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# *Comparison of the Dynamics of Bile Emptying by Quantitative Hepatobiliary Scintigraphy Before and After Cholecystectomy in Patients With Uncomplicated Gallstone Disease*

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**Purpose: Quantitative hepatobiliary scintigraphy, a noninvasive method frequently used to diagnose several biliary tract disorders, shows abnormalities in bile secretion and outflow. It is well known that there are wide variations in the normal pattern of bile emptying, but the effect of cholecystectomy on the bile flow has not yet been investigated. The goal of the current study was to examine the dynamics and normal variations of bile flow by quantitative hepatobiliary scintigraphy before and after cholecystectomy in a group of patients with uncomplicated gallstone disease.**

**Methods: Twenty patients were evaluated before and after cholecystectomy through cholecystokinin octapeptide–augmented quantitative hepatobiliary scintigraphy, and quantitative parameters of bile emptying ($T_{max}$: time to peak activity, $T_{1/2}$: half-emptying time before and after cholecystokinin octapeptide and duodenum appearance time) were determined and then compared.**

**Results: Before operation, the bile outflow displayed wide variations, with a moderately delayed common bile duct emptying time in some patients. After cholecystectomy, the $T_{1/2}$ of the common bile duct decreased significantly when compared with the preoperative status, with only minor patient-to-patient variation, indicating uniformly faster bile emptying (common bile duct $T_{1/2}$ before and after operation: 30.5 ± 14.8 and 18.8 ± 2.6 min, respectively). Cholecystokinin octapeptide administration caused rapid bile outflow from the common bile duct, with a significant decrease in the $T_{1/2}$ parameters before and after cholecystectomy.**

**Conclusions: In patients with their gallbladders in situ, the bile emptying rate showed wide variations and may be moderately slow without distal common bile duct obstruction. After cholecystectomy, the rate of bile emptying accelerated and showed only minor variations, thereby increasing the sensitivity of quantitative hepatobiliary scintigraphy for showing partial biliary obstruction.**

**Key Words: Bile Emptying, Cholecystectomy, Cholecystokinin, Gallbladder Motility, Quantitative Hepatobiliary Scintigraphy, Sphincter of Oddi Motility.**

QUANTITATIVE HEPATOBILIARY SCINTIGRAPHY (QHBS) has become a well-established method in the diagnosis of acute cholecystitis and in the differential diagnosis of jaundice, including the verification of intrahepatic or extrahepatic biliary obstruction (1). In patients with postcholecystectomy syndrome, with the application of cholecystokinin octapeptide (CCK-8) or amyl nitrite augmentation, QHBS recently proved to be the best noninvasive test for diagnosing sphincter of Oddi (SO) dysfunction (2,3). Furthermore, gallbladder emptying can also be estimated by measuring the gallbladder ejection fraction after a fatty meal or CCK-8 stimulation during QHBS (4). Of the quantitative parameters of QHBS, time variables of the common bile duct ($T_{max}$ and $T_{1/2}$ of the common bile duct [CBD]) and duodenum appearance time are regarded as the most sensitive parameters for diagnosing partial biliary obstruction at the level of the SO (3).

Although we know that gallbladder function is closely related to the interdigestive phase of the migrating mo-

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tor complex of the duodenum (5), significantly less is known about the interdigestive variations and normal rate of bile flow and emptying. However, the diagnosis of partial CBD obstruction caused by bile duct stricture, stones, or SO dysfunction requires a full knowledge of the normal pattern of bile outflow in patients with and without the gallbladder in situ. Although the normal variations of hepatobiliary imaging were reported earlier by Krishnamurthy et al. (6) and Williams et al. (7), no study has compared the results of CCK-8–augmented QHBS before and after cholecystectomy in the same group of patients with uncomplicated gallstone disease.

Accordingly, the aims of the current study were to define the dynamics and normal variations of the transpapillary bile flow by QHBS in patients with uncomplicated gallstone disease before and after cholecystectomy, and to investigate the effect of gallbladder removal and CCK-8 administration on the CBD emptying rates.

## Patients and Methods

### *Patients*

Twenty patients (1 man and 19 women; ages 29 to 70 years; mean age, 51 years) with symptomatic but uncomplicated gallstone disease were evaluated from 1 month before to 3 months after cholecystectomy. Single or multiple stones were demonstrated by abdominal ultrasonography in the gallbladder in all patients, but none of them had any sign of biliary obstruction or CBD stones. The CBD diameter was normal in all patients. All patients had normal results of liver function tests, and they were completely free of symptoms after surgery.

### *Methods*

Quantitative hepatobiliary scintigraphy was performed on all 20 patients before and after cholecystectomy according to the same method. After fasting overnight, 100 MBq (2.7 mCi) Tc-99m EHIDA was injected intravenously. Digital images were recorded continuously, at one frame per minute for 120 minutes, and saved into the computer. From the 60th minute, 0.3 ng/body weight $kg^{-1}/min^{-1}$ CCK-8 (cholecystokinin octapeptide; Squibb Diagnostics) was administered intravenously as a continuous infusion during the following 60 minutes.

### *Analysis of the Results*

Time–activity curves were generated from regions of interest defined as follows: right peripheral liver parenchyma, hepatic hilum, CBD, gallbladder (before operation), and duodenum. Parameters of time to peak activity ($T_{max}$), half-time of excretion ($T_{1/2}$), and duodenum appearance time were calculated. The $T_{1/2}$ of the CBD was determined repeatedly, before and during CCK-8 administration (CBD $T_{1/2}$ and CBD $T_{1/2}$-CCK). Before operation, the maximal gallbladder ejection fraction (%) was also calculated when CCK-8 was administered.

### *Statistics*

Results are expressed as the mean ± SD. For statistical evaluation, paired Student *t* tests was used and the significance level was set at 0.05.

TABLE 1. *Means and Standard Deviations of the Common Bile Duct Emptying Parameters*

| | Preoperative (mean ± SD) (min) | Postoperative (mean ± SD) (min) |
|---|---|---|
| CBD $T_{max}$ | 26.1 ± 6.8 | 21.6 ± 4.6 |
| CBD $T_{1/2}$ | 30.5 ± 14.8 | 18.8 ± 2.6 |
| DAT | 30.7 ± 16.0 | 16.6 ± 3.0 |

### *Ethics*

The study was approved by the local ethics committee in accordance with the Helsinki Declaration, and informed consent was obtained from each patient before they were enrolled in the study.

## Results

Before operation, gallbladder filling started within 60 minutes in 18 of the 20 patients, and within 30 minutes in 14 of them. Before administration of CCK-8 at time 60 minutes, spontaneous gallbladder emptying was detected in five patients. Duodenal activity appeared before 60 minutes in 18 of the 20 patients, and in 12 patients the duodenum appearance time was less than 30 minutes. The gallbladder ejection fraction was more than 35% in seven patients, and the average gallbladder ejection fraction was 43.2% ± 29.2%. The hepatic uptake and secretion of the isotope was normal in all cases, but the CBD emptying rate showed wide variations, so accordingly the $T_{1/2}$ of the CBD was more than 35 minutes in seven patients and more than 45 minutes in three cases. However, the $T_{1/2}$ of the CBD was less then 35 minutes in all those five patients with spontaneous gallbladder emptying before CCK-8 administration.

After cholecystectomy, the rate of bile emptying was normal in all patients and showed only minor variations. The $T_{1/2}$ of the CBD and also the duodenum appearance time were less than 30 minutes in all patients. Table 1 lists the means and SDs of the CBD emptying parameters ($T_{max}$, $T_{1/2}$, and duodenum appearance time) before and after cholecystectomy.

A comparison of the quantitative parameters before and after cholecystectomy revealed that bile emptying was accelerated after surgery. The $T_{max}$ of the CBD and the $T_{1/2}$ of hepatic hilum and CBD were significantly decreased after the operation when compared with the preoperative results ($P = 0.0285$, 0.0007, and 0.003, respectively; (Table 1 and Figs. 1 to 3). The duodenum appearance time was also significantly decreased after cholecystectomy ($P = 0.0004$; Table 1). We must emphasize that these differences were insignificant at the level of the hepatic parenchyma, and thus it seems not to

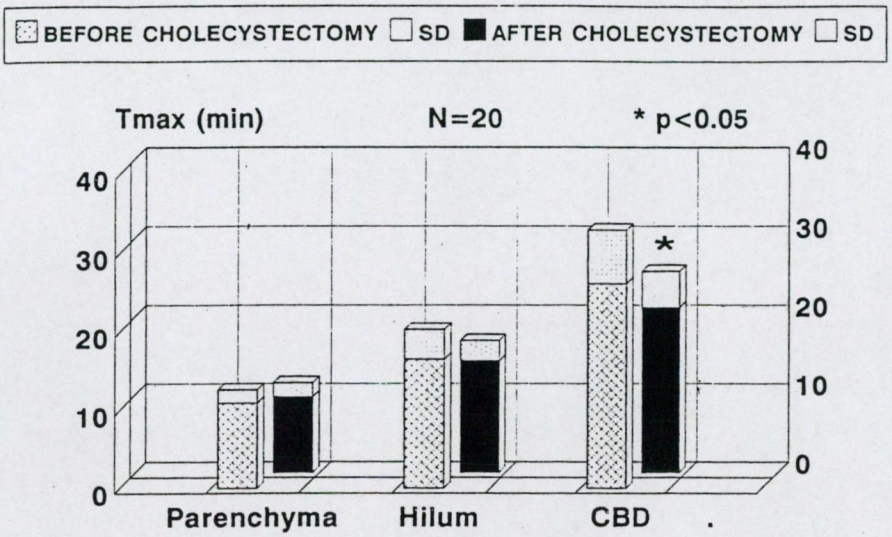


Fig. 1. Effects of cholecystectomy on the times to peak activity ($T_{max}$) of the liver parenchyma, hepatic hilum, and common bile duct.

be a result of changes in the hepatic bile secretion caused by cholecystectomy.

The administration of CCK—8 caused a rapid bile outflow from the CBD, with a significant decrease of the $T_{1/2}$ parameters before and after cholecystectomy, CBD $T_{1/2}$: 30.5±14.8 min and 18.8+2.6 minutes versus CBD $T_{1/2}$-CCK: 18.9±7.2 minutes and 13.5+2.1 minutes, respectively (Fig. 4). No paradoxical response (*i.e.*, permanent stoppage of the transpapillary bile flow during CCK-8 administration) was detected.

## Discussion

The combination of several factors, such as hepatic bile secretion, the contractile state of the gallbladder, and also the SO motor activity determine the bile outflow from the CBD into the duodenum (8). Although bile is secreted continuously from the liver, the secretion rate depends strongly on the pressure gradient of the biliary tree. Functional coordination between the gallbladder and the SO is of great importance in the mechanism of pressure equalization in the biliary tract. Bile secretion from the liver decreases when the CBD pressure increases, and thus the pressure is maintained at a relatively low level, even in the presence of partial biliary obstruction (9). Despite the continuous secretion of bile by the liver, its entry into the duodenum is periodic and it depends on the actual need. If the function of the gallbladder is intact, the secreted bile from the liver drains in two directions. One fraction enters the duodenum directly, whereas the other fraction fills the gallbladder. Before operation, the biliary tract is a low-

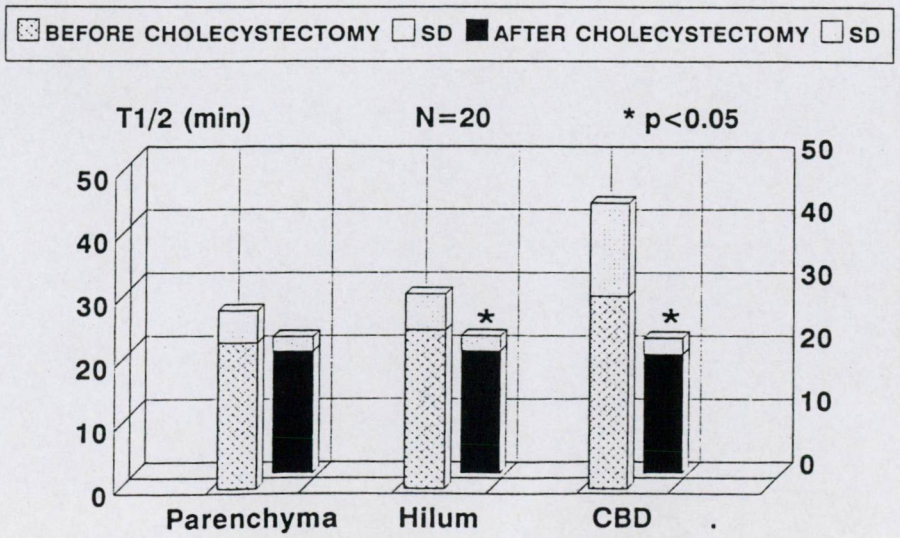


Fig. 2. Effect of cholecystectomy on the half-times of emptying ($T_{1/2}$) of the liver parenchyma, hepatic hilum, and common bile duct.

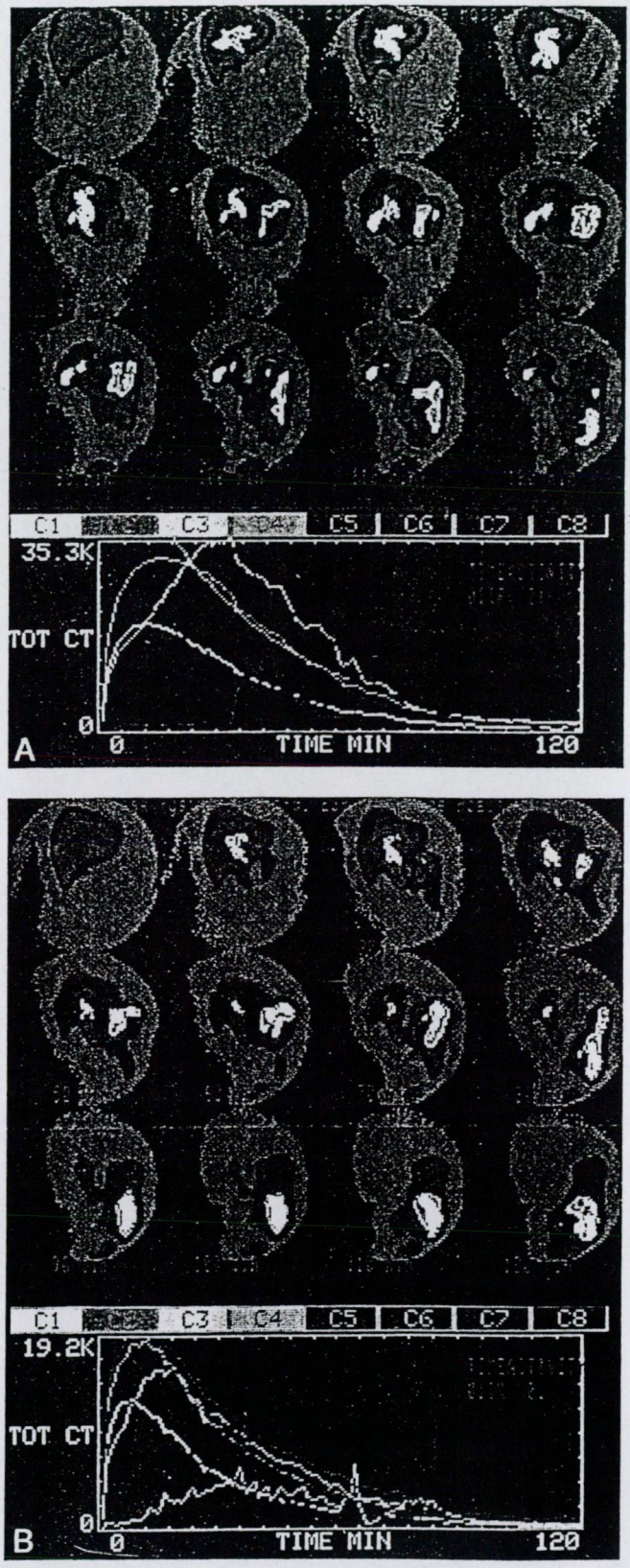


Fig. 3. Representative hepatobiliary scintigram of a patient before (A) and after (B) cholecystectomy. Note the obvious acceleration of the isotope emptying after operation.

pressure system, in which only minimal pressure changes occur despite substantial changes in the bile flow (10). The resistance of the SO can be regarded as a principal factor in the regulation of the pressure of the CBD. If the tone of the SO is increased, it produces a pressure gradient between the CBD and the gallbladder, which leads to gallbladder filling in the interdigestive state. On the other hand, if the pressure of the SO decreases, a larger proportion of the secreted bile can enter the duodenum directly (11). Therefore, in patients with the gallbladder in situ, wide variations in the bile emptying rate from the CBD into the duodenum may be physiologic.

Cyclic filling and emptying of the gallbladder is also closely related to the actual phases of the migrating motor complex of the bowel during the interdigestive state. Gallbladder filling occurs during phases I and III of the migrating motor complex, and endogenous motilin-induced, partial gallbladder emptying occurs in the late phase II (12). After a fatty meal is eaten, the gallbladder empties with an active contraction, which is regulated mainly by the release of endogenous CCK, which simultaneously induces SO relaxation, therefore allowing maximal bile outflow from the CBD into the duodenum at the time of maximal gallbladder contraction (13).

After cholecystectomy, the bile output can be described by a simple two-compartment model, where all the bile secreted from the liver enters the CBD and drains through the SO into the duodenum, thereby producing a continuous flow. On the other hand, it is obvious that CBD pressure inevitably increases when the SO contractility is enhanced, such as in patients with SO dysfunction, which is a result of the loss of the pressure-equalizing function of the gallbladder (14). It has been shown that the distension of the gallbladder and to a certain extent of the CBD can induce prolonged inhibition of SO motility and baseline pressure (15,16). This suggests a local reflex between the gallbladder and the SO, and therefore cholecystectomy might result in a higher resistance of the SO, which is predisposing for the development of postcholecystectomy symptoms and SO dysfunction in a subgroup of patients. Considerably less is known about the effect of cholecystectomy on the net bile output. When the total bile salt output in controls was compared with that in patients whose gallbladders were removed, no significant difference was found, but the peak bile salt output showed wide fluctuations in patients with the gallbladder in situ (17). Our results showed that the removal of the gallbladder resulted in globally increased transpapillary bile flow and CBD emptying rate, and patient-to-patient variation of the bile emptying was decreased after cholecystectomy. This may also be explained by the fact that, during the gallbladder filling period with a closed SO, the CBD emptying into the gallbladder through the narrow cystic duct

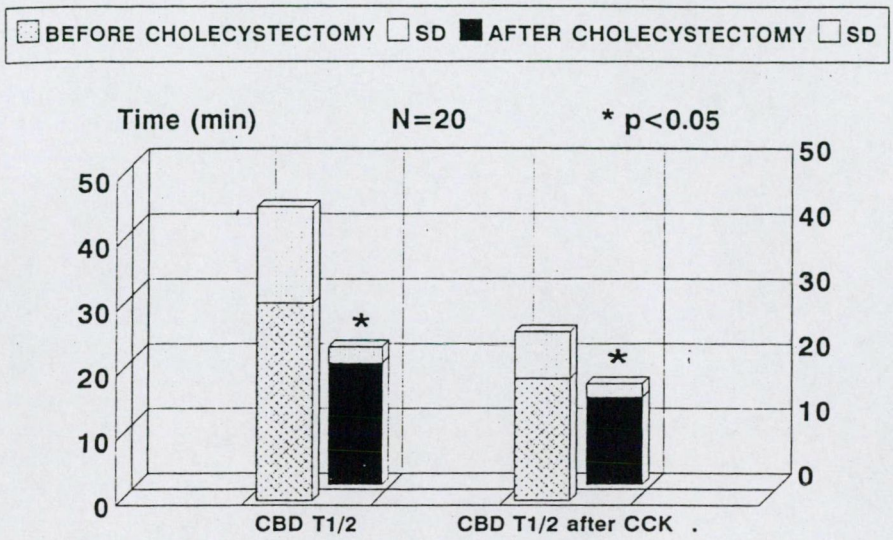


Fig. 4. Effects of cholecystokinin octapeptide administration on the $T_{1/2}$ parameters of the common bile duct.

is expected to be a considerably slower process than the bile emptying into the duodenum through an open SO. On the other hand, after cholecystectomy and without the periodic filling and emptying periods of the gallbladder, the actual phase of the duodenal migrating motor complex has probably no or only a minor influence on the bile emptying rate.

Finally, our results clearly showed that before operation sometimes only minimal bile outflow could be detected, even in the absence of biliary obstruction, and this phenomenon may lead to serious interpretation errors during the analysis of QHBS. However, after CCK-8 administration, the $T_{1/2}$ of the CBD was decreased significantly, to a constant level similar to that observed after operation. Consequently, in patients with the gallbladder in situ, dynamic studies with CCK or a fatty meal should be performed to differentiate fixed anatomic lesions from physiologic changes of the SO tone (18).

## Conclusions

The average bile emptying is accelerated after cholecystectomy compared with before operation. In patients with their gallbladders in situ, the bile emptying rate varied widely and can be moderately slow without CBD obstruction. After cholecystectomy, the bile emptying parameters of QHBS showed only minor variations in asymptomatic patients, thereby increasing the chance that abnormalities in patients with SO dysfunction would be exposed. These results should be considered when patients are examined who have their gallbladders in situ and potential CBD obstruction by QHBS.

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# EFFECT OF NITRIC OXIDE ON THE GALLBLADDER MOTILITY IN PATIENTS WITH ACALCULOUS BILIARY PAIN - A CHOLESCINTIGRAPHIC STUDY

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## Abstract

**Aim: The aim of the present study was to evaluate the influence of the exogenous nitric oxide donor glyceryl trinitrate on the caerulein-induced gallbladder contraction in patients with acalculous biliary pain. Patients and methods: Quantitative hepatobiliary scintigraphy was performed on 33 patients. From the 60. min caerulein ( 1 ng/bwkg/min for 10 min iv.) then from the 90. min the same dose of caerulein plus glyceryl trinitrate (0.5 mg sublingually) (21 patients) or placebo (12 patients) were administered and the gallbladder ejection fraction was measured repeatedly. Results: After the first dose of caerulein the gallbladder ejection fraction was less than 35% in 23 of 33 patients (non-responders), while it was more than 35% in the remaining 10 patients (responders). After the second dose of caerulein in 16 non-responder patients glyceryl trinitrate administration significantly increased the previously impaired gallbladder ejection fraction while in 7 non-responder patients placebo administration had no effect. Conclusion: Normalisation of the gallbladder ejection fraction in the majority of patients following glyceryl trinitrate administration suggests that impairment of gallbladder emptying is caused by a functional motility disorder rather than any organic disease.**

**Key words: acalculous biliary pain, gallbladder motility, gallbladder dyskinesia, nitric oxide, glyceryl trinitrate, caerulein, quantitative hepatobiliary scintigraphy.**

## Introduction

Patients with recurrent right upper quadrant abdominal pain and fatty food intolerance in the absence of demonstrable gallstones frequently present as a diagnostic and therapeutic challenge. A number of pathophysiological disorders may be responsible for the generation of acalculous biliary pain (ABP), e.g. chronic cholecystitis, cystic duct abnormalities, gallbladder (GB) dyskinesia and sphincter of Oddi dyskinesia. Cholecystography, abdominal ultrasonography (US), quantitative hepatobiliary scintigraphy (QHBS) and sphincter of Oddi (SO) manometry have been used to investigate patients with ABP (1, 2). The GB contraction induced by exogenous cholecystokinin (CCK) or CCK analogue (caerulein) administration can be measured by means of either US or QHBS, however currently methods involving QHBS are generally regarded as gold standard (3). QHBS offers the advantage over US of allowing simultaneous visualisation of the bile ducts, together with non-geometrical measurement of the GB contraction.

A subgroup of ABP patients exhibit an impaired GB emptying and the reproduction of biliary pain after CCK or caerulein administration. The term originally proposed to describe this condition by Cozzolino et al. (4) was cystic duct syndrome. Partial cystic duct obstruction caused by fibrosis, kinking and adhesions were the previously suspected factors in the pathomechanism of this syndrome, but a pure motility disorders such as GB dyskinesia were also suggested as a possible cause (5). Although GB dyskinesia, i.e. an uncoordinated GB contraction with spasm of the cystic sphincter muscles due to an excessive contractile response to CCK is an attractive theory, no human data are available as yet to lend support this pathomechanism.

Nitric oxide (NO) mediated non-adrenergic non-cholinergic (NANC) inhibitory nerves have been described in several regions of the gastrointestinal (GI) tract and also in the human GB and the sphincter of Oddi (6). Under basal conditions continuos release of the NO from the NANC nerve endings may influence the GB and the SO tonic and phasic activity. It is also well known, that the effect of NO on the sphincter areas of the GI tract is more enhanced, than on the other regions. Organic nitrates which exert their effect through NO have been shown to reduce the pressure of the sphincter of Oddi and to influence the GB contraction, but the combined effect of CCK and NO on GB motility has not been yet tested. We proposed, that simultaneous glyceryl trinitrate (GTN) administration might overcome the possible paradoxical contractile

response of the cystic duct sphincter due to caerulein and therefore it might improve the efficacy of the GB emptying.

**The aim of the present study** were to evaluate the effect of GTN on the caerulein-induced GB contraction in patients with ABP and suspected GB dyskinesia by means of QHBS and to asses the influence of GTN on the frequency of biliary pain evoked by caerulein.

## Patients and methods

33 patients with ABP were investigated. The selection criteria were chronic or intermittent, postprandial right upper quadrant pain, normal laboratory values (WBC count, ESR, AST, ALT, AP and se.amylase), negative abdominal ultrasound (US) and negative upper gastrointestinal endoscopy. Negative abdominal US was defined as a GB wall less than 1 mm thick, without sludge or stones in the GB. The study design was approved by the local University ethical committee.

QHBS was performed on all 33 ABP patients. The methodological aspects and the preliminary results have been presented at the EANM Congress in 1995 (7). After an overnight fast, 140 MBq technetium-99m-2,6-diethylphenylcarbamoylmethyl-diacetic acid (EHIDA) was injected intravenously. Changes in the activity over the upper part of the abdomen were recorded by a large field-of-view gamma-camera fitted with a low-energy, parallel hole collimator. Gamma-camera images (1 min each) were obtained at 5, 15, 25, 35, 45, 60, 75, 90 and 105 min in the anterior projection. Digital images were obtained simultaneously at one frame/min for 120 min, and recorded in a 64x64 matrix into the computer. In the first series of the experiments, from the 60. min caerulein (Takus) was administered intravenously in a dose of 1 ng/body weight/min, for 10 min (total administered dose 10 ng/body weight). Measurement of the GBEF after the first dose of caerulein allowed us to determine the motor function of the GB in patients with ABP. On the basis of our previous studies on healthy volunteers the GBEF response greater than 35% was considered to be normal (8). 23 of the 33 ABP patients had a GBEF response less than 35%, indicating an impaired GB emptying (non-responder [NR] group), while the remaining 10 patients had a well-functioning GB, with a GBEF response to caerulein stimulation more than 35% (responder [R] group).

In the second series of experiments, from the 90. min caerulein administration was repeated (1 ng/body weight/min for 10 min i.v.) in the presence of sublingually administered 0.5 mg glyceryl trinitrate (Nitromint subl. tabl.) in 21 consecutive patients, while the remaining 12 patients received placebo. Time - activity curves were generated from the GB region of interest, and corrected for the background activity and the physical decay of the radionuclide, and the GB ejection fraction (GBEF, %) and the half-time of emptying during the ejection period (HTE) were calculated from the data obtained after the first and the second stimuli, during the time periods from 60 to 90 and 90 to 120 min, respectively. Subjective complaints were also recorded. The GBEF was calculated according to the method described by Krishnamurthy (9). Values were expressed as means $\pm$ SD. For statistical evaluation, the paired Student t test was applied. The significance level was set at $p<0.05$.

## Results

23 of the 33 ABP patients had a GBEF response less than 35% after the first dose of caerulein, indicating an impaired GB emptying (group NR). In 7 of these 23 NR patients GBEF and HTE parameters remained unchanged following caerulein and placebo co-administration, demonstrating that this combination was not able to modify the previously impaired GB emptying, and caused no significant differences in the GBEF and HTE parameters between the first (caerulein) vs. the second (caerulein plus placebo) stimuli: 14.6$\pm$9.5% vs. 13.1$\pm$9.4% and 80.6$\pm$16.5 min vs. 76.1$\pm$20.1 min, respectively (Figure 1).

In 16 of 23 NR patients, caerulein and GTN co-administration improved or normalised the previously impaired GB emptying, with significant differences in the GBEF and HTE parameters between the first (caerulein) vs. the second (caerulein plus GTN) stimuli: 20.3$\pm$10.3% vs. 39.1$\pm$22.4% and 61.7$\pm$25.6 min vs. 39.6$\pm$35.9 min (Figure 2 and Figure 5).

10 of the 33 ABP patients had a well-functioning GB, with a GBEF response more than 35% after the first dose of caerulein stimulation (R group). In 5 out of 10 R patients caerulein and placebo co-administration did not modify the previously normal GB emptying, with no significant differences in the GBEF and HTE parameters between the first (caerulein) vs. the second (caerulein plus placebo) stimuli: 61.3$\pm$24.8% vs. 60.8$\pm$21.2% and 12.8$\pm$12.3 min vs. 10.3$\pm$9.6 min (Figure 3 and Figure 6).

In the remaining 5 out of 10 R patients with a normal GBEF, caerulein and GTN together caused further increase in both GBEF

and HTE, with significant differences between the first (caerulein) vs. the second (caerulein plus GTN) stimuli: 47.3±14.7% vs. 83.3±11.2% and 16.5±7.5 min vs. 6.8±4.3 min (Figure 4).

In 16 NR patients whose GBEF showed improvement following GTN and caerulein co-administration on the static hepatobiliary scans we could frequently observe a scintigraphic sign, which we called GB remodelling. This means that during the first caerulein infusion the GB configuration was spherical or oval in shape and there was no obvious visual evidence of GB emptying, however during the GTN and caerulein co-administration the GB configuration was changed to pear shape with a simultaneous decrease in the amount of the isotope in the GB area (Figure 7).

11 of the 33 ABP patients in the NR group parallel with the impaired GB emptying indicated mild right upper quadrant or epigastrial pain after the first dose of caerulein. However in the small group of R patients with normal GBEF no biliary pain response was observed. During the second series of experiments placebo co-administration was applied in 4 patients did not affect the caerulein-induced biliary pain, however GTN was applied in the remaining 7 patients abolished pain sensation, as well as normalised the GB emptying..

**Discussion**

The GB motility is controlled by various neural and humoral factors. Endogenous CCK is regarded as the most potent physiologic stimulator of the postprandial GB contraction (10). The gastrointestinal hormone motilin also induces a GB contraction, but analysis of the plasma peaks demonstrated that it acts mainly during the interdigestive periods by provoking repetitive GB contractions at the time of migrating motor complexes (11). Besides hormonal effects, the parasympathetic nerve stimulation causes GB contraction directly or in response to CCK or motilin action (12).

The synthetic CCK octapeptide (Sincalide), and the decapeptide caerulein (Takus) have similar pharmacological properties, with very short serum half-lives of about 2.5 min. The exogenous CCK-induced GB emptying lasts for 4-6 serum half-lives, and about 20 min after their administration the serum concentrations are undetectable. It has been shown that during physiological circumstances GB contraction requires the constant presence of CCK in the serum to maintain its emptying, and it will cease to empty in the absence of CCK (13).

QHBS combined with exogenous CCK administration was previously validated as an accurate method for the measurement of GB motility, with satisfactory reproducibility of both parametric variables and patterns of emptying (14). It has also been shown that pre-treatment with exogenous CCK does not preclude GB contraction evaluation with a second dose of CCK (15, 16). In our QHBS procedure the very short serum half-life of caerulein allowed us to evaluate the GB contraction two times during the same imaging study. In order to validate this method, in the second phase of the study we administered placebo together with caerulein. The results in the placebo group proved that repetitive administration of equivalent doses of caerulein evoked equivalent GBEFs both in patients with normal and with impaired GB emptying.

The dosage and the rate of administration of the exogenous CCK may critically influence the GB contraction. Several previous investigations have demonstrated the advantages of continuous, low dose CCK infusion over the bolus method, which is considered to be more physiological, results in more complete emptying and fewer side-effects, and has a lower variability (17). Accordingly, we applied a 10 min infusion with a total dose of 0.01 ug/body weight, which can be regarded as a golden mean.

A disordered motility of the GB has been assumed to produce recurrent biliary pain in patients without gallstones (18, 19, 20, 21). Although several prospective studies failed to reveal a significant correlation between the presence or the severity of the histopathology of chronic cholecystitis and the CCK-induced GB contraction (22, 23), cholecystectomy alleviates symptoms in the majority of patients with ABP and abnormal cholescintigraphy (24, 25). These previous results suggest that there is a good theoretical chance that pure GB motility abnormalities may exist without significant GB inflammation and produce biliary symptoms. One recent publication reported a strong association between poor GB emptying and cholesterol microlithiasis in the bile, which is a well-established etiologic factor of gallstone formation (26). The mechanism of poor GB emptying during exogenous CCK stimulation could be a decreased by the number or the sensitivity of CCK receptors in the GB, or may be explained by an inappropriate contraction of the GB smooth muscle wall due to inflammatory changes or an increased cystic duct resistance. The resistance of the cystic duct can be pathologically enhanced due to mechanical obstruction caused by

inflammatory oedema, microlithiasis, sludge or stone formation and due to functional disorders such as hypersensitivity of the cystic duct sphincter to CCK. Sphincter of Oddi dyskinesia with a paradoxical response to CCK (contraction or the absence of relaxation) may also be the cause of poor GB evacuation (27). The fact that there was no apparent accumulation of the radionuclide in the common bile duct after CCK administration in our patients, makes the latter pathomechanism unlikely.

NANC inhibitory nerves have been described both in the human GB and in the sphincter of Oddi (28, 29). Recent data have suggested that NO acts as an inhibitory neurotransmitter in the NANC neural pathways of the biliary tract (7, 8, 28, 30). Resting GB pressure and CCK induced contraction are enhanced by specific inhibition of NO synthase in guinea pigs (8), however NO does not suppress the GB muscle tonicity in cats (30). Although the exact role of the NANC innervation of the biliary tract has not been established, continuos release of NO from nerve endings may modulate the SO and GB tonic and phasic activity under resting conditions (8). Nitrosovasodilatators as GTN acts indirectly on the smooth muscle via the release of NO either spontaneously or as a result of enzymatic conversion. The intracellular mechanisms of smooth muscle relaxation due to exogenous or endogenous NO are probably mediated by the same intracellular mechanism, by stimulating the activity of soluble guanylate cyclase thereby elevating the tissue levels of cyclic guanosine and adenosine monophosphate (cGMP and cAMP) (31). In this way, exogenous NO may induce relaxation of the GB wall, however this effect must be more enhanced in the sphincter region (cystic sphincter of the GB neck), and thus simultaneous exogenous CCK administration can not only overcome the relaxing effect of NO and causes GB wall contraction, but also produce a more complete GB emptying. It is well known, that nitrosovasodilatators are the most potent relaxants of the sphincter of Oddi too (32, 33), and this may also contribute in the mechanism of enhanced GB evacuation.

Our results provided the first evidence that the NO donor GTN causes a significant improvement in the caerulein-induced GB emptying in patients with ABP. Normalisation of the GBEF in the majority of ABP patients following GTN administration strongly suggests that impairment of GB emptying, which frequently associated with biliary pain response after caerulein administration is caused by a functional spasm of the cystic duct rather than any organic GB disease. We also demonstrated a new scintigraphic sign so called GB remodelling, which strongly supports this pathomechanism and may be a visual evidence of the functional spasm of the cystic duct and the GB neck area. This pure motility disorder, which can be called as GB dyskinesia may be responsible for the abnormal GB function and subjective complaints frequently seen in patients with ABP.

**In conclusion**, QHBS combined with simultaneous caerulein plus GTN administration has an important clinical implication in the diagnosis of GB dyskinesia, and thus GTN therapy may be recommended in the management of these patients.

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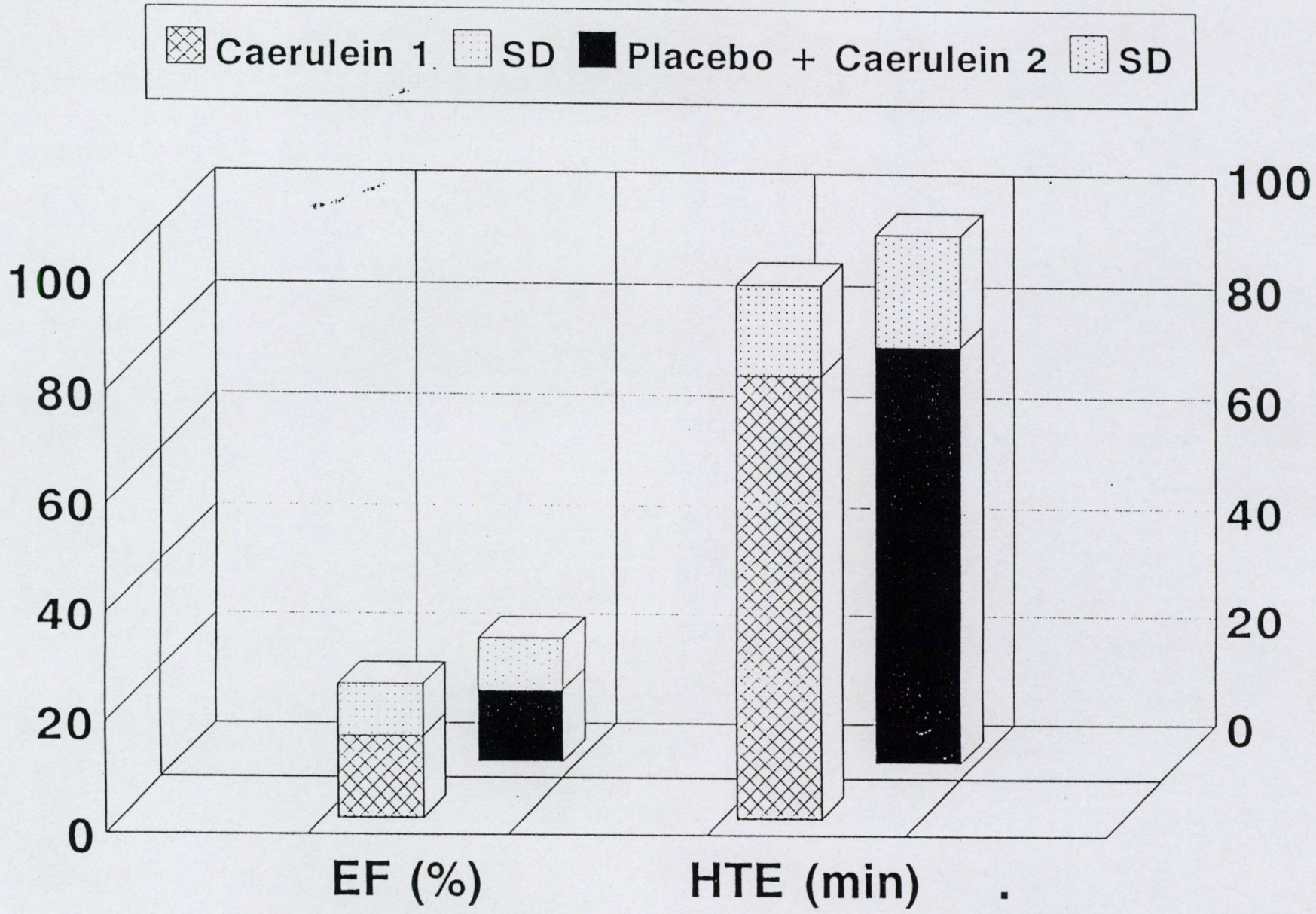
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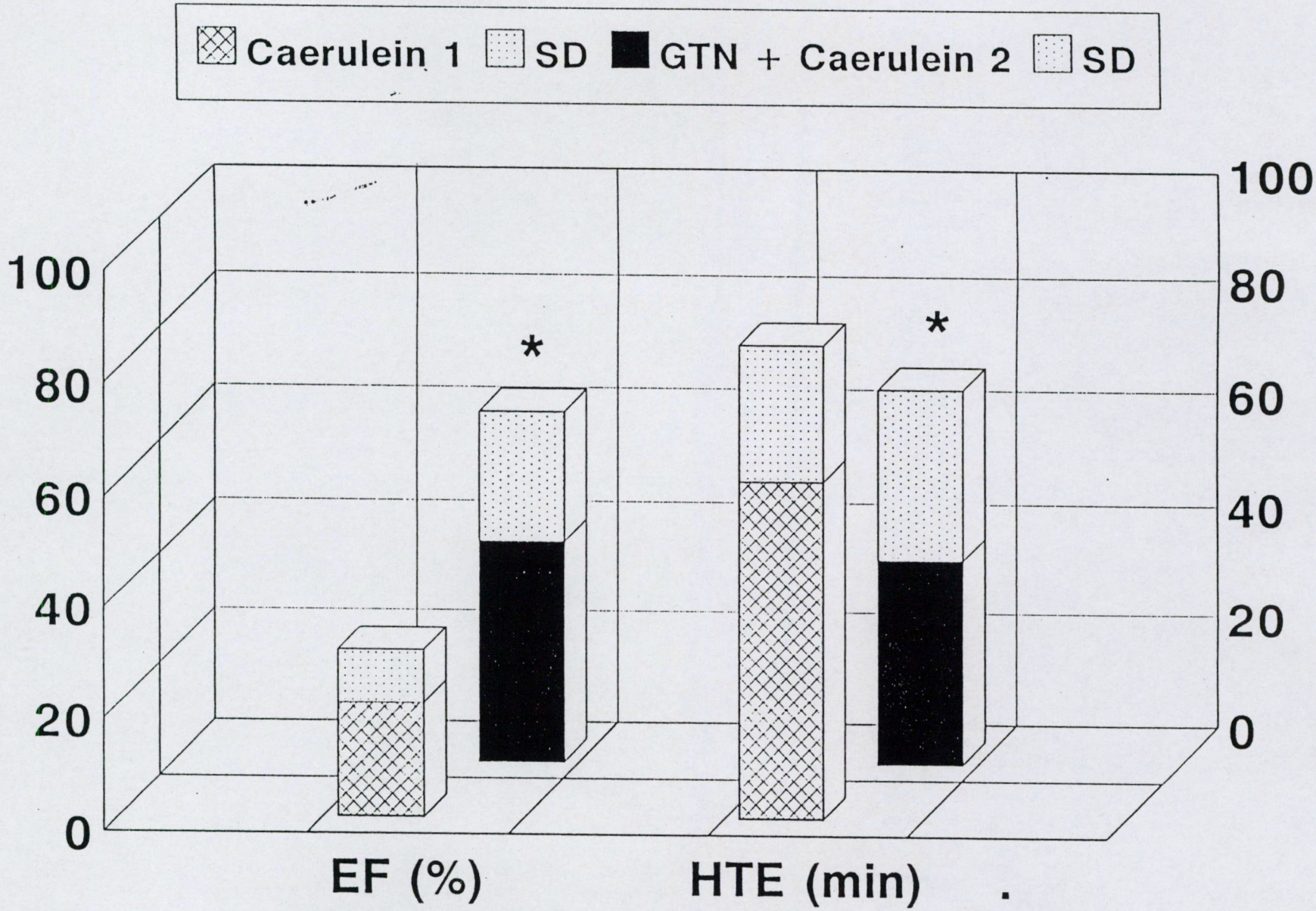
SD
Placebo + Caerulein 2
SD
100
80
60
40
20
0
100
80
60
40
20
0
EF (%)
HTE (min)

Figure 1. N=7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SD
GTN + Caerulein 2
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80
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100
80
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20
0
EF (%)
HTE (min)

Figure 2.

N=16

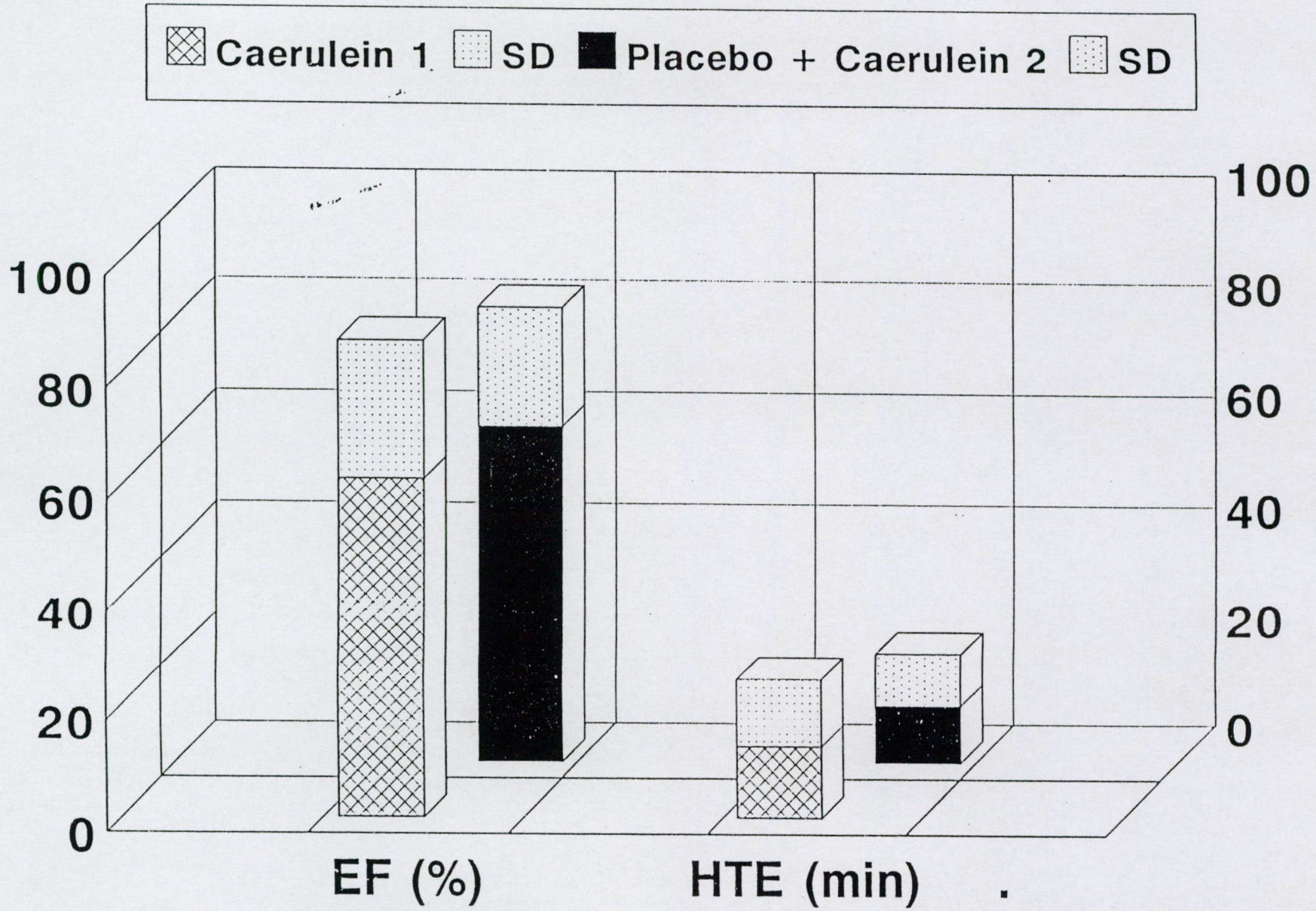

Caerulein 1
SD
Placebo + Caerulein 2
SD
100
80
60
40
20
0
100
80
60
40
20
0
EF (%)
HTE (min)

Figure 3.

N=5

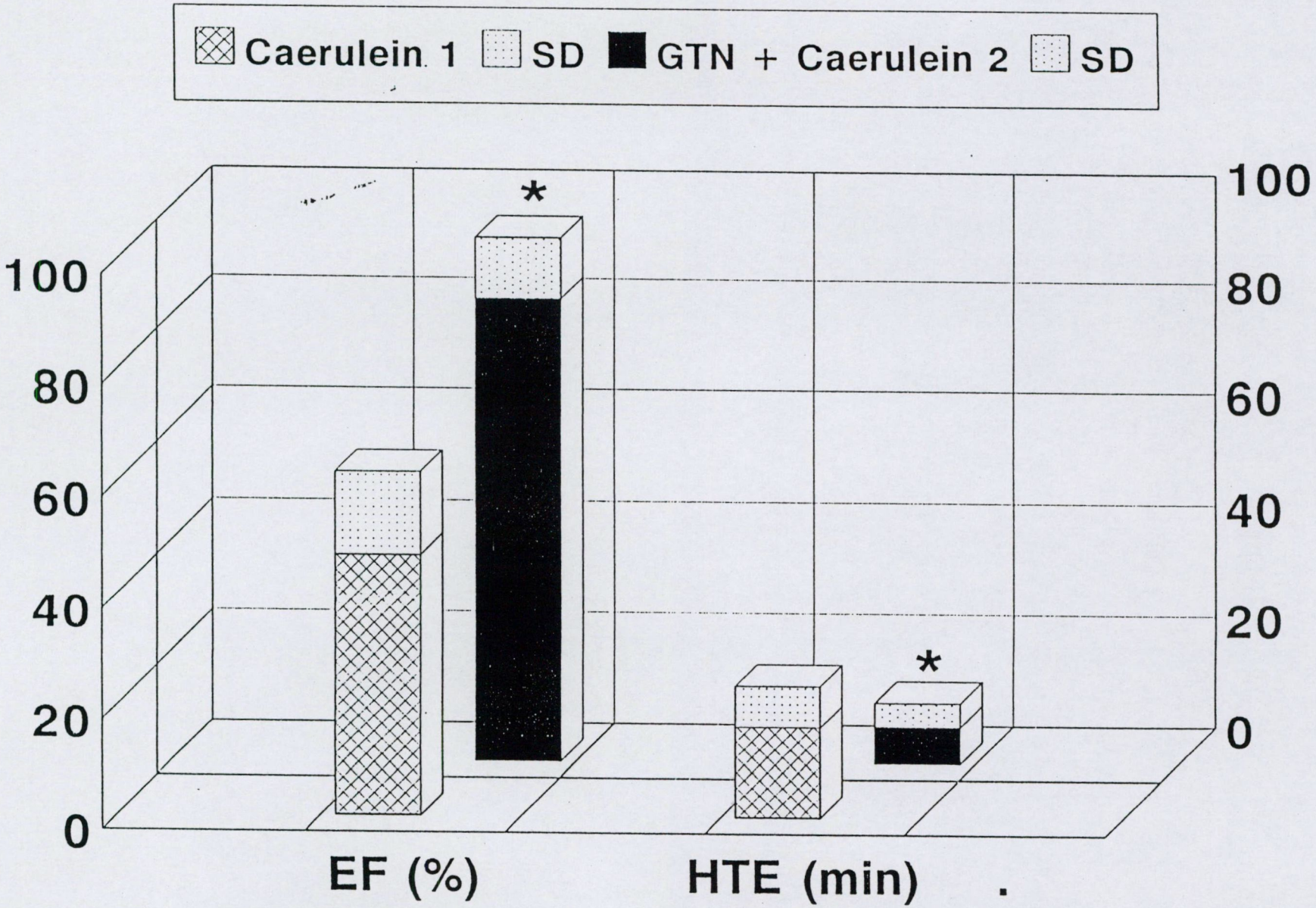
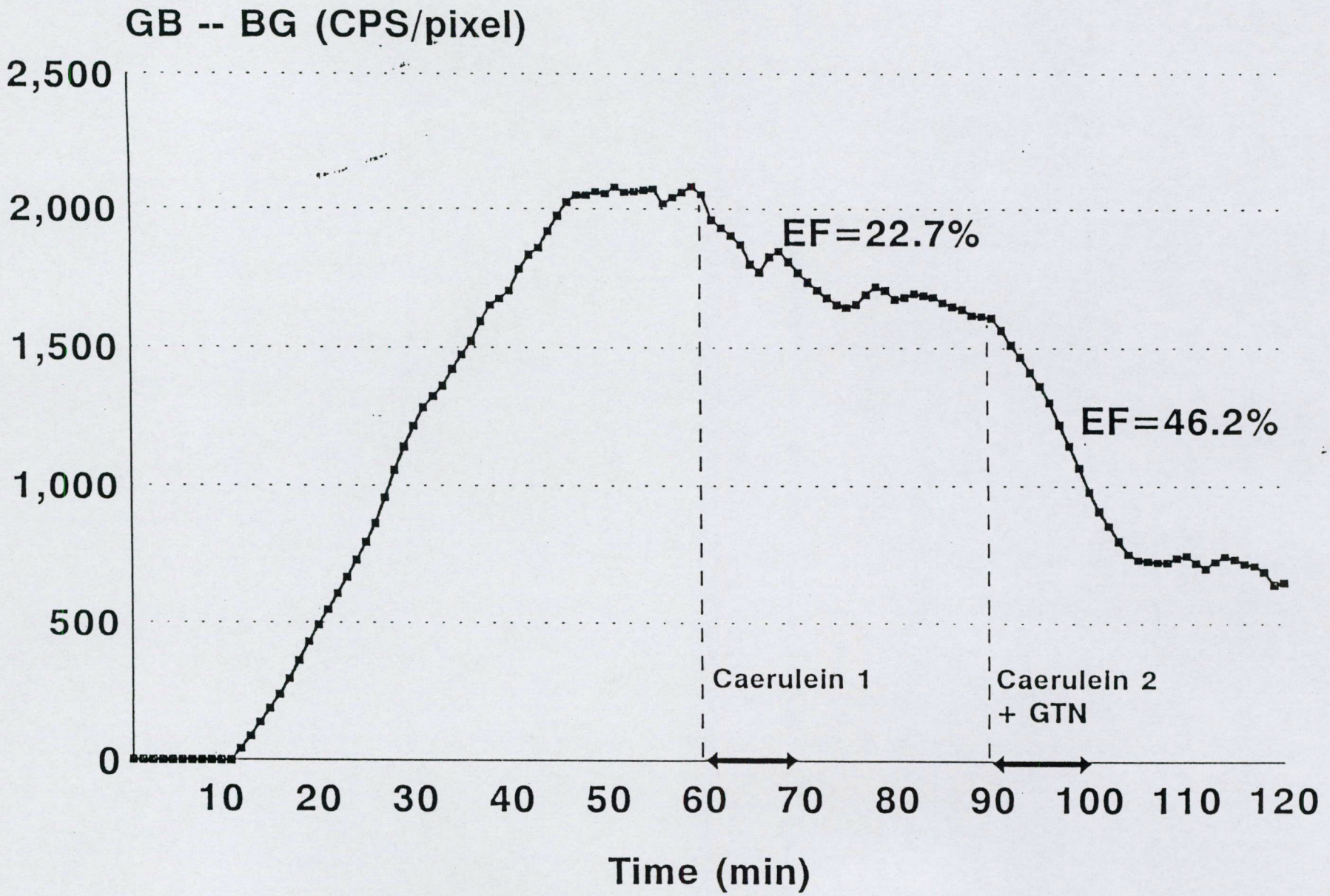

Caerulein 1
SD
GTN + Caerulein 2
SD
100
80
60
40
20
0
*
*
100
80
60
40
20
0
EF (%)
HTE (min)

Figure 4.

N=5


GB -- BG (CPS/pixel)
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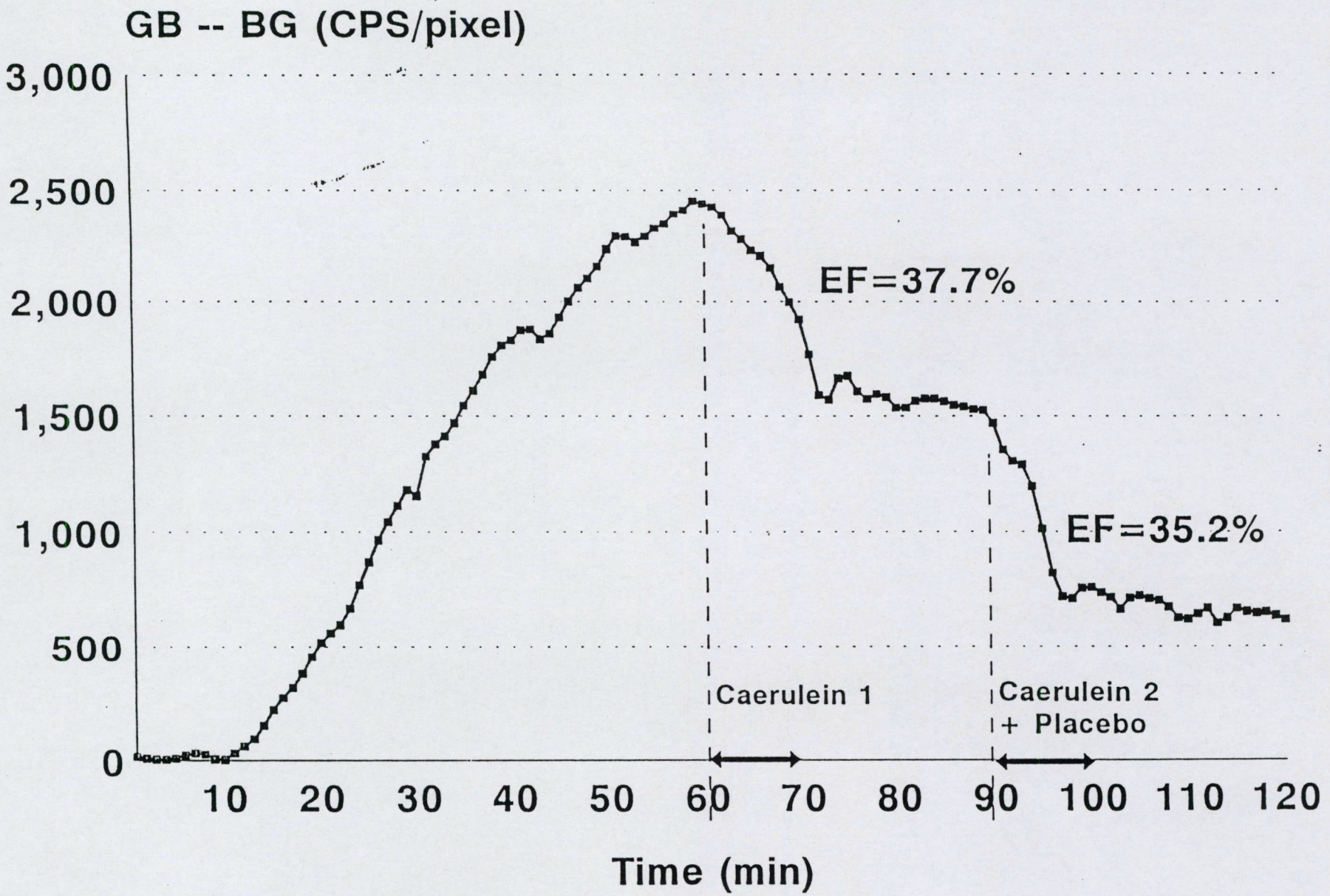
2,000
1,500
1,000
500
0
EF=22.7%
EF=46.2%
Caerulein 1
Caerulein 2
+ GTN
10
20
30
40
50
60
70
80
90
100
110
120
Time (min)

Figure 5


GB -- BG (CPS/pixel)
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2,000
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1,000
500
0
EF=37.7%
EF=35.2%
Caerulein 1
Caerulein 2
+ Placebo
10
20
30
40
50
60
70
80
90
100
110
120
Time (min)

Figure 6.

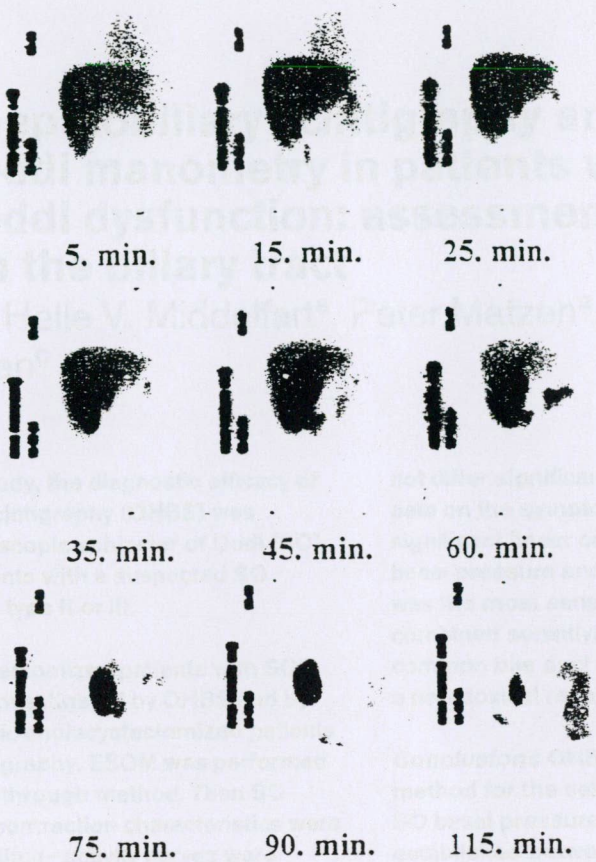



Figure 7.

is to divide them into the following three groups on the basis of the clinical presentation, the laboratory results and the ERCP findings. SOD group I patients present with abdominal pain, abnormally elevated liver enzymes, a dilated CBD and a delayed contrast drainage time. SOD group II patients have abdominal pain and at least one more of the above-mentioned criteria. SOD group III patients have only abdominal pain and none of the other criteria [5]. The introduction of endoscopic SO manometry (ESOM) into clinical practice can be regarded as a major step both for the exploration of the physiological motor function of the human SO and also for the diagnosis of SOD [6]. Several motility abnormalities of the SO have been described, such as an increased basal pressure, an increased amplitude of phasic contractions (PCs), an increased number of retrograde PCs, an increased frequency of PCs, an increased pressure of the CBD and a paradoxical response to cholecystokinin administration [7–9]. However, the manometric evidence of an elevated SO basal pressure, i.e. SO stenosis, is regarded as the most important diagnostic finding, since it affords a good reproducibility, and has proved to be a reliable predictor of a satisfactory therapeutic outcome in patients scheduled for endoscopic sphincterotomy [10].

Hepatobiliary scintigraphy based on static gamma camera pictures was initially recommended for the non-invasive diagnosis of SO motility disorders [11,12]. Krishnamurthy *et al.* then developed a computerized method for quantitative analysis of the dynamics of bile flow, referred to as quantitative hepatobiliary scintigraphy (QHBS) [13]. In cholecystectomized patients, QHBS has proved to be a sensitive technique for the diagnosis of abnormalities of bile secretion and transpapillary bile flow, with excellent reproducibility [14]. However, clinical acceptance of the diagnostic role of QHBS has progressed only slowly, because of the lack of controlled studies in which the parameters of ESOM and QHBS were compared. There is still uncertainty as to which is the most sensitive scintigraphic parameter for the selection of patients with an elevated SO basal pressure and how measurements should be made. Accordingly, the aims of the present study were to compare the diagnostic usefulness of QHBS and ESOM in cholecystectomized patients with SOD (biliary type II or III) and also to assess the flow–pressure relationship in the biliary tract by searching for a possible correlation between the quantitative parameters.

## Methods

### Patients studied

We investigated 20 cholecystectomized patients (17 females and 3 males, mean age 50 years) with PCS by means of QHBS and ESOM. All 20 patients were referred to the Hvidovre Hospital with suspicion of SOD. All patients had chronic RUQ pain similar to that before the operation, and 57% of them had concomitant dyspeptic symptoms. Apart from the diagnostic tests necessary to exclude extra-biliary organic diseases, a diagnostic ERCP had been performed a few weeks earlier in all patients before inclusion in the present study. The ERCP was normal in the majority of patients, two displayed a moderate CBD dilation without any obvious cause, and three had moderately elevated AST on admission. According to the Geenen classification, our patients belonged in the SOD biliary type II or III groups. QHBS and ESOM were performed during the same week in the majority of our patients, always starting with scintigraphy. We also investigated 20 asymptomatic cholecystectomized patients of similar age and sex (19 females and 1 male, mean age 51 years) by QHBS three months after uncomplicated laparoscopic cholecystectomy, and the results of these investigations served as controls for the scintigraphic study.

### Procedures

ESOM was performed by a standard method [15]. Following an overnight fast, sedation was induced with 2.5–7.5 mg intravenous midazolam (Dormicum®, Roche, Germany). No other drugs were given. Duodenoscopy was then performed with a video duodenoscope JF-130 (Olympus). For SO pressure measurements, a standard triple-lumen manometric catheter was used (Arndorfer ERCP Manometric Catheter, 3 ch, ER3GW, Zinetics Medical, Utah, USA, and Medtronic Synectics Medical, Stockholm, Sweden) with an external diameter of 1.7 mm and side-holes spaced 2 mm apart. All capillary channels were constantly perfused with sterile water at a rate of 0.4 ml/min from a dual-chamber pressure pump with a 15 psi (103.42 KPa) over-pressure in the water reservoir. The pressures were transmitted by external transducers and the video pictures from the endoscope were recorded simultaneously on a Synectic Polygraph computer system with a time-correlated basis, using the Synectic Polygram Windows 1.1 software. Selective deep cannulation of the CBD was achieved with a standard-tip Wilson–Cook ERCP catheter. The position of the catheter was assessed by aspiration of a small amount of bile through the catheter, then a flexible-tip guide wire (Wilson–Cook HSF 25/400) was introduced deeply into the bile tract. Next, the ERCP catheter was changed for the ESOM catheter over the guide wire, which was kept in place. The duodenal pressure was recorded before and immediately after the SO measurements to establish the average zero reference pressure. After the ESOM catheter had been placed into the CBD, the guide wire was removed and the CBD pressure was recorded for a minimum of 2 min to exclude the periods of initial hyperactivity of the SO. A stationary pull-through measurement of the SO segment was then made. During the station pull-through

recording, the ESOM catheter was withdrawn into the SO zone and retained there for a mean time of 5 min. Then the SO basal pressure, the PC amplitude, frequency and peristalsis were measured.

QHBS was performed with our standard method in all patients. After an overnight fast, 100 MBq 99mTc-*N*-2,6-dimethylphenylcarbamoylmethyliminodiacetic acid (99mTc-EHIDA) was injected intravenously. Changes in the activity over the right upper part of the abdomen were recorded by a Siemens Orbita gamma camera fitted with a parallel-hole collimator. Gamma camera images were obtained in the anterior projection with the patient lying supine beneath. Digital images were recorded continuously, at one frame/min for 120 min, and saved in a VAX computer. From the 60th min, 5 ng/kg body weight/min caerulein (Takus®, Pharmitalia, Italy) was administered intravenously for 10 min in all 20 patients with PCS in order to enhance the sensitivity of QHBS.

### Analysis of the results

During the QHBS analysis, after the image processing, time–activity curves (TACs) were generated from regions of interest (ROIs) defined as follows: right peripheral liver parenchyma (LP), hepatic hilum (HH), CBD and duodenum. TACs were then generated and quantitative parameters of time to peak activity ($T_{max}$) and half-time of excretion ($T_{\frac{1}{2}}$) over each ROI were calculated. The $T_{\frac{1}{2}}$ of the CBD was calculated for both pre- and post-caerulein periods. The hilum-to-duodenum transit time (HDTT) and the duodenum appearance time (DAT) were also determined. Schematic presentations of these methods of quantification are displayed graphically in Fig. 1.

For ESOM, the SO basal pressure and the amplitude, frequency, duration and propagation of the PCs were measured in each channel, and mean pressure values were then calculated. For the SO basal pressure calculation during the station pull-through technique, we used only that manometric channel reproducibly located in the mid-portion of the SO, and there we determined the average basal pressure between the PCs after careful exclusion of all periods with obvious manometric artefacts. A mean SO basal pressure > 40 mmHg was considered to be abnormal and diagnostic for SO stenosis.

### Statistics

All results are expressed as means + one standard deviation (1 SD). For statistical evaluation, the unpaired Student's *t* test was used. For calculation of the correlation between QHBS and ESOM parameters, the Spearman rank correlation method was applied. The significance level was set at 0.05, and the upper limit of normal values of the scintigraphic parameters at the mean + two standard deviations, calculated from the results in the asymptomatic control group. The sensitivity and specificity of each scintigraphic parameter were then determined.

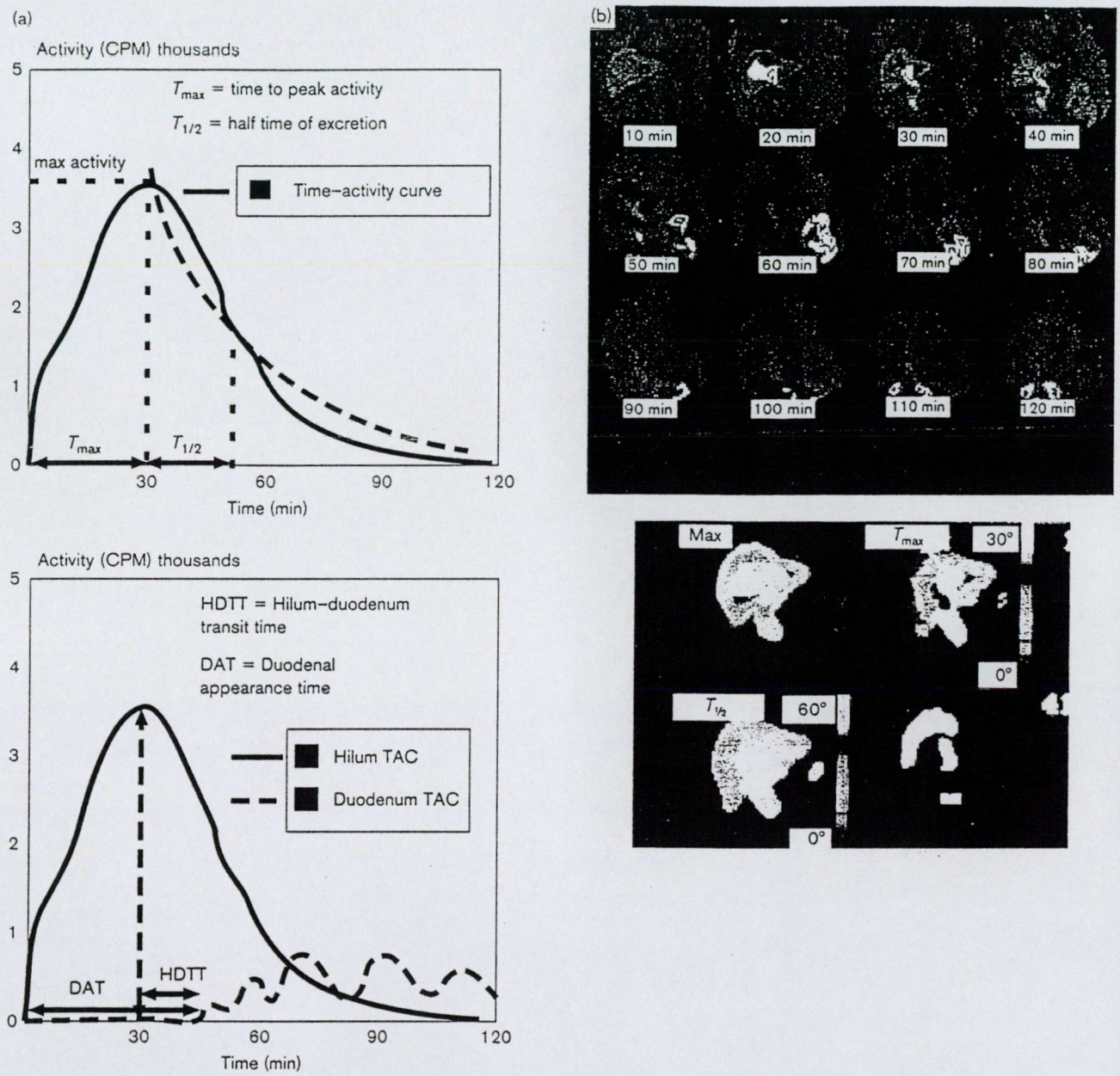
The study was approved by the local ethics committee and was conducted in accordance with the Helsinki II Declaration. Informed consent was obtained from each subject before inclusion into the study.

## Results

QHBS was performed in all cases, but ESOM could only be completed in 15 patients, five in the SOD biliary group II and the remaining 10 in the SOD biliary group III. Drop-outs were due to poor patient co-operation in three cases and technical difficulties (inability to introduce the manometric device into the papilla) in two cases. Nine of the 15 symptomatic patients exhibited an elevated basal pressure (> 40 mmHg) on ESOM, while in the remaining six patients the basal pressure was normal. The individual ESOM results regarding the basal pressure and the PC amplitude are shown in Fig. 2. The average amplitude of the PCs was normal in all patients. Predominantly retrograde PC peristalsis was found in four patients, all but one accompanied by an elevated basal pressure. No tachyoddia was recorded, the frequency of the PCs ranged from 1 to 4.5 per min.

In the 15 patients with SOD and successful ESOM, we were able to compare the manometric results with the QHBS parameters. On the basis of the ESOM results, we divided the patients into two groups: nine patients with an elevated SO basal pressure (> 40 mmHg) and six patients with normal SO basal pressure (< 40 mmHg). The QHBS parameters in the two patient groups with SOD were then compared with the results for 20 asymptomatic cholecystectomized controls. In patients with an elevated SO basal pressure (> 40 mmHg), QHBS parameters, such as $T_{max}$ and $T_{\frac{1}{2}}$ calculated from the ROIs over the CBD, HDTT and DAT proved to be significantly increased compared to the controls: $28.7 \pm 4.3$ versus $21.1 \pm 4.6$ min corresponding to the CBD at $T_{max}$, $39.7 \pm 15.4$ versus $18.8 \pm 2.6$ min corresponding to the CBD at $T_{\frac{1}{2}}$, $9.0 \pm 3.6$ versus $2.3 \pm 1.3$ min corresponding to HDTT and $27.1 \pm 4.9$ versus $16.6 \pm 3.0$ min corresponding to DAT, respectively (Figs 3–5). On the static pictures of hepatobiliary scintigraphy, a slight isotope accumulation in the biliary tree can be detected in the majority of SOD patients with an elevated SO basal pressure, but accurate assessment of the bile flow dynamics was not possible without quantification (Figs 6 and 7). By contrast, the hepatobiliary scintigram was normal in the six patients with a normal SO basal pressure and the QHBS parameters did not differ significantly when

Fig. 1



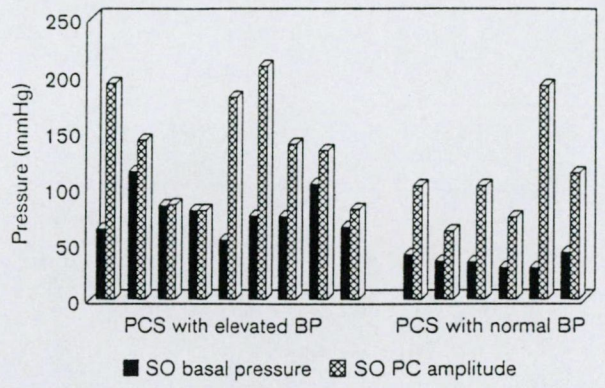

(a) Schematic representation of parameters of QHBS calculated from time–activity curves ($T_{max}$, $T_{\frac{1}{2}}$, HDTT and DAT). (b) Schematic representation of ROIs for time–activity curve calculations during QHBS.

compared to the asymptomatic cholecystectomized controls (Figs 3–5).

In order to establish a possible relation between the flow parameters derived from QHBS and the pressure values calculated from ESOM, we systematically compared our quantitative parameters by the Spearman rank correlation method. For the pooled data on the 15 patients with SOD, a statistically significant linear correlation was found between the SO basal pressure and all of the QHBS parameters: LP $T_{max}$ ($R = 0.69$, $P = 0.005$), LP $T_{\frac{1}{2}}$ ($R = 0.84$, $P = 0.00009$), HH $T_{max}$ ($R = 0.82$, $P = 0.0002$), HH $T_{\frac{1}{2}}$ ($R = 0.79$, $P = 0.0005$), CBD $T_{max}$ ($R = 0.65$, $P = 0.008$), CBD $T_{\frac{1}{2}}$ ($R = 0.68$, $P = 0.005$), HDTT ($R = 0.72$, $P = 0.003$) and DAT ($R = 0.89$, $P = 0.00001$) (Fig. 8). However, no statistical relationship was detected between the QHBS parameters and the amplitude, frequency and propagation characteristics of the SO PCs.

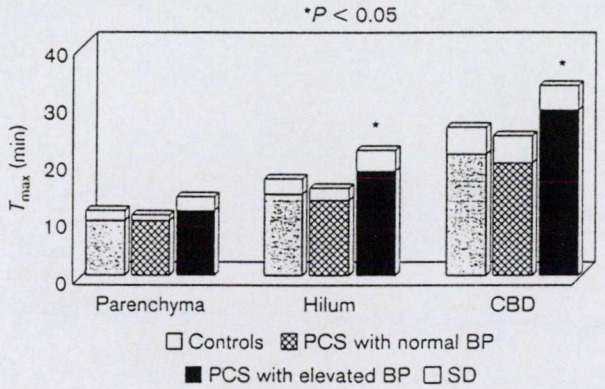
Calculation of the upper confidence limits of the normal values (mean + 2 SD) of each QHBS parameter

Fig. 2



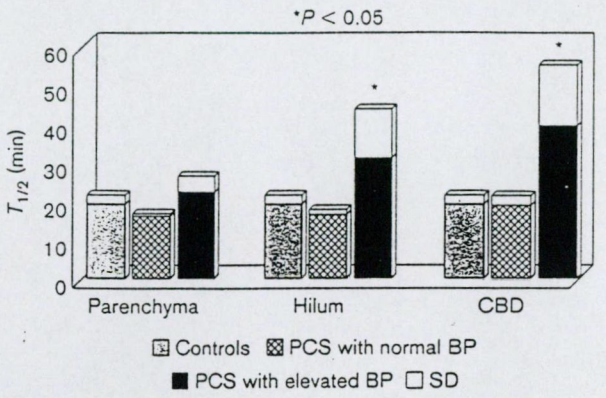

Individual results of ESOM in 15 PCS patients.

Fig. 3



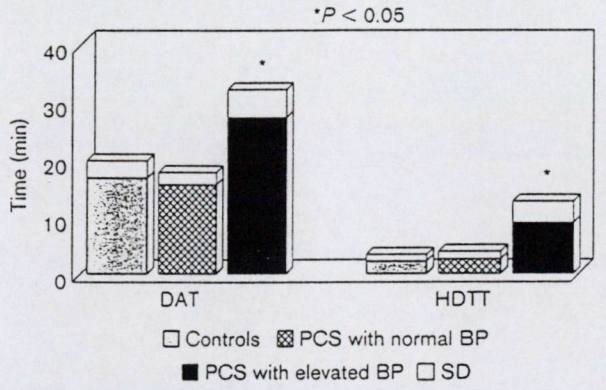

Comparison of $T_{max}$ parameters of the liver parenchyma, hepatic hilum and CBD in PCS patients with elevated basal pressure with PCS patients with normal basal pressure and also to asymptomatic cholecystectomized controls.

Fig. 4




Comparison of $T_{\frac{1}{2}}$ parameters of the liver parenchyma, hepatic hilum and CBD in PCS patients with elevated basal pressure with PCS patients with normal basal pressure and also to asymptomatic cholecystectomized controls.

Fig. 5

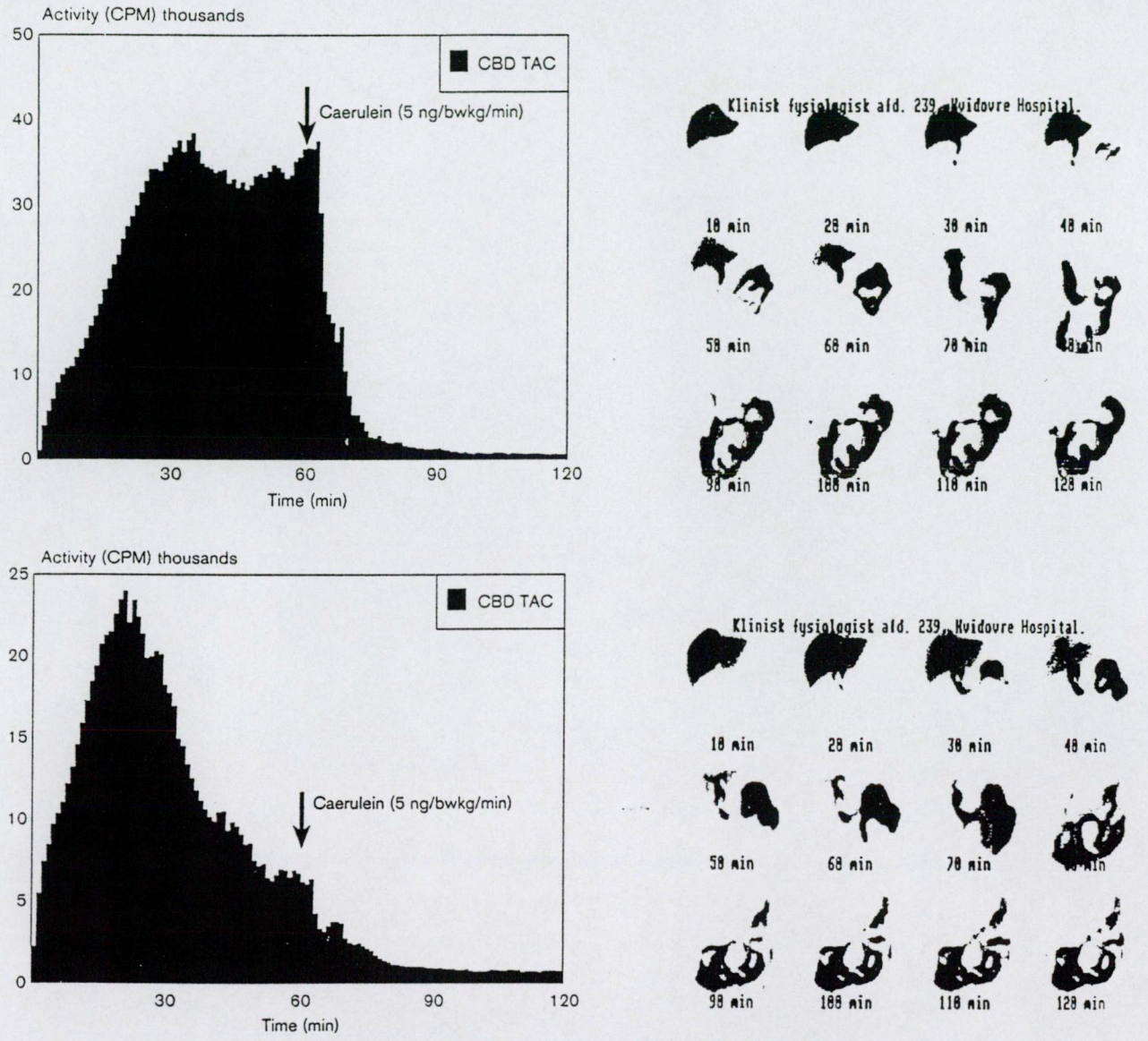



Comparison of HDTT and DAT parameters of the liver parenchyma, hepatic hilum and CBD in PCS patients with elevated basal pressure with PCS patients with normal basal pressure and also to asymptomatic cholecystectomized controls.

in the control group allowed us to determine the sensitivity and specificity of QHBS in the diagnosis of SOD with elevated basal pressure. Although HDTT was the most sensitive scintigraphic parameter, $T_{max}$ of the CBD, $T_{\frac{1}{2}}$ of the HH and CBD, and DAT also proved to have excellent sensitivity (Table 1). In fact, the combined sensitivity of $T_{max}$ and $T_{\frac{1}{2}}$ of the CBD reached 100%, so by the application of both these scintigraphic parameters we were able to select all patients who had an elevated SO basal pressure on ESOM. The specificity was 100% for all QHBS parameters, which was obviously due to the highly preselected patient population with a normal liver function and ERCP.

After administration of the cholecystokinin analogue caerulein during QHBS, the rate of bile excretion from the CBD was accelerated and the $T_{\frac{1}{2}}$ for the CBD not only decreased significantly, but also normalized in all 20 patients with SOD. This effect of caerulein was equivocal and independent of the previous scintigraphic or the manometric result (Figs 6 and 9). No scintigraphic sign of a paradoxical response to cholecystokinin (i.e. accumulation of the isotope due to SO spasm instead of relaxation) was detected, although five patients complained of biliary-type abdominal pain after caerulein administration, which was associated with a significant duodeno-gastric reflux of radiolabelled bile in two of them. Therefore, caerulein administration did not increase the sensitivity of QHBS in the diagnosis of SOD, but instead diminished the previous trans-papillary bile flow differences.

Fig. 6

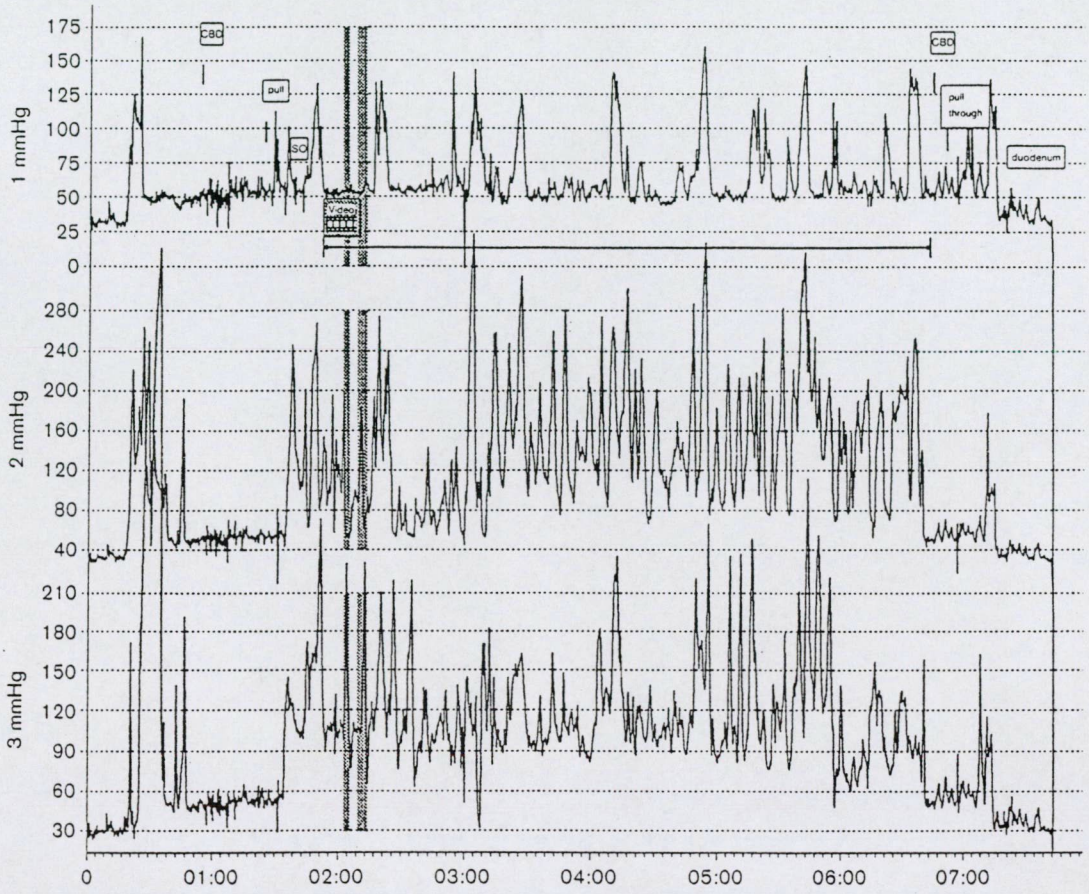



Recording of TAC generated from the ROIs of the CBD and hepatobiliary scintograms of a PCS patient with elevated SO pressure (upper panel) and normal SO pressure (lower panel). The hepatobiliary scintogram depicts an isotope accumulation in the biliary tree and the TAC of the CBD reveals slower trans-papillary bile transit in the patient with SOD and an elevated SO pressure. Note that caerulein administration at the 60th minute causes rapid emptying of the isotope from the CBD.

## Discussion

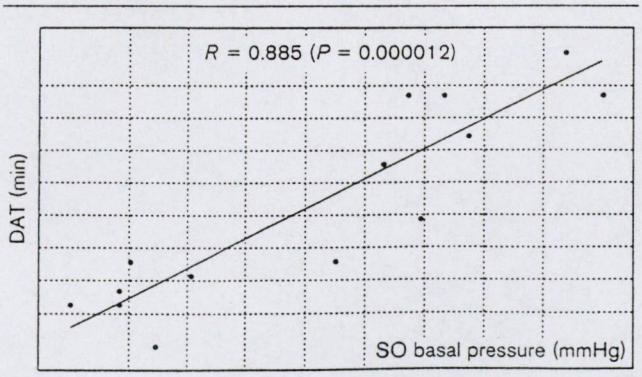
ESOM is the gold standard for identification of the subgroup of patients with abnormal basal pressure of the SO; however, the technique is not without disadvantages. ESOM is an expensive and not uniformly available procedure. Furthermore, the difficulty of performing an acceptable manometric study necessitates close co-operation between an experienced endoscopist and a motility expert. ESOM has been shown to be a reproducible technique in healthy persons and patients with SO stenosis (i.e. elevated SO basal pressure), but the reproducibility has sometimes been unsatisfactory in patients with SO dyskinesia. Moreover, ESOM increases the risk of procedure-related pancreatitis to a level above that expected for standard ERCP. The frequency of ESOM-associated pancreatitis in the general patient population is about 8%, but it has been reported to be as high as 28% in subgroups of patients with SOD, which is a functional gastrointestinal motor disorder [17]. Severe acute necrotizing pancreatitis is an uncommon but possible complication [18]. In terms of the risk–benefit principle of the

Fig. 7




Recording of 3 channel station-pull-through ESOM in a PCS patient with elevated SO pressure and SOD.

Fig. 8



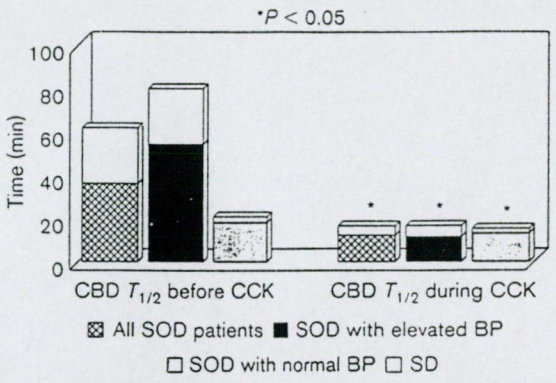

Correlation between SO basal pressure determined by ESOM and DAT calculated from QHBS in 15 PCS patients.

Table 1 **Upper limit of normal values and calculated sensitivity of each QHBS parameter in the diagnosis of elevated SO pressure and SOD**

| | Upper limit (mean ± 2 SD) | Sensitivity |
|---|---|---|
| Liver parenchyma $T_{max}$ (min) | 13 | 33% |
| Liver parenchyma $T_{\frac{1}{2}}$ (min) | 24 | 33% |
| Hepatic hilum $T_{max}$ (min) | 20 | 22% |
| Hepatic hilum $T_{\frac{1}{2}}$ (min) | 24 | 67% |
| Common bile duct $T_{max}$ (min) | 30 | 67% |
| Common bile duct $T_{\frac{1}{2}}$ (min) | 24 | 78% |
| Duodenal appearance time (min) | 23 | 78% |
| Hilum–duodenum transit (min) | 5 | 89% |

diagnostic work-up, these potentially serious complications of ESOM stress the importance of seeking other non-invasive techniques for the investigation of patients with SOD. In our series of 15 consecutive ESOM cases, slight abdominal discomfort with a transient serum amylase elevation was detected in five patients, but all of them could be discharged from hospital on the day after the ESOM procedure. The cost of an ambulatory ESOM is about 5–10 times as much as the cost of QHBS. Furthermore, it is estimated that, if ESOM were employed to screen patients with post-cholecystectomy pain, 7.2 studies would be performed for every case of SOD detected. This efficacy ratio is unacceptable for an invasive and expensive procedure

Fig. 9




Effect of CCK analogue caerulein on the trans-papillary bile flow in PCS patients by comparison of $T_{\frac{1}{2}}$ parameters of the CBD before and after caerulein administration.

that is both difficult and associated with potentially dangerous complications.

A non-invasive, simple and widely available method is therefore needed for the diagnosis of SOD. In this respect, QHBS is an ideal substitute for ESOM: it can be performed with low radiation exposure and without procedure-related complications. The radiation dose of QHBS is approximately 3 mSv in effective dose equivalent, which is less than the dose of annual background radiation. The efficacy of QHBS has been investigated in a few previous uncontrolled studies for the differential diagnosis of PCS, for the selection of patients with SOD, for making therapeutic decisions in patients with SOD and for the follow-up of these patients after medical or endoscopic therapy [19–28]. However, due to the lack of controlled studies and the following controversies most motility experts still do not fully accept that scintigraphy is an accurate diagnostic test in patients with SOD [29,30].

First of all, the results of those studies conducted to investigate the usefulness of scintigraphy in the differential diagnosis of PCS are controversial [11,12,19,20]. QHBS is an ideal method for the detection of low-grade biliary obstruction, but it cannot differentiate between organic (i.e. stone or stricture) and functional (SOD) disorders. We therefore developed a method where amyl nitrite augmentation can be applied during QHBS, and the evoked SO relaxation can be detected [16]. In this way, functional and organic causes of biliary obstruction can be differentiated in most cases. In the present study, we administered caerulein during a similar QHBS acquisition protocol, and surprisingly this also proved to be a relaxation test. Consequently, the clinical utility and place of QHBS must be evaluated in relation to the degree of biliary obstruction, and ERCP must be performed in all cases when the obstruction is high grade, or QHBS and the clinical picture suggest organic causes of biliary obstruction. After the exclusion of organic causes, the probability of SOD is high when a negative ERCP is accompanied by a positive QHBS.

Secondly, it is also a crucial question whether QHBS is an adequate method for the selection of SOD patients and to replace invasive ESOM [21–25]. Previous investigations have proved that QHBS has excellent sensitivity (83–100%) and specificity (100%) for the diagnosis of SOD as compared with the results of ESOM [24,25]. The main criticism regarding those studies is that they were performed on a group of patients with SOD of biliary type I or II (obvious biliary obstruction), and most of the patients had CBD dilatation. However, a dilated CBD was generally associated with a slower trans-papillary bile transit [19]. Our study yielded comparable scintigraphic results, but we investigated patients with SOD of biliary type II or III, and most of them presented with a normal CBD diameter. The second weak point is the uniformly 100% specificity, which is outstanding. The obvious reason for this phenomenon is the highly pre-selected patient population, which is caused by the exclusion of other organic gastrointestinal disorders on patient selection. In our opinion, the diagnosis of functional gastrointestinal disorders should be exclusive, and this is therefore a natural consequence of a correct diagnostic work-up. Moreover, QHBS and ESOM should be applied as functional methods and not to investigate morphology or to differentiate between organic biliary disorders. Organic biliary disorders should be excluded by a diagnostic ERCP or magnetic resonance cholangiopancreatography (MRCP). Considering the relatively high risk of post-ERCP pancreatitis in patients with SOD, in the future ERCP should be replaced by the non-invasive MRCP for this purpose. Our results proved an excellent correlation between the QHBS parameters and the SO basal pressure determined by ESOM, which suggests that in this respect these methods are comparable. After the separation of patients with SOD on the basis of the SO basal pressure determined by ESOM, the quantitative parameters of HH and CBD emptying were significantly different and clearly separated from the controls. These results lead us to accept that, after the exclusion of organic disorders, QHBS is a reliable method for the identification of SOD patients with an elevated BP from the PCS group, and it can be used to replace invasive manometry.

In the present study, we administered the cholecystokinin analogue caerulein during the emptying phase of QHBS as a provocation test to evoke a paradoxical response of the SO (i.e. spasm) and therefore to increase the sensitivity [9,23,24]. However, no scinti-

graphic sign of a paradoxical response to caerulein was detected and the trans-papillary bile flow was accelerated in each patient, which was probably induced by prompt SO relaxation. These results are in contrast with previous investigations which suggested that the administration of cholecystokinin might increase the accuracy of QHBS [23,24]. One explanation could be that in the previous studies the timing and dosage of cholecystokinin administration were different. Moreover, in manometric studies, paradoxical response of the SO in patients with SOD is found to be a relatively rare phenomenon, detected only in 13–19% of SOD patients, and therefore it probably cannot be used as a provocation test in the general patient population [9]. Instead, cholecystokinin induces SO relaxation in the majority of patients with SOD and elevated SO basal pressure, as has become obvious from the present study.

Finally, some remarks may be made with regard to whether it is justified to rely only on the results of QHBS in the planning of a high-risk operative endoscopic procedure such as endoscopic sphincterotomy in patients with SOD. A few uncontrolled follow-up studies have proved that endoscopic sphincterotomy (EST) based on the abnormal results of QHBS is an effective therapeutic approach in SOD patients [26–28]. It is also obvious that EST induces optimal symptomatic improvement only in those SOD patients who display an elevated SO basal pressure on ESOM. More importantly, in the present study, the SO basal pressure and the QHBS parameters exhibited an excellent correlation and QHBS was able to detect those patients whose SO basal pressure was elevated with a sensitivity of about 80–100%. Therefore, we suggest that in patients with SOD of biliary type II or III, a low-grade biliary obstruction demonstrated on QHBS could be an indication for EST, although in questionable cases (normal QHBS) one should progress to performing ESOM. However, in patients with SOD biliary type I (i.e. CBD dilation with obvious obstructive signs and elevated liver enzymes) neither ESOM nor QHBS is necessary and EST should be performed immediately at the time of ERCP.

In conclusion, QHBS is a useful non-invasive diagnostic method for the selection of SOD patients with an elevated SO basal pressure. A significant correlation has been established between the trans-papillary bile flow measured by QHBS and the SO basal pressure determined by ESOM. Therefore, QHBS might be recommended as the method of choice for the selection of SOD patients who should be offered EST.

## Acknowledgements

Valuable contributions by the medical and nursing staff of the Endoscopic and Nuclear Medicine Departments of Hvidovre Hospital are acknowledged. During this study in the Hvidovre Hospital, Dr Madácsy was the recipient of an Eötvös Fellowship from the Hungarian Ministry of Education.

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Original Article

# Video Manometry of the Sphincter of Oddi: A New Aid for Interpreting Manometric Tracings and Excluding Manometric Artefacts

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***Background and Study Aims*: Endoscopic sphincter of Oddi manometry (ESOM) allows direct assessment of motor function in the sphincter of Oddi. However, variations in examination conditions and duodenal motility may have a critical effect on the results of ESOM. The aim of the present study was to develop a new method – sphincter of Oddi video manometry – based on simultaneous ESOM and real-time endoscopic image analysis, and to investigate the usefulness of video manometry for detecting manometric artefacts during ESOM.**

***Patients and Methods*: Seven consecutive patients who had undergone cholecystectomy and were referred with a suspicion of sphincter of Oddi dysfunction were investigated. Sphincter of Oddi pressure and endoscopic images (20 frames/s) were recorded simultaneously on a Synectics PC Polygraf computer system with a time-correlated basis, and then compared.**

***Results*: On ESOM, 69 sphincter of Oddi phasic contractions were identified, with an average amplitude of 153.9 ± 85.0 mmHg and a duration of 7.9 ± 1.2 seconds. Visual analysis of the real-time endoscopic images, replayed in cine loop by the computer, revealed 236 separate duodenal contractions, with an average frequency of 3.5 ± 2.4/min (range: 1–12/min). On the ESOM tracing, 78% of the duodenal contractions had a corresponding pressure wave with an average duration of 2.8 ± 0.4 seconds and an amplitude of 71.9 ± 16.7 mmHg. Other artefacts on the ESOM tracings, such as catheter movements, pseudocontractions, hyperventilation, or retching, were also easily recognized using simultaneous ESOM and real-time endoscopic image analysis.**

***Conclusions*: Video manometry of the sphincter of Oddi is a promising new method for improving the analysis and documentation of ESOM tracings. It has several advantages over the conventional technique, allowing visual detection of duodenal activity and enabling enhanced recognition of other manometric artefacts.**

## Introduction

Manometry is the only diagnostic method that allows direct assessment of motor function in the sphincter of Oddi. Accurate pressure measurement in the sphincter of Oddi through the endoscope has become possible following the miniaturization of manometry catheters and the development of low-compliance fluid perfusion pressure–recording systems [1]. The sphincter of Oddi can be identified during endoscopic sphincter of Oddi manometry (ESOM) as a zone of stepwise pressure elevation (baseline pressure) relative to duodenal pressure and common bile duct pressure, with superimposed phasic contractions [2]. Sphincter of Oddi dysfunction (SOD) can be defined as abnormal sphincter of Oddi contractility, which may manifest clinically as upper right abdominal pain, or as signs and symptoms of recurrent partial biliary obstruction or pancreatitis [3]. Several manometric changes have been described in patients with SOD, such as increased baseline pressure, increased amplitude or frequency of phasic contractions, an increased number or retrograde propagation of the phasic contractions, and a paradoxical response to cholecystokinin administration [3].

Although ESOM is regarded as the gold standard for diagnosing SOD, the technique is not without problems. ESOM is a troublesome procedure for the endoscopist and also for the patient, since premedication needs to be minimized. Moreover, the difficulty of carrying out an acceptable manometric study requires close cooperation between an experienced endoscopist and a motility expert. Correct interpretation of the ESOM tracings is also often difficult [4]. ESOM has been shown to be a reproducible technique

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in healthy persons and in patients with sphincter of Oddi stenosis, but reproducibility has sometimes been unsatisfactory in patients with sphincter of Oddi dyskinesia [5]. One possible explanation frequently put forward is that, due to the intermittent nature of the disease, the pressure profile may differ on separate occasions. However, there are other rarely mentioned factors that may influence reproducibility. One is the possible dependence of the sphincter of Oddi pressure profile on duodenal contractions and on cyclic phases of the duodenal migrating motor complex (MMC). The other problem is the possible misinterpretation of tracings caused by the frequent artefacts, such as initial hyperactivity, catheter movement, retching, and hyperventilation [6]. Variations in the examination conditions and duodenal motility may therefore have a critical influence on the pressure profile of the sphincter of Oddi.

The aims of the present study were therefore to develop a new method – video manometry of the sphincter of Oddi – based on simultaneous manometric pressure and real-time endoscopic image analysis during the ESOM procedure; to investigate the usefulness of video manometry in detecting manometric artefacts during ESOM; and to analyze the effects of duodenal contractions on the sphincter of Oddi manometric pressure profile using video manometry.

## Patients and Methods

### *Patients*

Video manometry of the sphincter of Oddi was carried out in seven consecutive female patients who had undergone cholecystectomy (mean age 56, range 44–66) who were referred to our hospital with chronic upper right quadrant pain and a suspicion of SOD. On the Geenen classification, the patients belonged to the SOD groups for biliary types II or III, but none of them had dilation of the common bile duct. Prior to ESOM, all of the patients had normal findings on upper gastrointestinal endoscopy and abdominal ultrasonography.

### *Methods*

After an overnight fast, sedation was induced with 2.5–7.5 mg intravenous midazolam (Dormicum). No other drugs were administered. Duodenoscopy was then conducted using a video duodenoscope (Olympus JF-130). For sphincter of Oddi pressure measurements, a standard triple-lumen manometric catheter was used (ERCP manometric catheter, Synectics Medical, Sweden), with an external diameter of 1.7 mm and sideholes spaced 2 mm apart. All capillary channels were constantly perfused with sterile water at a rate of 0.33 ml/min from a dual-chamber pressure pump (MUI Scientific Pump Perfusion System, Mississauga, Ontario, Canada) with 14 psi overpressure in the water reservoir. The pressures transmitted by the external transducers and the video image from the endoscope were recorded simultaneously on a Synectics PC Polygraf computer system with a time-correlated basis, using the Synectics Polygram for Windows 1.1 program.

Selective deep cannulation of the common bile duct was achieved with a standard endoscopic retrograde cholangiopancreatography (ERCP) catheter, and a flexible-tip guide wire (Wilson-Cook HSF 25/400) was then introduced high up into the bile tract. Next, the ERCP catheter was exchanged for the ESOM catheter over the guide wire, which was left in place. The duodenal pressure was recorded to establish a zero reference pressure both at the beginning and after completion of the sphincter of Oddi recording period for at least 30 seconds. After the ESOM catheter had been positioned high in the common bile duct, the guide wire was removed and the common bile duct pressure was recorded. During the station pull-through recording, the ESOM catheter was withdrawn into the sphincter of Oddi zone and retained there for a mean of nine minutes. Finally, the catheter was pushed back into the common bile duct, and a rapid pull-through over the sphincter of Oddi zone was carried out. During the ESOM study, the digital video-endoscopic monitor picture was saved continuously on the computer at a frame rate of 15 images/s. The ESOM and real-time endoscopic image analysis results were evaluated separately and then compared.

### *Analysis*

On ESOM, the sphincter of Oddi baseline pressure and the amplitude, frequency, duration, and propagation of the phasic contractions were measured. For the sphincter of Oddi baseline calculation during the station pull-through technique, only the manometric channel located in the mid-portion of the sphincter of Oddi was used, and the average and maximum pressures were measured there as well. During real-time endoscopic image analysis, the position, duration, number, and frequency of duodenal contractions were determined, and the corresponding sequence of the ESOM recording was then carefully analyzed to search for simultaneous pressure waves. Using visual analysis, the duodenal contractions were graded as minor (small-bowel movements in the peripapillary area) or major (peristaltic movements causing complete occlusion of the duodenal lumen). If a pressure wave was found on the ESOM at the exact time of a duodenal contraction observed during real-time endoscopic image analysis, then its appearance in each individual manometric channel and its amplitude, duration, and propagation were determined. Artefacts induced on the ESOM tracings by catheter movements, hyperventilation, or retching were readily recognized using simultaneous real-time endoscopic image analysis. The occurrence of these artefacts was scored as none (0), few (1), or several (2), for each patient.

### *Statistics and Ethics*

The unpaired Student's *t*-test was used for statistical evaluation, and the level of significance was set at 0.05%. The study was approved by the local ethics committee, and it

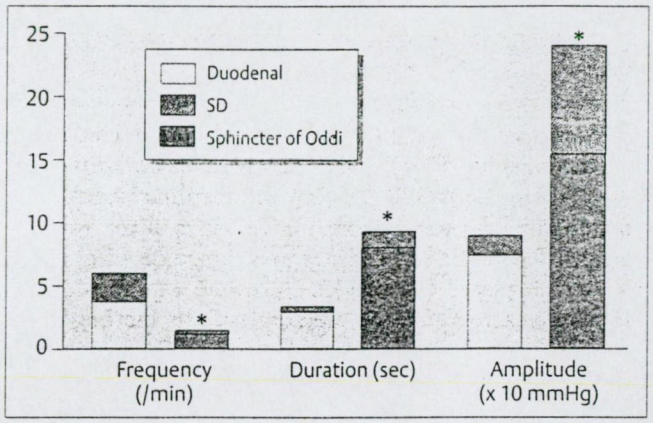


**Figure 1** Important manometric characteristics of phasic contractions originating from the sphincter of Oddi and from the duodenum, such as amplitude, duration and frequency. Note the significant differences between these variables. SD: standard deviation

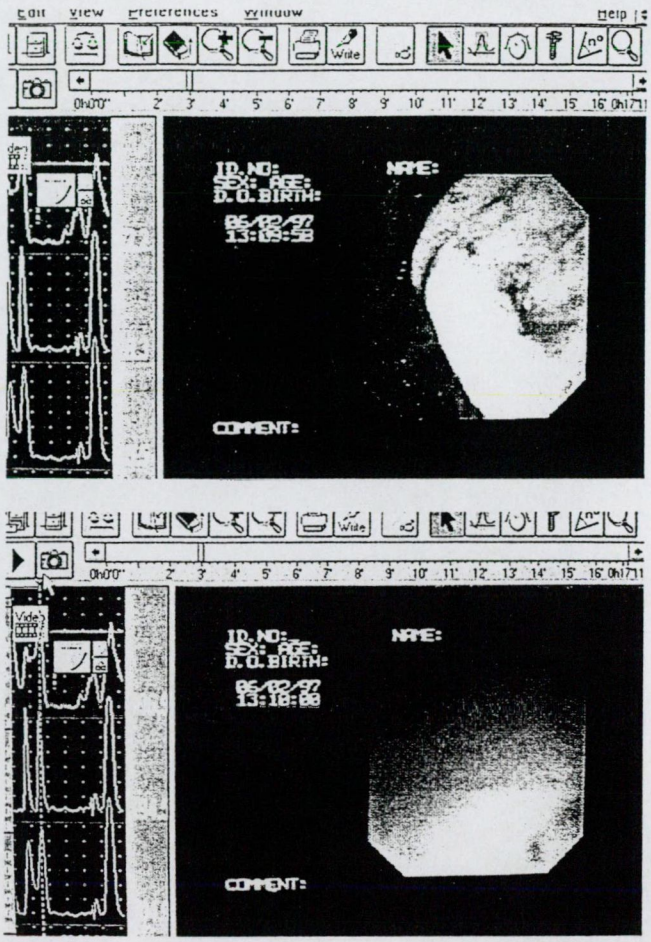


**Figure 2** Video-manometric images of a typical manometric artefact caused by retching. Note the sudden, simultaneous, relatively high and brief pressure rise on all three manometric channels, with a simultaneously obscured endoscopic image (**b**)

was conducted in accordance with the Helsinki Declaration. Informed consent was obtained from each patient before inclusion in the study, after verbal and written information had been provided.

## Results

The average length of the simultaneous video-endoscopic and sphincter of Oddi manometric recording time was 11.5 minutes per patient. On the ESOM, 69 phasic contractions of the sphincter of Oddi were identified, with an average amplitude of $153.9 \pm 85.0$ mmHg and duration of $7.9 \pm 1.2$ seconds. The frequency of the phasic contractions ranged from 0.8/min to 3.0/min. The baseline pressure of the sphincter of Oddi was elevated (more than 35 mmHg) in two of the seven patients.

Real-time analysis of the endoscopic images was carried out by replaying the saved analogue images in cine loop on the computer without watching the pressure curve. During this process, 236 separate duodenal contractions were detected; 120 of these (51%) were judged to be minor contractions (small duodenal movements or contractions of the peripapillary duodenal wall). The remaining 49% were assessed as major contractions (peristaltic duodenal contraction initiating complete lumen occlusion). The average frequency of the duodenal contractions was $3.5 \pm 2.4$/min, with a range of 1–12/min.

When the real-time endoscopic image analysis results were compared with the ESOM tracing, a corresponding pressure wave was detected in 78% of duodenal contractions on the ESOM tracing, with an average amplitude of $71.9 \pm 16.7$ mmHg and a duration of $2.8 \pm 0.4$ seconds. However, the manometric characteristics (amplitude, duration, and frequency) of the phasic contractions originating from the sphincter of Oddi and from the duodenum were significantly different (Figure 1). A large proportion (42%) of the 236 duodenal contractions were manifested in only one or two manometric channels, while 36% were observed in all and 22% in none of them. Of the 144 duodenal contractions that were clearly visible in more than one channel, allowing the virtual propagation to be determined, 37% exhibited anterograde propagation, 49% simultaneous propagation, and 14% retrograde propagation on the ESOM tracing. However, the speed of this virtual propagation of the duodenal contractions was considerably slower than the propagation of the phasic contractions originating from the sphincter of Oddi (Figures 4, 6).

Artefacts caused on the ESOM tracings by retching (Figure 2), catheter movement–induced pseudocontractions (Figure 3), duodenal contractions (Figure 4), or hyperventilation (Figure 5) were easily recognized and differentiated from real sphincter of Oddi contractions (Figure 6) on the basis of video manometry. Retching caused a sudden, simultaneous, high and narrow pressure rise in all three channels, with an amplitude of up to 200 mmHg and a duration of less than two seconds (Figure 2). Movements of the manometric catheter also gave rise to the phenomenon of pseudocontractions. These in-and-out movements of the catheter, due to the transmitted effect of respiration, caused pressure waves on the ESOM tracing with an am-

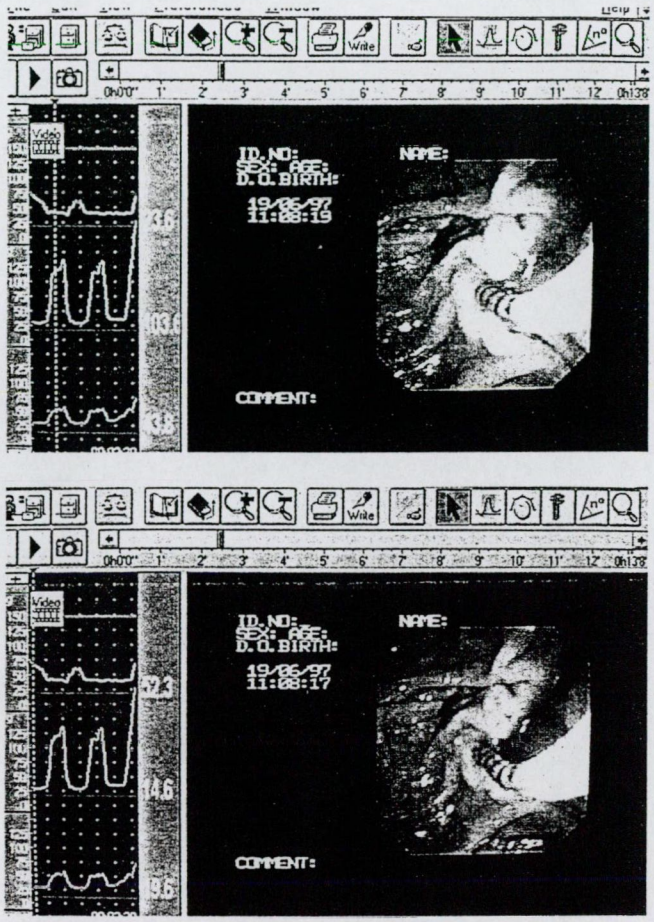


**Figure 3** Video-manometric images of small pseudocontractions induced by in-and-out catheter movements. Without the aid of video manometry, this artefact is easily misinterpreted as genuine sphincter of Oddi activity. On the video-endoscopic image, different numbers of black ring marks can be visualized outside of the papilla of Vater when **a** and **b** are compared. Note that the pressure waves are exactly simultaneous on all manometric channels, and that they also show a reciprocal or mirror phenomenon in channels one and three

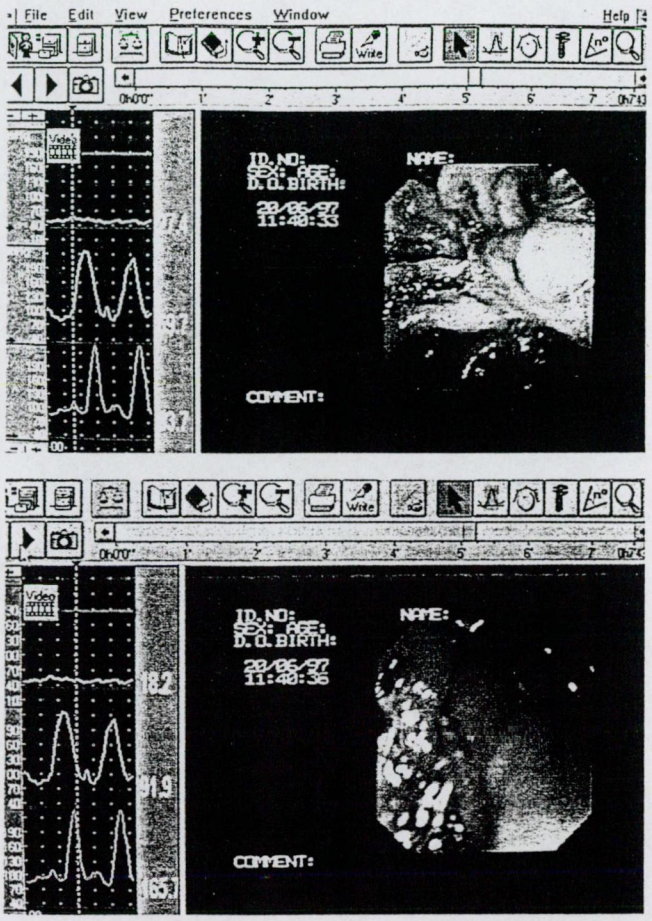


**Figure 4** Video-manometric images of duodenal contractions manifested on the sphincter of Oddi manometric curve. Note that pressure waves originating from duodenal peristaltic activity have a lower amplitude, shorter duration, and slower propagation than sphincter of Oddi contractions. Simultaneous duodenal peristalsis is obvious on the video-endoscopic images

plitude and duration quite similar to those of genuine sphincter of Oddi or duodenal contractions. However, we found that these pseudocontractions were always exactly simultaneous in all channels, and they also showed a reciprocal or mirror phenomenon in channels one and three (Figure 3). Duodenal contractions were easily distinguished from genuine sphincter of Oddi contractions by their lower amplitude, shorter duration, and slower propagation (Figure 4). The manometric appearance of hyperventilation was quite unique, since it caused only fine undulations of the manometric curve, with an amplitude of 20–40 mmHg and a frequency of 16–20/min (Figure 5). The availability of the real-time endoscopic images was found to be extremely useful during the ESOM analysis. With the continuous monitoring of the catheter position, it was possible to detect the site of the measurement and establish an explanation for most of the unexpected baseline undulations, which are frequently caused by catheter movements (Figure 7). The frequencies of these artefacts were scored dur-

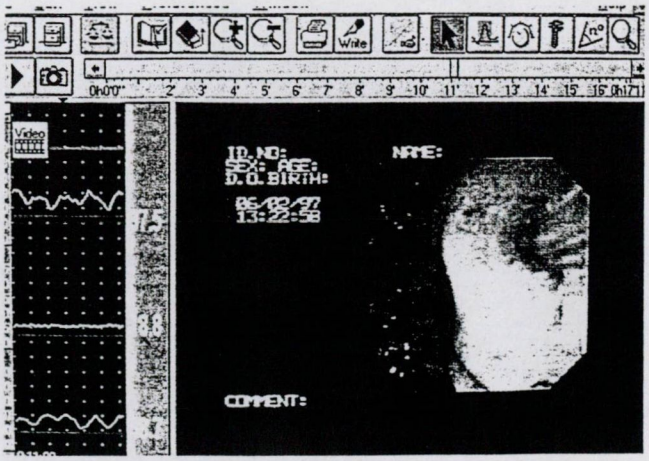


**Figure 5** Hyperventilation-induced fine undulation can be demonstrated on the pressure curve of the common bile duct, which is due to the transmitted effect of respiration on intra abdominal pressure

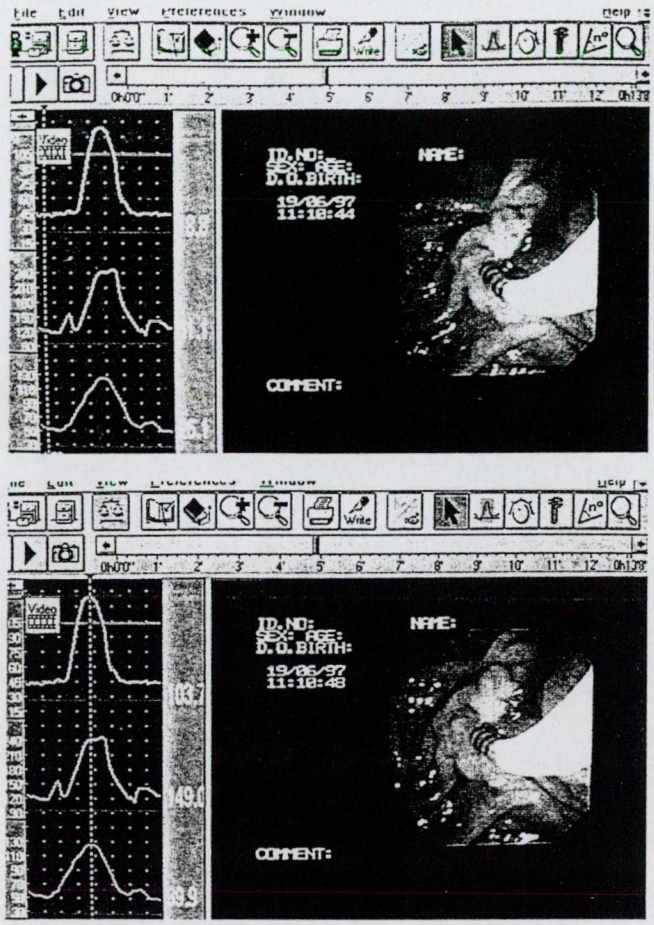


**Figure 6** Video-manometric images of phasic contraction of the sphincter of Oddi. The simultaneous video-endoscopic image shows no sign of duodenal activity

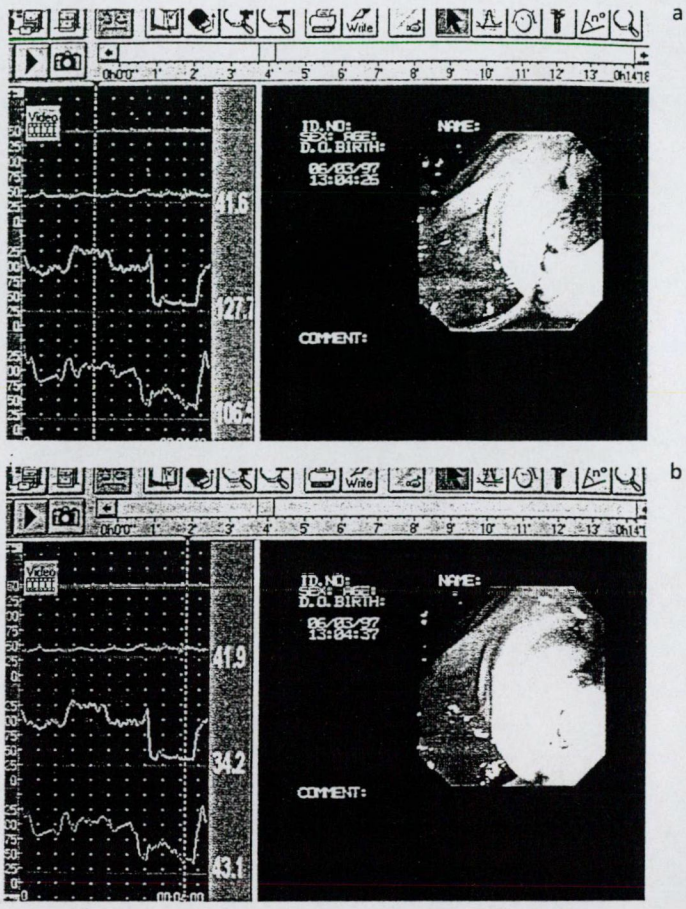


**Figure 7** Video-manometric images of a major baseline undulation caused by a sudden catheter movement into the common bile duct. The change in the catheter position and in the site of the pressure measurement can be easily documented by video manometry

ing the ESOM tracing analysis and then compared. The most frequent artefacts were due to duodenal contractions and catheter movements with pseudocontractions (average scores 1.8 and 1.5, respectively), followed by hyperventilation (average score 0.7) and retching (average score 0.5).

Finally, the manometric tracings were compared with and without video information on which artefacts such as duodenal contractions, retching and catheter movements had been marked. The number of events detected without video information was then calculated as a percentage of all those detected with video manometry. Eighty-seven of 236 duodenal contractions (37%) and 34 of 40 retching episodes (85%) were apparent without video information. With practice, 100% of the large catheter movements (into the common bile duct and out of the sphincter of Oddi) can be recognized without video information, but small baseline undulations and pseudocontractions due to fine catheter movements (sometimes induced only by the rhythmic activity of respiration) can be explained and understood only with the aid of video manometry.

## Discussion

Several manometric abnormalities have been described in patients with possible SOD. However, controlled studies in patients with postcholecystectomy pain have shown that symptomatic relief was obtained after endoscopic sphincterotomy only in patients with an elevated sphincter of Oddi baseline pressure [7], and none of the other manometric criteria for SOD have been proved to have prognostic value [3]. Although the intraobserver and interobserver reproducibility of ESOM has been found to be reasonably good [5,8], correct analysis of the sphincter of Oddi pressure profile can be rather difficult in any specific patient. First of all, from a manometric point of view, correct determination of the baseline pressure of a sphincter anywhere in the gastrointestinal tract may involve several problems. Some of these are related to the sphincter characteristics, such as longitudinal and transverse pressure profile asymmetry, while others relate to the manometric technique itself, such as catheter movement during the station pull-through technique and reflex sphincter contractions during the rapid pull-through technique [9]. This is particularly true for the sphincter of Oddi, which is rather short and

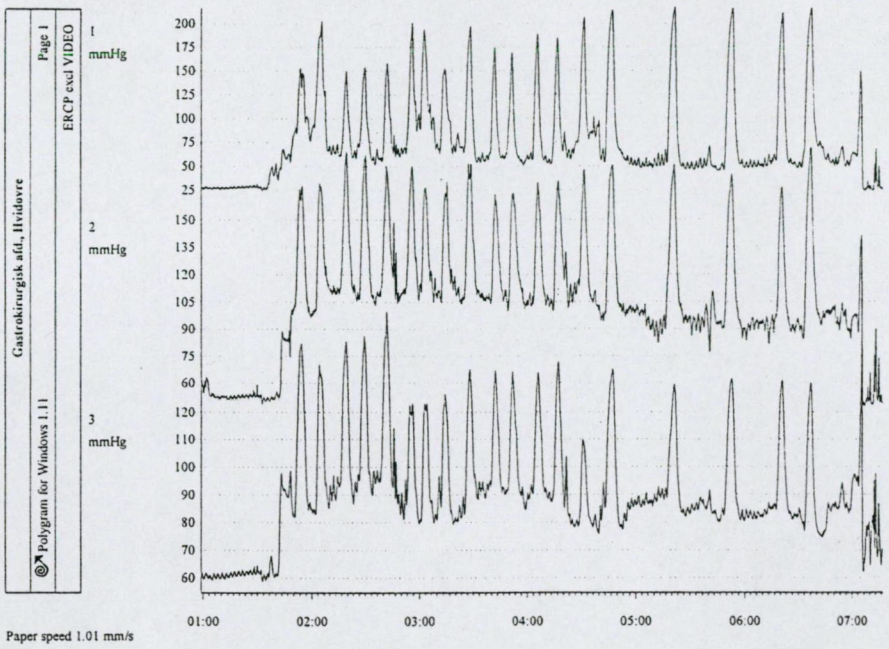


**Figure 8** An original station pull-through sphincter of Oddi manometric tracing that contains no manometric artefacts, and is therefore exceptionally easy to read and interpret. Unfortunately, this is a rare example

narrow, with a marked axis deviation at the junction of the superior sphincter of the common bile duct and the inferior sphincter of the common channel [10]. We prefer the station pull-through technique to the rapid pull-through technique to measure sphincter of Oddi basal pressure, since it has the advantage of allowing precise longitudinal pressure mapping of the sphincter of Oddi, with calculation of the average and maximal basal pressure as well. However, when applying this method, it is extremely important to know the catheter position and to keep the manometric catheter in exactly the same place for a certain period of time – which is sometimes impossible, or may require small corrections to be carried out by the endoscopist. The potential offered by real-time endoscopic image analysis for monitoring the depth of insertion of the manometric catheter is therefore a genuine advantage in video manometry, allowing the basal pressure measurements to be reviewed and false pressure values to be excluded.

Secondly, there is a problem associated with duodenal activity, and this problem also has two important aspects: the possible influence of the actual stage of the interdigestive MMC on sphincter of Oddi motor activity; and the direct effect of duodenal contractions on the sphincter of Oddi pressure profile. Data from animal and human experiments have shown that phasic activity in the sphincter of Oddi is closely associated with the interdigestive phases of the MMC [11]. It has also been reported that there is a transient rise in biliary pressure in phase III (the activity front) of the duodenal MMC, probably because of the simultaneous increase in sphincter of Oddi motor activity [12]. However, the increased number of major duodenal contractions during phase III of the MMC may induce a rise in biliary pressure by passively occluding the intraduodenal segment of the sphincter of Oddi, thereby decreasing the bile outflow into the duodenum. The results of the present study support this explanation, as it was found that the duodenal contractions are not only visible on the ESOM tracing, but can also cause pressure waves with a sufficiently high amplitude and long duration to be able to influence bile outflow. The duodenal contractions that are manifested on the ESOM tracing may therefore have physiological significance, even without sphincter of Oddi motor activity.

Finally, there are well-known, troublesome, but little-discussed artefacts that make ESOM tracings difficult to analyze, and which lead to variations in reproducibility. The use of video manometry does not alter the results of ESOM if the interpretation is correct and if the manometric tracing does not contain any artefacts (Figure **8**). The method can be used to prevent false interpretation of ESOM recordings that are affected by several manometric artefacts, which are more frequently recorded in humans (Figure **9**). We believe that catheter movement is the most problematic issue, in addition to duodenal contractions, since it can make the baseline pressure unstable and can lead to the formation of pseudocontractions. With the advent of video manometry, the position of the catheter can be continuously monitored by watching the ring marks on the manometric catheter outside the papilla, and artefacts arising from the catheter movement can be excluded. In the present series, most of the artefacts occurred during periods of frequent duodenal contractile activity. We believe that these periods are not suitable for ESOM recording, and should be excluded from the final analysis.

## Conclusion

Video manometry of the sphincter of Oddi is a promising and innovative method that can be used to help analyze the tracing, to exclude manometric artefacts, and to improve

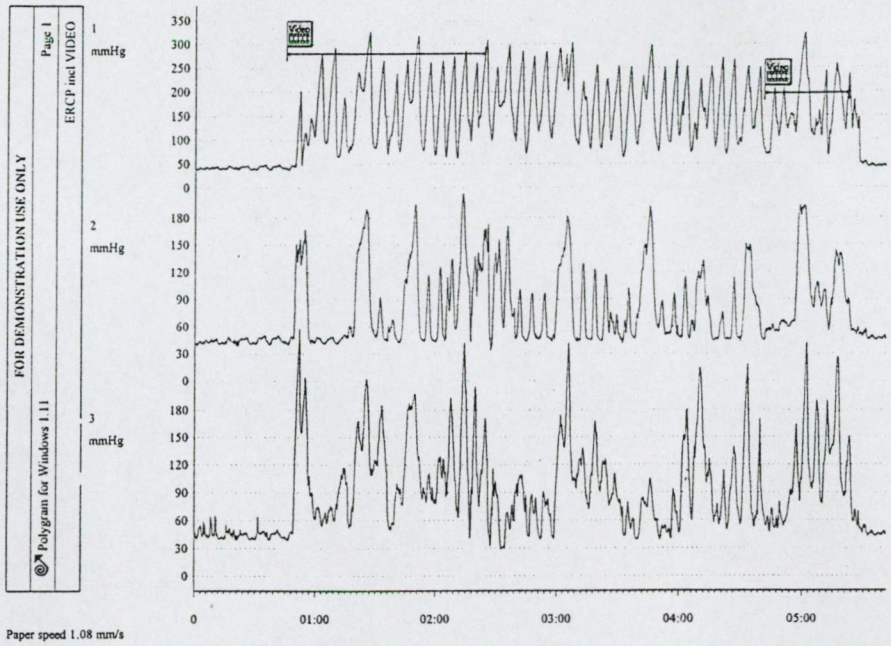


**Figure 9** An original station pull-through sphincter of Oddi manometric tracing showing several different types of manometric artefact, which are frequently recorded in everyday clinical practice in humans

documentation of the tracing. It has several advantages over the conventional technique, enabling visual detection of duodenal activity and allowing a review of the depth of insertion of the manometric catheter during station pull-through measurement of sphincter of Oddi basal pressure. The use of video manometry in clinical practice may therefore be recommended. However, further studies will be needed to prove the effectiveness of the technique in improving the diagnostic accuracy and reproducibility of endoscopic sphincter of Oddi manometry.

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# Differentiation between organic stenosis and functional dyskinesia of the sphincter of Oddi with amyl nitrite-augmented quantitative hepatobiliary scintigraphy

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**Abstract.** Recurrent biliary pain after cholecystectomy is presumably due to sphincter of Oddi dysfunction (SOD). There is no ideal non-invasive test for SOD, and the diagnosis often relies on invasive procedures such as sphincter of Oddi (SO) manometry. Amyl nitrite-augmented quantitative hepatobiliary scintigraphy (QHBS) was performed on nine asymptomatic volunteers and 22 patients with SOD of biliary types I and II. Normal QHBS parameters were established in the asymptomatic volunteers. QHBS revealed a partial obstructive pattern in nine patients in whom SO stenosis was suspected and in 13 patients in whom SO dyskinesia was suspected. This obstructive pattern remained unchanged in the former group, but was completely relieved in the latter group of patients on amyl nitrite administration. In conclusion, amyl nitrite-augmented QHBS proved to be a useful non-invasive method in the diagnosis of SOD of biliary types I and II and permitted differentiation between organic stenosis and functional motor abnormalities of the SO.

*Key words:* Quantitative hepatobiliary scintigraphy – Amyl nitrite – Sphincter of Oddi dysfunction

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## Introduction

Cholecystectomy is usually associated with an excellent therapeutic outcome. A small number of patients, however, continue to have a variety of gastrointestinal symptoms. The term used to describe this condition is post-cholecystectomy syndrome (PCS) [1]. Patients with PCS form a heterogeneous group whose problems include organic and functional disorders of non-biliary and of biliary tract origin. The latter group includes retained common bile duct (CBD) stones, CBD stricture, papillary tumours, cystic duct remnant and sphincter of Oddi (SO) dysfunction [2, 3].

On the basis of the pathogenic mechanism, sphincter of Oddi dysfunctions (SODs) can be further classified into two entities: sphincter of Oddi stenosis (structural SOD) and sphincter of Oddi dyskinesia (functional SOD) [4, 5]. Since it is usually difficult to distinguish between primary functional and structural abnormalities, Geenen, Hogan and Sherman classified patients with SOD into three groups [5, 6]. In patients with *SOD biliary type I* structural abnormalities (organic stenosis) predominate. These patients usually have typical biliary pain and abnormally elevated liver function test data. Endoscopic retrograde cholangiopancreatography (ERCP) typically reveals obstructive signs (dilated CBD and delayed contrast excretion time), and manometry shows an elevated SO basal pressure. The possible pathophysiological disorders responsible for SO stenosis are sphincter fibrosis, sphincter hypertrophy, chronic papillitis or adenomyosis. Patients with *SOD biliary type II* have biliary-type pain but have only one of the above-mentioned criteria. In this group the aetiology is difficult to ascertain: the disorder may be functional or structural. The basal SO pressure is often normal; if elevated, the sphincter of Oddi is still able to relax during amyl nitrite, cholecystokinin (CCK) or glucagon administration. Patients with *SOD biliary type III* have only biliary-type pain and no other abnormalities. This group is referred to as true functional SOD, or SO dyskinesia, and SO manometric study is recommended for the diagnosis, which may reveal tachyoddia, retrograde contractions or a paradoxical response to CCK administration. The sphincter is characteristically hypersensitive to several stimuli, e.g. morphine or a fatty meal. It is still very difficult to distinguish between primary structural and functional abnormalities, for the basal SO pressure can be elevated in either group. Relaxation following administration of a smooth muscle relaxant suggests that the problem is functional [5, 7–9].

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Although SO manometry remains the gold standard for the diagnosis of SOD, the technique of SO manometry is not without problems. It is a difficult and time-consuming endoscopic procedure, the success rate is approximately 75% and it may be associated with acute pancreatitis in 1%–5% of the patients [10]. Due to these difficulties, other non-invasive methods have already been applied for the detection of SO dyskinesia. Provocation tests, such as the Debray and Nardi tests [11, 12] were used for several years in the diagnosis of SO dyskinesia. Since the judgement is based upon the subjective complaints, these tests alone proved unreliable in selecting patients with functional SOD [13], and they were therefore combined with measurements of serum enzymes, including aspartate aminotransferase and amylase levels, and with quantitative hepatobiliary scintigraphy (QHBS) [14]. Fatty-meal ultrasonography and cholecystokinin- and secretin-aided ultrasonography have recently been introduced and have proved quite specific but only moderately sensitive tests for the identification of patients with SOD [15, 16]. QHBS has been reported to be a useful, non-invasive technique for the detection of patients with partial bile duct obstructions resulting from a structural disorder or SOD [17–21]. However, the value of QHBS in differentiating between structural and purely functional SODs has not been tested to date. The aim of this study was to determine whether amyl nitrite-augmented QHBS can be used as a non-invasive technique in the differentiation of structural and functional SODs.

## Materials and methods

Amyl nitrite-augmented QHBS was performed on 22 female patients with SOD of biliary types I and II (mean age: 52 years; range: 32–69 years) and nine healthy female volunteers (mean age: 49 years; range: 44–65 years), who underwent cholecystectomy 8.8 ± 8.5 years before they were admitted. In patients with SOD liver function tests, abdominal ultrasonography, gastroduodenoscopy and ERCP were performed. Organic and functional extrabiliary disorders and also organic biliary disorders other than SOD were excluded. The selection criteria in patients with SOD of types I and II were: typical biliary pain in the postprandial period, and the meeting of at least one more SOD classification criterion (abnormal liver function tests: alkaline phosphatase, alanine aminotransferase or aspartate aminotransferase >1.5 times upper limit of normal; delayed contrast drainage time during ERCP >45 min; dilated common bile duct measured by ultrasonography >10 mm). The selection criteria in healthy volunteers were: no gastrointestinal symptoms after cholecystectomy, normal liver function test results and negative abdominal ultrasonography.

*Quantitative hepatobiliary scintigraphy.* QHBS was performed in all 31 subjects. After an overnight fast, 140 MBq technetium-99m 2,6-diethylphenylcarbamoylmethyl-diacetic acid (EHIDA) was given intravenously. Changes in the activity over the upper part of the abdomen were recorded by a large field-of-view gamma camera fitted with a low-energy, high-resolution, parallel-hole collimator. Gamma camera images (1 min each) were obtained at 5, 15, 25, 35, 45, 60, 75 and 90 min in the anterior projection. Digital images were obtained simultaneously at one frame/min for 90 min, and recorded in a 64 × 64 matrix into the computer. From the 60th minute until the end of the examination, amyl nitrite (dosage: 1 ml for each patient form the 45 mg/ml solution) inhalation was applied continuously. Time-activity curves were generated from regions of interest (ROIs) selected as follows: right peripheral liver parenchyma, hepatic hilum, CBD and duodenum. The time to peak activity ($T_{max}$) and the half-time of excretion ($T_{1/2}$) were calculated for each of the time-activity curves. $T_{1/2}$ was obtained by applying an automatic exponential fit to the time-activity curves. $T_{1/2}$ was calculated for both pre- and post-amyl nitrite periods ($T_{1/2}$ and $T_{1/2a}$). The time of first appearance of the activity in the duodenum (DAT) was also registered. For statistical evaluation, the unpaired Student's t-test was used, except for the analysis of the effect of amyl nitrite on the $T_{1/2}$ from the CBD ($T_{1/2}$ compared to $T_{1/2a}$), where the paired Student's t-test was applied. Significance was achieved at $P<0.05$. All results are given as mean and standard error of the mean (mean ± SE), except for the normal values, which are given as mean and two times the standard deviation (mean ± 2SD).

**Table 1.** QHBS parameters in control group ($n$=9). Normal values of $T_{max}$ and $T_{1/2}$, defined as mean ± 2SD

| | Liver parenchyma | Hepatic hilum | Common bile duct |
|---|---|---|---|
| $T_{max}$ | 12.7 min | 17.6 min | 30.8 min |
| ± 2SD | 5.8 min | 8.0 min | 16.6 min |
| $T_{1/2}$ | 25.0 min | 25.5 min | 26.5 min |
| ± 2SD | 6.6 min | 9.8 min | 13.8 min |

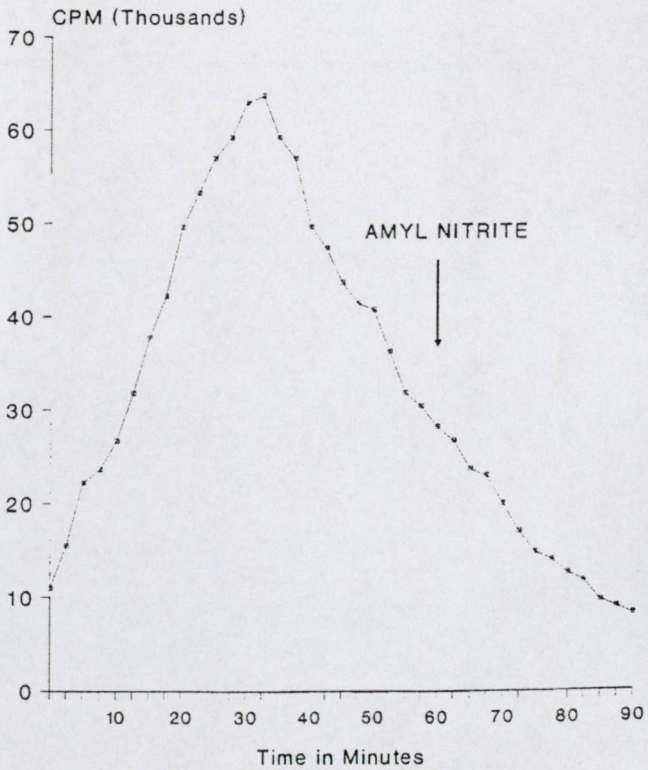


**Fig. 1.** Representative recording of a time-activity curve generated from the ROI detected over the CBD of a healthy volunteer (control group) ($T_{max}$:32.5 min; $T_{1/2}$:25 min; $T_{1/2a}$:16 min)

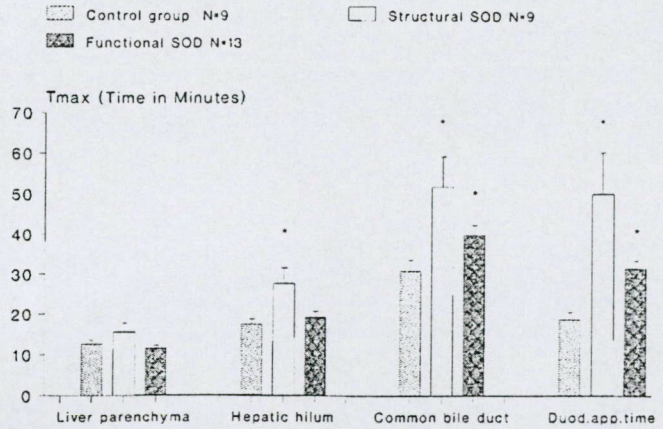


**Fig. 2.** $T_{max}$ of liver parenchyma, hepatic hilum, CBD and duodenum appearance time in control group (n=9) and in patients with SOD ($n$=22). (*$P$<0.05, siginificant differences relative to control group)

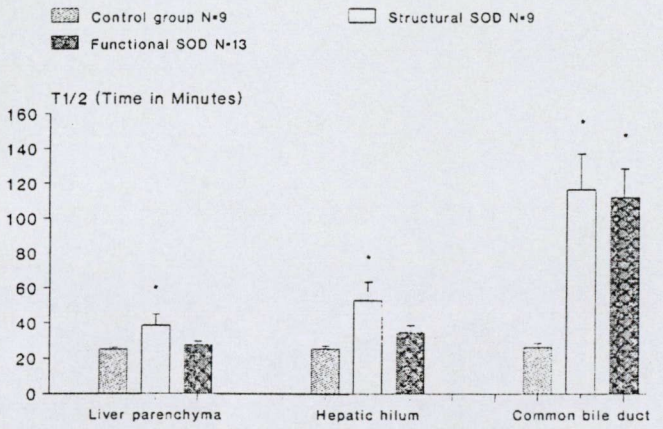


**Fig. 3.** $T_{1/2}$ of liver parenchyma, hepatic hilum and CBD in control group ($n$=9) and in patients with SOD ($n$=22). (*P<0.05, significant differences relative to control group)

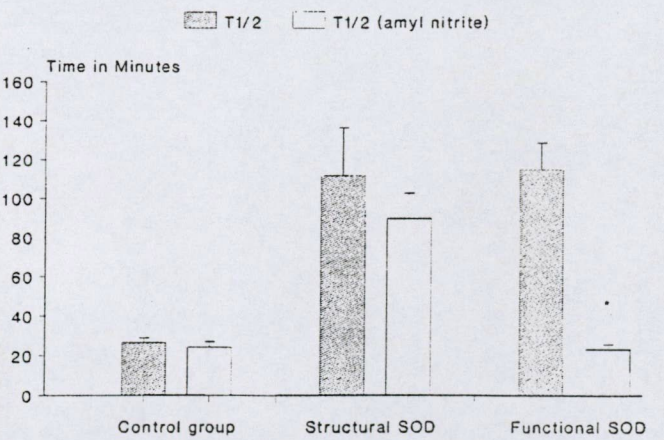


**Fig. 4.** Effect of amyl nitrite on $T_{1/2}$for the time-activity curve generated from the ROI detected over the CBD in the control group ($n$=9) and in patients with structural SOD ($n$=9) and functional SOD($n$=13). (*P<0.05, significant differences relative to control group)

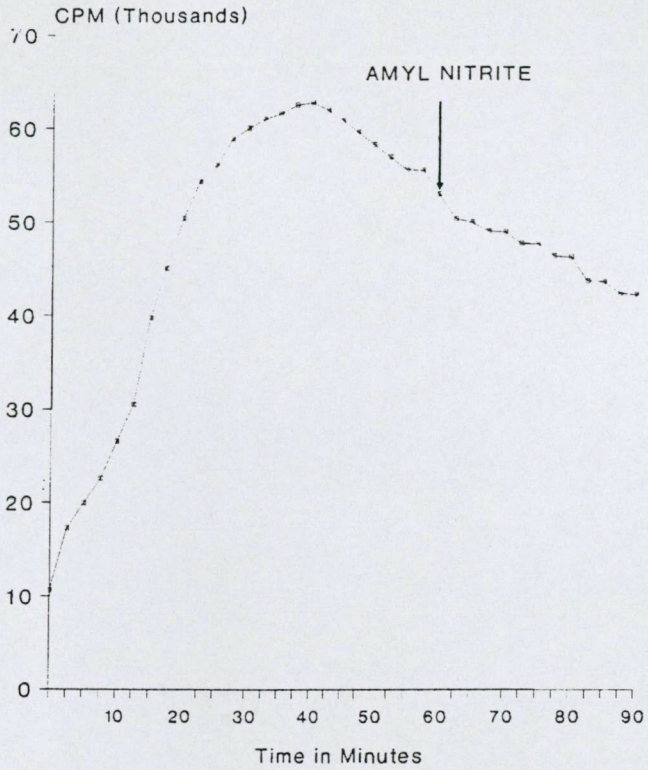


**Fig. 5.** Representative recording of a time-activity curve generated from the ROI detected over the CBD of a patient with SO stenosis (structural SOD). ($T_{max}$: 40 min;$T_{1/2}$: 144 min: $T_{1/2a}$: 140 min)

## Results

Normal values of $T_{max}$ and $T_{1/2}$ (defined as mean ± 2SD) obtained from QHBS on the nine asymptomatic volunteers (control group) are shown in Table 1. Amyl nitrite administration did not influence $T_{1/2}$ for the CBD significantly (see Fig. 4). A typical time-activity curve, generated from the ROI detected over the CBD, is to be seen in Fig. 1.

On the basis of the results of amyl nitrite-augmented QHBS, patients with SOD can be divided into two groups:

1. In nine patients with SO stenosis (structural SOD), $T_{max}$ and $T_{1/2}$ calculated from the ROIs over the hepatic hilum and CBD were significantly higher, and the DAT also proved to be significantly longer than for the controls (Figs. 2, 3). The hepatobiliary scintigram revealed a marked accumulation of the isotope in the biliary tree, which persisted until the end of the study. Amyl nitrite inhalation did not cause a significant decrease in $T_{1/2a}$ for the CBD time-activity curves (Fig. 4). A time-activity curve of the CBD and a hepatobiliary scintigram characteristic of SO stenosis are shown in Figs. 5 and 6, respectively.
2. In 13 patients with SO dyskinesia (functional SOD) $T_{max}$ and $T_{1/2}$ for the CBD were significantly higher than for the controls. The DAT was also significantly longer in this group (Figs. 2, 3). In all 13 patients, the rate of

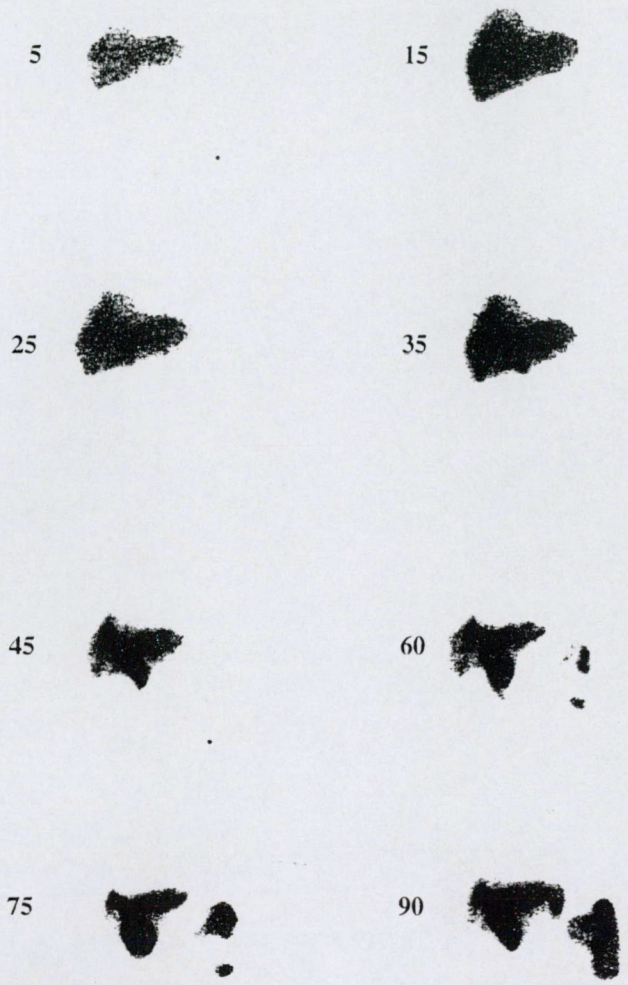


**Fig. 6.** Hepatobiliary scintigram in a patient with organic stenosis of the SO (structural SOD). Biliary tree activity is initially visualized at 25 min. The CBD and intrahepatic biliary tree appear prominently at 45 min and do not change during amyl nitrite administration up to 90 min. The small bowel is first visualized at 60 min

CBD excretion was accelerated and $T_{1/2a}$ for the CBD not only decreased significantly but also normalized during amyl nitrite administration (Fig. 4). On the hepatobiliary scintigram, the CBD and intrahepatic biliary tree were prominent up to 60 min, but a marked decline in activity was observed after amyl nitrite administration. A typical time-activity curve of the CBD and a hepatobiliary scintigram are shown in Figs. 7 and 8, respectively.

The CBD diameter measured by ultrasonography did not differ significantly between patients with structural and patients with functional SOD (10.5 ± 4.0 mm and 7.7 ± 3.5 mm, respectively).

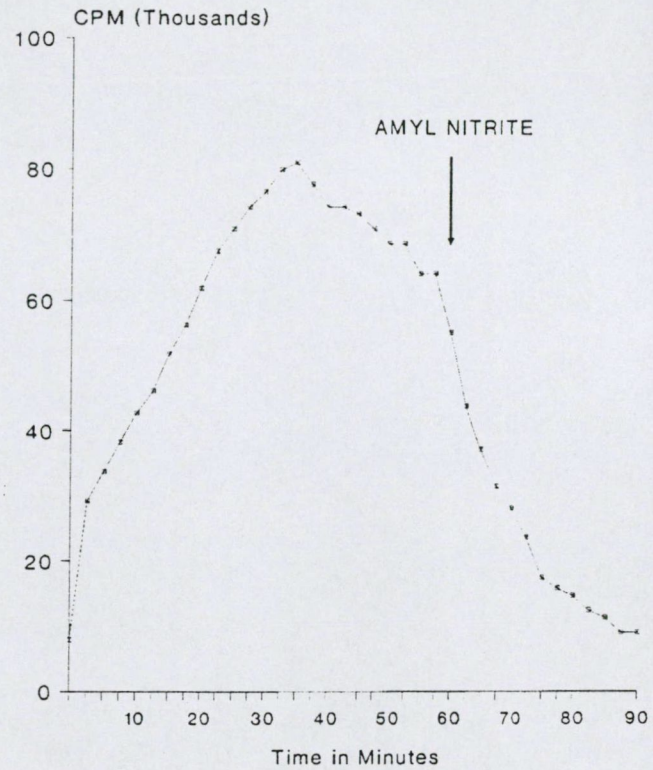


**Fig. 7.** Representative recording of a time-activity curve generated from ROI detected over the CBD of a patient with SO dyskinesia (functional SOD). ($T_{max}$: 35 min; $T_{1/2}$: 94 min; $T_{1/2a}$: 11 min)

## Discussion

Hepatobiliary scintigraphy has been recommended for the non-invasive diagnosis of SO motility disorders by many authors [16–21]. Varró et al. combined the choleretic-morphine provocation test (Debray) with hepatobiliary scintigraphy [22, 23]. Krishnamurthy et al. [24] developed a method to analyse the dynamics of hepatic bile flow quantitatively, this being referred to as QHBS. Others, including Drane and Johnson [25], Shaffer et al. [19] and Sostre et al. [20], combined QHBS with the administration of CCK or CCK analogues.

Nitrate therapy was introduced in the treatment of SOD in 1983 [26]. In the course of endoscopic manometry, Staritz et al. [27] demonstrated that glyceryl trinitrate substantially decreases the papillary baseline pressure and papillary contraction amplitude in SOD patients. On the basis of the results of endoscopic manometry, Hogan and Geenan [5] stated that reduction of the elevated basal pressure or phasic contraction amplitude following inhalation of amyl nitrite suggests dyskinesia rather than stenosis of the SO. Nitroglycerin proved to be the most potent sphincter-relaxing agent and has been successfully used in the treatment of SO dyskinesia [28, 29]. Endogenous nitric oxide has been shown to play a major role in the non-adrenergic non-cholinergic relaxation of SO, especially in regions close to the duodenal papilla [30]. The intracellular mechanism of the amyl nitrite-induced SO relaxation is not well understood. It has

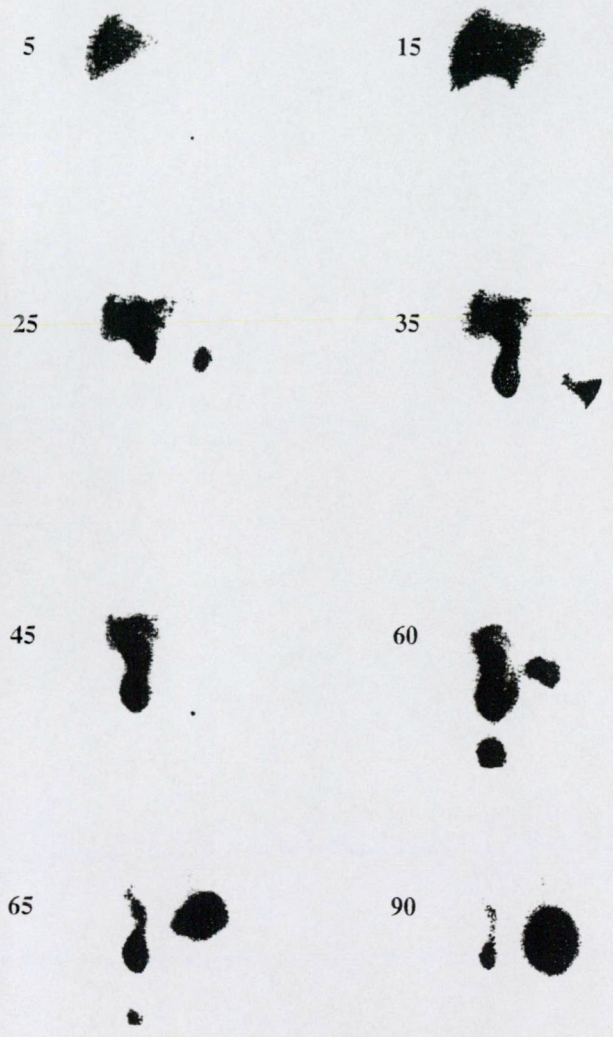


**Fig. 8.** Hepatobiliary scintigram in a patient with SO dyskinesia (functional SOD). Biliary tree activity is first visualized at 15 min. The CBD and intrahepatic biliary tree appear prominently from 25 min up to 60 min. The small bowel is first visualized at 25 min. Note the marked activity decline after amyl nitrite administration

been extensively investigated in vascular smooth muscle, and amyl nitrite has been shown to induce relaxation through activation of soluble guanylate cyclase. According to our in vitro studies, however, nitroglycerin was found to increase both cGMP and cAMP content in isolated rabbit SO, suggesting that an increase in the level of both cyclic nucleotides might be responsible for glyceryl trinitrate-induced SO relaxation [31].

The rationale of this study was based upon the assumption that amyl nitrite administration will cause relaxation in all functional obstructions of the SO, and the bile flow changes due to the action of amyl nitrite will be detected by QHBS.

Normal QHBS parameters were established in the asymptomatic volunteers. These values therefore may be used to characterize normal controls.

QHBS revealed a marked obstructive pattern in nine patients with SOD of biliary types I or II, and amyl nitrite did not cause significant changes in $T_{1/2}$ for the CBD. These results are in accordance with those where QHBS was used alone [17, 19] and are strongly suggestive of organic stenosis of the SO. Amyl nitrite-augmented QHBS therefore may be recommended as a non-invasive technique for the detection of organic stenosis at the level of the SO.

In 13 patients with SOD of biliary types I or II, QHBS revealed a partial obstruction pattern in the transpapillary bile flow, which was completely relieved by amyl nitrite administration, indicating a functional obstruction at the level of the SO in the preprandial period.

In the majority of cases, the evaluation of the static images was sufficient for detection of the partial biliary obstruction and of the effect of amyl nitrite. However, quantitative analysis is essential, for estimation of the rate of biliary tract emptying on the basis of static images is extremely uncertain, particularly in patients with SOD and a possibly dilated CBD. The $T_{1/2}$ of the CBD proved to be the most important quantitative parameter for the diagnosis of SOD, which must normalize fully during the administration of amyl nitrite in patients with functional SOD.

At an early stage of SOD, the hypersensitive SO responds to morphine provocation with spasms and typical pain. At this stage, manometry usually shows a normal basal pressure, and this form of SOD was termed pure hypertensive SOD by Varro and Lonovics [32]. Another classification, introduced by Hogan and Geenen [5] and Sherman et al. [6], defined these motor abnormalities as type III or "possible" SOD, and biliary type III SOD, respectively.

In a later stage, partial stenosis may develop, but the SO is still able to respond to different stimuli. In this stage, the basal SO pressure also may be elevated in painless periods of the disease. This stage is referred to as mixed hypertensive SOD by Varro and Lonovics [32], while according to the manometric classification it is defined as type II or "presumptive" SOD [5] or biliary type II SOD [6]. Our dyskinetic patients, exhibiting an obstructive pattern on QHBS with a good response to amyl nitrite, may belong in this group.

In the end stage of SOD, organic stenosis is unequivocally present, and obstructive signs and an elevated SO pressure are detected. This stage is classified as stenosis of the SO [32], type I or "definitive" SOD [5] or biliary type I SOD [6]. The group of patients in whom QHBS revealed a marked obstructive pattern without significant response to amyl nitrite seems to be the equivalent of this group.

Differentiation between stenosis and dyskinesia of the SO might modify the therapeutic strategy for the disease, since much benefit from the endoscopic sphincte-

rotomy is achieved in patients with elevated basal SO pressure and organic stenosis [5]; however, in patients with SO dyskinesia medical therapy should be tried as a first choice.

*In conclusion:* Amyl nitrite-augmented QHBS proved to be a useful method in the diagnosis of SOD of biliary types I and II. This method permitted non-invasive differentiation between organic stenosis and functional motor abnormalities of the SO.

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Original article

# Evaluation of results of the prostigmine-morphine test with quantitative hepatobiliary scintigraphy: a new method for the diagnosis of sphincter of Oddi dyskinesia

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**Abstract.** Attempts have long been made to use the prostigmine-morphine provocation test for the selection of postcholecystectomy patients suffering from sphincter of Oddi (SO) dyskinesia. Since the whole procedure is based upon the evaluation of subjective complaints, this test has frequently been criticized. To improve the diagnostic value of this method, we have visualized SO spasms during prostigmine-morphine provocation by means of quantitative hepatobiliary scintigraphy (QHBS). Twenty-two cholecystectomized patients with typical postprandial biliary pain were included in this study. In the first series of studies, QHBS with technetium-99m 2,6-diethylphenylcarbamoylmethyl-diacetic acid was performed in each patient 2 days before prostigmine-morphine provocation. The time to peak activity ($T_{max}$) and the half-time of excretion ($T_{1/2}$) over the liver parenchyma (LP), hepatic hilum (HH) and common bile duct (CBD), and the duodenum appearance time (DAT), were determined and served as control values. In the second series of experiments, sphincter spasms were evoked by prostigmine-morphine administration and visualized by means of QHBS. The same parameters were evaluated and serum levels of aspartate aminotransferase (AST) were determined simultaneously at regular intervals. In 12 patients who responded to prostigmine-morphine provocation with typical biliary pain and a significant AST elevation (Nardi positive group) the hepatobiliary scintigram demonstrated a marked biliary obstruction. $T_{max}$ and $T_{1/2}$ over the LP, HH and CBD were significantly increased, while DAT was significantly longer relative to the corresponding data obtained without provocation. Four of the remaining ten patients indicated atypical abdominal pain during prostigmine-morphine provocation, but the AST level remained unchanged in all ten (Nardi negative group). In this group, QHBS revealed a slower, but free transpapillary flow of the tracer: although $T_{1/2}$ over the LP, HH and CBD appeared to be significantly higher than without provocation. $T_{max}$ did not change and an obstructive pattern was not detected on the hepatobiliary scintigram. When QHBS parameters determined during prostigmine-morphine provocation were compared for the Nardi positive and Nardi negative groups, with the exception of $T_{max}$ over the LP they were significantly different. QHBS combined with the prostigmine-morphine provocation test proved to be a useful non-invasive method for the detection of pathological sphincter spasms in patients with SO dyskinesia. Application of this method is therefore strongly recommended in the diagnosis of SO dyskinesia.

**Key words:** Quantitative hepatobiliary scintigraphy – Sphincter of Oddi dyskinesia – Prostigmine-morphine test

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## Introduction

In approximately 5%–10% of cholecystectomized patients, symptoms similar to those present before the operation recur. Following the exclusion of organic and functional extrabiliary disorders, sphincter of Oddi dysfunction (SOD) may be considered as one possible cause of the postprandial biliary pain. On the basis of the pathogenic mechanism, SOD is divided into two forms: structural and functional [1–3]. In structural SOD or SO stenosis, endoscopic retrograde cholangiopancreatography (ERCP) and hepatobiliary scintigraphy show obstructive signs, while manometry reveals a fixed elevation of the basal SO pressure [4, 5]. In functional SOD or SO dyskinesia, no abnormalities are detected on ERCP. The basal SO pressure is often normal. If it is elevated, the SO is still able to relax during amyl nitrite, cholecystokinin (CCK) or glucagon administration [6]. In this group of patients, amyl nitrite-augmented quantitative hepatobiliary scintigraphy (QHBS) may indicate a par-

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tial obstruction, which is completely relieved by amyl nitrite administration [5]. Different manometric abnormalities have been reported to characterize SO dyskinesia, including tachyoddia, retrograde SO contractions and a paradoxical response to CCK administration, and SO manometry soon became a widely accepted method in the diagnosis of functional SO motility disorders [7, 8]. However, in patients with SO dyskinesia the manometric results can be poorly reproducible, which is perhaps due to the episodic nature of the disorder [9]. In these patients, postprandial biliary pain is a characteristic complaint, which can be mimicked by morphine administration. Special provocation tests, including the Debray and Nardi tests, have therefore been developed to confirm the diagnosis of SO dyskinesia [10–12]. Since assessment of the results of these tests is based upon the analysis of subjective complaints, and the Nardi test alone is thought to be unreliable [13], we have developed a new non-invasive method in which the prostigmine-morphine provocation test is combined with QHBS. The rationale of this is based upon the assumption that, in patients with SO dyskinesia, morphine administration will cause a prolonged and vigorous SO spasm, and the resulting blockage of the bile flow can be detected by means of QHBS.

## Materials and methods

The study was performed on 22 female cholecystectomized patients (mean age: 49 years; range: 35–60 years) who had typical biliary pain in the postprandial period. Organic biliary and extrabiliary and also functional extrabiliary disorders were excluded. Abdominal ultrasonography and ERCP revealed no abnormalities, and all liver function tests were normal. In all 22 patients, QHBS performed 2 days before the provocation test demonstrated normal biliary excretion in pain-free periods, and these results served as controls. In all 22 patients, a functional SOD was suspected.

*QHBS combined with the prostigmine-morphine test.* After an overnight fast, 10 mg morphine was administered subcutaneously. Thirty minutes later, 0.5 mg prostigmine was injected intramuscularly, with 140 MBq technetium-99m 2,6-diethylphenylcarbamoylmethyldiacetic acid (EHIDA) intravenously. Subjective complaints were recorded, and the serum levels of aspartate aminotransferase (AST) were determined at the beginning and 2, 4 and 6 h following morphine administration. The changes in radioactivity over the upper part of the abdomen were recorded by a large field-of-view gamma camera fitted with a low-energy, high-resolution, parallel-hole collimator. Gamma camera images (1 min each) were obtained at 5, 15, 35, 45, 60, 75 and 90 min in the anterior projection. Computer data acquisition was started simultaneously at the time of injection. Digital images were obtained at one frame/min for 90 min, and recorded in a 64×64 matrix. Time-activity curves were generated from regions of interest (ROIs) selected as follows: right peripheral liver parenchyma (LP), hepatic hilum (HH), common bile duct (CBD) and duodenum (D). The time to peak activity ($T_{max}$) and the half-time of excretion ($T_{1/2}$) were calculated for each time-activity curve. $T_{1/2}$ for the time-activity curve over the CBD was defined as a maximum of 360 min for statistical analysis. The time of first appearance of the activity in the duodenum (DAT) was also registered. For statistical evaluation, paired and unpaired Student's *t* tests were used. Significance was achieved at $P<0.05$. All results are given as the mean and the standard error of the mean (mean±SE). The results of QHBS alone (i.e. without the provocation test), performed 2 days earlier, with equivalent acquisition parameters, served as controls.

## Results

The quantitative parameters ($T_{max}$, $T_{1/2}$, DAT) of QHBS performed 2 days before the provocation test (control study) were within our normal limits in all 22 patients [5], in whom the transpapillary flow was normal in pain-free periods.

Of the 22 patients, 12 responded to prostigmine-morphine administration with typical biliary pain and an AST elevation. In all 12, $T_{max}$ and $T_{1/2}$ calculated from the ROIs over the LP, HH and CBD were significantly higher and DAT also proved to be significantly longer than the controls (Fig. 1–3). The time-activity curves over the CBD demonstrated a characteristic obstructive pattern, and no bowel activity appeared until 60 min

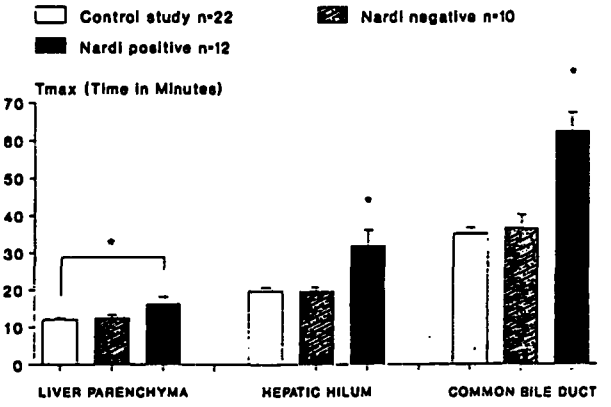


**Fig. 1.** Time to peak activity ($T_{max}$) of the liver parenchyma, hepatic hilum and common bile duct in the control study ($n$=22), and in Nardi negative ($n$=10) and Nardi positive ($n$=12) patients. *$P<0.05$, significant differences

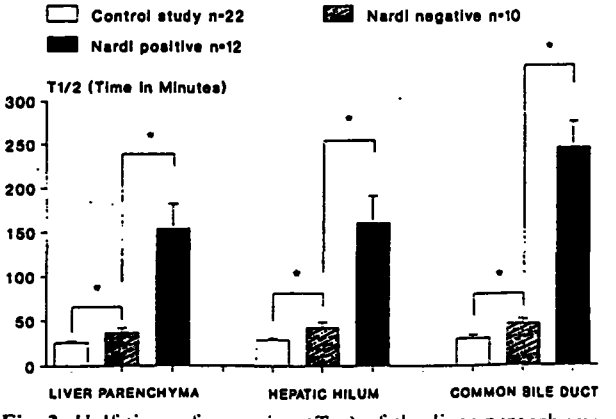


**Fig. 2.** Half-time of excretion ($T_{1/2}$) of the liver parenchyma, hepatic hilum and common bile duct in the control study ($n$=22), and in Nardi negative ($n$=10) and Nardi positive ($n$=12) patients. *$P<0.05$, significant differences

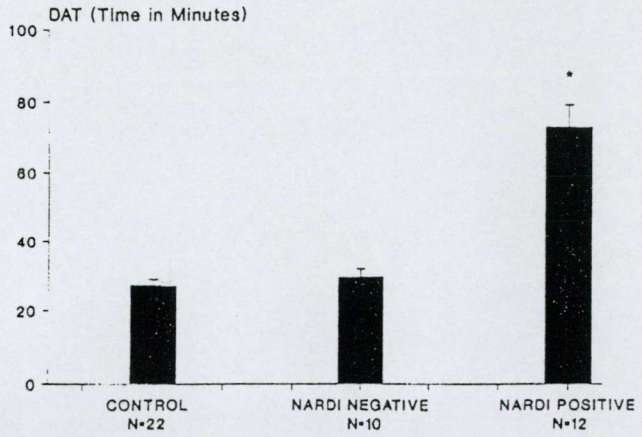


**Fig. 3.** Duodenum appearance time (DAT) in the control study ($n$=22), and in Nardi negative ($n$=10) and Nardi positive ($n$=12) patients. * $P$<0.05, significant differences

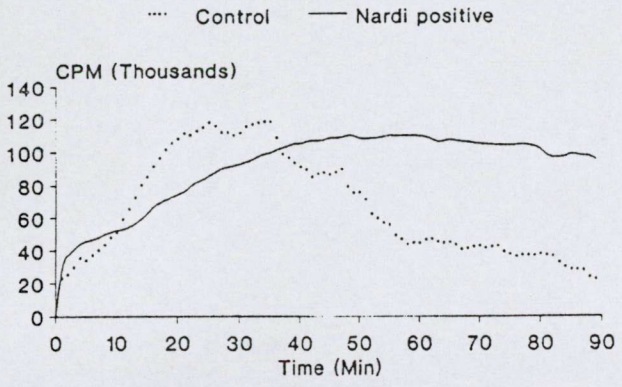


**Fig. 4.** Representative recording of time-activity curves generated from the ROI over the CBD of a patient during the control study and during a positive prostigmine-morphine test. Control study: $T_{max}$: 36; $T_{1/2}$: 27; Nardi test: $T_{max}$: 55; $T_{1/2}$: 167 min

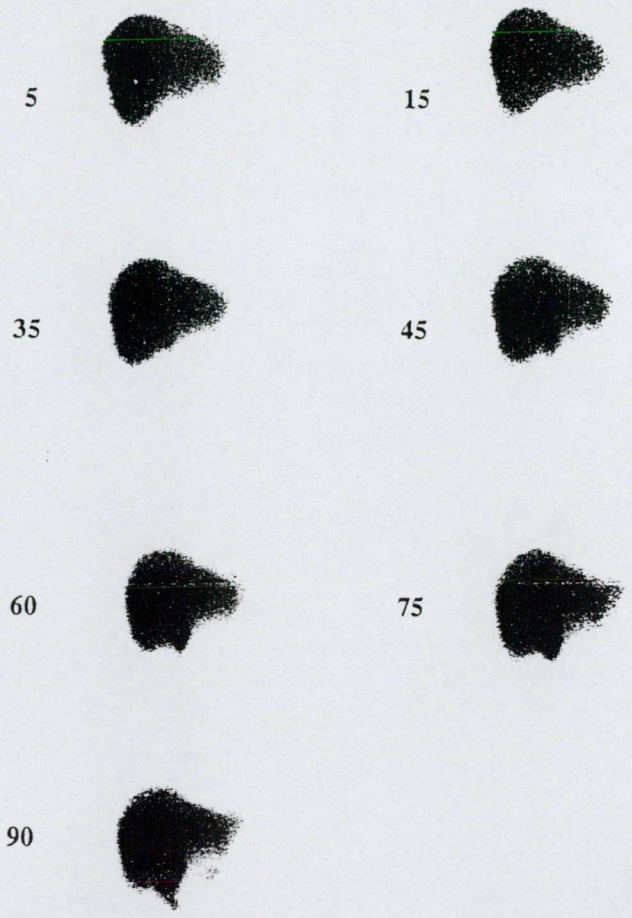


**Fig. 5.** Hepatobiliary scintigram in a patient with a positive prostigmine-morphine test and SO spasm. Note the marked accumulation of the isotope in the biliary tree, which persisted until the end of the study. No bowel activity appeared until 60 min

(Fig. 4). The hepatobiliary scintigram revealed a marked accumulation of the isotope in the biliary tree, which persisted until the end of the study (Fig. 5). The AST levels were significantly increased in all 12 patients, but only eight of them exhibited at least a twofold elevation (Fig. 6). On the basis of the results of QHBS and AST determination the provocation tests were considered to be positive in all 12 patients.

Four of the remaining ten patients observed abdominal pain during prostigmine-morphine provocation, but none of them exhibited significant AST changes (Fig. 6). In these ten patients, DAT and $T_{max}$ calculated from the ROIs over the LP, HH and CBD did not undergo significant changes, whereas $T_{1/2}$ increased slightly but significantly relative to the controls, indicating the well-known SO-contracting effect of morphine (Figs. 1, 2 and 3). Although analysis of the time-activity curves revealed the slower emptying of the isotope from the liver, the transpapillary flow of the radiotracer proved to be free (Fig. 7). The CBD was prominent on the hepatobiliary scintigram, but a clear decline in CBD activity was detected after 45 min (Fig. 8), and DAT was normal in all these patients. On the basis of the results of QHBS and AST determinations, the provocation test was considered to be negative in these ten patients.

The results of QHBS in the Nardi positive and negative groups differed significantly. In patients who gave a positive provocation test, $T_{max}$ for the HH and CBD, $T_{1/2}$ for the LP, HH and CBD, and also DAT were significantly higher than for the Nardi negative group (Fig. 1–3). These marked differences in the quantitative parameters of hepatobiliary scintigraphy allow an objective prediction of the result of the prostigmine-morphine provocation test.

## Discussion

Hepatobiliary scintigraphy is a widely accepted method for the evaluation of biliary dynamics. Krishnamurthy et al. developed a quantitative method for analysis of the dynamics of hepatic bile flow [14]. In patients with

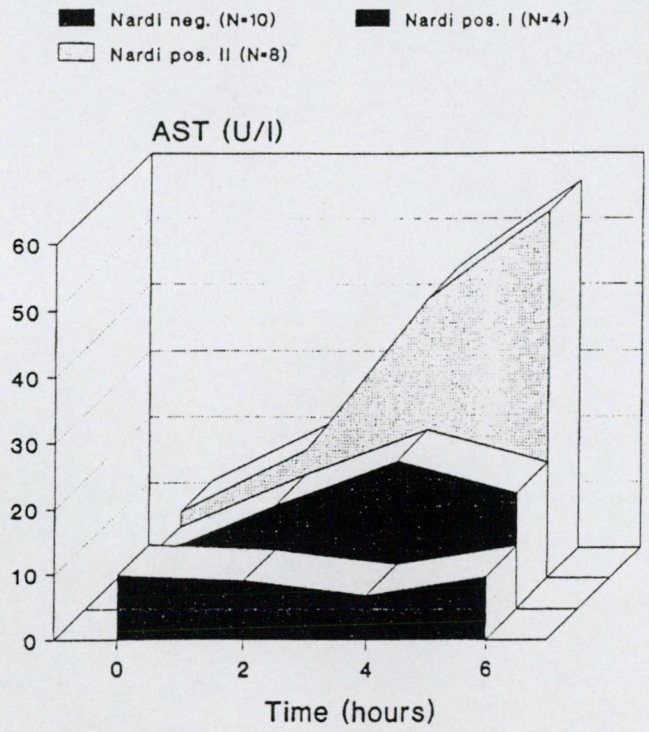


**Fig. 6.** Mean values of serial AST determinations in Nardi negative patients ($n$=10), Nardi positive patients ($n$=8) and Nardi positive patients with obstructive signs on QHBS, but less than a two-fold AST elevation ($n$=4)

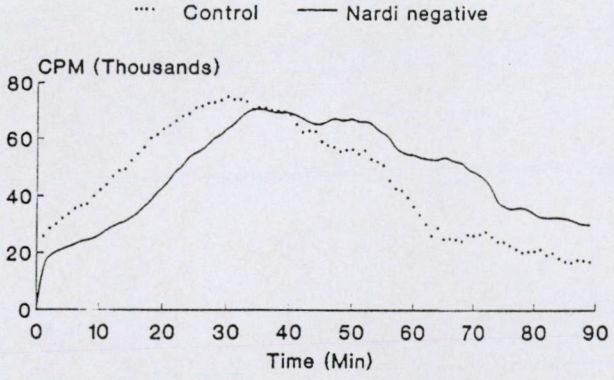


**Fig. 7.** Representative recording of time-activity curves generated from the ROI detected over the CBD of a patient during the control study and during a negative prostigmine-morphine test. Control study: $T_{max}$: 30, $T_{1/2}$: 25; Nardi test: $T_{max}$: 35, $T_{1/2}$: 45 min

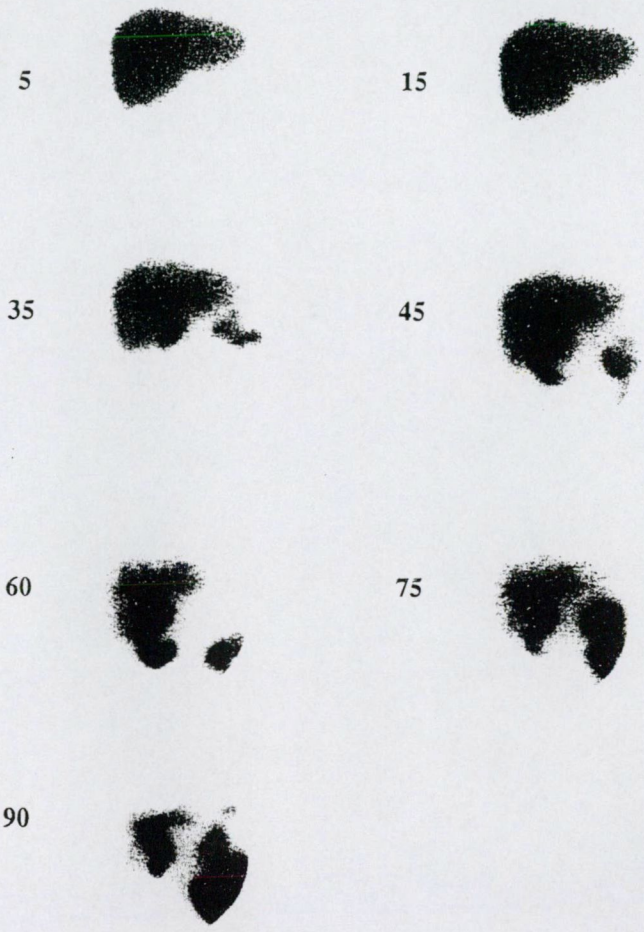


**Fig. 8.** Hepatobiliary scintigram in a patient with a negative prostigmine-morphine test. The CBD was prominent, but a clear decline in activity was detected after 45 min, and the duodenal appearance time was normal (35 min)

structural SOD, hepatobiliary scintigraphy usually revealed an obstructive pattern [15], but in a considerable proportion of functional SOD patients it failed to detect any abnormalities [16]. For this reason, in order to select patients with functional SOD, QHBS was combined with the administration of CCK [17, 18]. Fatty-meal ultrasonography and CCK- and secretin-aided ultrasonography have also been recommended for the diagnosis of SOD, but none of these has been widely accepted [19, 20]. Although SO manometry has become the gold standard in the diagnosis of functional SOD, this method also has several drawbacks, including unsuccessful cannulation, time consumption, the danger of pancreatitis and problems with reproducibility, and it therefore cannot be used routinely. There is a great need for a single non-invasive, widely available procedure which is capable of diagnosing functional SOD.

Provocation tests, such as the Debray and Nardi tests, have been used for several years in the evaluation of SO dyskinesia [10, 11]. The prostigmine-morphine test utilizes the synergistic stimulatory effect of a cholinergic agonist and morphine on the SO, with a diagnostic assessment of whether pain and enzyme abnormalities are produced by prolonged SO spasm in patients with a suspected SOD. Morphine and the cholinergic agonist prostigmine have similar intracellular mechanisms of action since they cause an SO contraction through the $Ca^{2+}$-calmodulin and the protein kinase C cascade. The SO-contracting effect of morphine is demonstrated by manometric measurements, which reveal that morphine increases the frequency of phasic contractions and the baseline pressure of the SO. This effect is inhibited by naloxone, but not by atropine, suggesting a direct smooth muscle

effect of morphine. Hogan reported that small doses of morphine increase the frequency of the phasic contractions, but have a minimal effect on the basal pressure, whereas larger doses cause a generalized SO spasm [21–23]. The prostigmine-morphine test, the codeine test or endoscopic retrograde cholangiopancreatographic filling pain test are of similar value as provocation methods. The usefulness of these tests has been criticized, since they may furnish a certain number of false-positive results, and the assessment is based upon the subjective complaints of the patients [13, 24].

Attempts have therefore long been made to make these tests more objective, i.e. to find methods which prove that a spasm of the SO really does exist at the time of the provoked pain. Tanaka et al. [25] and Madura et al. [26] observed a marked rise in CBD pressure by means of manometry during morphine administration. This was associated with typical biliary pain in cholecystectomized patients with SO dyskinesia. Varró et al. visualized the biliary ducts in the course of the morphine-choleretic (Debray) provocation test with $^{99m}$Tc-hepato-iminodiacetic acid and demonstrated that stoppage of the outflow paralleled the appearance of pain [28]. The morphine-choleretic test was combined with an estimation of the serum transaminase level, and the test was considered positive when a significant (at least twofold) elevation of the level of this enzyme occurred a few hours after provocation [27, 28]. Rises in plasma AST after morphine administration are similar to those after morphine-neostigmine administration. Changes in plasma levels of liver enzymes are clearly related to morphine-induced changes in SO motility, since an AST elevation is not observed in patients with a gall bladder in situ, and it is abolished by endoscopic papillotomy [29]. The frequencies of abnormal manometric results and an elevated basal pressure are significantly higher in patients with biliary pain who exhibit an AST rise during the Nardi test [30].

Our results indicated the QHBS can be used to visualize the prolonged SO spasm during prostigmine-morphine provocation. In the Nardi positive group, QHBS revealed a characteristic obstructive pattern over the CBD, proving that a sphincter spasm really does exist. In Nardi negative patients, prostigmine-morphine administration caused only a slight deceleration of CBD excretion, indicating a slightly increased SO resistance to CBD emptying.

QHBS proved to be a useful method for evaluation of the results of the prostigmine-morphine provocation test. This method allows a clear distinction of patients with a physiological response to morphine administration from those who respond with a pathological sphincter spasm.

Both QHBS and AST determination can be used to detect the sphincter spasm during the provocation test. In four of the 12 Nardi positive patients, the AST elevation was less than twofold, which was earlier thought not to be diagnostic. However, in these four patients QHBS proved the occurrence of a biliary obstruction and SO spasm. None of the ten patients who gave negative isotope results exhibited significant AST changes. QHBS seems slightly more sensitive but equally as specific as AST determination for the detection of morphine-induced SO spasms.

On the other hand, abdominal pain is a very common symptom during the Nardi test. However, abdominal pain alone proves unreliable for the selection of Nardi positive patients. In our series, 16 patients had upper abdominal pain during prostigmine-morphine provocation, whereas only 12 had an SO spasm according to the isotope study, as evidence that abdominal pain alone is not a specific sign. In those four Nardi negative patients who indicated abdominal pain without an SO spasm, an intestinal smooth muscle spasm may be a possible explanation for the origin of the abdominal pain.

Finally, a few words concerning our diagnostic strategy in patients in whom there is a clinical suspicion of SOD. In patients with SOD and obstructive signs on hepatobiliary scintigraphy or ERCP, amyl nitrite-augmented QHBS should be performed in order to differentiate organic stenosis from functional motor abnormalities of the SO [5]. Patients with purely functional SO dyskinesia have only biliary pain and no other abnormalities. In this group, the prostigmine-morphine provocation test combined with QHBS should be performed in order to select patients for invasive SO manometry, which is currently recommended for the exact diagnosis.

*In conclusion*, QHBS combined with prostigmine-morphine provocation proved a useful non-invasive method for the detection of pathological SO spasms in patients with SO dyskinesia. Since application of this method may improve the diagnostic accuracy of the conventional Nardi test, it is strongly recommended in the diagnosis of functional SO dyskinesia.

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