Gastric and gall bladder emptying of a mixed meal are not coordinated in liver cirrhosis – a simultaneous sonographic study

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Abstract

Background and aim—An impaired contractility has been suggested as a contributor to the increased incidence of gallstones in liver cirrhosis, but the few studies on gall bladder emptying in cirrhotics offered contradictory results. Ingestion of a meal triggers the physiological pathway of gall bladder emptying; therefore, it was decided to analyse postprandial kinetics by investigating simultaneously the rates of gastric and gall bladder emptying of a mixed meal in patients with liver cirrhosis.

Methods—Gastric and gall bladder emptying were measured using ultrasound techniques after a solid-liquid meal (14 g fat, 425 kcal) in 24 patients with liver cirrhosis and in 12 controls. None of the subjects had gall bladder disease. Sequential changes in cross sectional area of the gastric antrum and in gall bladder volume were represented as a monoexponential process after the test meal. Cirrhotic patients were analysed according to the severity of disease (Child classes). The presence of portal gastropathy was assessed by endoscopy. Differences between groups were assessed using the two tailed Student's *t* test for unpaired observations and the correlations by linear regression (Pearson's coefficient).

Results—It was found that gastric emptying after the solid-liquid meal was delayed in cirrhotic patients compared with controls. Gall bladder emptying was significantly diminished in cirrhotic patients: the area under curve was greater in Child A (p=0·01), Child B (p=0·04), and Child C (p=0·014) cirrhotics compared with controls. No correlation was found between the variables of gastric and gall bladder emptying. Gall bladder refilling began earlier in cirrhotics than in controls, before completion of gastric emptying.

Conclusions—These results indicate the lack of coordination between gastric and gall bladder emptying in liver cirrhosis. They also support the hypothesis that diminished gall bladder contractility might contribute to the increased gallstone formation in liver cirrhosis.

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Liver cirrhosis is associated with a high prevalence of gallstones, as a result of hypersplenism and alterations in hepatic metabolism. Impaired gall bladder motility has also been suggested as a contributor to this increased incidence of gallstones, but the few studies on gall bladder emptying in cirrhotics offered contradictory results.[1-5]

Postprandial gall bladder emptying is mainly coordinated by the rate of gastric emptying of food into the duodenum, with subsequent cholecystokinin (CCK) release.[6 7] An accelerated gastric emptying in portal hypertension, found in some studies, has been attributed to a decreased compliance and/or altered motility of the gastric antrum.[8-12] Wegener *et al* did not find significant changes in gastric emptying and whole gut transit in alcoholic cirrhotics when compared with controls.[13] Isobe *et al*, on the contrary, have shown that gastric emptying half time was significantly higher in patients with liver cirrhosis than in controls[14] and recently, delayed gastric emptying was described in cirrhotic patients with antral vascular ectasia.[15]

We undertook the present investigation in order to find out whether gall bladder emptying was impaired in liver cirrhosis and to analyse the temporal and quantitative relation between gastric and gall bladder emptying in this disease. Sonography is increasingly used for the estimation of gastric emptying and is the "gold standard" for the study of gall bladder motility. We carried out real time ultrasonography for the simultaneous measurement of gastric and gall bladder emptying.

Subjects

We studied 24 patients with liver cirrhosis admitted to our clinic and 12 controls, hospitalised patients without liver diseases. Subjects cholecystectomised or having gall bladder diseases were not included in the study. None had undergone prior gastric or ileal surgery and none was overtly diabetic.

The diagnosis of liver cirrhosis was made by histological and/or laparoscopic examination in 15 patients. In the other patients, in whom biopsy was contraindicated or refused, liver cirrhosis was diagnosed on the basis of clinical, biochemical, ultrasonographic features, and/or presence of oesophageal varices. The size of varices was assigned as described by Raws *et al*.[16] Aetiology of cirrhosis was established by history of alcohol intake, presence of HBsAg or anti-HCV antibodies and the liver histology. Cirrhotics were allocated to Child classes using

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TABLE I *Characteristics of patients included in the study*

| | Controls | Liver cirrhosis | | |
		Child A	Child B	Child C
No of patients:	12	8	8	8
Male	7	5	7	4
Female	5	3	1	4
Age (mean (SD)) (years)	50·7 (8·2)	46·9 (10·3)	45·6 (7·2)	51·9 (6·9)
Aetiology of cirrhosis:				
Viral		2	1	1
Alcoholic		2	4	3
Viral+alcoholic		3	1	2
Cryptogenic		1	2	2
Oesophageal varices:				
Absent		1	1	1
1st degree		3	1	–
2nd degree		2	6	5
3rd degree		2	–	2
Gastroduodenal lesions:				
Portal gastropathy	–	–	–	2
Duodenal ulcer	–	–	–	1
Gastric ulcer	–	–	–	1

clinical and biochemical factors (eight patients in each class). The characteristics of the patients included in the study are shown in Table I.

Informed consent was obtained from each subject before examination.

Method

Gastric and gall bladder emtpying were assessed by ultrasound monitoring. All measurements were undertaken by the same operator (DLD).

Gastric emptying was evaluated according to the method of Bolondi *et al*,[17] based on the measurement of antral area in a sagittal section inside the gastric wall through the aortic-mesenteric vein plane.

The gall bladder was scanned to visualise its longest axis, width, and depth. Gall bladder volume was calculated using the ellipsoid formula.[18]

The study began at 10 am. The subjects fasted for at least 12 hours before the study. None took any medication 24 hours before the study which might have influenced gastrointestinal motility, and none smoked on the morning of the investigation. Patients were instructed to assume the upright position between measuring periods.

After measuring the basal antral area and gall bladder volume, each subject was requested to consume a mixed (solid-liquid meal) consisting of one slice of bread (30 g), 10 g butter, one boiled egg, 300 ml tea with 25 g sucrose. This was equivalent to 14 g fat and 465 kcal. The test meal was finished within 3 or 4 minutes.

The following variables for gastric emptying were evaluated immediately (time 0) and every 15 minutes until 90 minutes after the test meal: antral distension (percentage of antral area increase after finishing the meal), minimal postprandial area, and the area under the emptying curve (AUC_{ST}–percentage of basal area at 90 minutes).[19] The half time (T/2) of gastric emptying was calculated from the linear part of the emptying curve (usually between time 0 and 60 minutes).

Gall bladder function was assessed by analysing at 15 minute intervals (until 90 minutes) after the test meal the following

variables: fasting gall bladder volume (FV), minimal residual volume (RV–smallest volume after the test meal), gall bladder ejection fraction (FV–RV/FV×100) and the area under emptying curve (AUC_{GB}–proportional to the degree of gastric emptying during 90 minutes and expressed as percentage of FV). The half contraction time of the gall bladder (T/2) was calculated in all patients during the time period in which the values were linear with time (usually between 0 and 45 minutes).

Analysis

Antral areas and gall bladder volumes were expressed as absolute values (cm^2 or cm^3) and as percentage of the respective values at 0 minutes (100%).

Data were expressed as mean (SD).

Differences between groups were analysed using the two tailed Student's t test for unpaired observations, with statistical significance set at the $p<0.05$ level. Correlations were evaluated by linear regression (Pearson's correlation coefficient).

Results

The aetiology of liver cirrhosis was alcoholic in nine patients (37·5%), viral in four (16·6%), mixed–alcoholic and viral B or C in six (25%), and cryptogenic in five (20·8%). The fibre endoscopy revealed portal hypertensive gastrophy in two of the Child C class patients, and a linear or cicatriceal gastric and duodenal ulcer in another two Child C class patients (Table I). Endoscopy was normal in the remaining liver cirrhosis patients and in controls.

We found a strong inverse correlation between antral postprandial distension and AUC_{ST} both in controls ($r=-0·747$, $p=0·005$) and in cirrhotics ($r=-0·738$, $p=0·036$). The postprandial antral distension was non-significantly decreased in Child B and C class patients compared with controls ($p=0·075$). The AUC_{ST} was greater in Child B and C patients (significantly for Child B patients) than in controls (Table II), indicating impaired gastric emptying. The T/2 of the stomach was similar in controls and cirrhotic patients and did not correlate with the degree of portal hypertension (indicated by the size of oesophageal varices) (Table III).

Fasting gall bladder volume was larger in Child class C cirrhotics (47·5 (25) cm^3) than in controls (27·4 (16·7) cm^3) ($p=0·041$), but for class A or B patients the difference

TABLE II *Variables of gastric emptying of the mixed test meal in cirrhotics (Child class A, B and C) and controls (means (SD))*

	Antral postprandial distension (%)	Gastric T/2 (min)	AUC_{ST} (% antral area at 90 min)
Controls	323·3 (113·9)	18·6 (9·7)	52·6 (7·8)
Cirrhosis A	325·0 (100·7)	18·4 (10·9)	59·5 (15·5)
Cirrhosis B	286·1 (91·4)	23·3 (11·9)	62·7 (8·5)*
Cirrhosis C	238·7 (66·4)	17·2 (10·9)	61·3 (14·3)

*p=0·013.

TABLE III *Relation between size of varices and half emptying time (T/2) of the stomach*

Oesophageal varices (degree)	T/2 of the stomach (min) (mean (SD))	p Value
absent	20·7 (12·4)	NS
1	22·9 (6·5)	NS
2	18·4 (10·6)	NS
3	16·2 (11·3)	NS
4	20·5 (10·2)	NS

NS=non-significant.

TABLE IV *Variables of gall bladder motor function after a mixed test meal in cirrhotics and controls (mean (SD))*

	FV (ml)	RV (ml)	EF (%)	T/2 (min)	AUC (% FV 90 min)
Controls	27·5 (16·7)	11·2 (7·4)	70·3 (14·8)	15·8 (5·9)	48·4 (14·0)
Cirrhosis A	30·7 (13·9)	20·1 (13·6)	48·5 (14·1)*	19·9 (5·3)	65·3 (13·0)*
Cirrhosis B	31·8 (9·3)	13·1 (6·7)	56·4 (15·7)*	20·9 (11·8)	61·3 (10·5)*
Cirrhosis C	47·6 (25·0)*	22·3 (14·6)*	49·5 (9·3)*	22·1 (11·3)	64·7 (11·6)*

*p<0·05 versus controls.

compared with controls was not significant (Table IV).

Five controls (41·6% of controls) and 15 liver cirrhosis patients (62·5% of liver cirrhosis patients) began to empty their gall bladder before meal completion and in anticipation of gastric emptying (p>0·50).

The RV was significantly larger in Child C cirrhotics than controls (p=0·037). The T/2 of the gall bladder was similar in cirrhotics and controls, but the AUC$_{GB}$ was significantly greater compared with controls in Child A (p=0·01), Child B (p=0·04) and Child C (p=0·014) cirrhotics, indicating reduced gall

bladder emptying. The gall bladder ejection fraction was also significantly reduced in cirrhotics (Table IV).

We found no correlation between T/2 of the gall bladder and age, FV or ejection fraction in controls and liver cirrhosis patients. We noted a strong inverse correlation between gall bladder ejection fraction and AUC$_{GB}$ in liver cirrhosis patients in Child A, B, and C class (r=−0·925, −0·910 and −0·890; p=0·001) and in controls (r=−0·859, p=0·0008).

The sequential changes in antral area and gall bladder volume could be represented as a monoexponential process after the test meal between time 0 and 60 (or 45) minutes (Figs 1–4). The gastric and gall bladder emptying curves run almost parallel towards the minimal volumes, splitting during the gall bladder refilling phase. Nevertheless, we found no correlation between variables of gastric and gall bladder emptying: gastric and gall bladder T/2 (p=0·8) or AUC$_{GB}$ and AUC$_{ST}$ (p=0·3) in cirrhotic patients. The gastric emptying curves indicated a delayed emptying in liver cirrhosis patients but reaching similar magnitude at 90 minutes (about 60% emptying) as in controls. Gall bladder emptying curves showed a slower emptying with a reduced magnitude in all cirrhotics versus controls.

Discussion

Gastric emptying is an important physiological motor function of the stomach, as the gastric emptying rate determines the rate at which nutrients are delivered to and assimilated by the small intestine. Gastric meal emptying induces postprandial cholecystokinin release
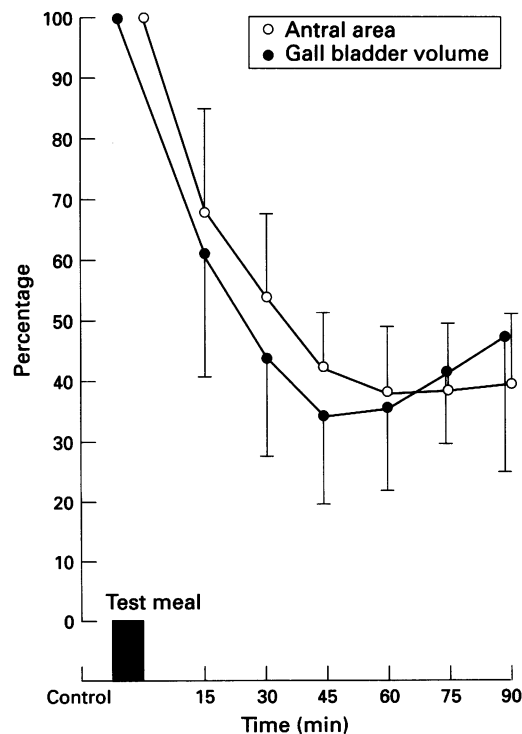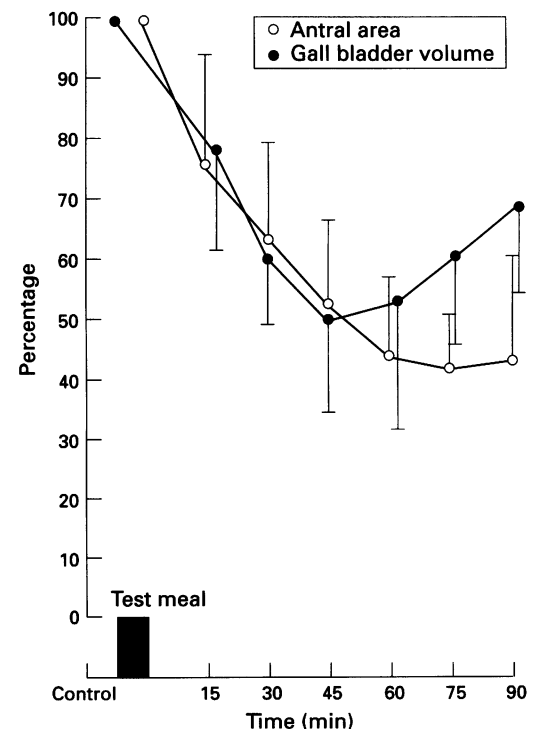

Figure 1: Mean emptying curves of the stomach and the gall bladder determined by sonography in controls. Data are plotted as mean percentage of the residual antral cross sectional area and residual gall bladder volume (expressed as percentage of the respective values at 0 minutes, 100%). Bars=SD.

Figure 2: Emptying curves of the stomach and the gall bladder determined by sonography in patients with Child class A liver cirrhosis (mean (SD)).
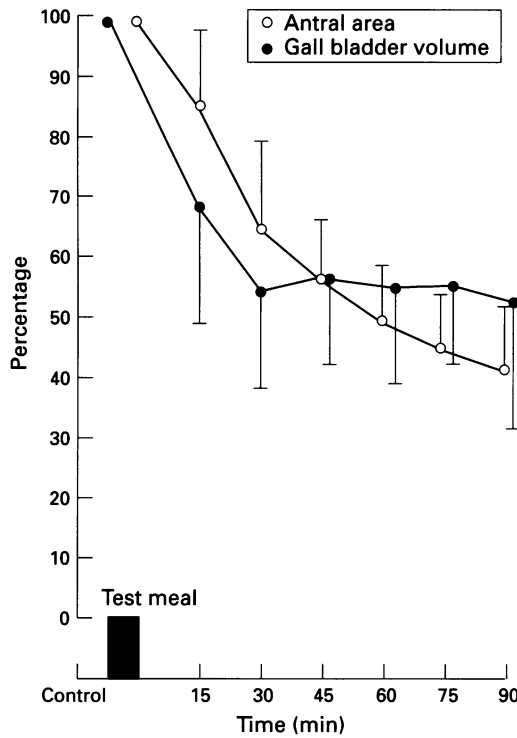
Figure 3: Emptying curves of the stomach and gall bladder determined by sonography in patients with Child class B liver cirrhosis (mean (SD)).

and gall bladder contraction. It has been shown that the rate at which food enters the proximal duodenum modifies the gall bladder emptying rate without affecting the amount of contraction, which seems instead to be more closely related to the calorie/fat content of the meal.[7] [20-22] The two (fast and slow) phases of gall bladder emptying are followed by gall
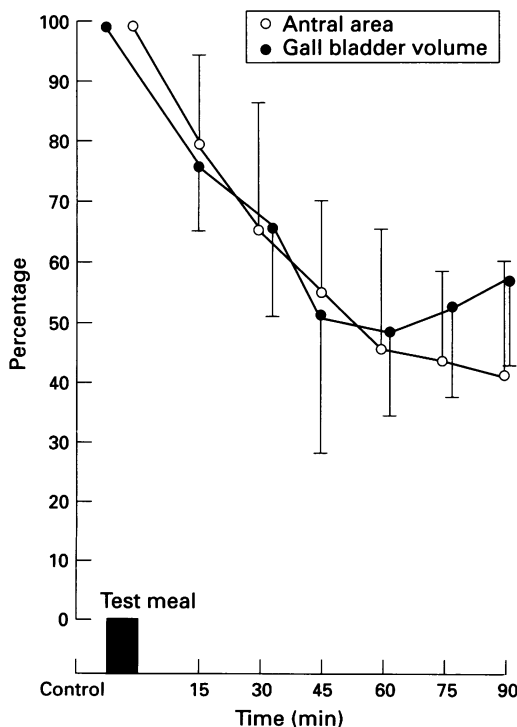

Figure 4: Emptying curves of the stomach and gall bladder determined by sonography in patients with Child class C liver cirrhosis (mean (SD)).

bladder refilling; this usually beginning when gastric emptying is completed.[6]

We used a mixed meal to evaluate both gastric and gall bladder emptying. This solid-liquid meal containing 14 g fat has already been shown to cause a significant decrease in normal gall bladder volume[20] [22]: for liquid meals, 10 g fat was found to be the threshold quantity necessary to induce maximal gall bladder contraction.[23] The characteristics of the test meal used in our patients seem suitable to evaluate the relation between gastric and gall bladder emptying, and the simultaneous ultrasound measurement of both events may offer important clues in assessing gall bladder function in health and disease.[21] [24] No such evaluation has been performed in patients with liver cirrhosis.

The best known method for the study of gastric emptying is scintigraphy.[25] However, ultrasonography has been increasingly used for the measurement of gastric motility, including gastric emptying. Different studies, using various test meals, reported very good correlations between these techniques.[26-28] The sonographic method, which is simple, reproducible, reliable, and does not necessitate exposure to radiation also allows for the simultaneous evaluation of gall bladder emptying. Indeed, gastric and gall bladder emptying have recently been studied mostly by ultrasound.[20] [24] [29] This method is promising for the evaluation of the relation of gall bladder emptying to gastric emptying as a routine practice,[24] and suited best the aim of our study.

We did not find an accelerated gastric emptying in liver cirrhosis patients as suggested in some experimental and clinical studies using liquid[8] [10] [11] or solid-liquid meals.[8] [9] [12] The accelerated gastric emptying in portal hypertension was first explained by altered gastric compliance due to submucosal oedema[8] and later by altered antral motility.[9] Hypothetically, accelerated gastric emptying might account for diminished gall bladder contraction in cirrhotics, as it results in a rapid passage of the meal through the duodenum, with lower release and earlier cessation of the effect of CCK and other peptides that contract the gall bladder.

Gastric distension is the only natural stimulus known to increase gastric emptying.[9] Indeed, we found a strong inverse correlation between antral postprandial distension and the AUC_{ST}. Antral distension was not significantly different in our liver cirrhosis patients compared with controls, although it was reduced in Child C patients (in 25% of whom endoscopy revealed portal hypertensive gastropathy). The AUC_{ST} was greater in Child B and C patients than in controls, indicating impaired emptying. Our results are in agreement with those of Wegener et al,[13] who found a trend towards delayed gastric emptying in alcoholic cirrhotics compared with controls, although it did not reach statistical significance. In their patients, gastric emptying time was not related to the presence of liver cirrhosis or of autonomic neuropathy. The

autonomic neuropathy demonstrated in liver cirrhosis patients was equally common in alcohol related and non-alcohol related liver disease.[30] Our results are also similar to those of Isobe *et al*,[14] who described delayed gastric emptying in cirrhotics. Charneau *et al*[15] found delayed emptying only in cirrhotics with antral vascular ectasia. None of our cirrhotics had antral vascular ectasia, but two had portal hypertensive gastropathy.

Although delayed, gastric emptying after the test meal reached a similar magnitude in our liver cirrhosis patients at 90 minutes (60%) as in controls.

The spontaneous gall bladder emptying in advance of the ultrasonically assessed gastric emptying is due to the cephalic phase of gall bladder contraction mediated by cholinergic pathways. Vagal stimulation initiates gall bladder contraction independently of meal composition.[20] [31-33] A cholinergic vago-vagal pyloro-cholecystic reflex has also been postulated to contribute to gall bladder emptying in response to antral distension.[34] We found no difference between the proportion of liver cirrhosis patients and of controls in whom prompt gall bladder emptying occurred in anticipation of gastric emptying (a type I response as classified by Baxter *et al*).[7]

The three phases of gall bladder emptying after a solid-liquid meal – that is, the rapid contraction, the slow (tonic) and the refilling phases,[6] [7] [35] [36] were all identified in our subjects. In cirrhotics, the rapid phase was slowed down and associated with diminished maximal emptying (Figs 2–4) compared with controls. In the controls, refilling of the gall bladder began when gastric emptying was almost completed, a pattern similar to that found in healthy volunteers by Lawson *et al*.[6] In our liver cirrhosis patients, refilling of the gall bladder started earlier, when only 50% (cirrhosis B) or 75% (cirrhosis A and C) of the gastric contents were evacuated. This interesting finding, which deserves further investigation, indicates a lack of coordination between gastric and gall bladder emptying in liver cirrhosis and suggests that humoral stimulation ceases before gastric emptying is complete, and consecutively the gall bladder refills.

Whereas the existence of larger fasting gall bladder volumes in liver cirrhosis is commonly accepted[3-5] and was also found in this study for Child C class patients, conflicting results regarding gall bladder emptying in this disease have been mentioned in different studies. We found defective gall bladder contractility in cirrhotic patients in all Child classes, independent of liver cirrhosis aetiology. This hypocontractility could be the consequence of either defective release of CCK or diminished gall bladder response to CCK at the receptor site.

In cirrhotic patients, the level of CCK was found to be higher than in controls,[5] [37] presumably due to impaired hepatic degradation as nearly all CCK-8 is normally metabolised on its first passage through the liver.[38] Pompili *et al*[5] found increased plasma CCK concentrations and normal gall bladder contraction in well compensated liver cirrhosis patients after a solid-liquid meal (1000 kcal, 21% as fat). Davion and Capron found a normal gall bladder contraction in male patients with alcoholic cirrhosis after a Lundh test meal.[3] In a previous study, we also found unimpaired gall bladder motility in cirrhotics following a liquid meal (270 kcal, 12 g fat). The contradictory results could be due to the different types of meals used (solid and/or liquid) and to their different fat content.[21] [36] Previous studies have demonstrated that solids empty from the stomach more slowly than liquids. This alone may be responsible for the slower gall bladder emptying in response to a solid meal than an equivalent liquid meal, but other factors cannot be excluded.[21]

As CCK concentrations are normal or increased in liver cirrhosis patients, the diminished gall bladder contractility could be due to resistance of the gall bladder to the action of CCK at the receptor site in the presence of increased plasma concentrations of intestinal peptides such as VIP, somatostatin, glucagon and pancreatic polypeptide (PP), acting as relaxing substances on the gall bladder wall. Several hormones and peptides known to affect gastrointestinal motor function normally undergo first pass hepatic degradation and thus their plasma concentrations are increased in liver cirrhosis. This has been demonstrated for somatostatin, VIP, and glucagon,[39] [40] but no attempt has been made to correlate their plasma concentrations with gall bladder emptying in this disease. Increased concentrations of gall bladder relaxing peptides could be responsible for early gall bladder refilling observed in our patients with liver cirrhosis, before complete gastric emptying.

In conclusion, our results indicate delayed gastric emptying of a solid-liquid meal in cirrhotic patients compared with controls, and impaired gall bladder emptying in these patients, which was not related to the aetiology or severity of the disease. To our knowledge, this is the first simultaneous analysis of gastric and gall bladder emptying in liver cirrhosis patients and it indicated the lack of coordination between the two emptying rates. Our data also support the hypothesis that diminished gall bladder contractility might contribute to increased gallstone formation in liver cirrhosis.

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