Gastrointestinalis hormonok és farmakonok hatásának vizsgálata Oddi sphincteren

egyetemi doktori (PhD) értekezés

magyar nyelvű összefoglaló

Dr. Velősy Borbála

1998

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Az Oddi sphincter működése leginkább a szív szisztolés és diasztolés mozgásához hasonlítható, fázikus kontrakciók és relaxációk sorozatából áll. A sphincter zóna bazális nyomása kb. 10-25 Hgmm, a fázikus kontrakciók csúcsán eléri a 100-130 Hgmm-t. A fázikus kontrakciók általában antegrád irányúak, de szimultán, sőt retrográd kontrakciók is előfordulnak.

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Annak ellenére, hogy egyre nyilvánvalóbb az összefüggés az epehólyag és az Oddi sphincter motilitási zavarai között, klinikai entitásként ma még külön tárgyaljuk őket. Az epehólyag motilitási zavarai alapvetően két formára oszthatók: 1. epehólyag hypokinesis és 2. epehólyag dyskinesis.

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Eredmények

Az amyl nitrittel érzékenyített quantitativ hepatobiliaris scintigraphia alkalmasnak bizonyult arra, hogy különbséget tegyünk a functionalis és az organikus epeelfolyási nehezítettség között.

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Epehólyaggal rendelkező betegekben a "kő nélküli epés fájdalom" hátterében az izotópdiagnosztikai módszerrel sok esetben alacsony ejectiós frakciót találtunk CCK analóg (cerulein) adása után, ami az esetek egy részében nitrogén monoxid donor és cerulein együttes alkalmazásakor normalizálódott.

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Effects of gastrointestinal hormones and pharmacological agents on the sphincter of Oddi

egyetemi doktori (PhD) értekezés

Dr. Velősy Borbála

1998

Az értekezés a Szent-Györgyi Albert Orvostudományi Egyetem I. sz. Belgyógyászati Klinikáján készült az alábbi kutatási program keretein belül:

Program:

"A neuroendokrin rendszer működése ép és kóros körülmények között."
(Témavezető: Dr. Telegdy Gyula akadémikus, tanszékvezető egyetemi tanár)

Alprogram:

"A gastrointestinalis rendszer neuroendokrinologiája."
(Témavezető: Dr. Lonovics János tanszékvezető egyetemi tanár)

To my teachers and friends

Az értekezés alapjául szolgáló közlemények:

I.: Madácsy L, Velősy B, Lonovics J, Csernay L: Differentiation between organic stenosis and functional dyskinesia of the sphincter of Oddi with amyl nitrite-augmented quantitative hepatobiliary scintigraphy.
Eur. J. Nucl. Med. 21: 203-208, 1994.

Impact factor: 3.097 Idézettség: 2

II.: Madácsy L, Velősy B, Lonovics J, Csernay L: Evaluation of results of the prostigmine-morphine test with quantitative hepatobiliary scinitgraphy: a new method for the diagnosis of sphincter of Oddi dyskinesia.
Eur. J. Nucl. Med. 22: 227-232, 1995.

Impact factor: 3.097 Idézettség: 0

III.: Szilvássy Z, Nagy I, Madácsy L, Hajnal F, Velősy B, Takács T, Lonovics J: Beneficial effect of lovastatin on sphincter of Oddi dyskinesia in hypercholesterolemia and hypertriglyceridemia.
Am. J. Gastroenterol. 92: 900-902, 1997.

Impact factor: 3.178 Idézettség: 0

IV.: Velősy B, Madácsy L, Csernay L, Lonovics J: Effect of glyceryl trinitrate on the sphincter of Oddi spasm evoked by prostigmine-morphine administration.
Eur. J. Gastroenterol. and Hepatol. 9: 1109-1112, 1997.

Impact factor: 1.310 Idézettség: 0

V.: Velősy B, Madácsy L, Szepes A, Pávics L, Csernay L, Lonovics J: The effects of somatostatin and octreotide on the human sphincter of Oddi.
Submitted for publication.

Contents

Abbreviations

AST	aspartate aminotransferase
CBD	common bile duct
CCK	cholecystokinin
EF	ejection fraction
ERCP	endoscopic retrograde cholangio-pancreatography
GB	gallbladder
GBEF	gallbladder ejection fraction
GI	gastrointestinal
cGMP	cyclic guanosine monophosphate
GTN	glyceryl trinitrate
HH	hepatic hilum
LP	liver parenchyma
NANC	non-adrenergic non-cholinergic
NO	nitric oxide
eNOS	endothelial nitric oxide synthase
iNOS	inducible nitric oxide synthase
nNOS	neuronal nitric oxide synthase
OCT	octreotide
QHBS	quantitative hepatobiliary scintigraphy
ROI	region of interest
SO	sphincter of Oddi
SOD	sphincter of Oddi dysfunction
SOM	somatostatin
$T_{1/2}$	half-time of excretion
T_{max}	time-to-peak activity
VIP	vasoactive intestinal polypeptide

Preface

In 1987 Professor Vince Varró found in his library some copies of the old textbook of internal medicine written by Professor Hetényi and presented them to the young clinicians of his department. I was very proud to receive. When I read the chapter on gastrointestinal diseases, I was somewhat surprised to learn that it gave a quite correct description of the postcholecystectomy syndrome and the possible motility disorders of the sphincter of Oddi. Even the therapeutic approach to these symptoms did not differ considerably from the contemporary one.

In the past two decades, a huge quantity of knowledge has been collected by experts and scientists in the field of gastroenterology. It has been proved, that the gastrointestinal tract is the largest endocrine organ in the human body, and a number of gastrointestinal hormones and neuropeptides have been discovered. It has turned out that the nervous network situated in the gut wall is not a simple relay system of the autonomic nervous system: there is a "little brain of the gut", the enteric nervous system, which coordinates the motility of the gastrointestinal tract. The complexity of the actions of the neuropeptides, hormones and nervous system in the regulation of the gastrointestinal motility and function is not yet fully understood.

Our team has been concentrating on research work in a quite small, but important field of gastroenterology, sphincter of Oddi motility. The background of many clinical symptoms has been elucidated and the need to clarify the basic mechanisms of motility disorders has become more and more important. The extensive knowledge of our earlier teachers, mainly based on empirical observations, stimulated us to study the mechanism of sphincter of Oddi motility. This review presents some of the new findings made by our team.

INTRODUCTION

In humans, the biliary tree consists of the bile ducts (the canals of Hering, ductules, interlobular ducts, septal ducts, right and left lobar ducts and common bile duct (CBD) and the gallbladder (GB). In the area of the cystic duct of the GB and at the ending of the CBD entering the duodenum, there are sphincter-like structures. The latter is considered by many authors to be a real sphincter and is called the sphincter of Oddi (SO). The SO was first described by Ruggero Oddi (while still a medical student in 1887) in several species, including humans (1). The human SO is a segment of the distal CBD from 10 to 15 mm in length, which includes three relatively discrete zones of muscle called: 1. the sphincter choledochus, 2. the sphincter ampullae and 3. the sphincter pancreaticus. The SO consists of internal circular and external longitudinal muscle fascicles, the latter being in connection with the musculature of the duodenal wall.

The actions of the SO are relatively independent of the duodenum. The motor function of the SO is similar to that of the systole and diastole of the human heart, i.e. phasic contractions and relaxations occur. Manometric studies have shown that the SO exhibits a resting (basal) tone and phasic contractions (2). The resting pressure in the sphincter zone is 10-25 mmHg, while the phasic contraction waves have an amplitude of 100-130 mmHg. In the majority of cases, the propagation of the phasic contractions is antegrade, but simultaneous and retrograde contractions also occur. This motility pattern is seen in the interdigestive phase, while after a meal the SO opens and allows the bile to flow into the duodenum.

The motility of the biliary system is under neuronal and hormonal regulation. While the hormonal mechanisms have been studied in detail, less is known about the neuronal control. The GB and bile ducts are parasympathetically innervated by the vagal nerve, while the sympathetic nerves project from the coeliac ganglion. Histological studies have shown an extensive distribution of ganglia and nerve fibres in the different layers of the extrahepatic biliary tract. Immunohistochemical activities of several hormones, including substance P, vasoactive intestinal polypeptide (VIP) and somatostatin (SOM), have been demonstrated in the nerve fibres of the SO (3).

The neurohumoral regulation of the fasting and postprandial motility of the biliary system has been investigated extensively in recent years. The hormones and neuropeptides acting directly or indirectly on the GB and SO are listed in Tables 1 and 2.

Motilin is thought to have a major influence on the interdigestive GB motility, while cholecystokinin (CCK) is the principal factor which controls postprandial GB contraction. Under normal (healthy) circumstances the motilities of the GB and SO are well coordinated in both the interdigestive and postprandial phase. In humans, the SO acts primarily as a resistor; the suppression of the phasic contractions and the relaxation of the basal tone are necessary to allow the bile flow into the duodenum postprandially. Among several hormones and neuropeptides, CCK plays a central role in the humoral control of SO activity. In humans, the dominant action of CCK on the SO is an inhibitory one, via stimulation of non-adrenergic non-cholinergic (NANC) inhibitory neurons, while a far less potent stimulatory effect had been observed acting directly on smooth muscle cells. Until recently, VIP was proposed as the main NANC neurotransmitter in the SO, but recent observations have suggested, that nitric oxide (NO) is the final neurotransmitter which causes relaxation (4).

Any malfunction that occurs in the coordinated motions of the GB and SO may precipitate various symptoms, and the clinical picture of motility disorders may develop. The discovery of the connection between the dysfunction of the regulatory mechanisms and the quite heterogeneous clinical symptoms is one of the most important research findings in the past decade.

In spite of the close connection between the motility disorders of GB and SO, as clinical entities they have been described quite separately. The motility abnormalities of the GB may be divided into two main groups: GB hypokinesia and GB dyskinesia. The former is characterized by an impaired emptying, while the latter is the term describing uncoordinated contraction of the cystic duct area simultaneously with fundic contraction of the GB, resulting in biliary pain.

The cause of the typical biliary or pancreatic pain occurring in patients who have undergone cholecystectomy (if no organic disease is found) may be a motility disorder of the SO. The endoscopic manometry and ERCP findings led Hogan and Geenen (5) to categorize such patients into three subgroups: SO dysfunction (SOD) of types I, II and III. Sherman et al. introduced a modified classification for patients with SOD of biliary types I-III and pancreatic types I-III. (6) The details and the criteria of the classification are to be seen in Tables 3 and 4.

DIRECT ACTIONS

Cholecystokinin	Contraction
Gastrin	Contraction
Substance P	Contraction
Vasoactive Intestinal Polypeptide	Relaxation
Calcitonin Gene-Related Peptide	Relaxation
Bombesin/Gastrin Releasing Peptide	Contraction
Met-encephalin	Contraction
Neurotensin	Contraction

INDIRECT ACTIONS

Cholecystokinin	Contraction
Motilin	Contraction
Neurotensin	Contraction/Relaxation
Bombesin/Gastrin Releasing Peptide	Contraction
Pancreatic Polypeptide	Relaxation
Capsaicin	Contraction

Table 1.

List of hormones and neuropeptides with suspected direct or indirect actions on the gallbladder.

INDIRECT ACTIONS

Cholecystokinin	Relaxation
Gastrin	Relaxation
Secretin	Relaxation
Substance P	Relaxation
Bombesin/Gastrin Releasing Peptide	Relaxation
Met-encephalin	Relaxation
Glucagon	Relaxation
Motilin	Contraction
Morphine	Contraction
Somatostatin	Contraction
Pancreatic Polypeptide	Contraction

DIRECT ACTIONS

Cholecystokinin	Contraction
Morphine	Contraction
Substance P	Contraction
Vasoactive Intestinal Polypeptide	Relaxation

Table 2.

List of hormones and neuropeptides with suspected direct or indirect actions on the sphincter of Oddi.

SOD Biliary type

Type I.

1. Typical biliary-type pain
2. Liver enzymes (alkaline phosphatase and transaminases) > 1.5-2 x upper limits of normal ranges
3. Dilated common bile duct > 12 mm diameter
4. Prolonged biliary drainage time (> 45 min) with the patient in the supine position

Type II.

1. Typical biliary-type pain
2. Positive findings for one or two features (2, 3 or 4) from type I

Type III.

1. Typical biliary-type pain, but no other abnormalities

Table 3.

Sphincter of Oddi dysfunction - Biliary type (adapted from Sherman S. et al. Am J Gastroenterol 86: 586-590, 1991)

SOD Pancreatic type

Type I.

1. Recurrent pancreatitis and/or typical pancreatic-type pain
2. Amylase and/or lipase > 1.5-2 x upper limits of normal ranges
3. Dilated pancreatic duct (head >6 mm; body >5 mm)
4. Prolonged pancreatic drainage time (> 9 min) with the patient in the prone position

Type II.

1. Typical pancreatic-type pain
2. Positive findings for one or two features (2, 3 or 4) from type I

Type III.

1. Typical pancreatic-type pain, but no other abnormalities

Table 4.

Sphincter of Oddi dysfunction - Pancreatic type (adapted from Sherman S. et al. Am J Gastroenterol 86: 586-590, 1991)

This classification is in accordance with the observations of Varró and Lonovics (7), who proposed a theoretical classification based mainly upon the clinical findings: the term "hypertonic SO dyskinesia" may fit SOD of biliary type III, "mixed hypertonic SO dyskinesia" may cover the same entity as SOD of biliary type II and the end-stage of the disease has been called "SO sclerosis" which may be the equivalent to SOD of biliary type I.

The crucial questions in the care of patients with the above-mentioned diseases are how to make a correct diagnosis, how to select drugs which could help in the management of the symptoms, and how to verify the effects of treatment.

The aims of the studies reported on here were to introduce quite simple, non-invasive methods for the selection of patients with different types of SOD and to observe the effects of various compounds on the SO which could explain the development of the clinical symptoms. A further goal was the search for drugs which could help in the control of the pain of the patients and in the prevention of the development of symptoms.

METHODS

Radioisotopes have been widely used in diagnostic procedures in recent decades. For the study of bile transport and flow, radioactively labelled iminodiacetic acid and its analogues seemed to be most useful compounds. They are taken up by the liver cells and excreted into the bile. The dynamics of the bile flow can be monitored with a gamma-camera. The method of quantitative hepatobiliary scintigraphy (QHBS) was first described by Krishnamurthy et al. (8) This method provided a possibility for measurement of the quantitative parameters which were characteristic of the uptake, excretion and flow of the radiotracer into the bile in a non-invasive manner. Because of this advantage, QHBS has become a method of choice for the study of patients with motility disorders of the biliary tract.

With the kind help of colleagues at the Department of Nuclear Medicine, we adapted the original method. During the quantitative analysis of the time-activity curves, it was possible to measure quite separately the dynamics of the bile flow in the liver parenchyma, hepatic hilum and CBD. It is a well-known fact that the rate at which the bile enters the duodenum mainly depends on the motility of the SO. Because of the possibility of visualizing changes in the bile flow, we developed new methods (based on the original one) of measuring the effects of hormones and pharmacological agents on the SO.

The basic methodology of QHBS was as follows:

After an overnight fast, 140 MBq (3-4 mCi) 99mTc-2,6-diethylphenylcarbamoylmethyl-diacetic acid was administered intravenously. The patient was placed in the supine position. 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 in the anterior projection at 5, 15, 25, 35, 60, 75 and 90 min. Digital images were obtained simultaneously at one frame/min for 90 min and recorded in the computer in a 64x64 matrix. Time-activity curves were generated from regions of interest (ROIs) selected as follows: right peripheral liver

parenchyma (LP), hepatic hilum (HH), 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. The first appearance of the activity in the duodenum was also registered.

In cholecystectomized patients, the parameters of the time-activity curves over the CBD are the best indicators of the speed of transpapillary bile flow. Without an extrahepatic bile duct obstruction, the level of radioactivity in the CBD reaches its maximum before 45 min. Following a plateau phase, the level of radioactivity begin to decrease in an exponential manner. The slope depends on the flow rate through the SO, and the $T_{1/2}$ of the CBD demonstrates numerically how quickly the bile enters the duodenum. In accordance with this, we chose the 60th min of QHBS for the administration of different pharmacological agents suspected of rapidly influencing the flow rate through the SO. In the case of drugs with prolonged actions, we administered the different compounds at the beginning or 30 min before QHBS was started (the details will be discussed in the following section).

Imaging of the GB motility in patients without cholecystectomy is also possible with the same radioisotopes (9). The contraction of the GB after food intake (standardized meal) or exogenous administration of a CCK analogue (e.g. caerulein) can be measured. The ejection fraction (EF), calculated as the percentage difference between the maximum and the minimum radioactivity observed in the ROI over the GB, is regarded as normal if it is over 35%. Drugs with suspected effects on the motility of the biliary tree could also be administered during QHBS, but in this case a longer imaging period is necessary, this type of QHBS lasting 120 min.

Compounds suspected of influencing the SO

Glyceryl trinitrate (GTN)

As a NO donor amyl nitrite was administered continuously from the 60th min to the 90th min of QHBS, initially as an inhalation agent (1 ml per patient from 45 mg/ml solution). Later, the form of application of the drug was changed: in the 60th min of QHBS, 1 tablet of GTN containing 0.5 mg (Nitromint, Egis) was given to the patients sublingually. The two

formulations of the drug were equally efficient. To reach a continuously high serum level of NO (e.g. during provocation tests), GTN was given as an intravenous infusion (Nitrolingual 1 ug/kg/min for 120 min), started 30 min before QHBS.

Morphine and prostigmine

Morphine was used as an agent for provocation tests, together with prostigmine (Nardi test), 30 min before the QHBS was started, in a dose of 10 mg subcutaneously, followed 30 min later by 0.5 mg prostigmine intramuscularly.

Somatostatin (SOM)

Both the native hormone and its long-acting analogue have been used. Because of the short half-life of the native hormone, SOM was given as a continuous infusion. At the beginning of QHBS, a 250 microgram bolus (Stilamin, Serono) was given intravenously, followed by an intravenous infusion of 250 microgram/hr SOM until the end of the study. The long-acting analogue octreotide (OCT) (Sandostatin, Sandoz) exhibited a longer half-life, and it was therefore administered in a dose of 0.1 mg subcutaneously 30 min before QHBS was started.

Compounds suspected of influencing the GB emptying

Cholecystokinin (CCK)

Instead of the native hormone, we chose an analogue, caerulein (Takus, Farmitalia). It was given intravenously in a dose of 1 ng/kg/min for 10 min. The short infusion was started in the 60th and, if necessary, again in the 90th min of the QHBS. The repeated administration of caerulein had the same effect; no accumulation of the drug was observed.

For statistical evaluation paired and unpaired Student t-tests were used. Significance was achieved at $p<0.05$. All results were expressed as the mean and the standard error or standard deviation of the mean. Parameters obtained in the basic study of the same patients served as controls.

All the study protocols were approved by the local Ethical Committee of the University (SZOTE 62-6/92, 30-5/93, 5-29/93).

RESULTS

In all patients studied, organic biliary and extrabiliary diseases were excluded by previous examinations.

NO donors

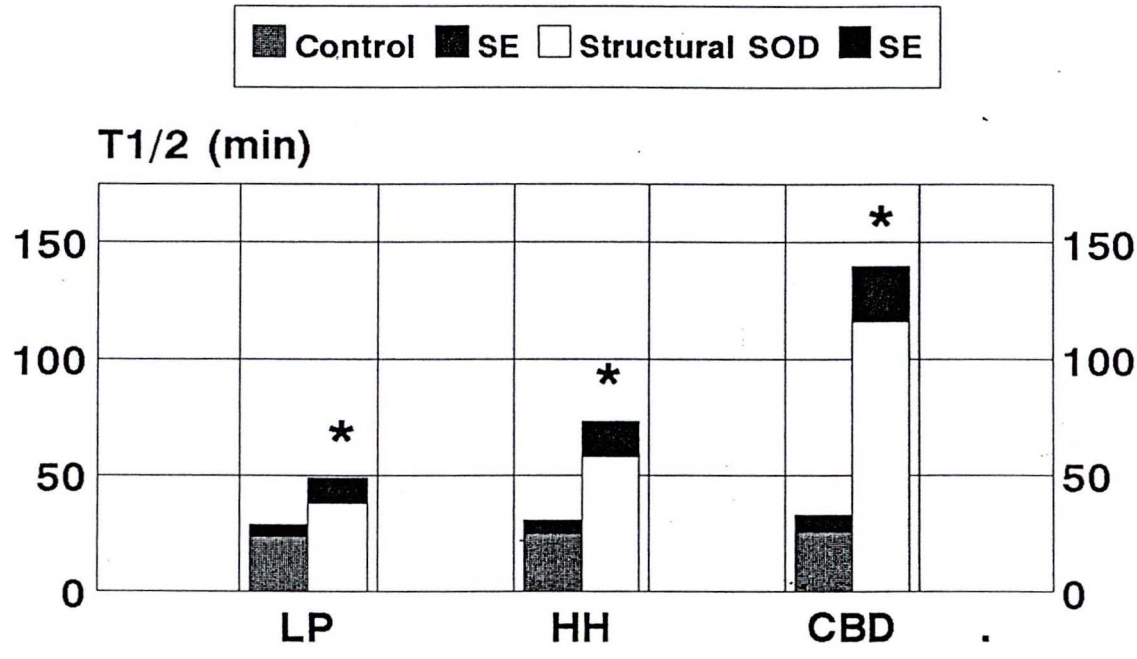
Amyl nitrite-augmented QHBS was performed on 22 female patients with suspected SOD of biliary type I or II, and 9 healthy female volunteers who had undergone cholecystectomy. The normal values of T_{max} and $T_{1/2}$ were obtained from QHBS on the 9 asymptomatic volunteers. In this group, amyl nitrite administration did not influence $T_{1/2}$ for the CBD significantly. On the basis of the amyl nitrite-augmented QHBS, patients with SOD could be divided into two groups:

In 9 patients with suspected SOD, $T_{1/2}$ calculated from the ROIs over the HH and the CBD were significantly higher as compared with the controls. QHBS 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 $T_{1/2}$ for the time-activity curves of the CBD (Figures 1, 3 and 4), indicating the presence of structural SOD.

In 13 patients with suspected SOD, T_{max} and $T_{1/2}$ for the CBD were significantly higher than for the controls, but in all these patients the rate of CBD excretion was accelerated and $T_{1/2}$ for the CBD decreased significantly during amyl nitrite administration (Figures 2, 3 and 5), suggesting a SOD of functional origin.

The results of this first study prompted us to use several other compounds with effects similar to that of amyl nitrite as NO donors. The details will be described in the results of the following studies.

Figure 1

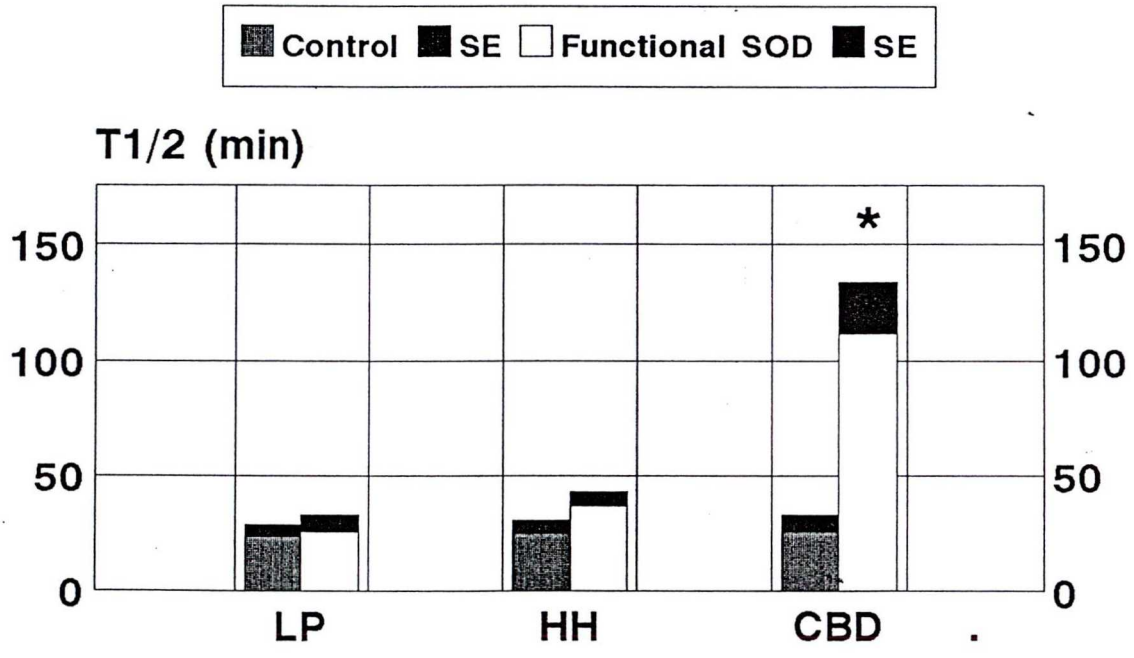


* p<0.05

Figure 1

$T_{1/2}$ calculated from the ROI over the CBD in the control group and in the 9 patients with structural SOD.

Figure 2

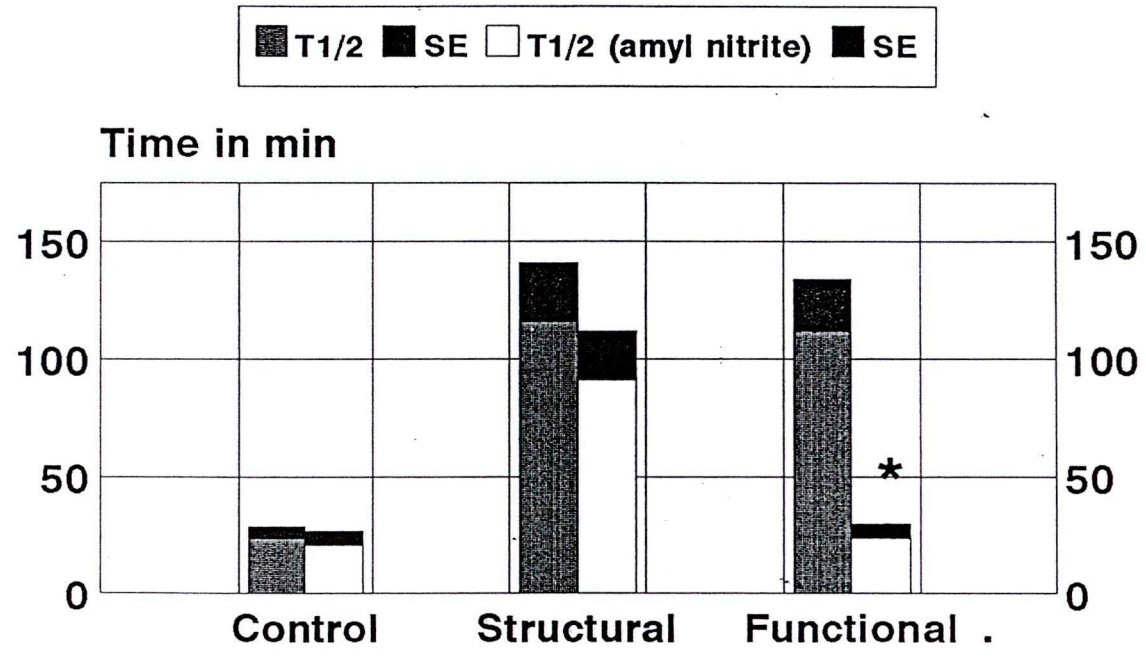


* p<0.05

Figure 2

$T_{1/2}$ calculated from the ROI over the CBD in the control group and in the 13 patients with functional SOD.

Figure 3



* p<0.05

Figure 3

$T_{1/2}$ of the CBD in control group and in patients with structural or functional SO dyskinesia. Note the significant decrease after amyl nitrite administration in patients with functional SOD.

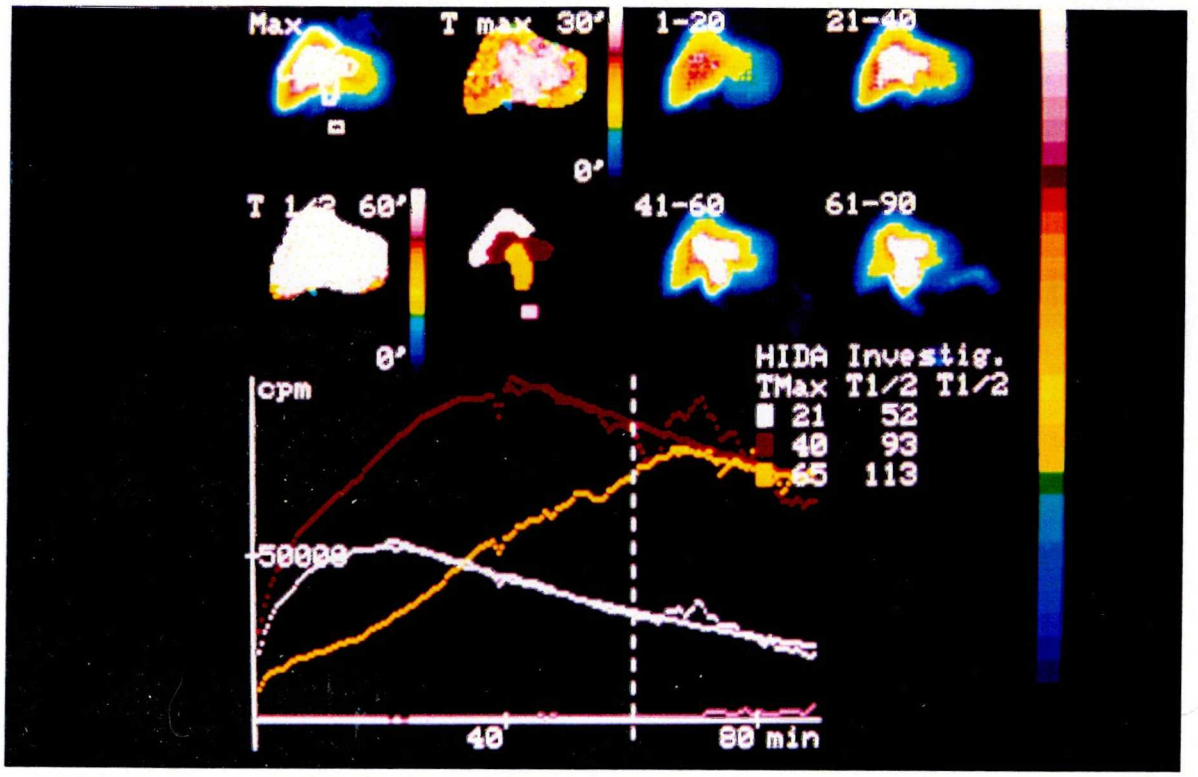


Figure 4

Representative QHBS recording for a patient with structural SOD. Amyl nitrite administration did not cause an acceleration of the transpapillary bile flow; the slope of the time-activity curve over the CBD remained unchanged (yellow line).

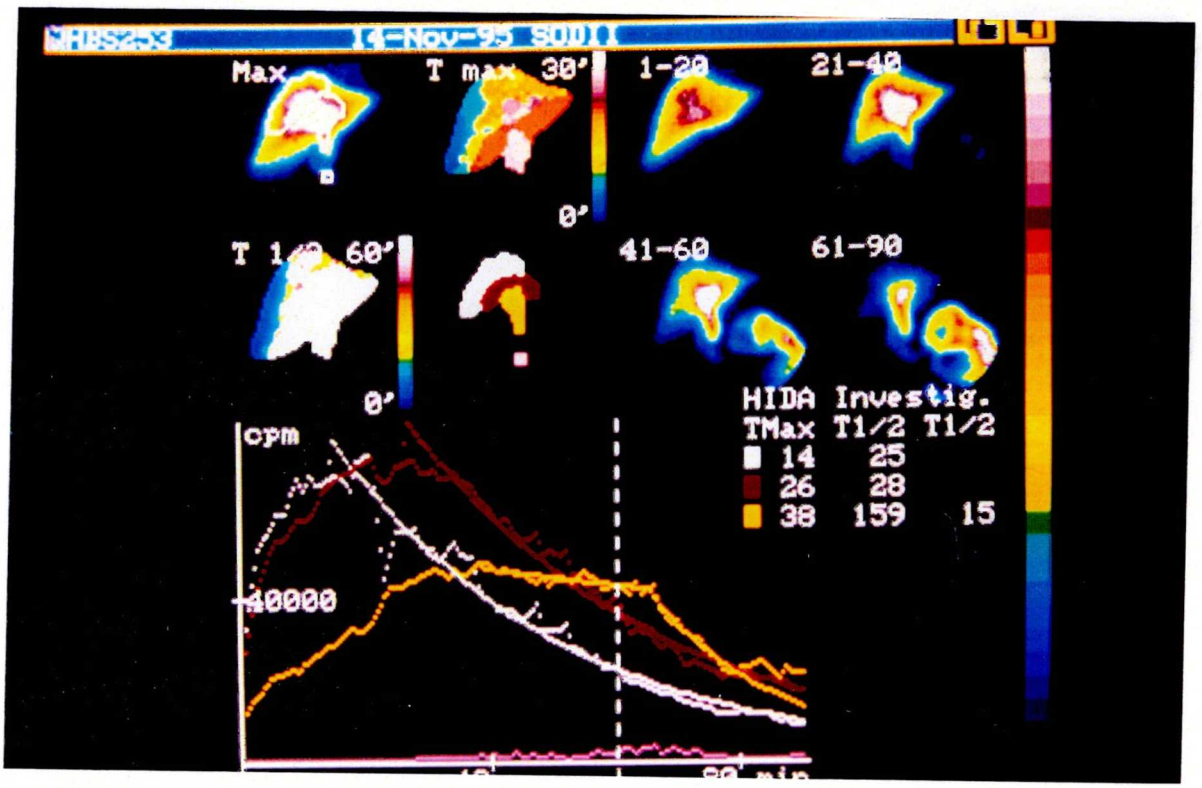


Figure 5

Representative QHBS recording for a patient with functional SOD. Amyl nitrite administration caused a marked acceleration of the transpapillary bile flow, as seen from the change in slope of the time-activity curve over the CBD (yellow line).

Morphine

Morphine was used during the Nardi test (10) together with prostigmine in 22 female cholecystectomized patients with suspected SOD, in whom QHBS showed free transpapillary flow. The results of the basic study (without provocation) performed 2 days previously served as controls in each patient. Subjective complaints were recorded and the serum aspartate aminotransferase (AST) levels were determined at the beginning and 2, 4 and 6 h following morphine administration.

Twelve of the 22 patients responded to prostigmine-morphine administration with typical biliary pain and an AST elevation. In all 12 patients, T_{max} and $T_{1/2}$ calculated from the ROIs over the LP, HH and CBD were significantly higher as compared to the data from the control study (Figure 6). The time-activity curves over the CBD demonstrated a characteristic obstructive pattern, and no bowel activity appeared until the 60 min (Figure 8). The AST levels were significantly increased in all 12 patients.

Four of the remaining 10 patients experienced abdominal pain during prostigmine-morphine provocation, but none of them exhibited significant AST changes. In these 10 patients, 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 (Figure 7). 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. On the basis of the QHBS and AST determination results, the provocation test was considered negative in these 10 patients (Figure 9).

The QHBS results in the Nardi-positive and negative groups differed significantly. Such marked differences in the quantitative parameters of QHBS allow an objective prediction of the result of the prostigmine-morphine provocation test.

Morphine and NO donors

In 9 female cholecystectomized Nardi-positive patients we combined QHBS and the Nardi test with continuous administration of GTN (Nitrolingual infusion). In this study, the data of the basic examination and the quantitative parameters of QHBS during the Nardi test served as controls in each patient.

In the absence of prostigmine-morphine provocation, QHBS demonstrated a free transpapillary passage in all 9 patients. Prostigmine-morphine provocation caused significant increases in T_{max} over the HH and CBD and in $T_{1/2}$ over the LP, HH and CBD, demonstrating a marked inhibition of transpapillary flow at the level of the SO (Figure 10). The sphincter spasm induced by prostigmine-morphine administration was associated with the appearance of biliary pain and a substantial AST level elevation (Figure 11). The increased QHBS parameters were completely normalized by GTN infusion (Figure 10). GTN not only prevented the prostigmine-morphine-induced SO spasm, but also completely abolished the appearance of subjective complaints and AST level elevations (Figures 11 and 12).

Figure 6

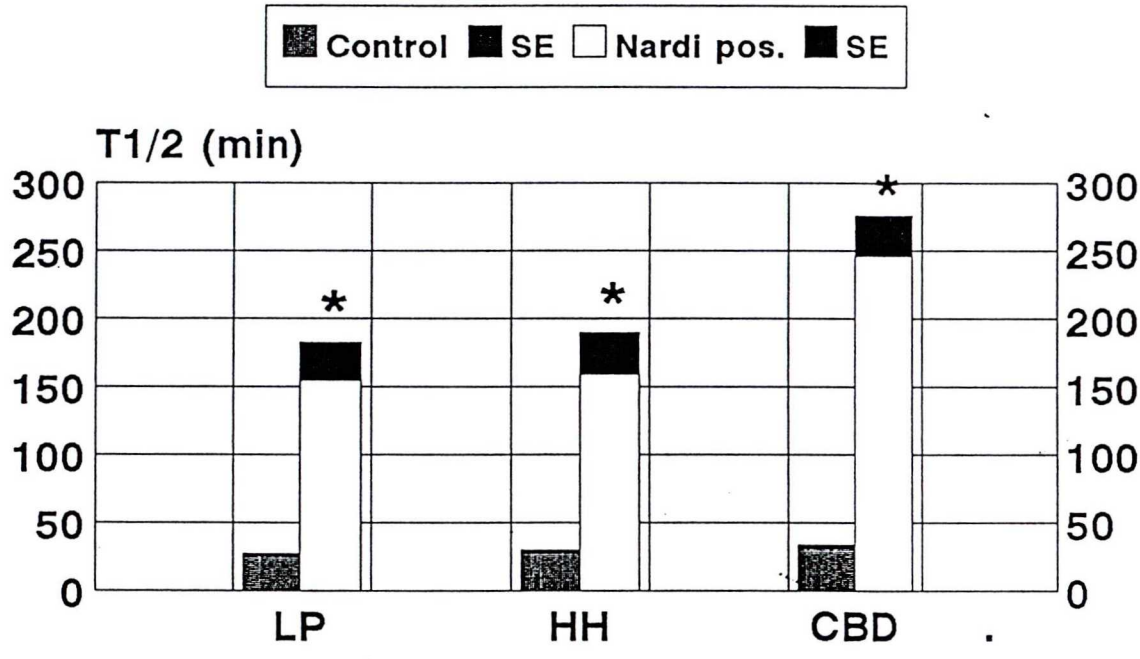


Figure 6

$T_{1/2}$ in the control group and in patients giving a positive Nardi test. Significant increases are seen in $T_{1/2}$ calculated from ROIs over the LP, HH and CBD.

Figure 7

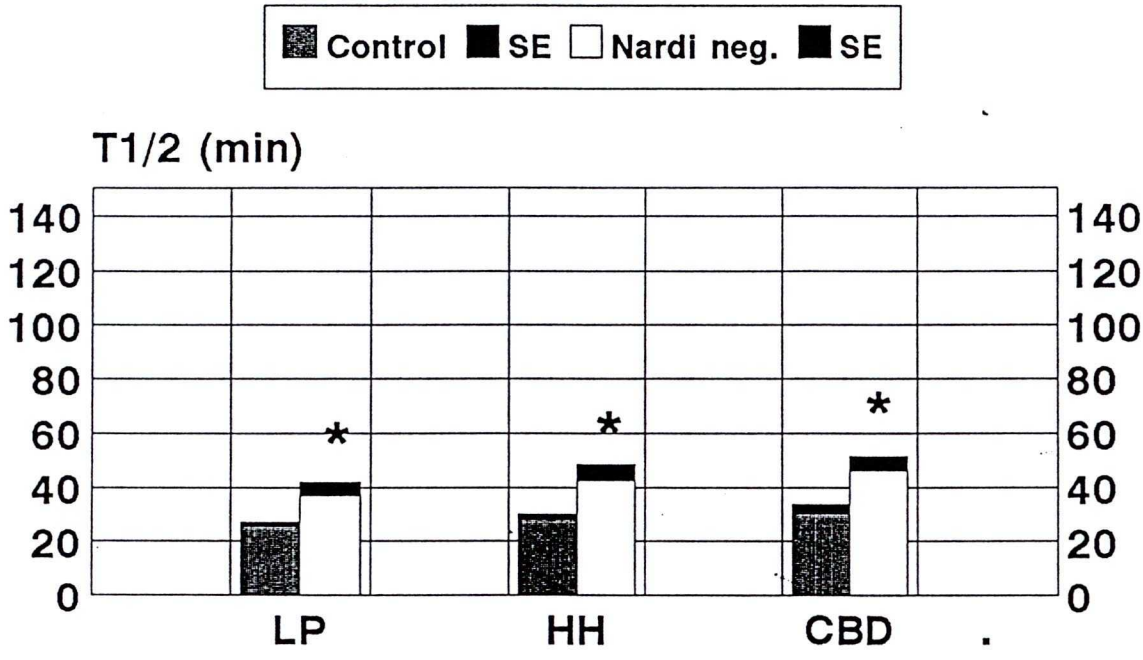


Figure 7

$T_{1/2}$ in the control group and in patients giving a negative Nardi test. The increases in $T_{1/2}$ calculated from ROIs over the LP, HH and CBD are significant as compared to the controls, but far less explicit than in patients giving a positive Nardi test.

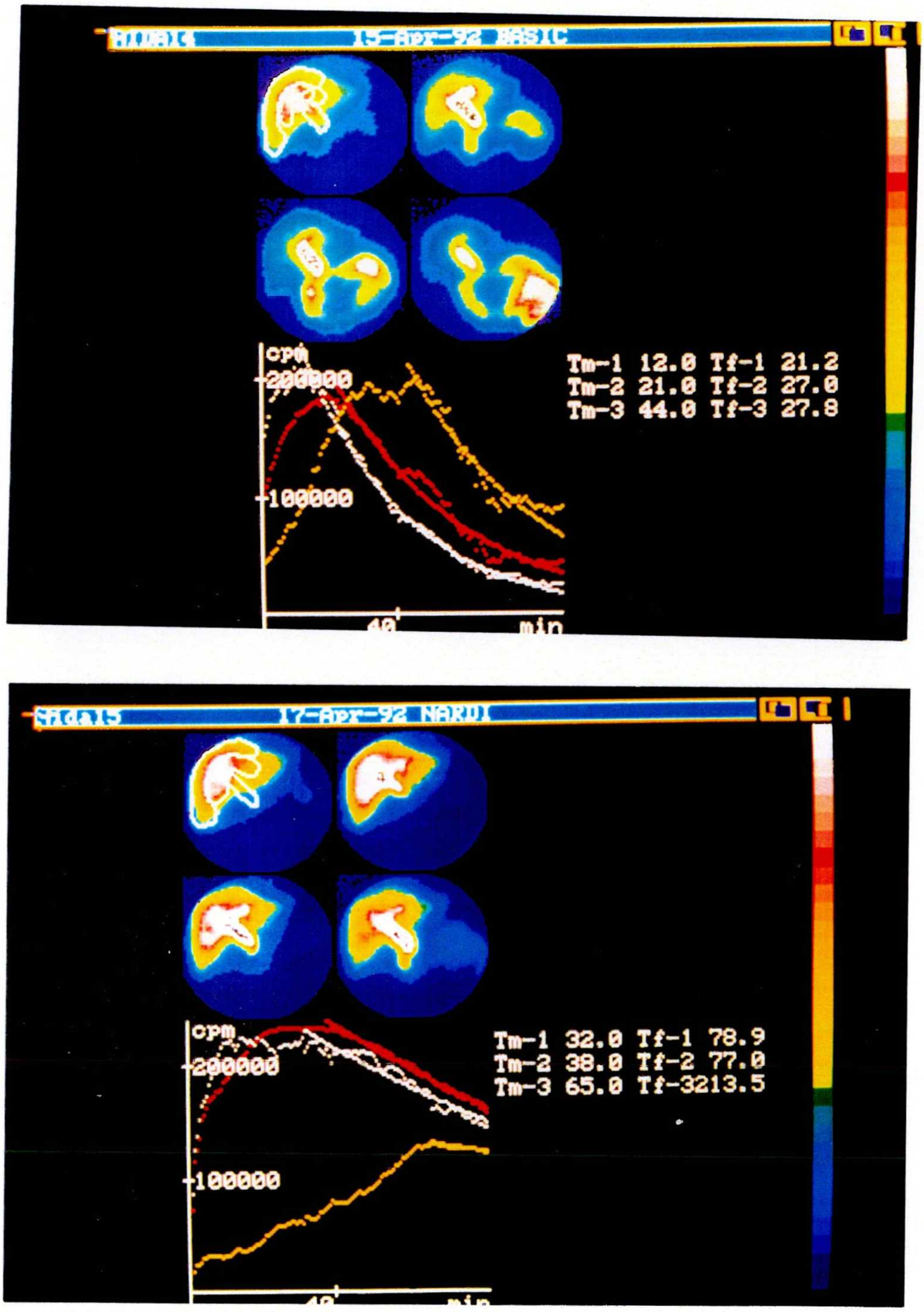


Figure 8

Representative QHBS recording for a patient during the basic study (upper panel) and during the Nardi test (lower panel). In the basic study, free transpapillary flow is shown (yellow line): $T_{1/2}$ over the CBD is normal. During the provocation test, QHBS demonstrates a marked accumulation of the radiotracer in the CBD: no bowel activity is seen until the end of the study. The Nardi test is considered positive.

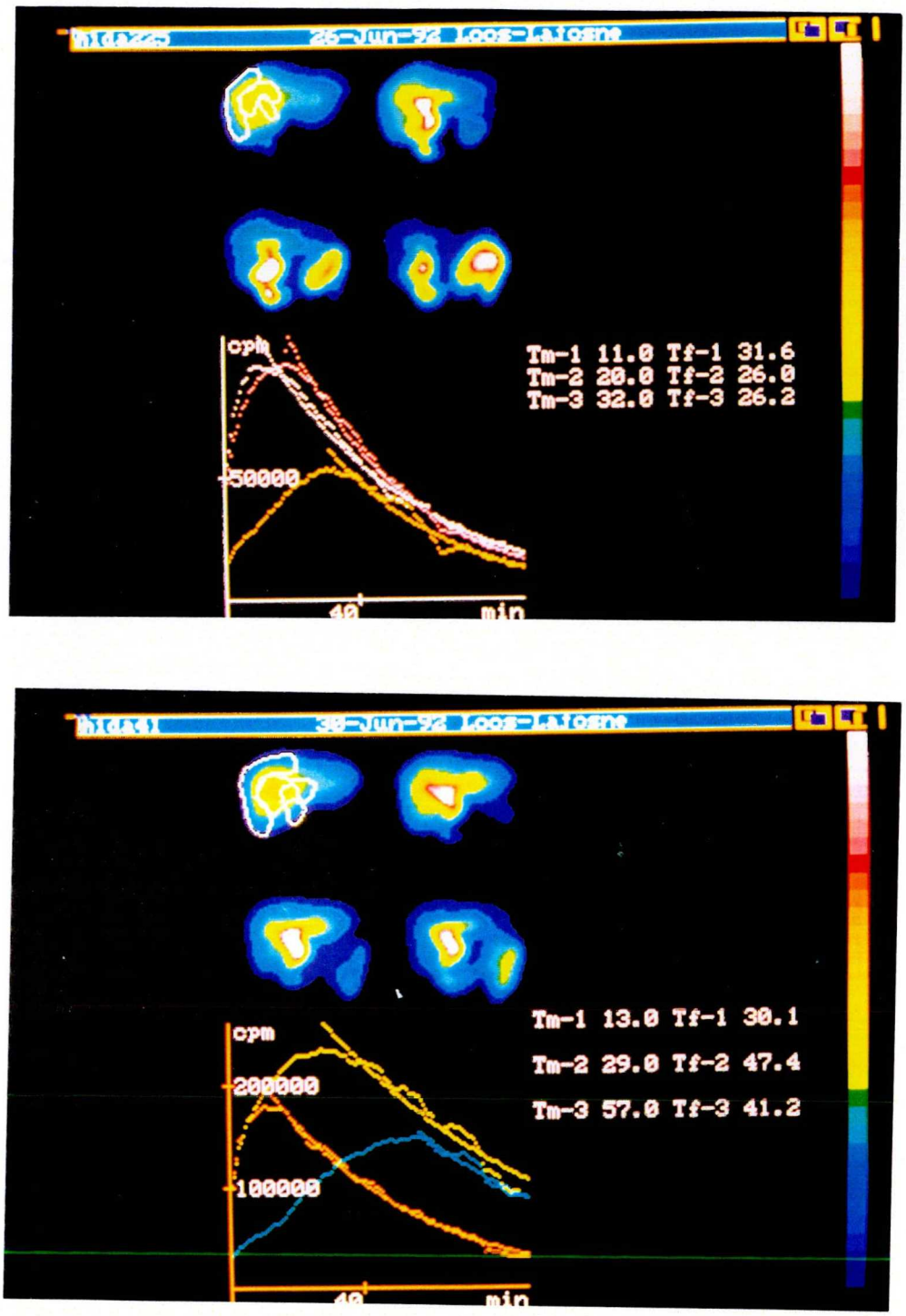
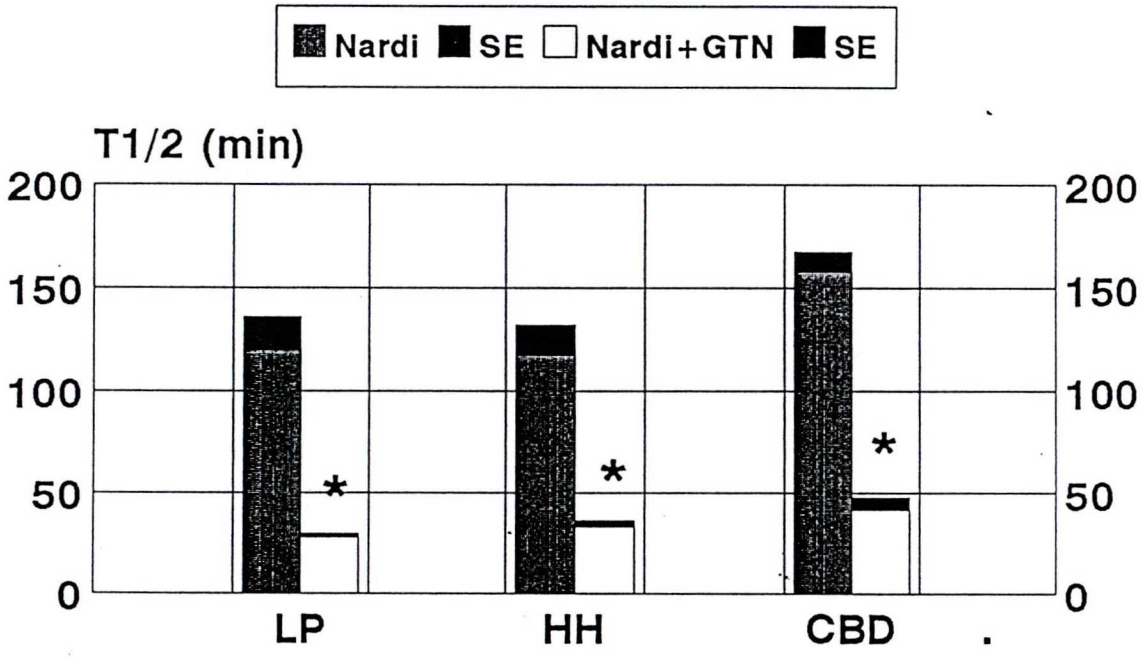


Figure 9

Representative QHBS recording for a patient during the basic study (upper panel) and during the Nardi test (lower panel). In the basic study, free transpapillary flow is shown (yellow line): $T_{1/2}$ over the CBD is normal. During the provocation test, QHBS demonstrates a slower, but free passage of the radiotracer in the CBD. The Nardi test is considered negative.

Figure 10



p<0.05

Figure 10

Effect of GTN infusion on $T_{1/2}$ during the Nardi test. In the presence of GTN, $T_{1/2}$ decreased significantly or even normalized over all the ROIs observed.

Figure 11

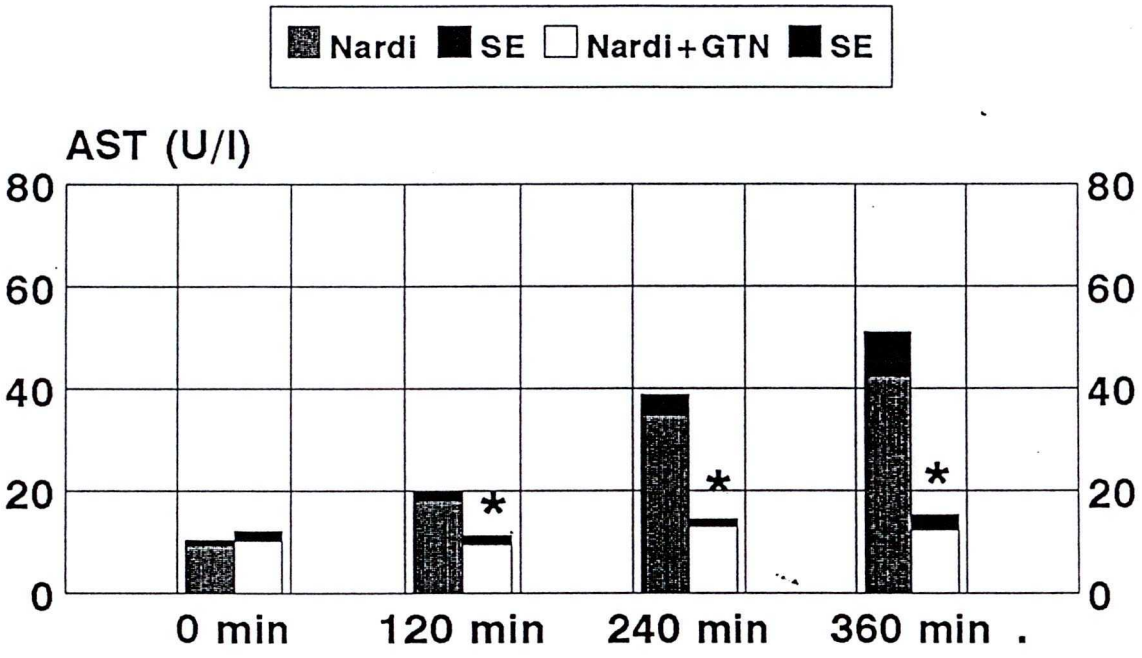


Figure 11

Effect of GTN infusion on serum AST levels during the Nardi test. In the presence of GTN, no increase in AST levels was observed.

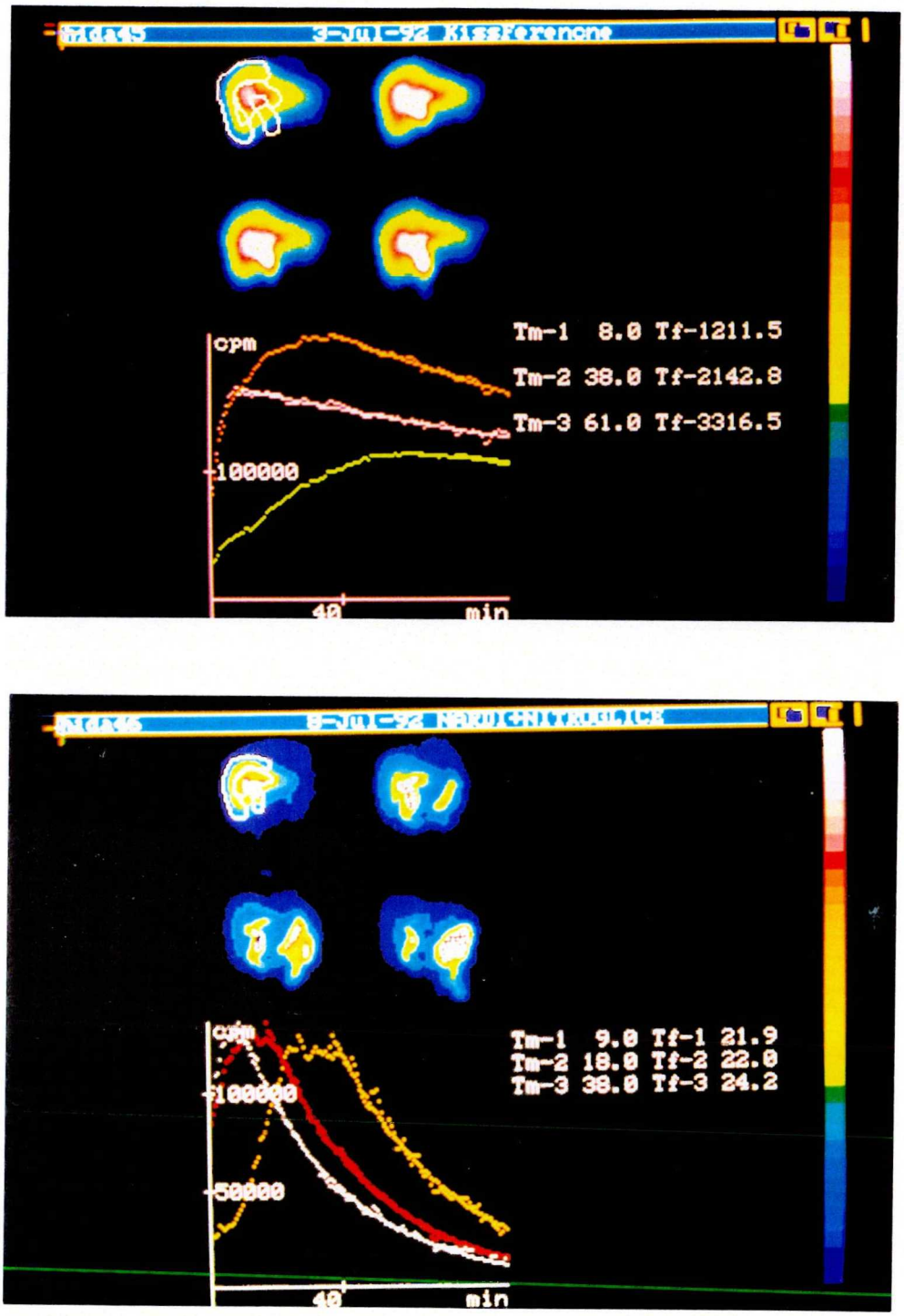


Figure 12

Representative QHBS recording for a patient during the Nardi test (upper panel) and during the Nardi test in the presence of GTN (lower panel). During the provocation test, a typical accumulation pattern is seen: $T_{1/2}$ is significantly increased. In the presence of GTN, the transpapillary passage is free: all the parameters are within the normal limits.

Somatostatin

Both native SOM and its long-acting analogue OCT were used. Fifteen female cholecystectomized patients were studied, 6 in the SOM group and 9 in the OCT group. QHBS revealed that 7 of the 9 patients in the OCT group, and 1 of the 6 patients in the SOM group exhibited a normal transpapillary bile transit in the basic study; the remainder of the patients (2 in the OCT group and 5 in the SOM group) had a slightly elevated $T_{1/2}$ over the CBD, but after GTN administration $T_{1/2}$ was normalized in all patients.

In the OCT group, $T_{1/2}$ over the HH and CBD were significantly increased during OCT administration as compared with the controls (Figure 13). After GTN administration, $T_{1/2}$ over the CBD decreased significantly as compared with the pre-GTN data, bud did not reach the level observed in the basic study (Figures 14 and 17).

In the SOM group, QHBS demonstrated an "accumulation pattern" in all patients during SOM administration, i.e. until 60 min no bowel activity was observed and $T_{1/2}$ over the CBD reached 180 min in all patients (defined as a maximum). Similarly as in the OCT group, $T_{1/2}$ over the HH was also significantly increased. After GTN administration, a marked decrease in $T_{1/2}$ over the CBD was seen in all patients (Figures 15 and 16).

CCK and NO donors

This study was carried out in patients with an intact GB, but typical acalculous biliary type pain. QHBS was performed in 33 female patients under the same conditions as described for the basic study, but the imaging period lasted for 120 min instead of 90 min. At the 60th min of QHBS, 10 ng/kg/min caerulein was administered intravenously for 10 min. At the 90th min, caerulein administration was repeated, but in 21 of the 33 patients in the presence of GTN (the patients received 1 tbl. Nitromint sublingually at the 85th min of QHBS). Time-activity curves were generated from the ROI over the GB and the GBEF was calculated after both the first and the second cerulein administration.

Ten of the 33 patients had a well-functioning GB, i.e. the GBEF after cerulein administration exceeded 35% (the limit regarded as normal). Five of these 10 patients received GTN together with the second dose of cerulein. The co-administration of cerulein and the NO donor caused a further increase in GBEF, with a significant difference between the first and second stimuli (Figure 18).

The remaining 23 of the 33 patients had a GBEF less than 35% after the first dose of cerulein. In 16of the 23 patients, co-administration of cerulein and GTN improved or normalized the previously impaired GB emptying, with significant differences between the GBEF observed after the first and the second cerulein administration (Figures 18 and 19).

Figure 13

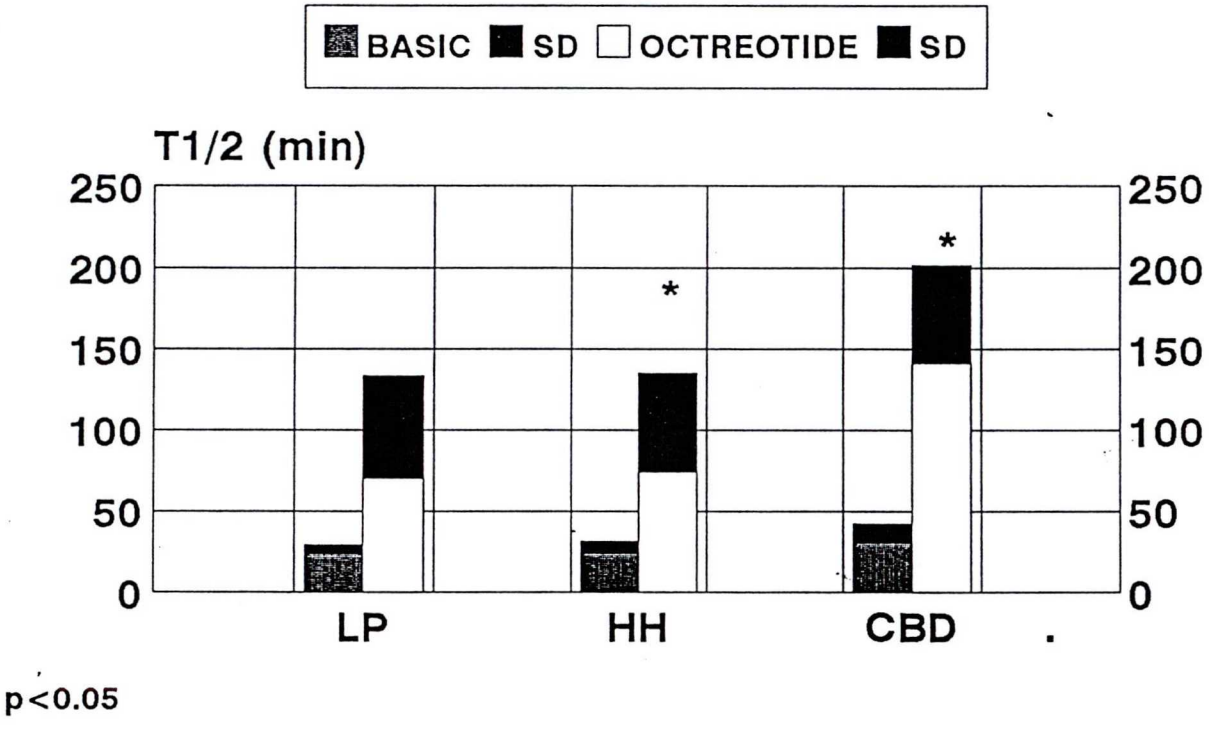
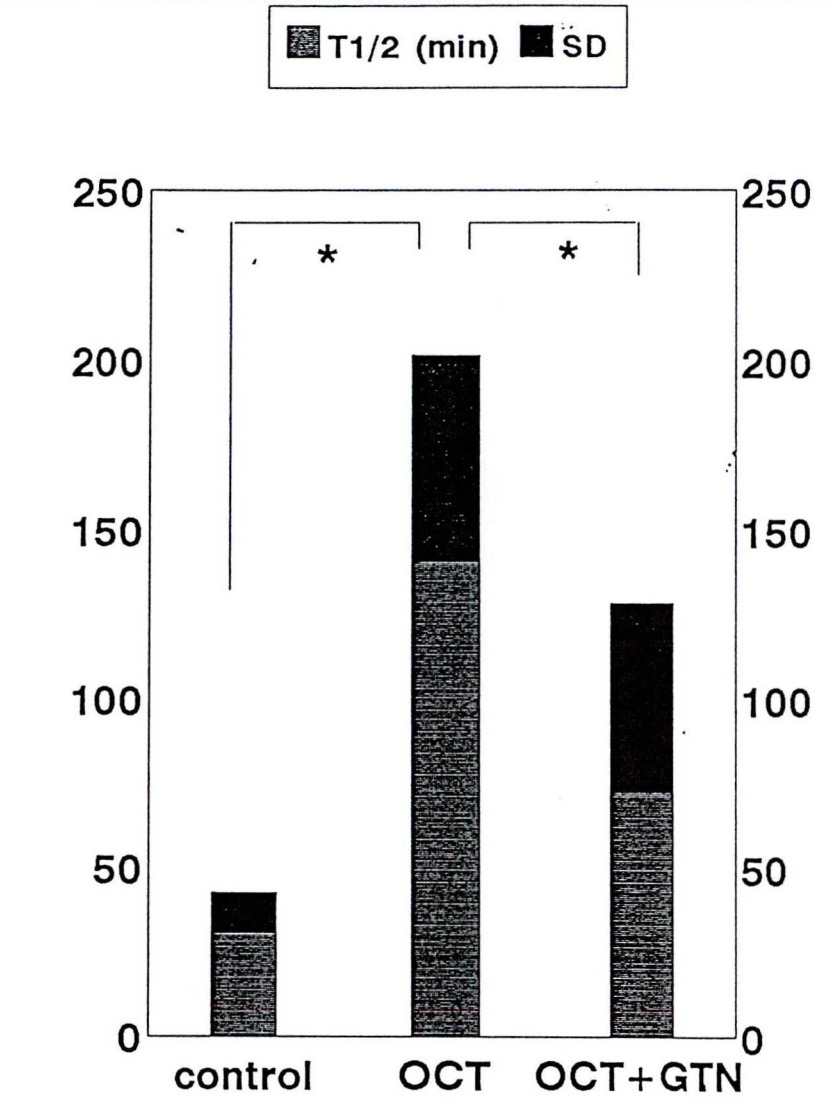


Figure 13

Changes in $T_{1/2}$ on QHBS during the basic study and in the presence of OCT. Note the significant increases in $T_{1/2}$ over the HH and CBD during OCT administration.

Figure 14



* p<0.05

Figure 14

Comparison of changes in $T_{1/2}$ over the CBD during the basic study (control) and in the presence of OCT. Note the significant decrease in $T_{1/2}$ during co-administration of OCT and GTN.

Figure 15

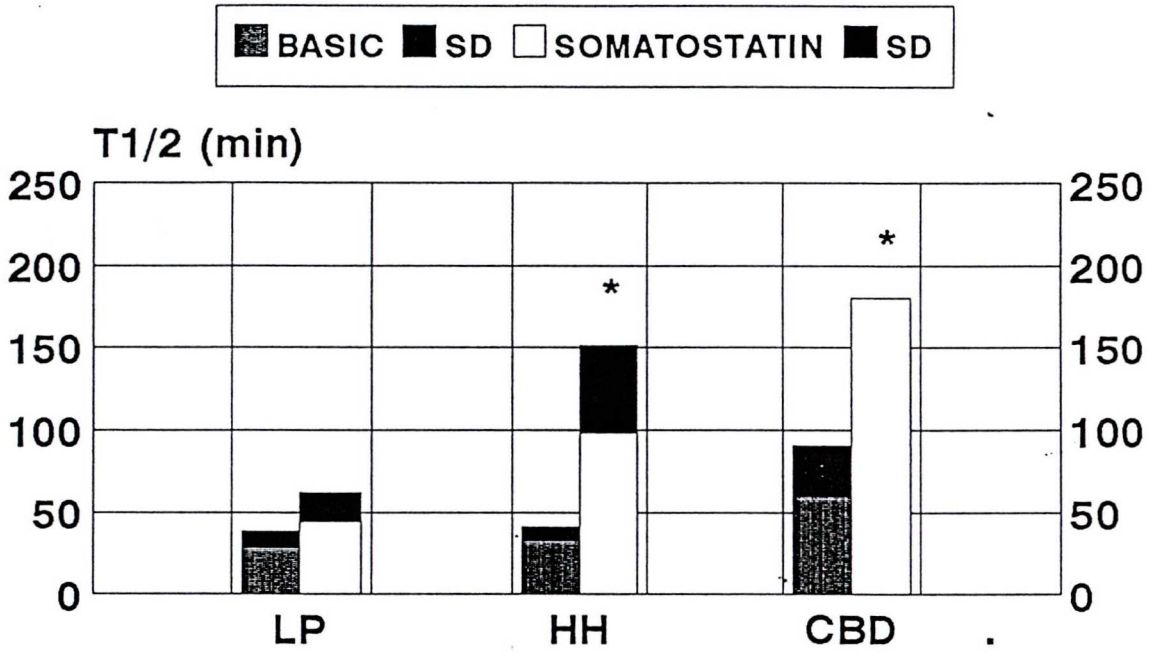


Figure 15

Changes in $T_{1/2}$ on QHBS during the basic study and in the presence of SOM. Note the significant increases in $T_{1/2}$ over the HH and CBD during SOM administration.

Figure 16

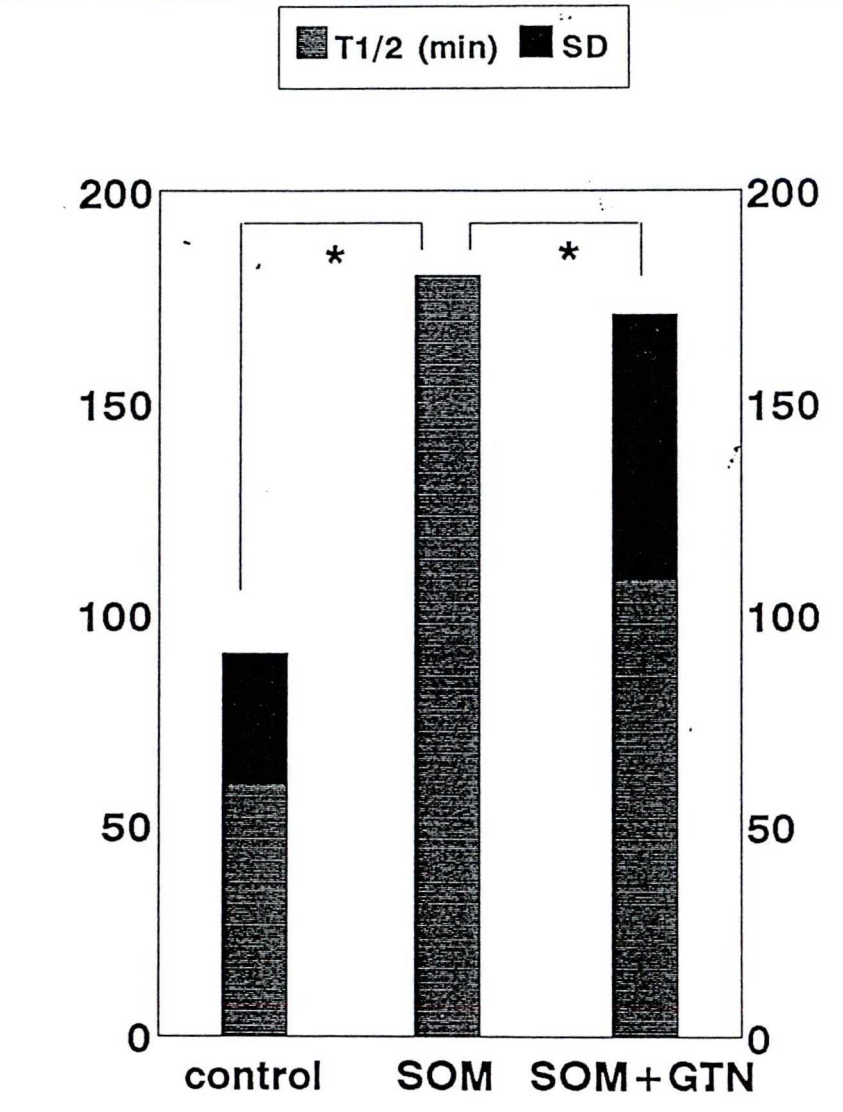


Figure 16

Comparison of changes in $T_{1/2}$ over the CBD during the basic study (control) and in the presence of SOM. Note the significant decrease in $T_{1/2}$ during co-administration of SOM and GTN.

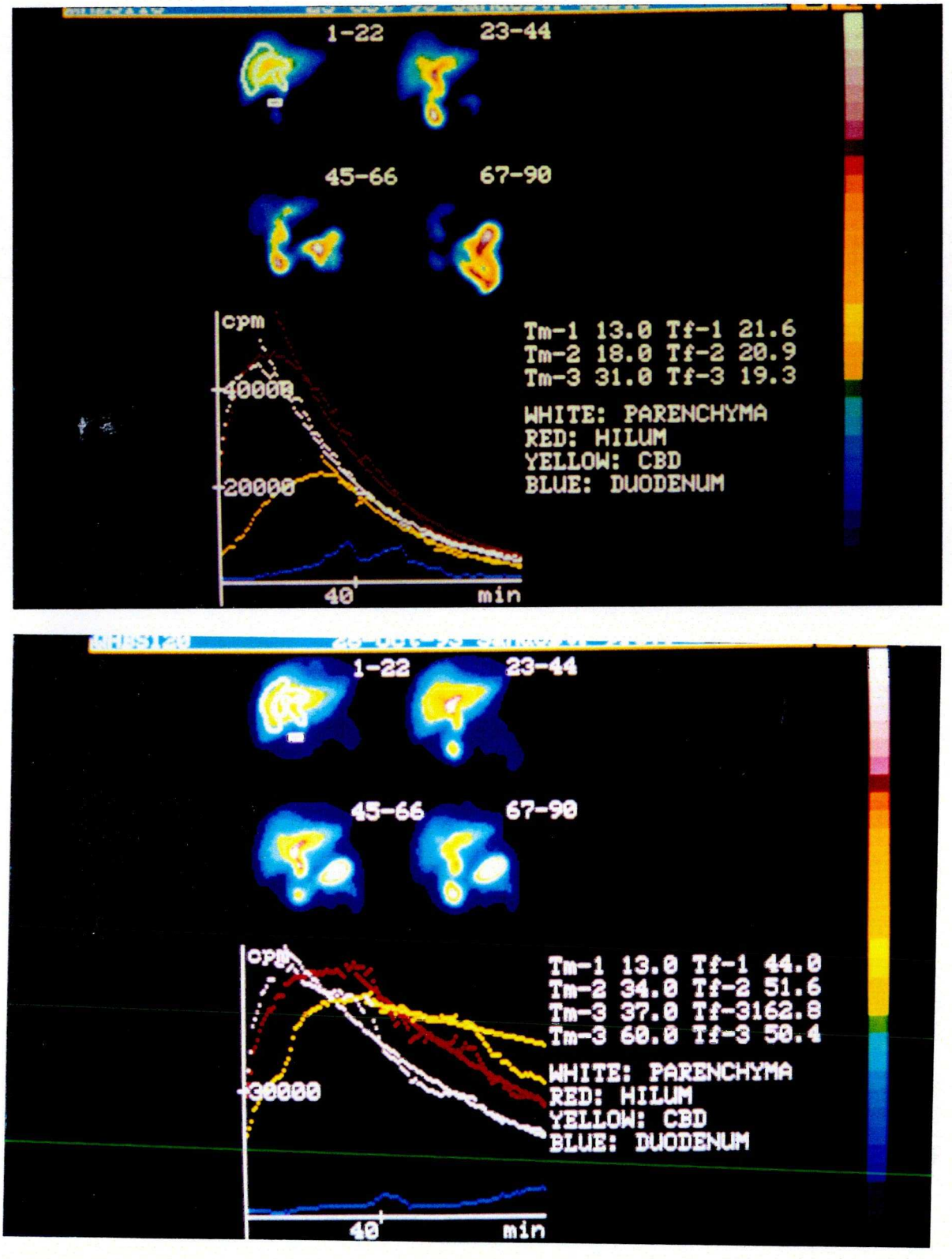


Figure 17

Representative QHBS recording for a patient during the basic study (upper panel) and in the presence of OCT (lower panel). OCT causes a typical accumulation pattern (yellow line), and $T_{1/2}$ over the CBD is significantly increased. After the administration of GTN at the 60th min, the transpapillary passage of the radiotracer accelerates, with a marked decrease in $T_{1/2}$.

Figure 18

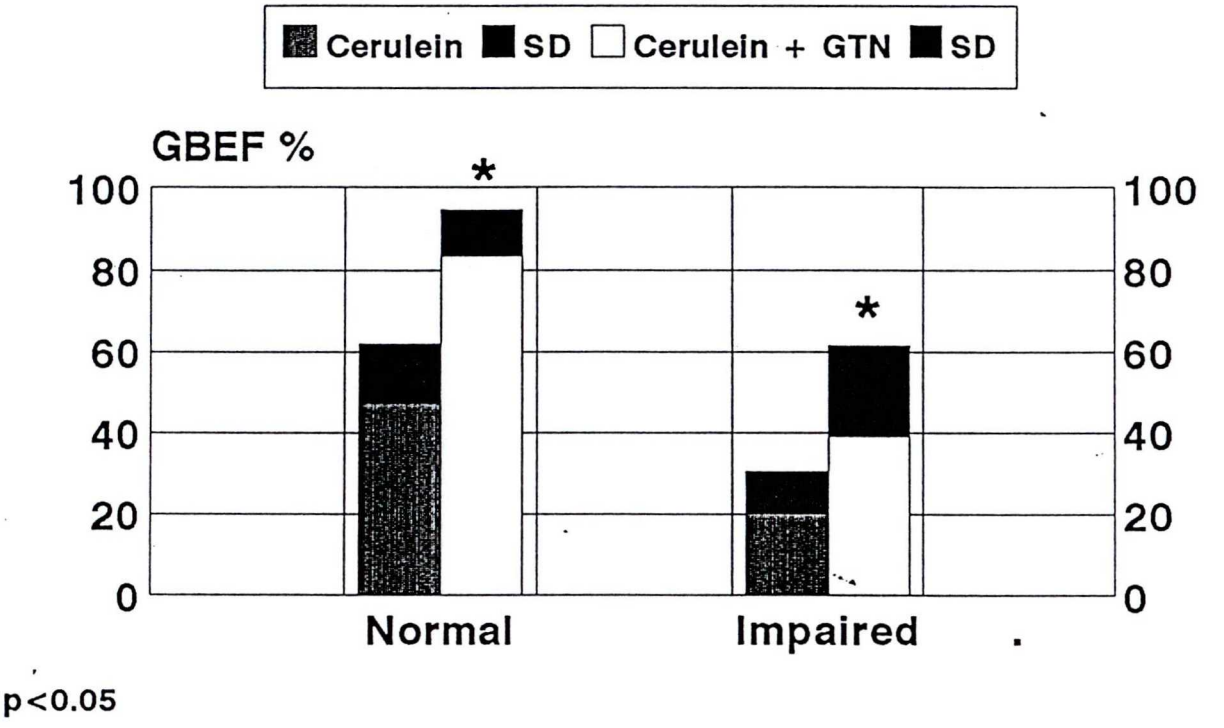


Figure 18

Effect of GTN co-administration on the cerulein-induced GBEF in patients with normal or impaired GB function.

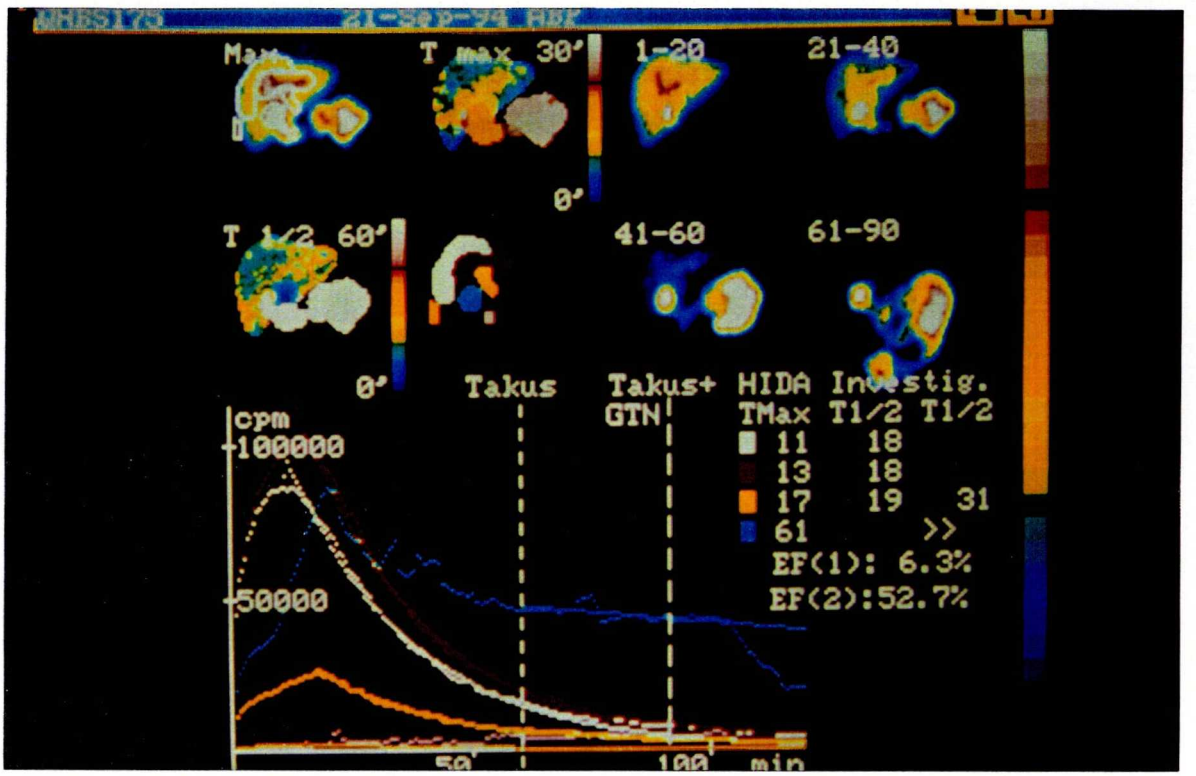


Figure 19

Representative QHBS for a patient with acalculous biliary pain and intact GB. Cerulein (Takus) administration caused only an impaired GBEF (blue line), while repeated administration of the same dose of Takus in the presence of GTN resulted in a normal GBEF (52.7%).

DISCUSSION

The diagnosis of SO dyskinesia is still an unresolved question in clinical gastroenterology. Endoscopic SO manometry has proved to be a widely-accepted and appropriate method for the differentiation of SOD of types I and II, whereas in patients with SOD of biliary type III this method has turned out to be poorly reproducible. Accordingly, other non-invasive methods, including provocation tests, still have their place in the diagnostic strategy of SO dyskinesia.

The original methodology of QHBS proved to be a valuable non-invasive tool for visualization of the bile flow. Our modifications of the basic method provided a possibility to study the effects of different compounds on the SO, i.e. to measure the changes in the speed of the transpapillary bile flow. Our search for drugs which could affect the SO motility in humans led us to test NO donors.

In 1987, it was demonstrated that the biological activity of the endothelium-derived relaxing factor, discovered by Furchgott and Zavadzki in 1980 (11), was in fact due to NO release (12) This endogenously synthesized gas has many important effects in regulating the vascular tone, in the pathophysiology of inflammation, in platelet aggregation, in the central nervous system and in control of the smooth muscle tone (13). The latter is one of the most important effects of NO seen in the gastrointestinal (GI) tract.

Three NO synthases have been described, an endothelial isoform (eNOS), a neuronal isoform (nNOS) and an inducible isoform (iNOS), the latter located mainly in macrophages. Two of these isoforms, eNOS and nNOS, are constitutive and calcium-calmodulin-dependent, while iNOS can be activated by cytokines and endotoxins. In biological systems, NO has a half-life of less than 5 sec; the biological actions are rapidly terminated by binding to oxyhaemoglobin or other haeme-containing proteins, but iNOS triggered by endotoxin or cytokines is able to produce NO for many hours without further stimulation. This phenomenon may be one of the factors responsible for the hypotension observed in toxic shock or liver cirrhosis (14).

Endogenous NO production occurs via an enzymatic pathway from L-arginine; it then binds to soluble guanylate cyclase and cause increase in cGMP production, with subsequent

relaxation of the smooth muscle (15). Recent findings in rabbits and guinea pigs have shown that the L-arginine-NO pathway has an important role in regulation of the GB contraction and the SO tone, and NO is produced locally by a constitutive NOS (14, 16).

Nitrovasodilators have been used in medical practice since 1879, originally for the treatment of angina pectoris. The action of these drugs is dependent on the release of NO, which may occur spontaneously or may require enzymatic reduction (17). Nitroglycerine (GTN) may be considered the prototype of this group of drugs.

In 1983, Bar-Meir et al. (18) reported a case with a papillary dysfunction, in which the patient responded to nitrate therapy with disappearance of the pain and decreases in both basal and phasic sphincter activity, as proved by endoscopic manometry. Staritz et al. (19) and Brandstatter (20) also demonstrated the SO-relaxing effect of GTN during endoscopic manometry in patients with biliary complaints. However, no literature data were available as to whether GTN affects the transpapillary bile flow in humans when it is given alone or in combination with other compounds.

Our results revealed that the administration of exogenous NO donors influences the motility of the human SO considerably.

Amyl nitrite-augmented QHBS permitted non-invasive differentiation between organic stenosis and functional motor abnormalities of the SO. These results indicated that there is a possibility to differentiate the group of patients who could benefit from endoscopic sphincterotomy (organic stenosis) and those in whom medical therapy should be the first choice (functional disorder). The clinical use of long-acting nitrates might be of relevance in the treatment of functional SO dyskinesia, but for an estimation of the long-term results controlled clinical trials are needed.

The SO-contracting effect of morphine in humans has been reported by many authors (5, 21). In clinical practice, provocation tests, e.g. the Nardi test, are based on the effect mentioned above (10). These tests have been criticized because of their low specificity. Simultaneous measurement of the changes in the serum AST levels improved the specificity, but the development of subjective complaints hampered the establishment of a clear decision between the positive and negative cases. Combination of the Nardi test with QHBS provided a possibility for visualization of the changes in the transpapillary bile flow in a non-invasive

manner and permitted the differentiation of patients with a prolonged, vigorous SO spasm from patients in whom only the "physiological effect" of morphine was seen at the level of the SO.

The administration of GTN during the Nardi test demonstrated clearly that the effect of this exogenous NO donor was able to overcome even the prostigmine-morphine-induced SO spasm and it also completely abolished the appearance of subjective complaints and AST level elevations in all patients. These data strengthen the hypothesis that nitrates could be very useful drugs in the treatment of motility disorders caused by intermittent spasm of the SO.

SOM plays an important regulatory role in the human GI tract, suppressing the release of several GI hormones, including CCK, pancreatic polypeptide, secretin, gastrin, insulin and glucagon, or inhibiting the effects of these substances. Since the discovery of its long-acting analogue OCT the two compounds have been widely used in the treatment of various GI diseases (22). OCT treatment is considered to be very effective in the case of hormone-producing GI tumours, e.g. VIP-omas (23). Similarly, in the treatment of variceal bleeding, both SOM and OCT have a beneficial effect equivalent to that of endoscopic sclerotherapy, and the rates of complications are even less (24). In contrast, in the therapy of acute or post-ERCP pancreatitis, the results of SOM treatment remain controversial and multi-centre trials have failed to prove its beneficial effect (25-27). One of the most important side-effects of long-term OCT treatment is gallstone formation. The cause of this phenomenon could be the altered bile formation, or the decreased GB motility, as a consequence of the inhibitory effect of SOM on the GB motility or CCK release (28-30). The study by Binmoeller et al. revealed that OCT exerts a significant stimulatory effect on the human SO, as measured by endoscopic SO manometry (31). The beneficial effect of SOM in the prevention of post-ERCP pancreatitis led Jenkins and Berein (32) to conclude that this may be explained by the SO-relaxing effect of SOM observed in prairie dogs (33). Many authors have reported that SOM or its analogue OCT increases the SO basal pressure and phasic contractile activity (31, 34-37), but it was not clear whether these changes are associated with an impairment in the bile flow or not.

Our data indicated that both SOM and OCT cause a marked inhibition of the bile flow as measured by QHBS. The fact that a significantly increased $T_{1/2}$ (which is the best indicator of the speed of bile flow during QHBS) was seen mainly in the distal part of the biliary tree, i.e. the HH and CBD, but not the LP, suggests that the effects of SOM compounds on the excretion of bile are far less explicit than the inhibitory effects at the level of the CBD, which is

caused by the prolonged contraction of the SO. The SO spasm caused by either OCT or SOM was resolved by co-administration of GTN, as indicated by a significantly accelerated transpapillary bile flow, seen on QHBS. Our results confirm that the most important effect of SOM compounds on the biliary tract is a prolonged spasm at the level of the SO, and also suggest a possible therapeutic use of NO donors together with SOM compounds in the treatment of acute or post-ERCP pancreatitis.

There are a number of patients who have typical biliary pain, but no gallstones are found in the biliary tree. This pain is called "acalculous biliary pain" and many disorders may be responsible for its development, e.g. chronic cholecystitis, cystic duct abnormalities or motility disorders of the SO or GB or both. The cause of GB dyskinesia is thought to be the uncoordinated contraction of the GB neck area with an impaired GB emptying. The "cystic duct syndrome" was first described as a clinical entity with an organic background (fibrosis, kinking, etc.), but later a purely functional disorder was also suspected (38, 43). Hepatobiliary scintigraphy has been introduced in the diagnostic procedure for these patients, but the low GBEF did not predict the clinical outcome after elective cholecystectomy; on the basis of the original method, it was not possible to select patients with organic or functional disease (39).

Our data have revealed, that patients with acalculous biliary pain may exhibit either normal or impaired GB emptying after CCK stimulation. However, there are several patients with low GBEF, in whom the co-administration of NO donors with a second dose of the CCK analogue caerulein caused a significant increase in GBEF, suggesting a functional disorder of the biliary tree. Other authors have demonstrated, that the repeated administration of CCK (without other drugs) did not cause any changes in GBEF (40). The question remains open as to whether the "isolated" dysfunction of SO, the GB or a complex motility disorder of both is responsible for the development of acalculous biliary pain, but our results have provided the first evidence of a pure motility disorder in the background of the cystic duct syndrome in humans (41).

All the results mentioned above suggest the beneficial effects of NO donors in various motility disorders. Nevertheless, the unquestionable effect of NO could be altered by other factors. Our colleagues working on basic scientific research have demonstrated an impaired nitrergic relaxation of the SO of hypercholesterolaemic rabbits (42). In a case report, we described an impaired SO relaxation function in a patient with hypercholesterolaemia and

hypertriglyceridaemia. After a 3-month treatment with dietary restrictions and 20 mg lovastatin per day, the serum lipid levels of the patient were normalized, and there was an improvement in the relaxation function of the SO during QHBS after GTN administration. (No. III). This case report also demonstrates the complexity of the factors that can affect the motility of the biliary tree.

In conclusion, our results may be summarized with the following statements: It was possible to find a non-invasive method for the differentiation of patients with organic or functional disorders of the SO. QHBS is considered to be a useful method for visualization of the transpapillary bile flow and allowed measurements of the effects of many compounds on the SO. We have demonstrated the beneficial effects of NO donors on the motility disorders of the GB and SO in many circumstances. Our findings suggest that the use of nitrate compounds may be of relevance in the long-term treatment of motility disorders of the human biliary tract. We hope that our results will promote further research work in this field.

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