and Emptying in Patients With Gallstones That Either Dissolved or Failed on Bile Acid Therapy Compared With Controls Without Gallstones*[a]

Group	Filling (%)	Emptying		
		Ejection fraction	$t_{1/2}$ (min)	t_{lag} (min)
Dissolution (n = 13)				
Pre Rx	68.8 ± 7.5	0.71 ± 0.07	14.8 ± 2.8	6.4 ± 1.2
Rx (3 mo)	56.8 ± 6.9	0.44 ± 0.08	25.3 ± 1.9	8.6 ± 2.5
Rx + dissolution	59.6 ± 8.7	0.60 ± 0.09	19.5 ± 3.4	10.3 ± 3.6
Post Rx	58.2 ± 5.6	0.79 ± 0.05	13.5 ± 2.7	5.4 ± 0.8
Failure (n = 18)				
Pre Rx	66.5 ± 4.7	0.64 ± 0.07	15.5 ± 2.5	7.6 ± 1.8
Rx (3 mo)	39.2 ± 7.1	0.46 ± 0.10	19.5 ± 3.5	13.1 ± 2.2
Rx (15–18 mo)	52.3 ± 12.4	0.25 ± 0.15	25.0 ± 3.2	20.3 ± 4.8
Controls (n = 52)	74.4 ± 2.3	0.73 ± 0.02	11.3 ± 0.6	5.0 ± 0.5
Exclusions (n = 6)	74.1 ± 8.6	0.55 ± 0.01	16.3 ± 4.5	6.7 ± 1.3

Rx, therapy with bile acids. [a] Values are mean ± SE.

ever had the percentage of filling drop to zero. At subsequent stages of dissolution, there was no consistent trend in gallbladder filling. By contrast, filling in the failure group decreased 41% (p < 0.001) after 3 mo of therapy. In 5 patients, the percentage of filling dropped to zero and in 1 patient this persisted even after 16 mo. (Standard 2-day oral cholecystograms reaffirmed the greatly impaired filling by either not visualizing or, in 1 patient, showing faint visualization.)
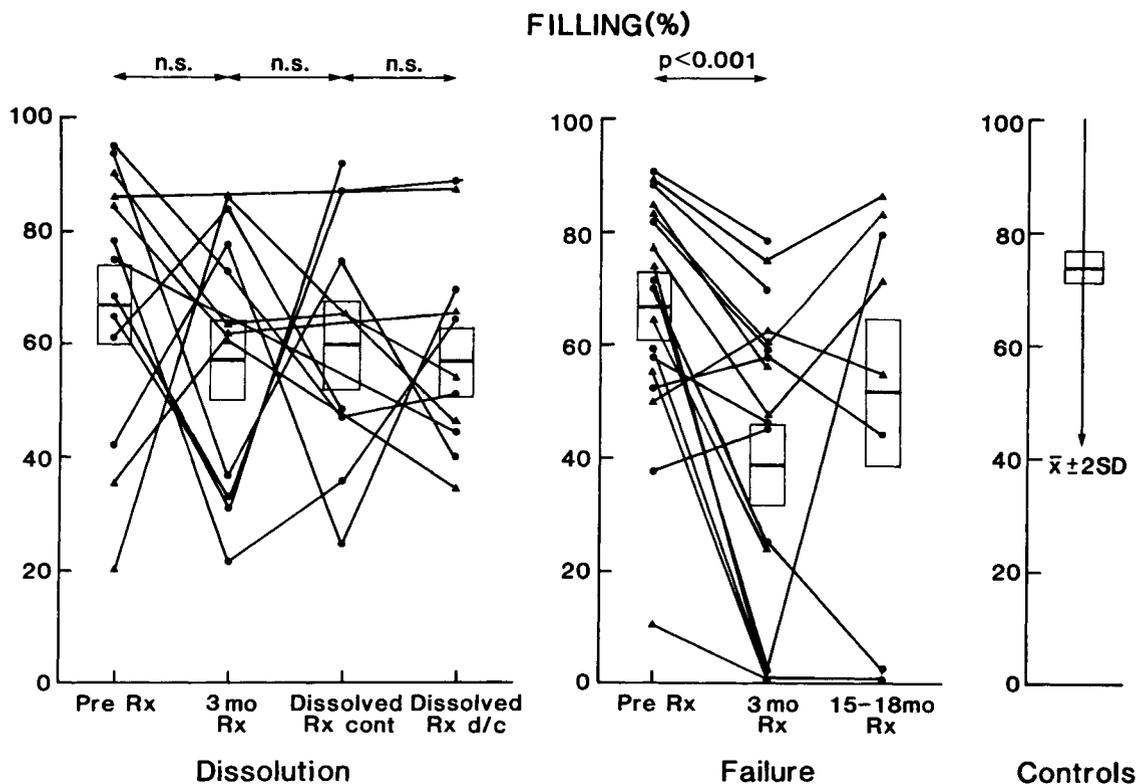

Figure 1. Gallbladder percentage of filling in 13 patients in the dissolution group and 18 patients in the failure group compared with 52 controls. Diisopropyliminodiacetic acid scan was performed in the dissolution group before therapy with bile acids (pre Rx), after 3 mo of bile acid therapy (3 mo Rx), after complete gallstone dissolution (dissolved Rx cont), and 1 mo after discontinuation of bile acids (dissolved Rx d/c). The failure group had scans before therapy (pre Rx), after 3 mo of bile acid therapy (3 mo Rx), and after 15–18 mo of therapy (15–18 mo Rx). The bars denote mean ± SE. In the controls the arrow denotes 2 SD from the mean. Circles represent patients treated with CDCA and triangles represent patients treated with UDCA.
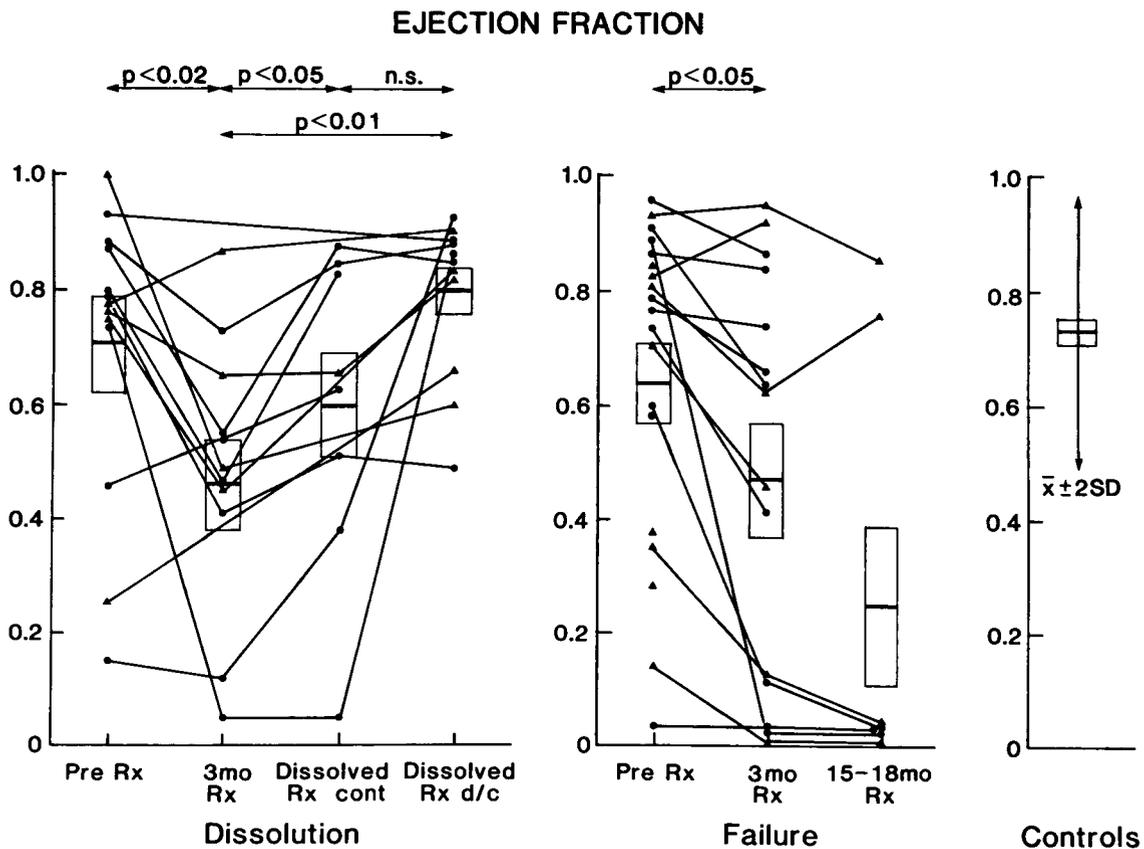
EJECTION FRACTION

Figure 2. Ejection fraction of gallbladder emptying in 13 patients in the dissolution group and 18 patients in the failure group compared with 52 controls. Legend description as in Figure 1. No emptying data could be provided in the 3 patients in the failure group who did not exhibit filling at 3 mo, or the 2 patients with no filling at 15–18 mo.

Gallbladder Emptying

The fraction of gallbladder bile ejected (Figure 2) and the $t_{1/2}$ (Figure 3) both represent the efficiency of gallbladder emptying. For all 31 gallstone patients, the overall ejection fraction (0.67 ± 0.05) was significantly ($p < 0.05$) less than the control values. When analyzed separately the failure group averaged 10% less than the dissolution group, although the difference was not significant (Table 2). There was no relation between reduced filling and impaired emptying.

The effect of gallstone size and ejection fraction on successful versus failed medical therapy is illustrated in Figure 4. In those patients whose ejection fraction was within the normal range above 0.49 (mean $-$ 2 SD of control), 9 of 10 patients in the dissolution group and 6 of 13 patients in the failure group had gallstones smaller than 1 cm; this was not statistically different. In the group with poor contractility, dissolution was achieved in 3 of 5 patients with small gallstones but in none of the 3 patients with the large stones (1–2 cm). The only significant difference found was that small stones were more likely to be dissolved ($p < 0.05$).

The pretreatment $t_{1/2}$ for the combined treatment groups (15.0 ± 1.7 min) was longer ($p < 0.05$) than for controls (11.3 ± 0.6 min). Separate analysis revealed that the mean $t_{1/2}$ was prolonged 24% in the dissolution group and 37% in the failure group compared with controls, although these differences were not significant. Three patients in the dissolution group and 6 patients in the failure group had $t_{1/2}$ beyond normal values (mean + 2 SD) at >20.5 s (Figure 3).

Treatment with bile acids altered gallbladder emptying. After 3 mo on bile acids, the ejection fraction in the 31 treated gallstone patients decreased from 0.67 ± 0.05 to 0.45 ± 0.06 ($p < 0.01$), while the $t_{1/2}$ increased from 15.0 ± 1.7 to 22.5 ± 1.9 min ($p < 0.01$). Bile acids also affected both measurements within each of the two treatment groups. In the dissolution group, 3 mo of therapy reduced the ejection fraction by 38% and prolonged the $t_{1/2}$ by 71% ($p < 0.02$ and $p < 0.01$, respectively). Similarly, in the failure group, bile acid therapy was associated with a 27% reduction in the ejection fraction ($p < 0.02$) and a significant ($p < 0.05$) prolongation of the $t_{1/2}$ by 26% (Table 2). For those patients without evidence of gallstone dissolution who had a third
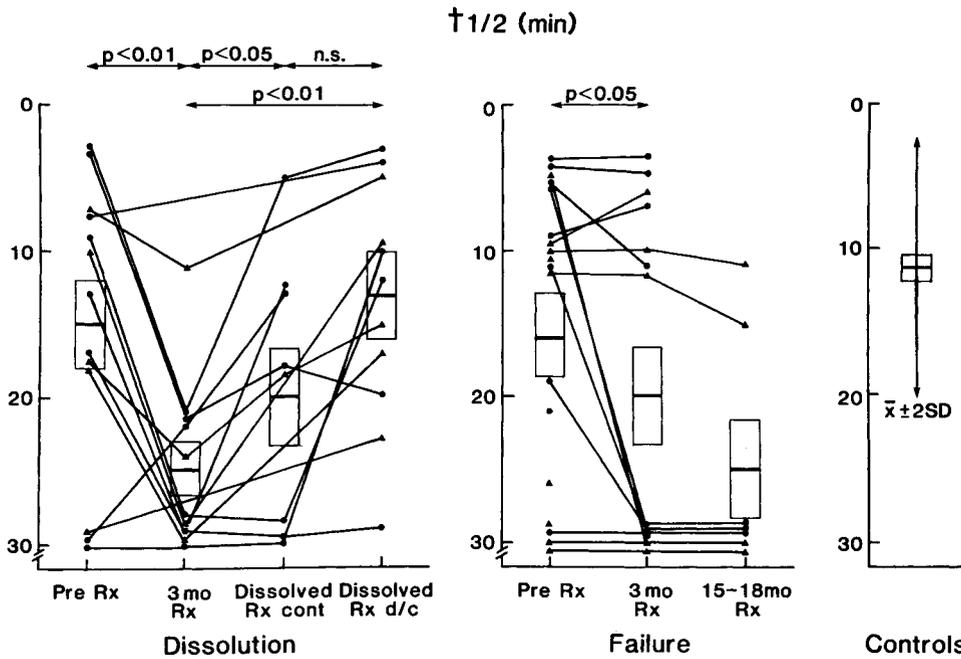
Figure 3. $t_{1/2}$ (minutes) of gallbladder emptying in 13 patients in the dissolution group and 18 patients in the failure group compared with 52 controls. Legend description as in Figure 1.

DISIDA scan done after 15–18 mo of bile acid therapy, emptying became markedly impaired in 7 patients, with virtually no response to CCK in 5 during all periods of therapy (Figures 2 and 3). In the eighth
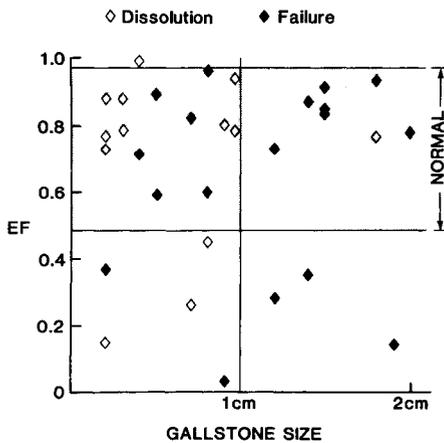

Figure 4. Relationship between gallstone size and ejection fraction relative to successful versus failed bile acid therapy. Open diamonds represent patients in the dissolution group and closed diamonds represent patients in the failure group. When the ejection fraction was within the normal range [above 0.49 (mean − 2 SD) of control], 9 of 10 of the patients in the dissolution group and 6 of 13 patients in the failure group had small gallstones (<1 cm). With poor contractility, 3 of 5 patients with small gallstones achieved dissolution, but none of the 3 with large stones did. The only significant difference found was that small stones were more likely to be dissolved (p < 0.05).
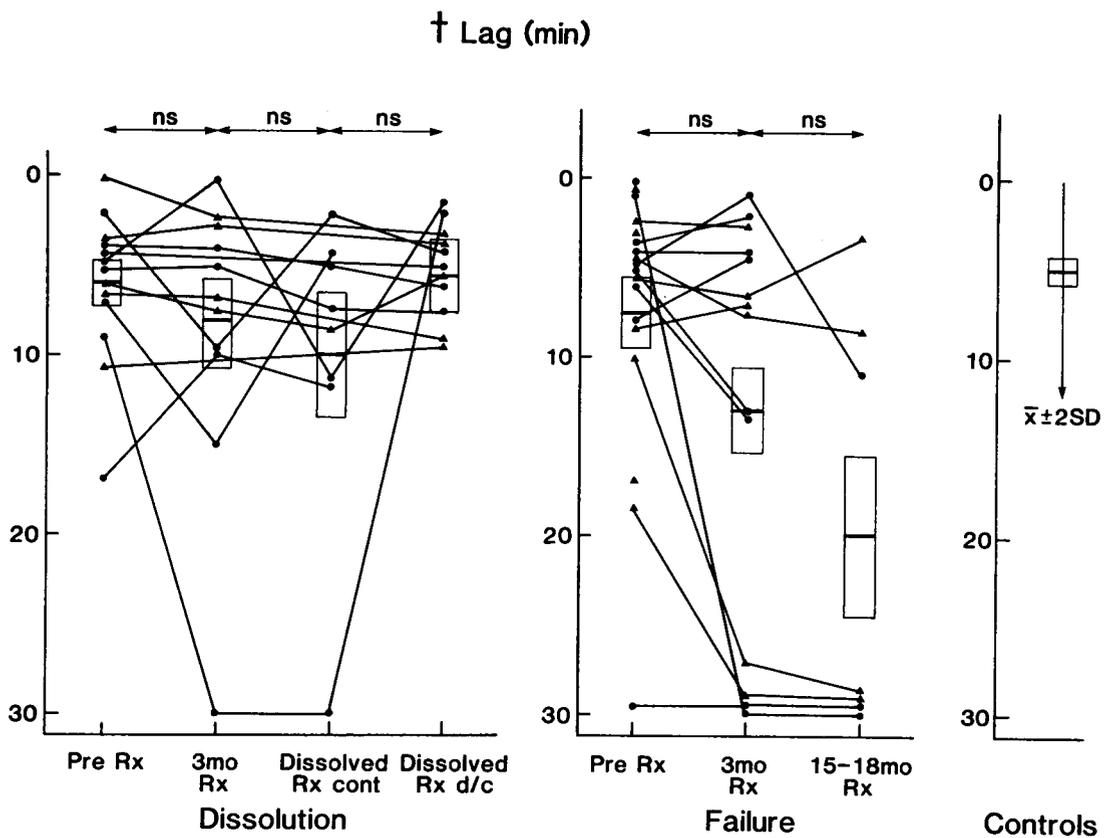
patient, the gallbladder did not fill so that emptying was not analyzed.

In contrast, complete gallstone dissolution was associated with improved emptying: the ejection fraction rose 36% (p < 0.05) and $t_{1/2}$ improved 30% (p < 0.05) while on bile acid therapy. Upon subsequent discontinuation of bile acids there was an additional 32% increase of the ejection fraction, which in some instances exceeded the pretreatment values (Figure 2). Also, $t_{1/2}$ further improved by 32% (Figure 3). There was no difference between pretreatment and postdissolution mean ejection fractions, with one exception. All three subnormal emptying values on entry into the study came well into the normal range once gallstones were dissolved or bile acid therapy was discontinued, or both.

In both the dissolution and failure groups, no difference in measures of gallbladder function were evident when CDCA therapy was compared with UDCA therapy.

An index of gallbladder sensitivity to CCK (4), t_{lag}, was analyzed (Table 2) but the only significant difference was a prolonged t_{lag} in the 31 gallstone patients (7.0 ± 1.1 min) versus the control value of 5.0 ± 0.5 min (p < 0.05). The general trends with introduction of bile acid therapy, after achieving dissolution, and then stopping treatment were similar to those found with the ejection fraction and the $t_{1/2}$ measurements (Figure 5).

The 6 patients excluded from the study had gallbladder filling and emptying values similar to those of the study patients (Table 2).

† Lag (min)

Figure 5. t_{lag} (minutes) of gallbladder emptying in 13 patients in the dissolution group and 18 patients in the failure group compared with 52 controls. Legend description as in Figure 1.

Discussion

We have found that treatment with bile acids adversely affects gallbladder filling and emptying in patients with radiolucent gallstones. Complete gallstone dissolution improves gallbladder contractility despite continued therapy and further improvement becomes evident after stopping the bile acids. No significant differences in gallbladder function were seen between CDCA and UDCA.

The inhibitory action of bile acids on gallbladder emptying was evident both at the onset of treatment, when bile acid therapy depressed emptying, and after discontinuing bile acids, when improvement occurred. Slower and less complete gallbladder emptying has been reported previously in gallstone patients placed on UDCA, and has been used to explain the reduction in biliary colic found during treatment (3). Symptomatic improvement in patients with bile reflux gastritis has also been documented with UDCA (18). The action of bile acids on biliary and gastrointestinal smooth muscle is unknown, but a general inhibitory effect has been demonstrated at least for vascular smooth muscle (19,20).

That there was no difference in gallbladder filling between the two gallstone groups and the control

subjects is not surprising. The patients with radiolucent gallstones were selected for bile acid therapy only if their gallbladder visualized on oral cholecystography, meaning the gallbladder must fill and concentrate the radiographic dye. Thus relatively normal filling was expected because of this selection bias. Treatment with bile acids decreased filling overall, but the effect was more apparent in the failure group where, after 3 mo of therapy, no filling was apparent in 5 patients. One of these 5 patients underwent a third study after 16 mo and filling was still not apparent. One other subject in the failure group also showed no filling at 15–18 mo. In the prairie dog model of cholesterol gallstones, gallbladder filling decreases in the late stages once stones have formed, perhaps related to increased resistance or stone obstruction at the cystic duct (16); the effect of bile acids on gallbladder function has not been studied in animals. The progressive deterioration in gallbladder filling in some patients whose gallstones failed to dissolve may therefore represent advancing disease. A less likely explanation for nonfilling in general is the periodic emptying of the gallbladder that normally occurs in close association with the interdigestive migratory contractions of the upper gastrointestinal tract (21). Although the 30-min ob-

servation period is short, any sudden interruption in gallbladder filling by emptying would be apparent. None occurred in this treatment group to explain complete absence of filling. Further, nonfilling was confirmed by oral cholecystography on a separate occasion. In contrast, none of the dissolution group ever showed absence of filling while on bile acid therapy. The basis for reduced gallbladder filling in gallstone patients, although tending to discriminate success versus failure with bile acid therapy, is unclear. Filling depends on hepatic bile secretion, a differential resistance in the biliary system enabling entry through the cystic duct rather than exiting via common bile duct and sphincter of Oddi, and a receptive gallbladder capable of accommodating added hepatic bile. The latter depends on gallbladder concentrating function and receptive relaxation (22). Any or all of these mechanisms could be affected by bile acid therapy, or a small stone could simply obstruct the cystic duct. If bile acid therapy induces an inhibitory smooth muscle effect as its predominant effect, a more relaxed sphincter of Oddi relative to any decrease in gallbladder-cystic duct tone would be expected to preferentially facilitate the exit of hepatic bile directly into the duodenum.

Defective gallbladder evacuation in patients with gallstones has been well-established (1,2,4) and confirmed in the present study. The exact cause is not clear but probably represents multiple factors (e.g., a possible inhibitory action of lithogenic bile, inflammation and fibrosis of the gallbladder wall, and/or mechanical factors associated with the physical presence of abnormal sediment, mucins, or the stones per se). In animal models of cholesterol gallstone disease, gallbladder motility is compromised even before cholesterol crystals or gallstones appear (23). The development of cholesterol stones, however, may further impair contractility (23), although prosthetic stones in animal experiments have a relatively modest inhibitory effect (24). The current study suggests that the physical presence of gallstones has a role. Despite the inhibitory effect of bile acids, gallbladder emptying improved in our patients once stone dissolution was complete. Thus gallstones even in the unobstructed gallbladder may inhibit gallbladder emptying. This is not simply a matter of volume displacement, as gallstone size and number are not factors defining impaired gallbladder evacuation (4).

The present results also confirmed our previous observation that a distinct subgroup of patients with cholelithiasis exhibits abnormal emptying (4). Of 37 patients who entered the study, 12 had ejection fractions that fell below the normal limits. That only one-third emptied suboptimally and gallbladder filling was normal may reflect the selection bias for the medical therapy of cholelithiasis. The 6 patients lost from the study had distinctly abnormal emptying characteristics on their one and only pretreatment scan (Table 2). Two underwent cholecystectomy in other centers within a few months, indicating that they likely had active gallbladder disease which was reflected by poor emptying. A spectrum of disease severity likely exists in unselected cases.

The effectiveness of CDCA and UDCA in gallstone dissolution has been well documented (6,9,12). Differences in patient selection, dosage, and duration of therapy have been responsible for the wide range in success rate (14%–80%). The best prognostic indicator of success to date has been gallstone size. Small radiolucent gallstones, particularly if floating, are more likely to dissolve (6,12). Our study, despite its relatively small numbers, also was able to confirm the predictive value of stone size.

Another determinant of efficacy, however, was sought in our study using cholescintigraphic measurements. Pretreatment scans did not prove to be predictive for gallstone dissolution; gallstone size remains the most important predictor in pretreatment assessment. Three successful dissolutions occurred despite abnormal emptying, but all involved small stones. All 3 patients with stones >1 cm plus abnormal emptying failed (Figure 4). Small stones combined with a good ejection fraction, however, did not guarantee a successful outcome: 6 of 18 failures occurred despite being in this category, although 9 of 13 of the successful patients also exhibited these features. A somewhat better index was the response to bile acid therapy. In the patients in the failure group the sole feature suggesting a poor prognosis was a drop in gallbladder filling to zero after 3 mo of bile acid therapy. No patient in the dissolution group exhibited such a decrease.

In summary, this study demonstrates that treatment with bile acids has a detrimental effect on gallbladder emptying and also on filling in gallstone patients, particularly those who fail to eventually dissolve their stones. No differences in this action were observed between UDCA and CDCA. Upon gallstone dissolution, gallbladder contractility improves and is further enhanced after discontinuing the bile acids. Cholescintigraphy was of no value in predicting the outcome of such medical therapy.

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