Correlation between gall bladder fasting volume and postprandial emptying in patients with gall stones and healthy controls

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Abstract

To evaluate whether the extent of postprandial gall bladder emptying is correlated with gall bladder fasting volume, gall bladder motility was studied in 56 patients with cholesterol gall stone and 19 control patients. Gall bladder volumes were determined sonographically, while cholecystokinin plasma values were measured radioimmunologically. Twenty three per cent of gall stone patients were classified as pathological contractors (residual fraction $>$ mean $+2$ SD of controls) and 77% as normal contractors. Normal but not pathological contractor patients exhibited larger gall bladder fasting volumes (mean (SEM)) (24.7 (1.7) ml) than controls (15.3 (1.2) ml, $p < 0.001$). In normal contractor patients and controls fasting volume was closely related with ejection volume ($r = 0.97$, $p < 0.001$) and residual volume ($r = 0.80$, $p < 0.001$). Although ejection volume was enlarged in normal contractor patients it did not compensate the increase in fasting volume. Thus, residual volumes were considerably increased not only in pathological contractors (12.7 (2.5) ml, $p < 0.001$) but also in normal contractor patients (7.0 (0.5) v 4.6 (0.6) ml, $p < 0.001$). Postprandial cholecystokinin secretion did not differ between patients and controls. It is concluded, that in normal contractor patients gall bladder fasting volume is closely correlated with ejection and residual volume. Thus, fasting volume may be an essential factor affecting postprandial gall bladder emptying. Large fasting volumes in cholesterol gall stone disease could thereby contribute to bile retention, which facilitates gall stone growth.

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The importance of gall bladder motility in the debate on the various causes of gall stones in humans is still to be determined.¹ Convincing evidence exists that impaired gall bladder motor function is an important determinant of gall stone formation during longterm parenteral nutrition,² pregnancy,³ somatostatinoma,⁴ and somatostatin treatment.⁵ Applying different techniques in small or highly selected groups of gall stone patients, different investigators reported decreased,⁶⁻¹⁴ normal,¹⁵⁻¹⁷ or even increased¹⁸ gall bladder emptying by comparison with healthy controls. Moreover, it has been postulated that two distinct subgroups of gall stone patients can be identified with regard to gall bladder emptying (normal contractors, pathological contractors), who may differ with respect to gall stone pathogenesis.^{14 19 20} In addition,

recent reports suggest that gall stone patients may be characterised by enlarged fasting volumes.^{9 11 19}

We therefore speculated that gall bladder fasting volume might be an essential factor in the regulation of gall bladder motility. To evaluate whether gall bladder motor function is correlated with gall bladder fasting volume we studied the relation between fasting volume and postprandial emptying as well as postprandial cholecystokinin (CCK) secretion in a large group of cholesterol gall stone patients and healthy subjects. Gall stone patients were divided into normal and pathological contractor patients to show different aspects of changed gall bladder motility in these groups compared with controls.

Patients and methods

PATIENTS

Gall bladder motility was assessed in 56 patients with radiolucent gall stones and 19 healthy controls. Both groups did not differ with regard to clinical characteristics (Table I). All gall stone patients were evaluated in our outpatient clinic for indications of gall stone treatment. Twenty three patients (41%) suffered from biliary pain, while the other 33 patients (59%) had no biliary symptoms. No patient presented with clinical or laboratory signs of biliary complications. To allow a valid motility investigation to be done the patency of the cystic duct was proved by opacification of the gall bladder on oral cholecystogram. Total stone volume ($\Sigma[4\pi r_i^3]/3$ with r_i = half of largest diameter of each stone on ultrasound) was 19 (2)% of gall bladder fasting volume. In all subjects the gall bladder wall and common bile duct was normal when examined by ultrasound. No patient had any history of disease or operations known to affect gall bladder motility or took any drugs. Informed consent was obtained from all patients and healthy subjects and the study protocol was approved by the ethics committee of the Medical Faculty of the University of Munich.

GALL BLADDER EMPTYING

Gall bladder volumes were determined sonographically (curved array transducer 3.5 MHz, CS 9000, Picker International, Germany) and calculated according to the sum of cylinders method.²¹ Intraindividual variation of gall bladder volume measurements was less than 5%. Gall stone patients and controls were studied between 8 am and 10 am after an overnight fast. Fasting volumes were determined at times -15,

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Figure 2: Correlation of fasting volume (FV) of the gall bladder and postprandial ejection volume (EV) in normal contractor gall stone patients (●) and controls (○). Pathological contractor patients shown by (■).

Figure 3: Residual fraction (RF) of the gall bladder before and 30, 60, and 90 minutes after a standard liquid test meal in gall stone patients (normal (n=43) and pathological (n=13) contractor patients) and controls (n=19). Mean (SEM), * $p < 0.05$ with controls.

Figure 4: Correlation of fasting volume (FV) of the gall bladder and postprandial residual volume (RV) in normal contractor gall stone patients (●) and controls (○). Pathological contractor patients shown by (■).

larger than in controls. Thirty minute ejection volumes were significantly increased in normal contractor patients compared with controls (Table II). Furthermore, gall stone patients were characterised by a larger postprandial residual volume (Table II). In normal contractor patients the residual volume was increased by nearly 50% compared with controls, whereas pathological contractors showed even larger residual volumes (Fig 1).

Normal and pathological contractor patients as well as controls did not differ with regard to either basal or maximal postprandial CCK plasma values or integrated CCK secretion (Table III).

Although 47% of normal contractor patients but only 23% of pathological contractor patients reported episodes of biliary pain, this trend did not reach statistical significance (Table I).

Discussion

This study shows a close correlation of gall bladder fasting volume with postprandial ejection and residual volume in healthy subjects and gall stone patients with normal gall bladder contractility. Thus, fasting volume may be an essential factor of gall bladder motility affecting postprandial emptying.

Normal contractor gall stone patients exhibited an appreciably increased fasting volume of the gall bladder, which was independent of stone volume. Only normal contractor patients, however, showed an enlarged mean fasting volume whereas pathological contractor patients did not. As it has been shown that in healthy subjects fasting volume is slightly related to body surface area and weight,²³ we carefully matched patients and controls for clinical characteristics (Table I). Furthermore, fasting gall bladder volume can vary up to 20% because of a small short term contraction and subsequent refilling associated with late phase II of the gastroduodenal migrating motor complex.²⁴ As, in our study, fasting volumes did not differ throughout a 15 minute period before the test meal was given, we assume that they were in a steady state at the start of the motility examination. Increased fasting volumes have been reported during pregnancy,³ after treatment with ursodeoxycholic acid,^{8,9,25,26} chenodeoxycholic acid,²⁶ somatostatin,²⁴ CCK antagonists,²⁷ neurotensin,²⁸ atropine,²⁹ and after truncal vagotomy.³⁰ Nevertheless, further studies are required to identify the mechanism of enlarged fasting volumes in gall stone patients.

In addition to other studies^{8,9,11,12,19} reporting increased postprandial residual volumes of the gall bladder in gall stone patients, we showed that not only pathological contractor patients but also normal contractor patients exhibit distinctly larger residual volumes than controls. This retention of bile in the gall bladder in most gall stone patients may facilitate the nucleation of cholesterol crystals and stone growth. Whereas increased residual volumes may be the final consequence of changed gall bladder motility in cholesterol gall stone disease the results of our study point to different underlying mechanisms in various subgroups of patients. In pathological contractor patients without cholecystitis

TABLE II Gall bladder emptying after a standard liquid test meal in gall stone patients and controls

	Gall stone patients			Controls n=19 (4)	p Values			
	Normal contractors n=43 (1)	Pathological contractors n=13 (2)	All n=56 (3)		(1-2)	(1-4)	(2-4)	(3-4)
FV (ml)	24.7 (1.7)	19.6 (2.5)	23.6 (1.5)	15.3 (1.2)	NS	p<0.001	NS	p<0.001
RV (ml)	7.0 (0.5)	12.7 (1.5)	8.3 (0.6)	4.6 (0.6)	p=0.02	p=0.02	p<0.001	p=0.002
RF (%)	29 (1)	69 (6)	38 (3)	30 (2)	p<0.001	NS	p<0.001	p=0.03
EV (ml)	17.7 (1.3)	6.9 (1.8)	15.2 (1.2)	10.7 (0.8)	p<0.001	p=0.001	NS	p=0.01
EV ₃₀ (ml)	14.9 (1.2)	4.8 (1.2)	12.5 (1.1)	10.6 (0.8)	p<0.001	p=0.02	p<0.001	NS

FV=fasting volume, RV=residual volume, RF=residual fraction, EV=total ejection volume, EV₃₀=30 minute ejection volume, Mean (SEM), NS=not significant.

impaired gall bladder emptying seems to be based on a functional defect of the gall bladder smooth muscle that is different from inflammation or fibrosis.³¹ On the other hand, in normal contractor patients enlarged residual volumes of the gall bladder are closely correlated with increased fasting volumes suggesting that expansion of the fasting volume may be an essential event during the formation and growth of gall stones. Prospective studies of subjects with large gall bladder fasting volumes are required to identify this finding as a risk factor or early indicator of gall stone formation.

Specifically, the correlation between gall bladder fasting volume and 30 minutes ejection volume suggests a physiological mechanism by which the gall bladder can eject greater bile volumes as fasting volumes increase. Theoretically, the distension of the gall bladder wall may either change the sensitivity to CCK and neural stimulation or may improve muscular contraction in a way similar to the Starling mechanism of the heart.³² Such an analogous mechanism is particularly interesting, as smooth muscle cells differ in many aspects from heart or skeletal muscle.³³ In support of this hypothesis Ryan and Cohen³⁴ showed in the opossum, that the pressure increments induced by CCK were increased at larger gall bladder volumes. Moreover, guinea pig gall bladder smooth muscle showed a length dependency of isometric stress in response to acetylcholine stimulation in vitro.³⁵ Our clinical data support the assumption of a comparable physiological characteristic in man. This mechanism, however, could not enhance ejection volume as much as it would be necessary to compensate for the increment in fasting volume. Thus, fasting volume also correlated directly with residual volume in normal contractors. As bile viscosity³⁶ and sphincter of Oddi and common bile duct pressures³⁷ do not differ between gall stone patients and controls an

enhanced ejection volume in normal contractors is unlikely to result from diminished outflow resistance.

Comparing postprandial CCK release in gall stone patients with and without impaired gall bladder emptying and healthy subjects no significant differences were obtained. These results show that changes in gall bladder motor function in gall stone patients are not associated with a modification of CCK secretion. Based on acute experiments it was proposed that bile influx into the duodenum may inhibit stimulated CCK secretion.³⁸ Consequently, non-contractor patients should secrete more CCK postprandially than normal contractor patients.^{19,20} Our data suggest, however, that in a chronic steady state of impaired gall bladder emptying such a phenomenon is not found or is at least overcome by adaptive mechanisms. Accordingly stimulated CCK plasma values are neither changed several weeks after cholecystectomy³⁹ nor do they differ between patients with chronic bile duct obstruction and healthy controls.⁴⁰

We conclude, that in normal postprandial gall bladder emptying, ejection volume and residual volume are closely correlated with fasting volume. Thus, fasting volume seems to be an essential factor affecting physiological gall bladder motility. Differences in fasting volume between groups will therefore require special consideration in future studies evaluating gall bladder emptying. In gall stone patients two different mechanisms, an insufficient physiological mechanism to cope with larger gall bladder volumes in normal contractor patients and an impaired gall bladder muscle function in pathological contractor patients, led to nearly a 50% increase in mean postprandial residual volume.

TABLE III Cholecystokinin plasma values in response to a standard liquid test meal in gall stone patients and controls

	Gall stone patients			
	Normal contractors n=43	Pathological contractors n=13	All n=56	Controls n=19
CCK _{bas} (pM)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)
CCK _{max} (pM)	5.8 (0.4)	5.5 (0.4)	5.7 (0.5)	5.1 (0.5)
CCK-AUC (pM×90 min)	221 (13)	242 (30)	226 (12)	184 (14)

CCK_{bas}=basal CCK concentration, CCK_{max}=maximal CCK concentration, CCK-AUC=area under the CCK-CCK_{bas} concentration/time curve for 90 minutes. No significant differences were obtained between any groups with regard to any given parameter. Mean (SEM).

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