Function and Dysfunction of the Sphincter of Oddi

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Abstract
In this review, the function of the sphincter of Oddi (SO) is detailed in terms of normal motility, neural and hormonal control of SO function, coordination between gallbladder and SO motility, and correlation of motility of the SO and the duodenum. In addition, SO function tests, such as the morphine Prostigmin test (Nardi test), perfusion manometry, microtransducer manometry, and cholescintigraphy, are explained. Subsequently, the pathophysiology, diagnosis, and treatment of SO dysfunction, including SO stenosis and dyskinesia, are described and discussed in detail. SO manometry and endoscopic sphincterotomy are effective to treat SO dysfunction, but symptoms of the patient must be severe enough to justify these invasive procedures for diagnosis and treatment.

Function of the Sphincter of Oddi

Motility of the Sphincter of Oddi
The upper gastrointestinal tract of most mammals shows a cyclic pattern of motility called the migrating motor complex (MMC) consisting of motor quiescence (phase I), intermittent irregular contractions (phase II), a brief band of strongest contractions with maximal frequency (phase III), and a short transitional period back to another phase I (phase IV) [1]. Phase III begins in the gastroduodenal region and slowly migrates down to the ileum, thus the name of the MMC. The MMC period lasts 100–120 min in humans.

The sphincter of Oddi (SO) shows rhythmical contractions (phasic waves) superimposed on tonic pressure (basal pressure). In a previous study, biliary pressure increased in concert with the duodenal MMC phase in patients after cholecystectomy [2], suggesting a flow-hampering function of the human SO. The physiological function of the SO in bile flow has long been believed to be different from species to species. The precise relationship between the SO phasic waves and bile flow has not been elucidated to date.

Neural Control of SO Function
The control of SO function is complex and consists of hormonal, extrinsic neural, intrinsic neural, and myogenic control. Hormonal control has been studied fairly well with regard to cholecystokinin, gastrin, secretin, and motilin, for example. On the other hand, neural control (mainly investigated by vagotomy, splanchnicectomy, and neural blockers) is more complex and intermingled. Nabae et al. [3] demonstrated that truncal vagotomy at the diaphragmatic level reduced SO basal pressure and increased the amplitude of phasic waves. Truncal vagot-
omomy also abolished an increase in the amplitude and a decrease in the frequency of phasic waves, which normally occur after meals. The high rate of gallstone formation after gastrectomy with truncal vagotomy may at least in part be attributable to these changes in SO motor function. On the contrary, vagal stimulation accelerates SO contractions similar to the effects of acetylcholine administration [4]. The pathophysiology of SO is complex and difficult to understand, because all the aforementioned mechanisms affect tonic and contractile SO functions.

**Hormonal Control of SO Function and Coordination between Gallbladder and SO Motility**

SO and gallbladder affect bile flow chiefly under the control of a variety of gastrointestinal hormones. The gallbladder contracts, while the SO relaxes, due to the action of cholecystokinin released from enteroendocrine cells of the duodenal mucosa, thereby mixing the bile and duodenal food content. Although the action of cholecystokinin on the SO used to be considered myogenic, Bauer et al. [5] demonstrated that the effect of cholecystokinin was not mediated by a direct myogenic action but by mural or extrinsic nerves, or hormones. In the SO of the opossum, which is considered to actively expel bile, action potentials have been generated in response to cholecystokinin, but hormonal effects may differ from species to species.

**Correlation of Motility of the SO and Duodenum**

Motilin released from the duodenal mucosa exerts a unique action which is quite different from other gastrointestinal hormones. When phase III migrates within the duodenum, the plasma concentration of motilin reaches its peak and coordinates gastrointestinal motor and secretory functions during fasting by augmenting and consolidating gastric phase III and contracting the gallbladder to expel the condensed bile into the duodenum [6, 7]. Exogenous motilin administered during phase II induces premature phase III [8].

Many previous reports have addressed the relationship between the MMC and SO motility [9]. When phase III goes through the duodenum, the SO shows strongest contractions synchronous to the duodenal smooth muscle. During this time the SO is apparently dependent on the duodenal musculature. During phase I, however, the SO continues to independently contract, while the duodenum is in complete quiescence.

**SO Function Tests**

Historical methods to test SO functions include intraoperative perfusion through a biliary catheter, cineradiography, and electromyography of the SO. Some tests which are currently available and practical are herein described.

**Morphine Prostigmin Test (Nardi Test)**

Morphine (10 mg) and Prostigmin (1 mg) are given intramuscularly to stimulate SO contraction and pancreatic secretion in part. A more than four times increase in the serum concentration of AST, ALT and/or amylase associated with generation of abdominal pain are regarded as positive. Although this test is simple and practical, it has been claimed that the specificity and reproducibility of this test are rather low, because it may produce SO spasm associated with nonspecific abdominal pain due to bowel spasm [10].

**Perfusion Manometry**

Perfusion manometry using a side hole catheter coupled with a pneumatic/hydraulically capillary infusion system enabled us to conduct a variety of research in the diagnosis and pathophysiology of SO motility disorders in the early 1980s. Employing a triple-lumen catheter with three side holes located 2 mm apart, Touli et al. [11] demonstrated that 55–60% of the SO phasic waves exhibited downward propagation, and proposed manometric criteria for the diagnosis of SO dysfunction (table 1). Aspiration of one of the triple lumens and separate performance of manometry and sphincterotomy were reported to be effective to reduce a relatively high incidence of acute pancreatitis as a complication of manometry [12]. A remarkable recent advance is the development of a ‘sleeve’ catheter which can be retained within the human SO and thus allows for prolonged SO manometry [13].

| **Table 1. Manometric criteria of SO dysfunction** |
|-------------------------|-----------------|
| Basal pressure          | ≥40 mm Hg       |
| Frequency of phasic waves | >7/min (tachyoddia) |
| Rate of retrograde propagation | >50%            |
| Response to cholecystokinin | paradoxical    |

(Dys)functions of the Sphincter of Oddi
Microtransducer Manometry

High-fidelity semiconductor manometry is possible in the SO, bile duct, and pancreatic duct [14]. Although the high costs are a drawback of the microtransducer, the apparatus is simple and associated with fewer artifacts without the need for a perfusion system. Ogawa and Tanaka [2] and Tanaka et al. [15, 16] developed a new method of prolonged biliary manometry by placing a microtransducer catheter within the bile duct, thus enabling us to conduct pharmacological studies with stimulation by morphine and cerulein and biliary pressure variation associated with the MMC.

Cholescintigraphy

Cholescintigraphy with the use of a radioisotope secreted into the bile (e.g. 99mTc-DISIDA) is a noninvasive method to study SO function. However, cholescintigraphy does not accurately reflect SO function when the gallbladder is in place. In patients with previous cholecystectomy SO functions are evaluated by using hepatic hilum-to-duodenum transit time or a more complex scoring method. The role of these methods is often determined by SO manometry as a gold standard, but their usefulness and reliability are still controversial. Craig et al. [17] showed that the sensitivity of cholescintigraphy in the diagnosis of SO dysfunction was only 13–38% compared with the manometric diagnosis with basal pressure >40 mm Hg as a gold standard.

SO Dysfunction

SO dysfunction causes intermittent or sustained biliary-type pain mostly after cholecystectomy. SO dysfunction includes benign SO stenosis accompanied by histological fibrosis in the SO and functional stenosis associated with no histological changes. Both of these types of SO dysfunction may produce either pain alone or pain associated with abnormal elevation in liver and/or pancreatic enzymes. The Milwaukee classification, which distinguishes three types of SO dysfunction according to the presence or absence of liver dysfunction, bile duct dilatation, and delayed drainage of contrast medium injected into the bile duct during endoscopic retrograde cholangiopancreatography (ERCP), in addition to abdominal pain is often used to characterize patients (table 2) [18]. Manometric abnormalities are noticed in 65–95% of type I patients, 50–63% of type II, and 12–28% of type III patients [19].

Benign SO Stenosis

Benign SO stenosis is characterized by hypertrophy of fibrous tissue within the SO, causing permanent stenosis and thus leading to bile duct dilatation, liver dysfunction, acute cholangitis, and/or formation of common bile duct stones. Endoscopic findings of the duodenal papilla are basically normal and ERCP cannulation is usually possible. However, delayed drainage (>45 min) of contrast medium injected into the bile duct during ERCP is often noticed. SO stenosis corresponds to type I of the Milwaukee classification, and the manometric diagnosis is made when SO basal pressure is >40 mm Hg. However, empirical clinical and manometric criteria are not completely consistent. One study reported that basal pressure is >40 mm Hg in 65–95% of type I patients [20]. The clinical response to endoscopic sphincterotomy is very good, usually resulting in complete relief. Current understanding is that we do not necessarily have to perform manometry in this group of patients, if the diagnosis is made by the aforementioned

<table>
<thead>
<tr>
<th>Type</th>
<th>Biliary-type pain</th>
<th>Abnormal LFT</th>
<th>Bile duct dilatation</th>
<th>Delayed drainage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Type II</td>
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<tr>
<td>Type III</td>
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LFT = Liver function test with ALT or AST >2× normal on two or more occasions; bile duct dilatation = common bile duct diameter >12 mm on ultrasonography or >10 mm on direct cholangiography; delayed drainage = drainage of contrast medium after ERCP delayed for >45 min.

* One or two factors positive.

Table 2. Milwaukee classification of SO dysfunction

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clinical criteria. On the contrary, negative manometry may be misleading in the diagnosis of type I SO dysfunction [19, 20].

SO Dyskinesia

The author would like to use the term SO dyskinesia to represent type II and III SO dysfunction of the Milwaukee classification. Manometry is really needed to make the diagnosis of SO dyskinesia, using criteria proposed by Toouli et al. [11] (table 1). SO manometry is reported to be abnormal in 50–63% of type II and 12–28% of type III patients [19]. SO dysfunction is an intermittent disease which becomes symptomatic from time to time. It is difficult to verify whether short-time SO manometry is reproducible and effective to document the intermittent pathology of SO dysfunction.

Endoscopic sphincterotomy was reported to be effective in patients with abnormal SO manometry in many publications. However, the effect of sphincterotomy has subsequently been questioned even in those with positive SO manometry. Toouli et al. [21] randomized 81 patients with suspected SO dysfunction after manometry to either endoscopic or sham sphincterotomy and followed them up with repeated SO manometry at 3 and 24 months. Since sphincterotomy relieved pain of SO stenosis (basal pressure >40 mm Hg; relief in 11 of 13 patients) more frequently than the sham procedure (relief in 5 of 13 patients), but not in those with dyskinesia or normal manometry, they concluded that sphincterotomy was useful only in patients with SO stenosis.

Endoscopic sphincterotomy is more often complicated by acute pancreatitis and/or perforation in patients with SO dyskinesia than in those with common bile duct stones. Thus, complete sphincterotomy is often difficult, and unexpectedly early restenosis may occur. Manoukian et al. [22] reported that 4 of 85 patients with type II SO dysfunction with abnormal basal pressure observed for 7 ± 3 years after sphincterotomy had recurrence of pain and showed SO basal pressure elevation again in only 4 months. Such very early recurrence may contribute

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Fig. 1. Pressure readings in the bile duct and duodenum recorded with a catheter having two microtransducers placed in the common bile duct and duodenum in a patient with SO dysfunction. a Dual pharmacological study with morphine and cerulein (a cholecystokinin analogue). Morphine (0.2 mg/kg i.m.) induces premature phase III activity in the duodenum and raises biliary pressure due to spasm of the SO. Cerulein (0.1 μg/kg i.v.) relaxes the SO and decreases biliary pressure. The severity of pain following morphine parallels the change in biliary pressure reflected by the pain score. After endoscopic sphincterotomy neither biliary pressure elevation nor pain appears even after the administration of morphine (data not shown). b Biliary pressure shows a transient but significant elevation during phase III of the duodenal MMC. This pressure elevation is associated with a reproduction of pain as demonstrated by pain scores. Pressure elevation and pain do not occur after endoscopic sphincterotomy (data not shown).
to the unfavorable long-term outcome of sphincterotomy in this group of patients.

The author considers that biliary-type pain in SO dysfunction originates from increased biliary intraluminal pressure. The diagnosis of SO dysfunction should rely on the reproduction of pain during pharmacologically induced or physiological elevation of biliary pressure. The rate of pain relief by sphincterotomy reached 92% after the diagnosis based on the reproduction of pain parallelly occurring during phase III of the duodenal MMC, a transient elevation in biliary pressure measured with duodenal pressure documenting the accompanied by reproduction of pain type of pain in patients. Although this method has a drawback, i.e. the long waiting time required for the appearance of spontaneous phase III of the duodenal MMC, sensitivity and specificity may be higher than for any other diagnostic tool of SO dysfunction. However, verification of the usefulness of this microtransducer in diagnosis needs a long study period, because only a few patients with suspected SO dysfunction are treated per year.

SO manometry and endoscopic sphincterotomy are effective to treat SO dysfunction, but symptoms of the patient must be severe enough to justify these invasive procedures for diagnosis and treatment. Recent studies reported that pediatric patients with relapsing abdominal pain may be managed by cholecintigraphy and/or SO manometry followed by sphincterotomy when indicated. However, most pediatric patients have their gallbladder in place, disabling the diagnostic utility of cholecintigraphy. Moreover, in children normal ranges of manometric parameters of the SO remain to be determined. Vitton et al. reported that many of the patients with SO dysfunction could be managed conservatively without sphincterotomy: cholecintigraphy was abnormal in 54% of 59 patients with postcholecystectomy pain but only 23% underwent sphincterotomy.

References


