SPHINCTER OF ODDI: UNDERSTANDING ITS’ CONTROL, FUNCTION AND DISEASE

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Abstract

The most common functional disorders of the biliary tract and pancreas relate to the activity of the sphincter of Oddi. The sphincter of Oddi is a small smooth muscle sphincter strategically placed at the junction of the bile duct, pancreatic duct and duodenum. Disorder in its motility is called sphincter of Oddi dysfunction. Clinically this presents either with recurrent abdominal pain or episodes of recurrent pancreatitis. Manometry may identify the motility abnormality and treatment by division of the sphincter is associated with good long term results.

Introduction

The most common functional disorders of the biliary tract and pancreas are associated with disordered motility of the sphincter of Oddi. Manometry of the sphincter has been central in our understanding of both normal and abnormal sphincter of Oddi activity.

Sphincter of Oddi Function

The sphincter of Oddi has three main functions; the regulation of flow into the duodenum, prevention of reflux from the duodenum to the bile and pancreatic duct and filling of the gallbladder. Manometric studies in humans have shown that there has a basal pressure of 10 mmHg over which are superimposed contractions with a frequency of 2~6/min and amplitude of 50~140 mmHg above duodenal pressure. These contractions are mainly in an antegrade direction (Fig. 1). Bile flow occurs mainly in between contractions when the pressure in the bile duct overcomes the low basal pressure. The phasic contractions expel small volumes of bile and thus maintain the opening of the bile duct free of crystals or debris. Furthermore, this prevents any reflux of duodenal content into the bile or pancreatic ducts. Modulation of the sphincter of Oddi basal pressure causes filling of the gallbladder and decrease causes flow of bile and pancreatic juice into the duodenum.

During fasting the sphincter of Oddi exhibits a cyclical activity pattern which is distinct from, but coincident with, duodenal inter-digestive activity. The sphincter of Oddi contracts throughout all phases of the inter-digestive cycle. The frequency increases just prior to Phase III of the duodenal activity, thus increasing the resistance of reflux of duodenal contents into the ducts. Feeding enhances the flow of bile through the sphincter with an overall
decrease in sphincteric pressure. In humans, this is characterized by a decrease in basal pressure, and a fall in contraction amplitude\(^1\). These changes produce a decrease in resistance and facilitate flow from the ducts into the duodenum.

**Control of Sphincter of Oddi Motility**

Like the gallbladder its control is complex and involves neural and hormonal pathways.

**1. Gut Hormones and Peptides**

Cholecystokinin produces inhibition of the phasic contraction and a decrease in basal pressure. The mechanism of its action appears to be via a stimulation of non-adrenergic, non-cholinergic inhibitory neurones. Secretin decreases the activity of the sphincter in most species with no effect on the rabbit or cat sphincter. In human it causes an initial excitation followed by relaxation. Other hormones and peptides such as Gastrin, Motilin and Octreotide have been reported to alter the contraction of the sphincter of Oddi.

**2. Neuronal Control**

Parasympathetic innervation is the main extrinsic innervation of the sphincter. Vagotomy experiments in animals have shown mixed results, with both excitatory and inhibitory effects.\(^2\) Vagal stimulation induces sphincter contraction. After administration of sympathetic blockers and atropine, vagal stimulation relaxes the sphincter suggesting a non-cholinergic non-adrenergic effect. These results indicate that vagal innervation to the sphincter is mainly excitatory, however there exists an underlying inhibitory action via non-cholinergic non-adrenergic nerves.

Sympathetic blockade on its own does not influence sphincter of Oddi activity, suggesting that the sympathetic system does not have a major regulatory role under normal circumstances. Intrinsic nerves have a prominent role in controlling sphincter of Oddi activity.

Studies have identified a role for nitric oxide as the major non-cholinergic non-adrenergic inhibitory transmitter acting on the sphincter of Oddi. Nitric oxide donors such as sodium nitroprusside induce relaxation of the possum sphincter, whereas inhibition of nitric oxide synthase with L-arginine analogues reduces the relaxation induced by

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\(^1\) Gut Hormones and Peptides

\(^2\) Neuronal Control
transmural electrical stimulation.

Electrical stimulation of the gallbladder produced a fall in sphincter of Oddi pressure in dogs. Subsequently studies in humans demonstrated that distention of the gallbladder decreased resistance to flow by reducing the amplitude and decreasing the basal pressure, thus promoting the flow of bile. This response of the sphincter of Oddi to gallbladder distention, cholecystic-sphincter of Oddi reflex, is mediated via neural connections between the gallbladder and the sphincter. This connection was abolished by application of local anaesthetic to the common bile duct.

Distention of the stomach causes sphincter of Oddi contraction, thus producing a resistance to reflux of duodenal contents through the sphincter of Oddi. It has been identified as the pylori-sphincter reflex. This response is abolished by atropine suggesting mediation by cholinergic nerves.

Distention or the installation of dilute hydrochloric acid into the duodenum of humans results in sphincter spasm. This entero-sphincter reflex is abolished by atropine.

**Clinical Presentation of Sphincter of Oddi Dysfunction**

Sphincter of Oddi dysfunction presents with symptoms and signs suggestive of either biliary or pancreatic disorder. Patients who present with biliary SO dysfunction typically experience recurrent biliary type pain. This often starts on average 4 to 5 years after cholecystectomy which is usually done for gallstone disease. Most of these patients are female. The episodes of pain are usually severe, and episodic. The patient may only experience 3 to 4 episodes of pain each year. The pain does not usually occur daily or weekly although some individuals may experience runs of pain episodes over a month or so and then not have another episode for a few months. In many instances the pain episodes may be associated with an abnormal rise in liver enzymes, either the AST or ALT or both. It is unusual to have a rise in bilirubin. Furthermore, some patients volunteer that the episode of pain was induced by opiate like drugs taken for pain relief. This is not a common association but one worth looking for, as the treatment is avoidance of the provoking substance.

Pancreatic sphincter of Oddi dysfunction presents as recurrent episodes of pancreatitis without obvious cause and these patients are often given the diagnostic label of idiopathic recurrent pancreatitis.

Similar to the patients with biliary SO dysfunction the majority of these patients are female and they have often had a cholecystectomy as empirical treatment for pancreatitis (ie on the assumption or demonstration of micro-lithiasis). However despite this treatment the episodes of recurrent pancreatitis persist and are often quite debilitating, often requiring hospital admission for the control of the symptoms.

**1. Investigation**

Manometry of the sphincter of Oddi underpins our understanding of the motility disorders associated with sphincter of Oddi dysfunction. It is the only objective measure which has stood the test of time in predicting outcome from treatment of SO dysfunction.

Successful sphincter of Oddi manometry is only achieved when the combined efforts of an experienced ERCP endoscopist are combined with the skills of an experienced clinician or scientist in manometry. Both aspects of the investigation require the skills of each, and often cannot be executed by a single individual. It has been my experience that in units where manometry has been tried and found wanting this important collaboration has not existed and the results have often been too difficult to interpret or the complication rate unacceptable, thus the proce-
dure has been abandoned.

It is also our experience that for optimal investigation the ERCP (ie the diagnostic investigation) and manometry need to be separated in time in order to optimise each of the procedures. Not only that but also this minimises the time of the study on each occasion and consequently reduces the complication rate. Both the endoscopist and the manometrist need to be patient during the procedure in order to achieve a successful tracing that can then be read using pre determined objective criteria. The person responsible for the manometry needs to control the procedure and instruct the endoscopist regarding positioning the recording catheter as well as the length of the recording. The manometrist needs to have an understanding of the recording equipment, ensure that the bubbles have been removed from the system, that the perfusion pressure is that appropriate for sphincter of Oddi study and that the patient has not been given drugs which may interfere with the recording.

Once the procedure has been completed (in our department usually after 10 to 15 minutes) the manometrist needs to objectively evaluate the recording and give a diagnosis using the previously defined criteria. The most clinically

Fig. 2. Manometric recording from the sphincter of Oddi demonstrating an abnormally elevated basal pressure.

Fig. 3. The sleeve SO manometry assembly - This is characterised by back perfusion so that fluid does not enter the ducts.
useful finding of abnormality is that of an abnormally elevated sphincter of Oddi basal pressure (equal or above 40 mmHg) (Fig. 2). This value defines an abnormal sphincter of Oddi amenable to treatment.

Sphincter of Oddi manometry has been associated with a variable complication rate which for pancreatitis ranges from 3% to 30%. The reasons for this complication are partly explained by technique as described above. However in addition it is thought that the perfusion of fluid in to the duct may contribute as well as the underlying etiology of the disorder.

In order to address some of these concerns we have developed a miniaturized sleeve assembly which records accurately SO pressures. The assembly is back perfused so that fluid does not enter the ducts hence removing perfusion as a possible cause of pancreatitis (Fig. 3). Furthermore, the sleeve produces a more stable manometric recording making interpretation of recordings easier for the non expert. Comparison studies with triple lumen manometry resulted in similar frequency in the diagnosis of SO dysfunction indicating that this catheter may replace triple lumen manometry.

**Management**

Apart from symptomatic treatment there is no effective medical therapy for these patients. Investigation of the sphincter of Oddi by manometry provide the only currently available objective means of identifying patients who will respond to treatment.

The most significant manometric abnormality recorded from either group of patients is an abnormally elevated sphincter basal pressure which signifies SO stenosis. For the biliary group the stenosis is in the biliary sphincter whilst for the pancreatic group it is either in both biliary and pancreatic sphincter or only in the pancreatic component.

**Treatment**

There have been 3 major studies that have clearly defined the role of sphincter of Oddi manometry in the selection of patients who will respond to treatment. Two prospective randomised studies, which included a control group of subjects who had no treatment have shown that when recordings from the biliary sphincter of Oddi show an abnormally elevated basal pressure then endoscopic sphincterotomy of the biliary sphincter is associated with excellent long term relief of symptoms in over 90% of patients. In patients with eligible clinical symptoms and signs neither a normal manometry nor one of the other abnormal manometric findings was associated with a positive clinical outcome following sphincterotomy. Furthermore no other investigation, (eg liver function tests, ultrasonography, biliary scintigraphy, morphine neostigmine test or botulinin toxin injection) have been shown to have the same specificity and sensitivity in predicting outcome as has manometry. Hence in this group of patients manometry of the biliary sphincter is currently the only objective investigation that selects patients who will respond to sphincterotomy.

For patients with recurrent pancreatitis there has been one prospective cohort study which has clearly demonstrated the role of manometry in patients who will respond to division of the sphincter of Oddi. In this study patients were selected for the operation of transduodenal sphincteroplasty and pancreatic septoplasty on the basis of the manometric findings. In patients in whom there was an abnormally elevated basal sphincter of Oddi pressure the sphincter
of Oddi in both the bile duct and pancreatic duct was divided.

Long term follow up has been associated with no further episodes of pancreatitis in over 90% of the patients. Manometry was the only objective test available that allowed selection of these patients for treatment.

More recently division of both the biliary and pancreatic sphincters has been achieved safely via an endoscopic approach. Initial data indicates that the endoscopic division does not provide comparable results to the operative approach. Comparative data in the form of a randomised trial are required.

Conclusion

Sphincter of Oddi dysfunction is an uncommon but significant disorder that produces recurrent biliary type symptoms and recurrent episodes of pancreatitis. Manometry of the sphincter of Oddi objectively identifies those patients who will respond to treatment by division of the Sphincter of Oddi.

References

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