Sphincter of Oddi dysfunction

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INTRODUCTION
Endoscopic retrograde cholangiopancreaticography (ERCP) was introduced in the seventies in Europe and Japan and has become an essential diagnostic and therapeutic tool for a number of biliary and pancreatic diseases. It allows us to define and alter sphincter anatomy. With refinement in the measurement of luminal pressures, it has become possible to record the manometric characteristics of the sphincter of Oddi (SO) in normal individuals and in patients with different diseases. Evidence has accumulated that a subgroup of patients with unexplained biliary and pancreatic symptoms have abnormal SO pressures or abnormal responses to pharmacological agents. This subject has stimulated considerable research into whether or not the sphincter of Oddi actually exists. Results of research over the last few years are in favour of clinical syndromes of sphincter of Oddi dysfunction and this evidence is presented in the following review.

ANATOMY AND PHYSIOLOGY
The major duodenal papilla is a smooth, nipple-like elevation on the postero-medial wall of the second part of the duodenum.1 The papillary orifice is located at the summit of the papilla of Vater. Biliary and pancreatic ducts in the papillary region are invested by specialized circular and longitudinal muscle fibres interdigitating with the juxta-ampullary fibres of the duodenal wall. This area, extending from 4 to 6 mm, is the sphincter of Oddi. The sphincter maintains a high pressure (about 5 mm Hg above the common bile duct pressure) and superimposed on the resting pressure are rhythmic phasic waves which occur at a frequency of 4 to 6 per minute. The SO works like the cardiac muscle and allows filling of the intrasphincteric segment during diastole (resting interphasic period) and empties its contents during systole (phasic contraction). Bile flow will be enhanced if the basal pressure is low, the frequency of phasic contractions is increased (tachyoddia), and the phasic contractions are of high amplitude. The bile flow is impeded if the basal pressure is elevated, the phasic contractions are few and of low amplitude, and the frequency of phasic contractions is markedly increased to reduce filling—a condition simulating the low cardiac output state in tachyarrhythmias.

MANOMETRY
Sphincter of Oddi manometry is performed in a conscious patient under light sedation without prior use of hyoscine butylbromide.2 The patient is advised to fast overnight, and to stop medication as this may alter the pressure profile. Forty-eight hours prior to the procedure, the papilla is visualized by a side viewing duodenoscope. The manometry catheter assembly is passed via the duodenoscope channel and the sphincter negotiated. Both bile and pancreatic ducts are entered separately and pressures recorded by a station pull-through technique in the ducts, across the SO and in the duodenum. Another catheter attached to the endoscope records the duodenal pressure continuously during the procedure. Each catheter is 1 mm in its outer diameter and has a side hole 0.8 mm in diameter made 5 mm from the blocked tip. The catheter is perfused by bubble-free water at a constant rate of 0.5 ml per minute. The pressure is recorded through a transducer on a pre-calibrated polygraph (Fig. 1). Earlier a single catheter was used to record ductal pressures but now the triple catheter assembly is used with side holes 2 mm apart. These catheters record sphincteric activity at three sites simultaneously to define whether peristalsis is antegrade, retrograde or simultaneous. Manometry records bile duct and pancreatic duct pressures as straight waves with mild undulations due to respiratory excursions. Once the catheter reaches the SO, the sphincteric activity is recorded as basal pressure with phasic activity (Fig. 2). Most of this phasic activity is antegrade as recorded by the multiple lumen catheter assembly. All pressures are calibrated with reference to a duodenal pressure of zero. At least three measurements are made and the pressures recorded are the mean of three readings. The various pressures usually obtained and their normal range are provided in Table I.

THE EFFECT OF PHARMACOLOGICAL AGENTS
The pharmacological agents whose effect on the SO has been studied include: morphine, nifedipine, hyoscine butylbromide (Buscopan) and nitrates.3,10-13 Morphine sulphate in a dose of 3 mg intravenously increases the frequency of phasic activity but has no measur-
Transducers

Precalibrated pressure app.

Catheters/Endoscope

Perfusion

Fig 1. SO manometric system.

SO manometry recording of a 25-year-old male without any gastrointestinal symptoms (D—duodenum).

Table I. SO manometry. Normal pressure values (all refer to a duodenal pressure of zero). Data collected from 12 volunteers

<table>
<thead>
<tr>
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<th>Pressure (mean ± 1SD)</th>
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<tr>
<td>BD—duodenal gradient</td>
<td>8.6 ± 1.2 mm Hg</td>
</tr>
<tr>
<td>PD—duodenal gradient</td>
<td>8.0 ± 2.0 mm Hg</td>
</tr>
<tr>
<td>SO Basal pressure</td>
<td>14.9 ± 1.0 mm Hg</td>
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<tr>
<td>SO Phasic contraction</td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td>53.0 ± 6.0 mm Hg</td>
</tr>
<tr>
<td>Frequency</td>
<td>6.5 ± 0.2/minute</td>
</tr>
<tr>
<td>Duration</td>
<td>6.0 second</td>
</tr>
<tr>
<td>Propagation %</td>
<td>55 (antegrade)</td>
</tr>
<tr>
<td></td>
<td>25 (simultaneous)</td>
</tr>
<tr>
<td></td>
<td>20 (retrograde)</td>
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able effect on the amplitude of ductal pressure and basal or phasic contractions (Fig. 3). In an intravenous dose of 6 mg or above, it increases the basal and phasic contraction of the SO. Patients with SO dysfunction have an exaggerated response to morphine and this forms the basis of the morphine—neostigmine test. This response may be related to the levels of the opioids or to an altered distribution of opioid receptors which influence motility in the biliary tract. However, the morphine—neostigmine test has failed to provide reproducible results and it lacks specificity for diseases of the SO. When compared with controls, patients who have suspected biliary dyskinesia and dilated bile ducts, besides spontaneous changes in the liver enzymes during episodes of pain, have a higher frequency of drug induced pain and a more frequent rise in serum concentrations of aspartate aminotransferase and amylase.

Nifedipine, 10 mg sublingually, has a slow effect on the SO, starting within 5 minutes of administration and extending beyond 15 minutes. It reduces the frequency of SO activity as well as the amplitude of its basal and phasic contractions. Consequently, the pressures in both bile and pancreatic ducts are also reduced (Fig. 4). While Guerlud et al. failed to show any effect on SO motor function with 10 mg of sublingual nifedipine, we found that 20 mg of nifedipine caused a moderate but significant decrease of the SO basal pressure in 8 volunteers and a marked effect on SO basal pressures in 9 patients with suspected biliary dyskinesia. A comparable decrease in the amplitude, duration and frequency of SO phasic contractions was also observed. Therefore, nifedipine is thought to be a useful drug in the treatment of biliary dyskinesia.

Hyoscine butylbromide, 40 mg intravenously, has a dramatic effect on SO activity, starting within 30 seconds of administration and lasting for 5 to 10 minutes. It abolishes the phasic activity of the SO and the bile duct—duodenal pressure gradient (Fig. 3) and is, therefore, an effective drug for treating symptomatic episodes of SO
dysfunction. However, as its action lasts only for a short duration, it is not suitable for long term treatment.

THE EFFECT OF HORMONES
The effect of cholecystokinin octapeptide (CCK-OP) on the SO has been studied extensively. CCK-OP inhibits the basal and phasic activity in normal subjects and in patients after cholecystectomy. This effect is mediated by stimulation of inhibitory nerves. In 5 of 30 patients with SO dysfunction and elevated basal pressures we found a paradoxical response of the SO to CCK-OP—sphincteric contraction rather than relaxation. This response may be related to the direct effect of the hormone on the SO as the effect on the inhibitory nerves may be lost following cholecystectomy. This we feel provides a clue to the possible pathogenesis of abdominal pain following fatty meals in these patients who also developed biliary pain when sphincteric spasm was elicited. There is also a report of abnormal circulatory levels of CCK-OP in patients with biliary dyskinesia but this has to be confirmed by other studies.

ENDOSCOPIC SPHINCTEROtomY
Endoscopic sphincterotomy eliminates the basal and phasic activity of the SO and abolishes the duodenal–bile duct pressure gradient (Fig. 5). Some studies have shown that it widens the SO to a mean diameter of 12±1.4 mm and the incision narrows down to 4.2±1.9 mm at one year and 2.1±0.5 mm at two years. The characteristics of the SO after endoscopic sphincterotomy can be divided into three groups.

Group 1
A papilla with minimal fibrosis or deformity; the SO diameter at 2 years being 60% of the original diameter. SO manometry reveals no basal or phasic sphincteric activity and no duodenal–bile duct pressure gradient.

Group 2
A papilla with marked deformity but minimal fibrosis; the SO diameter at 2 years being 30% of the original diameter. SO manometry reveals a resurgence of basal and phasic activity and the development of a duodenal–bile duct pressure gradient.
prevailing methods of investigation could not provide this group of patients more comprehensively. About half other imaging techniques it has become possible to study these symptoms. With the introduction of ERCP and a papilla with marked fibrosis and deformity; the SO gradient, the so called sphincteric stenosis. phasic activity and a high duodenal-bile duct pressure diameter at 2 years being 20% of the original diameter. evidence that stenosis or motility disorders produced undefined cause. A pain similar to biliary colic but of biliary dyskinesia and recurrent acute pancreatitis of to sphincter of Oddi dysfunction, viz. post-cholecystectomy CLINICAL CONDITIONS AND SPHINCTER DYSFUNCTION

At present two disease states are suspected to be related to sphincter of Oddi dysfunction, viz. post-cholecystectomy biliary dyskinesia and recurrent acute pancreatitis of undefined cause.\(^1,7,9\) A pain similar to biliary colic but of uncertain nature was recognized by surgeons more than half a century ago. These symptoms were thought to be caused by stenosis or a motility disorder involving the SO, and the entity was called biliary dyskinesia. However, prevailing methods of investigation could not provide evidence that stenosis or motility disorders produced these symptoms. With the introduction of ERCP and other imaging techniques it has become possible to study this group of patients more comprehensively. About half of them have minor symptoms after cholecystectomy but only 5% develop severe symptoms which necessitate further evaluation.\(^2\) In a study on 154 patients with cholecystectomy and recurrent upper abdominal symptoms we found that some organic disease was identified in 100 (Table II).\(^7\) We suspected the remaining 54 patients to have SO dysfunction and a critical analysis of the symptoms of 32 consecutive patients revealed that the disease caused considerable disability with multiple major episodes (mean±SD: 11±8; range 3 to 50) of right hypochondrial or epigastric pain over long periods (mean±SD: 7.5±5.2 years) requiring many admissions to the hospital and injections of intravenous analgesics. The pain appeared to be biliary in origin in 26 patients and pancreatic in 6. It was often precipitated by a heavy or a fatty meal. Jaundice was extremely rare in these patients. Many of them had a history of other disorders including migrainous headaches, menstrual difficulties and some had had multiple surgical procedures.\(^2\) Although other disorders such as peptic ulceration, urinary tract disease, liver disease and inflammatory bowel disease could have caused similar pain, we excluded these by ultrasound, upper and lower gastrointestinal endoscopy and intravenous pyelography.\(^7\) During symptomatic episodes many of these patients revealed elevated (up to twice normal) serum aspartate aminotransferase, alkaline phosphatase and amylase. ERCP showed a dilated common bile duct (>12 mm diameter and delayed drainage (>45 min) of contrast from the biliary tree. The majority of these patients had developed biliary symptoms months or years following cholecystectomy. However, some of them (5 out of 32) had had similar symptoms with an intact acalculous gall bladder.\(^7\) The criteria for the diagnosis of recurrent idiopathic acute pancreatitis have not been clearly defined but include patients with three or more episodes of acute pancreatitis in whom relevant investigations have excluded known precipitating causes.

Abnormal pressure profile

Sphincter of Oddi dysfunction results in impedance to the flow of bile into the duodenum, resulting in elevated biliary and pancreatic ductal pressures, dilatation of ducts and elevation of biliary and pancreatic enzymes. The sphincteric pathology may be organic or functional (the latter being either neurogenic or myogenic in origin). Broadly, five types of sphincteric manometric abnormalities have been described.\(^2,4,6-9\)

**Type I: Sphincteric stenosis**

Papillitis and papillary fibrosis result in narrowing of the sphincteric orifice. On SO manometry the basal pressure is raised and is not influenced by hyoscine butylbromide. The phasic waves are either absent or markedly attenuated. Stenosis occurs in patients with biliary lithiasis, in half the patients with recurrent acute pancreatitis and in a small selected group of patients with biliary pain following cholecystectomy. Endoscopic or surgical sphincterotomy may be effective in relieving pain.
Type II: Sphincteric spasm (Fig. 6)
In this condition there is hypertonicity of the SO with elevated basal pressures. Hyoscine butylbromide causes a lowering of the SO pressure.²,³ The phasic waves are few and of low amplitude—a common abnormality in patients with biliary pain following cholecystectomy. Nifedipine is effective in relieving symptoms in most of these patients. If nifedipine treatment fails, endoscopic sphincterotomy may yield good results.

Type III: Paradoxical response to CCK-OP
Infusion of CCK-OP causes an increase in basal sphincteric pressure with or without an increase in the amplitude and frequency of phasic contractions. This occurs in 16% of patients with suspected SO dysfunction. The response to endoscopic sphincterotomy is not good.

Type IV: Tachyoddia
There is an increase in frequency of phasic contractions of the SO (>8 per minute) and rapid sphincteric phasic contractions impede bile flow by reducing diastolic filling. This occurs in one-third of patients with suspected SO dysfunction. The response to endoscopic sphincterotomy has not been studied.

Type V: Abnormal propagation of phasic contractions
In this situation about two-thirds of SO phasic contractions are propagated retrogradely. This occurs in patients with biliary lithiasis and about a third of patients with suspected SO dysfunction. Retrograde contractions impede bile flow, increase biliary pressure and promote stagnation. The response to endoscopic sphincterotomy has also not been studied.

A CLINICAL ENTITY OR A MYTH!
Defining an abnormal pressure profile for the SO in patients with unexplained biliary pain does not prove a cause and effect relationship between the manometric findings and the patient’s symptoms because the clinical symptoms occur intermittently while the SO pressure and motility abnormalities are constant. However, if patients have such SO abnormalities they may be predisposed to respond abnormally to physiological stimuli. For example, patients with SO dysfunction respond to an infusion of CCK-OP with a paradoxical increase in SO pressure.¹⁵ Other evidence which links manometric abnormalities to the patients’ symptoms is provided by the results of endoscopic sphincterotomy.¹⁷,¹⁸ These patients benefited while others with normal SO pressures did not. There is thus circumstantial evidence to support the existence of a clinically symptomatic primary dysfunction of the SO in humans although conclusive proof is not yet available.

MANAGEMENT
What steps need to be taken in a patient who has unexplained biliary pain following cholecystectomy or recurrent acute pancreatitis for which a cause cannot be found even after thorough investigation (Table III)? First, the pattern of symptoms need detailed analysis and all possible causes of pain should be considered and relevant investigations ordered. There must be circumstantial evidence for SO dysfunction, viz. elevation of the serum levels of aspartate aminotransferase, alkaline phosphatase and amylase during symptomatic episodes. At ERCP the papilla should be carefully observed for scarring and deformity, and the ductal diameter and drainage assessed. The morphine–neostigmine test should be used as a provocative test to elicit pain so that elevation of the relevant serum enzymes are recorded.¹⁰ Biliary scintigraphy may help define functional obstruction at the papilla of Vater.¹⁹ Manometry is a valuable adjunct for evaluating patients with suspected SO dysfunction. It reveals abnormal pressure profiles in 50% of such patients. The procedure is used to classify the type of manometric abnormality
SUSPECTED SO DYSFUNCTION

SO MANOMETRY

HIGH BASAL PRESSURE

TACCHYODDIA

PARADOXIC RESPONSE TO CCK-OP

RETOGRADE PROPAGATION OF

PHASIC CONTRACTIONS

NORMAL

RESPONSE TO BUSCOPAN

NO RESPONSE TO BUSCOPAN

STENOSIS

DYSKINESIA

NIFEDIPINE

E.S.

S.S.

BALLOON DILATATION

E.S.

S.S.

TABLE 3 Sphincter of Oddi dysfunction. Flow chart on the result of SO manometry in patients with suspected SO dysfunction

REFERENCES


present. This might provide a clue to the pathogenesis of the SO dysfunction and may also be a guide to the therapy which is most likely to be effective. Sphincter stenosis is best treated by endoscopic sphincterotomy or surgical sphincteroplasty. Patients with sphincteric spasm or other manometric abnormalities should be treated with nifedipine started in a dose of 10 mg thrice daily and then increased until intolerance or symptomatic relief occurs. The majority of patients have an excellent response to this regime. A small group of patients have either drug side effects or fail to respond. Some of these do well after endoscopic sphincterotomy. Recently, balloon dilatation of the SO has been used as a therapeutic measure in SO dysfunction with encouraging results. Its advantage over endoscopic sphincterotomy is that it maintains the competence of the sphincter.

There is much to be learned about dysfunction of the SO and with the use of newer techniques the importance of this inaccessible muscle is being much better understood.


