

## Leading article

# What is sphincter of Oddi dysfunction?

### Summary

Ever since its description approximately 100 years ago, the sphincter of Oddi has been surrounded by controversy. First, whether it indeed existed, second, whether it had a significant physiological role in man and more recently whether abnormalities in its function give rise to a clinical syndrome. Data from animal and human studies, using sensitive techniques, have helped define the physiological role of the sphincter of Oddi, and more recent studies are determining the factors which control sphincter of Oddi function. These studies support Oddi's original description that the sphincter has a major role in the control of flow of bile and pancreatic juice into the duodenum, and equally importantly helps prevent the reflux of duodenal contents into the biliary and pancreatic ductal systems. The controversy of whether abnormalities in sphincter of Oddi motility result in clinical syndromes has not been totally resolved. Part of the difficulty has been inability to document normal and hence abnormal function of the sphincter. With the emergence of endoscopic biliary manometry as a sensitive and reproducible technique, however, the motility of the human sphincter of Oddi has come under closer scrutiny and allowed definition of possible disorders. We have used the term sphincter of Oddi dysfunction to define manometric abnormalities in patients who present with signs and symptoms consistent with a biliary or pancreatic ductal origin. Based on the manometry, we have subdivided the dysfunction into two groups; a group characterised by a stenotic pattern – that is, raised sphincter basal pressure – and a second group having a dyskinetic pattern – that is, paradoxical response to cholecystokin injection, rapid contraction frequency, high percentage of retrograde contractions, or short periods of raised basal pressure. It is apparent from the manometry but also from the clinical data that the patients are a heterogeneous group and thus any therapy would need to be tailored for each patient and abnormality. The most recent therapeutic data suggest that patients with the stenotic pattern on manometry respond to division of the sphincter, however, those patients with the dyskinetic manometric pattern show no significant effect after sphincterotomy. Further prospective trials evaluating therapeutic options are under way and their results are eagerly awaited.

Just over 100 years ago Rugero Oddi described the collection of smooth muscle at the lower end of the bile duct which now bears his name.<sup>1</sup> He postulated that this sphincter played a vital role in the control of flow of bile and pancreatic secretions and that abnormalities in its function would be associated with clinical syndromes. Since then, clinicians have given a

variety of names to symptomatology said to originate from a malfunctioning sphincter of Oddi. These names include odditis, biliary dyskinesia, post-cholecystectomy syndrome and sphincter of Oddi stenosis.<sup>2,3</sup> Precise definition of each of these entities is lacking and the plethora of clinical descriptions only serve to further confuse discussion. In an attempt to develop a terminology which may be reproducible we introduced the term sphincter of Oddi dysfunction to encompass all of the potential motility abnormalities of the sphincter and attempted to define subcategories based on objective manometric findings.<sup>4</sup> The nomenclature is also based on the existing understanding of the physiology of the sphincter of Oddi and several hypotheses on potential abnormalities of normal function which may lead to a dysfunctioning sphincter.

### Normal function

Understanding of the normal motility of the sphincter of Oddi has arisen from studies mainly in animals<sup>5</sup> and to a lesser extent in man.<sup>6</sup> Anatomical dissections show that the sphincter of Oddi differs between species and hence its normal physiological function might also be expected to be different between species. The human sphincter of Oddi is 6 to 10 mm in length and is situated almost entirely in the wall of the duodenum traversing an oblique course. Dogs, cats, and pigs have sphincters of smaller dimensions but differ from man in that the bile duct and pancreatic duct enter the duodenum separately. In the Australian possum and American opossum, the two ducts merge in a similar manner to man, but the sphincter has a long extraduodenal course which extends for up to 20 to 25 mm in length. The extraduodenal position of the sphincter of Oddi in the possum has made this animal suitable for detailed study in order to help understand the mechanisms of controlling flow across the sphincter.

Physiological studies in man<sup>7</sup> and animals<sup>8,9,10</sup> have shown that the sphincter of Oddi generates a small resistance of approximately 5 mm Hg at the opening of the bile duct and pancreatic duct. Superimposed on this tonal pressure are prominent phasic contractions (100 to 150 mm Hg) which are mainly orientated in an antegrade direction and contract at a frequency of two to six per minute. In possums the phasic contractions propel small volumes of fluid from the bile duct into the duodenum hence bile flows as a result of the phasic contractile activity with small amounts expelled passively between contractions.<sup>8</sup> In man, bile flow occurs mainly by a passive mechanism in between the phasic contractions, the contractions only serving to propel a small bolus of fluid and thus clearing the ductal opening.<sup>11</sup>

In both species the frequency of contractions varies during fasting and shows an increase just before phase III duodenal activity.<sup>11,12</sup> After feeding, the frequency of contractions increases in the possum<sup>12</sup> whilst in man the amplitude of the contractions decreases and the tone is reduced.<sup>11</sup> Both of these responses facilitate increased flow of bile from the bile duct into the duodenum; in the possum active propulsion is enhanced whilst in man passive flow between contractions is facilitated. These differences between the possum and man serve to illustrate species variations but also the complexity of the motility of the sphincter of Oddi. This complex motility is orchestrated by the interplay of neuronal and hormonal mechanisms, the precise details of which have not yet been elucidated.

## Clinical features

The diagnosis of sphincter of Oddi dysfunction is most usually considered in patients with persistent or recurrent biliary type symptoms after cholecystectomy.<sup>13</sup> Furthermore, patients with recurrent pancreatitis, where a cause cannot be determined, are also considered to be candidates for sphincter of Oddi dysfunction.<sup>14</sup> The prevalence of the disorder has not been defined. It is not known whether the disorder exists before cholecystectomy, is related to the problem which led to cholecystectomy, or results from changes brought about by cholecystectomy. It is not known whether the disorder is congenital or secondary to changes produced as a result of passage of gall stones or other debris through the sphincter of Oddi.

We have interviewed over 100 patients considered to be candidates of post-cholecystectomy sphincter of Oddi dysfunction. As a result of these interviews, a clinical pattern has emerged and alerts us to the possibility of the disorder so that the more invasive and objective investigations are performed.

The majority of patients are women, between the ages of 30 and 50 years. Symptoms occur approximately five years after cholecystectomy and are similar to those symptoms experienced before cholecystectomy and relieved by the operation. The major symptom is pain, which is usually epigastric radiating to the right upper quadrant and into the back. The pain is often related to a fatty type meal but also occurs spontaneously. In some patients the pain wakes the patient in the early morning hours. Patients fall into two major groups. One group of patients have distinct episodes of pain with intervals of weeks to months between episodes. Another group experience a more regular pain of moderate intensity almost daily, but in addition more severe episodes of pain occur at intervals of weeks or months. An interesting feature in a subgroup of these patients is a sensitivity to opiate containing medication, particularly codeine, morphine, and Omnopon. Even small doses of codeine such as occurs in certain cough mixtures may initiate a severe episode of pain. In another subgroup, the above features may be accompanied by a rise in serum amylase and a diagnosis of recurrent pancreatitis is made.

Inevitably, these patients undergo endoscopic retrograde cholangiopancreatography (ERCP) examination of the bile duct and pancreatic duct to exclude a morphological cause for the symptoms. In some, the endoscopist may note that the pain is reproduced by manipulation of the papilla and by injection of contrast into the bile duct.

Objective signs which support a diagnosis of sphincter of Oddi dysfunction include abnormal serum amylase or abnormal serum liver transaminases in association with an episode of pain. Furthermore, ERCP may reveal an abnormally dilated bile duct or pancreatic duct and delay in emptying of contrast from the bile duct into the duodenum. (Fig. 1). The majority of patients, however, will not have any objective signs to support the more subjective symptoms hence the need for development of objective investigations which may assist in the diagnosis of SO dysfunction.

## Investigations of sphincter of Oddi function

### ERCP

Definition of the anatomy of the bile duct and pancreatic duct is essential as

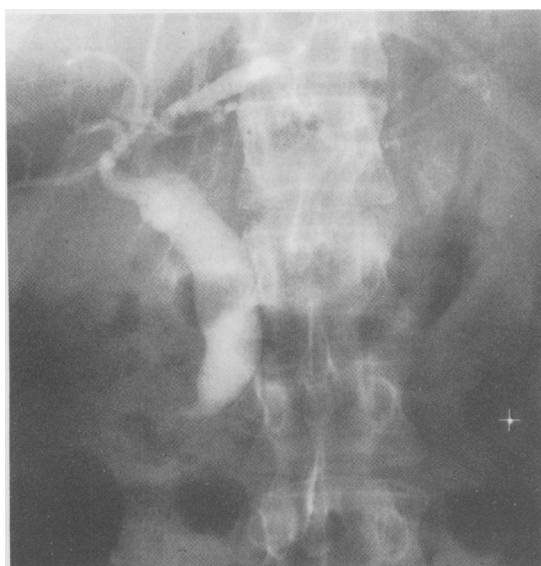


Fig. 1 Endoscopic retrograde cholangiogram on a patient with postcholecystectomy recurrent biliary type pain associated with raised liver enzymes during pain episodes. Cholangiogram shows a moderately dilated extrahepatic bile duct. At 45 minutes after introduction of contrast, there is little flow from the bile ducts.

Table Control data on biliary manometry

	Median	Range
Common bile duct (mm Hg)	5	0–15
Sphincter of Oddi		
Basal pressure (mm Hg)	15	5–35
Wave amplitude (mm Hg)	135	95–195
Wave frequency (n/min)	4	2–6
Wave direction		
Antegrade %	80	12–100
Simultaneous %	13	0–50
Retrograde %	9	0–50

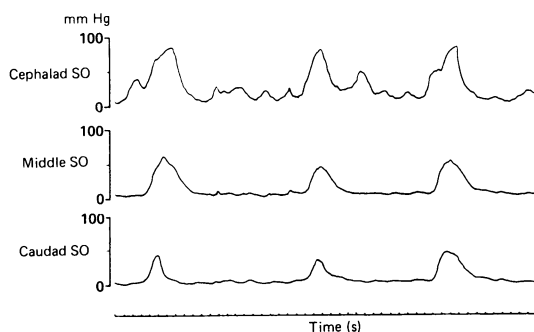


Fig. 2 Triple lumen catheter recording from the sphincter of Oddi, showing a normal tracing. Phasic contractions are superimposed on a modest basal pressure.

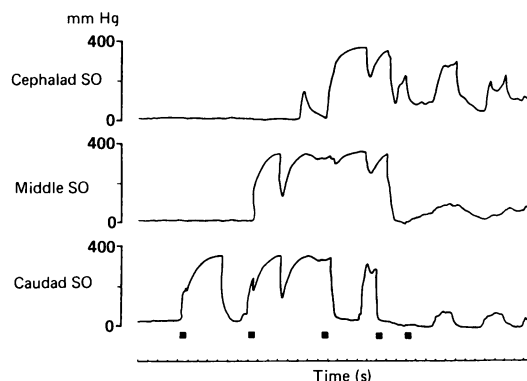


Fig. 3 Triple lumen catheter recording from the sphincter of Oddi in the patient illustrated in Fig. 1. The catheter is withdrawn from the bile duct across the sphincter into the duodenum in a stepwise manner indicated by the black marks. The tracing illustrates a high basal pressure recorded on all three lumens.

is exclusion of morphological abnormalities which may give rise to the symptoms. A cholangiogram will also determine duct diameter. A corrected diameter in excess of 12 mm is consistent with dilatation and may indicate a relative resistance to flow across the sphincter of Oddi. (Fig. 1).

#### MORPHINE NEOSTIGMINE TEST

This investigation was first described for the diagnosis of idiopathic recurrent pancreatitis, however, it has been adapted for screening of patients with suspected sphincter of Oddi dysfunction. Its sensitivity and specificity as assessed by results of therapy is very poor. Hence the investigation has not been considered useful in the diagnosis of sphincter of Oddi dysfunction. Given the fact that the term sphincter of Oddi dysfunction encompasses a variety of possible aetiological conditions,

however, which include patients with abnormal and normal responses to opiates plus fibrotic and non-fibrotic changes in the sphincter, it is not surprising that this test is not specific for all patients. In the identification and screening of patients with possible sphincter of Oddi dysfunction there is a need for a provocative test, as most patients experience only intermittent episodes of pain. The morphine neostigmine provocative test may identify a subgroup of patients with sphincter of Oddi dysfunction who are abnormally sensitive to opiates. The test is performed by administering morphine (0.12 mg/kg) and neostigmine (0.012 mg/kg) intramuscularly. Blood is taken at hourly intervals for five hours to determine serum liver enzyme concentrations. A positive test comprises reproduction of pain with a rise in liver enzymes (serum alanine transaminase or aspartate transaminase) to greater than double the upper limit of normal.<sup>15</sup>

#### DUCTAL DIAMETER AFTER SPECIFIC STIMULATION

In the search for provocative non-invasive investigations to screen patients suspected of sphincter of Oddi dysfunction, two investigations using ultrasound techniques have emerged as possible candidates.

Evaluation of pancreatic ductal size has been determined after administration of secretin (1U/kg) which produces maximal pancreatic juice flow. In the presence of a normally functioning sphincter of Oddi there is transient increase in pancreatic duct diameter as a result of increased flow. In the presence of sphincter of Oddi dysfunction, a prolonged increase in ductal diameter in excess of 20 minutes after secretin injection is observed.<sup>16</sup>

A similar test has recently been reported for the bile duct. The diameter of the bile duct is determined by ultrasound and alterations noted after a fatty meal. Prolonged dilatation of the bile duct after fatty meal stimulation suggests a relative stenosis of the sphincter.<sup>17</sup>

Current studies are under way to help define the sensitivity and specificity of the above investigations. It would be expected that in view of the heterogeneity of the possible mechanisms which make up sphincter of Oddi dysfunction that neither of the above investigations will prove to be highly specific and similar to the morphine neostigmine test, help to identify a subgroup of patients.

#### SCINTIGRAPHY

Radionuclide methods for assessing bile flow across the sphincter of Oddi potentially should provide the most significant and specific data of functional changes. Quantitative hepatobiliary scintigraphy after sphincter of Oddi provocation by specific stimulants may further enhance its diagnostic value. To date, however, most studies have presented data showing that scintigraphy is useful in the diagnosis of major stenosis but quite insensitive in differentiating patients with intermittent symptoms.<sup>17-19</sup>

#### MANOMETRY

Manometric evaluation of sphincter of Oddi function has produced the most recent advance in understanding of the normal function of the sphincter and also has allowed for identification of abnormalities in sphincter of Oddi motility. These manometric abnormalities have provided the basis for description of subgroups of patients with sphincter of Oddi dysfunction. Manometry is performed through an endoscopic route by adaptation of

ERCP techniques,<sup>21</sup> at operation by direct cannulation of the bile duct<sup>22</sup> and postoperatively in patients with T-tubes in the bile duct.<sup>23</sup>

A miniaturised triple lumen catheter perfused by a minimally compliant pneumohydraulic perfusion system may be positioned across the sphincter so that three lumens record pressure changes. A separate catheter records pressure changes from the duodenum. The sphincter of Oddi is characterised manometrically by regular phasic contractions superimposed on a modest basal tone (Fig 2). Studies in control subjects<sup>4</sup> and normal volunteers<sup>24, 25</sup> have defined the normal manometric profile of the sphincter of Oddi (Table).

Manometric abnormalities have been described in patients with clinical features consistent with sphincter of Oddi dysfunction and as a result two major subgroups have been identified based entirely on the manometric results.<sup>4</sup> The groups are as follows:

#### *Sphincter of Oddi stenosis*

Manometrically these patients have an abnormally raised basal pressure (>40 mm Hg). (Fig. 3) Emerging evidence suggests that there may be an association between raised basal pressure and duct diameter, plus abnormalities in liver enzymes in relation to episodes of pain. An association is also present with patients who have an abnormal fatty meal sonogram<sup>17</sup> and abnormal secretin stimulated pancreatic duct diameter.<sup>16</sup> The correlation between the various investigations is, however, not tight. Pathological correlation is lacking, however, and it is postulated that a high basal pressure may result from fibrotic stenosis, muscle hypertrophy or mucosal oedema.<sup>26</sup>

#### *Sphincter of Oddi dyskinesia*

Manometrically a variety of disorders are included in this group. So far, the following manometric dyskinetic abnormalities have been described;<sup>4</sup> paradoxical response to cholecystokinin octapeptide injection, rapid contraction frequency, episodes of raised basal pressure or an excess of retrograde contractions. Patients who respond abnormally to morphine or to a fatty meal stimulus may have these manometric abnormalities. Pathologically there have not been any reproducible abnormalities described. A possible defect in the enteric nervous system, however, may account for the paradoxical response seen after cholecystokinin-octapeptide administration.<sup>26</sup> This hypothetical neuronal defect may be similar to that described for achalasia of the oesophagus and awaits future confirmation.<sup>27</sup>

### **Treatment of sphincter of Oddi dysfunction**

As far as is known, sphincter of Oddi dysfunction is not a life threatening disorder. Undoubtedly patients suspected of having this disorder are severely debilitated. The mechanism for production of pain is unknown. It is postulated that the relative obstruction of flow through the sphincter of Oddi results in bile duct or pancreatic duct distension which in turn gives rise to either pain or pain and pancreatitis respectively. The observation of reproduction of the pain by manipulating the papilla of Vater at endoscopy, however, is difficult to reconcile with the above hypothesis. Similarly the lack of duct dilatation in a number of patients suspected to have the disorder does not readily fit in with a hypothesis of sphincter stenosis. Another confounding factor might be the possibility that sphincter of Oddi dysfunc-

tion is just one of a number of bowel motility disorders which might afflict any one individual and directing therapy at one part of the gastrointestinal tract would not be expected to cure all symptoms.

The first line of treatment usually tried in patients with suspected sphincter of Oddi dysfunction is administration of smooth muscle relaxant medications<sup>28 29</sup> such as hyoscine-N-butylbromide, mebeverine HCL, dicyclomine HCL, glyceril trinitrate—sorbide nitrate and nifedipine. Response to these medications is variable and there are no prospective studies showing significant long-standing successful outcomes. Glyceril trinitrate—sorbide nitrate and nifedipine are associated with significant symptomatic side effects which limits their utilisation.

The most effective form of therapy is division of the sphincter of Oddi either *via* endoscopy or transabdominal operation. Logic dictates that if the pain is produced by spasm of the sphincter then division of the sphincter should stop further episodes of pain. If the major problem relates solely to the biliary tract, all that needs to be divided is the choledochal part of the sphincter of Oddi.

In those patients who develop recurrent pancreatitis as a result of sphincter of Oddi dysfunction, however, then division of both the choledochal and pancreatic duct components of the sphincter of Oddi should be performed.<sup>30 31</sup>

A number of studies have evaluated the effect of sphincterotomy on patients with suspected sphincter of Oddi dysfunction. In one study, a group of patients underwent manometry of the sphincter of Oddi. A selected subgroup subsequently had an endoscopic sphincterotomy and their clinical response was evaluated in relation to the manometric findings. There was no significant correlation between manometry and clinical outcome.<sup>32</sup> In this study neither the patients nor the clinicians were blinded to the form of treatment. Furthermore, patient selection may have influenced the results as only those patients who had socially debilitating symptoms were offered sphincterotomy. This study does, however, question the results of a separate study which appraised clinical response in a group of patients who were randomly allocated to one of two groups – that is, sphincterotomy or sham sphincterotomy. All of these patients underwent sphincter of Oddi manometry before randomisation but the manometry was not used to determine treatment. On reviewing the manometry and correlating it with the clinical outcome, it was noted that patients with the stenotic pattern – that is, raised sphincter of Oddi basal pressure – were either cured or significantly improved, whilst those patients with the dyskinetic manometric changes showed no change after sphincterotomy.<sup>33</sup> Interestingly, all other objective parameters of sphincter stenosis, such as dilated duct or delayed emptying of contrast from the bile duct did not correlate with either the manometry or the clinical outcome. One would expect, however, that division of the sphincter of Oddi should be effective in the treatment of all types of sphincter of Oddi manometric abnormality as effective division should eliminate all forms of dysfunction.

The operation of transduodenal sphincteroplasty and pancreatic ductal septectomy has been performed in patients with sphincter of Oddi dysfunction producing recurrent pancreatitis. In these patients results comparable with those reported after endoscopic sphincterotomy for patients with raised basal pressure are reported.<sup>30 31</sup>

The selection of patients for appropriate and specific treatment has not been clearly defined.<sup>34</sup> Current studies are under way evaluating the effect of treatment based on manometric findings. The results of these prospective randomised double blinded studies are eagerly awaited and it is hoped will assist in defining appropriate therapy for patients with sphincter of Oddi dysfunction.

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