Functional disorders of the biliary tract and pancreas

E Corazziari, E A Shaffer, W J Hogan, S Sherman, J Touli

Abstract
The term “dysfunction” defines the motor disorders of the gall bladder and the sphincter of Oddi (SO) without note of the potential etiologic factors for the difficulty to differentiate purely functional alterations from subtle structural changes. Dysfunction of the gall bladder and/or SO produces similar patterns of biliopancreatic pain and SO dysfunction may occur in the presence of the gall bladder. The symptom-based diagnostic criteria of gall bladder and SO dysfunction are episodes of severe steady pain located in the epigastrium and right upper abdominal quadrant which last at least 30 minutes. Gall bladder and SO dysfunctions can cause significant clinical symptoms but do not explain many instances of biliopancreatic type of pain. The syndrome of functional abdominal pain should be differentiated from gall bladder and SO dysfunction. In the diagnostic workup, invasive investigations should be performed only in the presence of compelling clinical evidence and after non-invasive testing has yielded negative findings. Gall bladder dysfunction is suspected when laboratory, ultrasonographic, and microscopic bile examination have excluded the presence of gallstones and other structural abnormalities. The finding of decreased gall bladder emptying at cholecystokinin-cholescintigraphy is the only objective characteristic of gall bladder dysfunction. Symptomatic manifestation of SO dysfunction may be accompanied by features of biliary obstruction (biliary-type SO dysfunction) or significant elevation of pancreatic enzymes (pancreatic-type SO dysfunction). Biliary-type SO dysfunction occurs more frequently in post-cholecystectomy patients who have categorized into three types. Types I and II, but not type III, have biochemical and cholangiographic features of biliary obstruction. Pancreatic-type SO dysfunction is less well classified into types. When non-invasive investigations and endoscopic retrograde cholangiopancreatography show no structural abnormality, manometry of both gall bladder and pancreatic sphincter may be considered.

Normal gall bladder and sphincter of Oddi function
The gall bladder and the sphincter of Oddi (SO) act as an integrated unit to regulate bile flow from the liver through the biliary tract into the duodenum. The SO similarly controls pancreatic exocrine output. During fasting, hepatic bile enters the gall bladder for storage. The gall bladder accommodates this increase in volume through receptive relaxation without any significant rise in pressure and by concentrating bile to keep its volume small. The gall bladder evacuates bile by smooth muscle contraction, coordinated with reduced tone in the SO. During fasting, about 25% of the emptying of gall bladder contents occurs periodically every 100–120 minutes, mediated by motilin, which acts via vagal cholinergic nerves and is synchronized with the migratory motor complex of the intestine. Eating initiates over 75% of gall bladder emptying through neural (cephalic and local gastroduodenal reflexes) and hormonal (predominantly cholecystokinin (CCK) acting via cholinergic nerves) influences. Non-adrenergic, non-cholinergic inhibitory nerves produce SO relaxation through the release of vasoactive intestinal peptide (VIP) and nitric oxide, acting as post-ganglionic neurotransmitters. The neural supply to the biliary tract includes vagal efferent nerves releasing acetylcholine, sympathetic fibers releasing norepinephrine, and sensory nerves containing substance P. Sensory fibers influence the neural response, acting via the vagus through central reflexes. Derangements of any of these components may lead to intermittent upper abdominal pain, transient elevations of liver or pancreatic enzymes, common bile duct dilatation, or episodes of pancreatitis.

Definition of gall bladder and sphincter of Oddi dysfunction
Motor dysfunction of the gall bladder and SO has long been suspected as a major feature of several clinical entities that manifest with a similar pattern of upper abdominal pain (table 1). Unlike other functional gastrointestinal disorders, however, abnormalities are beginning to be identified by new technologies, although in many instances a cause-and-effect relationship has not been substantiated. Clinical symptoms may not coincide temporally with the demonstrated abnormality. Further, impaired gall bladder emptying occurs in many patients with cholesterol gallstones, yet most

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Keywords: biliary tract disease; sphincter of Oddi dysfunction; gallstone disease; pancreatitis; endoscopic retrograde cholangiopancreatography; cholecintigraphy; endoscopic ultrasonography; cholecystokinin; magnetic resonance cholangiopancreatography; Rome II

Abbreviations used in this paper: SO, sphincter of Oddi; CCK, cholecystokinin; VIP, vasoactive intestinal peptide; ERCP, endoscopic retrograde cholangiopancreatography.
Table 1 Functional gastrointestinal disorders

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The presumed mechanism for biliary pain is obstruction leading to distension and inflammation. This might result from incoordination between the gall bladder and either the cystic duct or the SO due to increased resistance or tone. Fibrosis and inflammation also can affect the SO, but any clinical relevance is unclear. Rather, for both the gall bladder and SO, motor contraction, sensory afferents, and obstruction/inflammation all likely play a role in biliary-type pain. Central projections from visceral nociceptors to the thalamus and cortex might lead to a more excitable state with hyperalgesia (severe pain evoked by mildly painful stimuli). Persistent central excitability might then result in allodynia where innocuous stimuli produce pain. The “hypersensitive biliary tract” may exist, but the anatomy of the biliary tract precludes ready access to assess this hypothesis scientifically.

Motor dysfunction currently is the most effectively studied of the sources of disorders; it is the only available measure of gall bladder and SO dysfunction. We therefore have adopted the term “dysfunctional disorders of the gall bladder and SO” without attempting to attribute its cause(s) or to identify often subtle morphological changes. This classification consists of:

1. gall bladder dysfunction, and
2. SO dysfunction, which may be subdivided into: (a) biliary-type and (b) pancreatic-type.

The following clinical observations should be considered with regard to gall bladder and SO dysfunction:

- gall bladder and SO dysfunction manifest symptomatically with the same type of pain;
- although the diagnosis of SO dysfunction is usually made following cholecystectomy, SO dysfunction can manifest clinically in patients with an intact biliary tract;
- psychosocial aspects appear to be variably interrelated with gall bladder and SO dysfunction;
- the syndrome of chronic functional abdominal pain may manifest with clinical characteristics similar to biliopancreatic type of pain.

### E1. Gall bladder dysfunction

The central symptom of gall bladder dysfunction is biliary-type pain. Currently, the only objective characteristic is decreased gall bladder emptying. Available techniques have not clarified its basis (perhaps there is more than one cause) and cannot exclude other entities such as impaired filling or an overly sensitive gall bladder.

#### EPIDEMIOLOGY

Gallstones are the most common affliction of the gall bladder, but only 10–20% of patients ever develop symptoms. Further, there is no association with dyspepsia. The frequency of biliary pain in those without gallstones may be as high as 7.6% of men and 20.7% of women, or as low as 2.4% overall, as reported in an ultrasonographic survey.

#### DIAGNOSTIC CRITERIA

Episodes of severe steady pain located in the epigastrium and right upper quadrant, and all of the following:

1. Episodes last 30 minutes or more;
2. Symptoms have occurred on one or more occasions in the previous 12 months;
3. The pain is steady and interrupts daily activities or requires consultation with a physician;
4. There is no evidence of structural abnormalities to explain the symptoms; and
5. There is abnormal gall bladder functioning with regard to emptying.

The presence of biliary sludge implies gall bladder dysfunction in the form of stasis from impaired emptying but may not necessarily explain the pain. In addition the pain may be associated with one or more of the following: nausea and vomiting; pain radiating to the back and/or right interscapular region; onset after...
meals; and/or awakens the patient at night. In some, these symptoms may be superimposed on a background of low-grade chronic abdominal pain of unknown etiology.

Rationale for Changes in Diagnostic Criteria

There are two major changes compared with the Rome I diagnostic criteria. The first refers to the specification of the duration, number of episodes of pain, and the time within which they occur:

1. 30 minutes has been more firmly established in the literature as the minimum duration of a biliary “colic”;
2. even a single pain episode may be so severe as to justify diagnostic investigation irrespective of the number of episodes, and
3. the frequency of biliary pain may be so irregular that a time window of only three months has been considered too restrictive.

The second change is point 5, the specification of the only established functional abnormality.

Clinical Evaluation

Screening Tests

Laboratory—Tests of liver biochemistries and pancreatic enzymes must be normal.

The following tests are necessary to eliminate calculous biliary disease, which can produce similar symptoms.

Ultrasoundography—Transabdominal ultrasonography of the upper abdomen is mandatory. The biliary tract and pancreas should be normal and gallstones or sludge absent. Ultrasonography readily detects stones equal to or greater than 3–5 mm in diameter or biliary sludge within the gall bladder, but it has a low sensitivity for smaller stones or biliary microcrystals. It also has a low yield for stones within the common bile duct. Endoscopic ultrasonography seems to be more sensitive than traditional transabdominal ultrasonography in detecting microlithiasis (tiny stones <3 mm) and sludge within the biliary tract, but the recommendation for its inclusion in standard workups requires further evaluation.

Microscopic bile examination—This procedure is necessary to exclude microlithiasis as a cause. Gall bladder bile can be obtained directly at the time of endoscopic retrograde cholangiopancreatography (ERCP) or by aspiration from the duodenum following stimulation (e.g., CCK-8 5 ng/kg i.v. over 10 minutes, or 50 ml MgSO$_4$ instilled into the duodenum). Two types of deposits may be evident: (1) cholesterol microcrystals, which are birefringent and rhomboid shaped, best visualized by polarizing microscopy; and (2) bilirubinate granules, which appear as red-brown deposits under conventional light microscopy.

Endoscopy—In the presence of normal laboratory and ultrasonographic findings, endoscopy is usually indicated to exclude upper gastrointestinal diseases.

Tests for gall bladder dysfunction

CCK-cholescintigraphy assessment of gall bladder emptying—This study continuously monitors the hepatic excretion of a radiopharmaceutical into the gall bladder and duodenum, using computer assistance to quantitate changes in radioactivity over the gall bladder. Filling of the gall bladder with radionuclide indicates patency of the cystic duct. Gall bladder emptying is expressed as the gall bladder ejection fraction, the percentage decrease in net gall bladder counts following CCK infusion (CCK-8 slowly infused at 20 ng/kg over 30 minutes). Reduced emptying, which defines gall bladder dysfunction, can arise from either depressed gall bladder contraction or increased resistance such as elevated tone in the SO. Furthermore, several other conditions that do not necessarily present with biliary colic can be associated with reduced gall bladder emptying. These range from intrinsic gall bladder disease (stones, cholecystitis) to neural and metabolic disorders, drugs, and even the irritable bowel syndrome. Although biliary-type pain is rarely elicited, the test appears to be a marker of this biliary disorder, based on evidence of the beneficial effect of cholecystectomy.

Transabdominal ultrasonography—This test measures gall bladder volume, which if followed serially after a stimulus (meal or CCK), reflects emptying. The technique is operator dependent and the results may not be reproducible in different centers. Ultrasonographic assessment of gall bladder emptying is currently not the standard for gall bladder dysfunction.

Pain provocation test—Stimulation tests with CCK to duplicate biliary pain have been used historically as a diagnostic investigation. Such tests have low sensitivity and specificity in selecting patients with gall bladder dysfunction who respond to therapy. This may relate to problems in the subjective assessment of pain and the use of bolus injections of CCK, which can induce intestinal contractions.

Diagnostic Workup

Biliary tract symptoms should be evaluated by liver biochemistry, pancreatic enzymes, and ultrasound examination of the abdomen. As a general recommendation we suggest that invasive investigations should be withheld in those patients in whom episodes are infrequent and not accompanied by increased liver function tests.

- If no abnormal findings are detected, CCK-cholescintigraphy should be used to assess gall bladder emptying. Abnormal gall bladder emptying (<40% ejection) indicates gall bladder dysfunction.
- If there is no obvious cause for impaired emptying, cholecystectomy is appropriate treatment.
- If gall bladder emptying is normal, bile for microscopic examination to detect cholesterol microcrystals and bilirubinate can be obtained by duodenal drainage, at the time of gastrointestinal endoscopy or during
ERCP. Magnetic resonance cholangiography or endoscopic ultrasound, where available, can be performed to detect lithiasis.

- If gall bladder emptying is normal, ERCP should be considered. In the absence of common bile duct stones or other abnormalities, SO manometry should be considered if clinically indicated. Evidence of SO dysfunction is an indication for treatment, which may include sphincterotomy.

### APPROACH TO TREATMENT

Medical therapy remains theoretical. It might take the form of: (1) altering gall bladder motor function (e.g., use of motility agents which enhance gall bladder contractility or ursodeoxycholic acid which worsens motility yet lessens the likelihood of biliary pain); (2) reducing visceral hyperalgesia or inflammation (e.g., with non-steroidal anti-inflammatory drugs); or (3) as a last resort, cholecystectomy. CCK-cholecintigraphy will identify those patients with impaired emptying. The challenge is to interpret the subgroup that will benefit from treatment. Laparoscopic cholecystectomy retains a role in the treatment of gall bladder dysfunction, although favorable outcomes may deteriorate with time, a potential placebo effect of surgery.

#### E2. Sphincter of Oddi dysfunction

Sphincter of Oddi dysfunction is the term used to define motility abnormalities of the SO. Because of its strategic position at the duodenal junction of the biliary duct and pancreatic duct, SO dysfunction may result in either biliary or pancreatic disorders. SO dysfunction may be present in patients with an intact biliary tract, but it has been more frequently reported following cholecystectomy.

#### E2a. Biliary-type SO dysfunction

Patients present with intermittent episodes of biliary-type pain, sometimes accompanied by biochemical features of transient biliary tract obstruction: elevated serum aminotransferases, alkaline phosphatase, or conjugated bilirubin. These postcholecystectomy patients have been arbitrarily classified according to clinical presentation, laboratory results, and ERCP findings:

- Patients with biliary-type I SO dysfunction present with pain, elevated liver function tests documented on two or more occasions, delayed contrast drainage, and a dilated common bile duct with a corrected diameter equal to or greater than 12 mm at ERCP.
- Type II patients present with pain and only one or two of the previously mentioned criteria.
- Type III patients have only recurrent biliary-type pain and none of the above criteria.

The predictability of SO dysfunction varies among these groups, being highest in types I (65–95%) and II (50–63%), but less so in type III (12–28%). Conversely, the probability that the syndrome of chronic functional abdominal pain (see chapters on Functional bowel disorders and Functional abdominal pain) manifests itself as biliary pain is higher in type III patients and less likely in type I.

#### E2b. Pancreatic-type SO dysfunction

Sphincter of Oddi dysfunction is less easily classified into types. In its more obvious form (like biliary-type I) pancreatic-type SO dysfunction may present with classic pancreatitis with epigastric pain, which often radiates to the back, and with evidence of elevated serum amylase or lipase. The absence of the traditional causes of pancreatitis (no stones or alcohol misuse) often yields the label of idiopathic recurrent pancreatitis. In a less obvious form (like biliary-type III SO dysfunction), the pain is similar but there is no increase in pancreatic enzymes; in many of these patients the symptomatology may be a manifestation of the syndrome of functional abdominal pain.

### EPIDEMIOLOGY

The prevalence of symptoms suggesting SO dysfunction is about 1.5% of patients after cholecystectomy, being more frequent in women. From another perspective, SO dysfunction appears in less than 1% of patients after cholecystectomy and in 14% of a selected group of patients complaining of postcholecystectomy symptoms. In patients with idiopathic recurrent pancreatitis, manometric evidence of SO dysfunction was found to vary between 39 and 90%. SO dysfunction can involve abnormalities in the biliary sphincter, pancreatic sphincter, or both. The true frequency thus depends on whether one or both sphincters are studied.

### DIAGNOSTIC CRITERIA

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1. Episodes last 30 minutes or more;
2. Symptoms have occurred on one or more occasions in the previous 12 months;
3. The pain is steady and interrupts daily activities or requires consultation with a physician; and
4. There is no evidence of structural abnormalities to explain the symptoms.

In addition the pain may be associated with one or more of the following:

- The diagnosis is supported by elevated serum aminotransferases, alkaline phosphatase, or conjugated bilirubin, and/or pancreatic enzymes (amylase/lipase).
- Acute recurrent pancreatitis can indicate pancreatic SO dysfunction.
- Other clinical features that may be associated with the pain episodes are: nausea and vomiting; pain radiating to the back and/or right interscapular regions (biliary) and/or pain partially alleviated by bending forward (pancreatic); onset after meals; awakens the patient at night.

Sphincter of Oddi dysfunction may exist in the presence of an intact biliary tract with the gall bladder intact. As the symptoms of SO or
Table 2  Pressure profile of the sphincter of Oddi measured at the common bile (CBD) and pancreatic (PD) ducts

<table>
<thead>
<tr>
<th></th>
<th>Normal* CBD</th>
<th>Abnormal† PD</th>
<th>CBD and PD</th>
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<tbody>
<tr>
<td>Duct pressure (mm Hg)</td>
<td>7.4 (1.7)</td>
<td>8.0 (1.6)</td>
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<tr>
<td>Basal pressure (mm Hg)</td>
<td>16.2 (5.8)</td>
<td>17.3 (5.8)</td>
<td>&gt;40</td>
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<tr>
<td>Phasic contractions</td>
<td></td>
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<tr>
<td>Amplitude (mm Hg)</td>
<td>136.5 (25.9)</td>
<td>127.5 (21.5)</td>
<td>&gt;350</td>
</tr>
<tr>
<td>Duration (seconds)</td>
<td>4.7 (0.9)</td>
<td>4.8 (0.7)</td>
<td>&gt;7</td>
</tr>
<tr>
<td>Frequency (minute)</td>
<td>5.7 (1.4)</td>
<td>5.8 (1.5)</td>
<td></td>
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<tr>
<td>Propagation sequence (%)</td>
<td>55 (10–100)</td>
<td>53 (10–90)</td>
<td>&gt;7</td>
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<tr>
<td>Simultaneous</td>
<td>34 (0–70)</td>
<td>35 (10–70)</td>
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<tr>
<td>Antegrade</td>
<td>11 (0–40)</td>
<td>12 (0–40)</td>
<td>&gt;50</td>
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<tr>
<td>Retrograde</td>
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*Values are mean (SD); ranges are given in parentheses.†Abnormal values for the CBD.

**Choleodochocintigraphy**—Following cholecystectomy, SO tone mainly regulates bile delivery into the duodenum. Dysfunction of the sphincter becomes manifest by a delay in the disappearance of radiopharmaceutical markers of bile from the biliary tract,29 or a prolonged transit of radiolabeled bile from the hepatic hilum to the duodenum.50 Choleodochocintigraphy is a useful screening method to select patients after cholecystectomy, in whom SO manometry might reveal abnormalities.

**Invasive tests**

**Endoscopic retrograde cholangiopancreatography**—Certain radiologic features at ERCP such as a common bile duct diameter exceeding 12 mm and delayed emptying of contrast media (>45 minutes) suggest SO dysfunction. Additional features are a dilated pancreatic duct (>5 mm) and delayed emptying of contrast media from the pancreatic duct (>10 minutes). However, variables such as premedication, lack of standardization, and the patient’s posture limit their value.

**SO manometry**—Perendoscopic manometry identifies the sphincter as the zone of elevated resting pressure between the duct (pancreatic or choledochal) and the duodenum. Phasic waves are superimposed (table 2).31 Manometric alterations of the SO include: increased basal pressure, increased amplitude of phasic waves, a paradoxical response to CCK, increased frequency of phasic waves, and an increased number of retrograde waves.24–27 32 Elevated basal SO pressure is diagnostic of either stenosis or spasm of the sphincter. With sphincteric spasm, SO pressure decreases after administering a smooth muscle relaxant.

**Diagnostic workup**

As a general recommendation we suggest that invasive investigations should be withheld in those patients in whom episodes are infrequent and not accompanied by increased liver function tests or pancreatic enzymes. Complications from invasive procedures such as ERCP and SO manometry are more frequent in patients with SO dysfunction and when performed by inexperienced endoscopists. The following recommendations apply only to skilled endoscopists, preferably in referral centers.

**Biliary-type SO dysfunction**—

- The evaluation of biliary pain in patients without gall bladders begins with laboratory analyses of liver function and pancreatic enzymes, plus elimination of potential structural causes by: transabdominal ultrasound, analysis of bile for microcrystals, magnetic resonance cholangiography, and endoscopic ultrasound (where available), and ERCP, depending upon the circumstances of the patient and the resources available.
- Choleodochoscintigraphy is a useful screening test before SO manometry.
- Patients with type I SO dysfunction may undergo endoscopic sphincterotomy without SO manometry. SO manometry is
recommended in type II and could be considered in type III dysfunction.

- If SO manometry is normal, look for causes other than SO dysfunction.
- SO stenosis should be treated by endoscopic sphincterotomy.
- In SO dyskinesia, a trial of drug therapy may be in order.

For patients with an intact gall bladder, the workup is part of the same diagnostic algorithm for gall bladder dysfunction.

**Pancreatic-type SO dysfunction**—

- When ERCP demonstrates no structural abnormality, manometry of both biliary and pancreatic sphincter is indicated.
- Finding biliary SO dysfunction leads to an endoscopic biliary sphincterotomy.
- For pancreatic SO dysfunction alone or with biliary SO dysfunction, standard therapy is operative sphincteroplasty and pancreatic septoplasty. Combined endoscopic biliary and pancreatic sphincterotomy is undergoing investigation.

**TREATMENT**

The therapeutic approach in patients with SO dysfunction aims to reduce the resistance to the flow of bile or pancreatic juice.

**Pharmacotherapy**

Some therapeutic agents have potential but there is limited evidence for their therapeutic usefulness.

- Hormones such as CCK and glucagon can transiently reduce SO tone.
- Calcium channel blockers such as nifedipine at 10–20 mg p.o. decreases the SO pressure and lessens phasic contractions in biliary dyskinesia, benefitting patients with type II SO dysfunction. 13
- Nitrates decrease sphincteric pressure and can alleviate the symptoms, at least in the short term. 14
- Botulinum toxin, a potent inhibitor of acetylcholine release, when injected into the sphincter reduces its pressure, improves bile flow, and provides some symptomatic relief. 15

Such medical therapies have several drawbacks. Calcium channel blockers and nitrates have significant side effects, whereas smooth muscle relaxants are unlikely to be of any benefit in patients with SO stenosis. Responses tend to be transient and long term reports are lacking.

**Sphincterotomy**

Endoscopic sphincterotomy is the most widely used therapeutic procedure for patients with biliary-type SO dysfunction, being less expensive and having lower morbidity than transduodenal surgery. Endoscopic sphincterotomy provides symptomatic relief in 55–95% of patients. The variable outcomes reflect the different criteria used, the methods of data collection (retrospective vs prospective), and the techniques used to determine benefit. Pancreatitis in 5–16% is the most common short term complication of endoscopic sphincterotomy, a rate higher than that for common duct stone extraction.

The even higher complication rate with hydrostatic balloon dilation and placement of biliary (or pancreatic) stents for temporary pain relief does not support their use.

For pancreatic-type SO dysfunction, severance of the pancreatic sphincter, not merely biliary sphincterotomy, may be necessary for a successful outcome. The surgical approach is via transduodenal sphincteroplasty and pancreatic duct septoplasty, yielding 70% improvement with a low risk of pancreaticitis but a high morbidity of 30%. 16 Endoscopic pancreatic sphincterotomy is another approach under investigation. All such approaches require further study.

**Conclusion**

Motility disorders of the gall bladder and SO can cause significant clinical symptoms but are not likely to explain many instances of biliary pain. Clearly, elucidation of the basis for such dysmotility and the detection of a putative hypersensitive biliary tract should sharpen our diagnostic tools, expand therapeutic options, and benefit those with this disabling problem.

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