

## A MATTER OF OPINION

# Sphincter of Oddi Dysfunction: Overdue for an Overhaul

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Sphincter of Oddi dysfunction (SOD) may be the most misunderstood and abused diagnosis in gastroenterology. U.S. referral centers for hepatobiliary and pancreatic (HBP) disorders see large numbers of patients with abdominal pain syndromes who have been told that they have SOD. The HBP clinic has become the final common pathway for many irritable bowel syndrome (IBS) patients. The classification of SOD is badly in need of an overhaul. It dates back to the landmark study of Geenen *et al.*, published in the *New England Journal of Medicine* in 1989 (1), in which 47 postcholecystectomy pain patients thought to have SOD were prospectively randomized to endoscopic sphincterotomy (ES) or sham sphincterotomy (Sham). Of 23 patients with increased biliary sphincter pressures, determined by sphincter of Oddi manometry (SOM), 10 of the original 11 who underwent ES remained pain-free at 4 yr. Seven others who subsequently underwent ES (after the study) also benefited. The authors concluded that 17 of 18 patients with SOD verified by manometry benefited from ES. However, patients with normal biliary sphincter pressures did not (results equivalent to Sham).

### SOD: ROSETTA STONE OR PANDORA'S BOX?

The 1989 paper (1) spawned a cottage industry for HBP centers, based on the so-called Milwaukee Criteria. Unfortunately, as seems to be the rule after promising initial data, subsequent studies were less encouraging about the results of SOM and ES in SOD. The patient population is much more heterogeneous than initially thought. SOM and ES for SOD have been associated with high rates of post-ERCP pancreatitis (PEP) in some published series (2, 3). A subset of SOD patients have pancreatic sphincter hypertension. SOM is indicated in the work-up of idiopathic recurrent acute pancreatitis when other structural and metabolic causes have been excluded (4). The putative role of SOD in pancreatitis is beyond the scope of this discussion, whose focus is biliary SOD (a.k.a. biliary dyskinesia). However, there is agreement that if SOM is being performed to investigate recurrent pancreatitis, both the biliary and pancreatic sphincter pressures should be measured. SOM is simply a “snapshot” of sphincter behavior during a very short window of time. A recent study of 12 patients with previously normal SOM showed evidence of

SOD in five (42%) retested after a median of 337 days (four had pancreatic sphincter hypertension, and one had elevated biliary and pancreatic sphincter pressures) (5). This observation reinforces earlier concerns about the reproducibility of SOM (6). To confound these issues even more, the sphincter of Oddi is not symmetrical, with implications for how pressures are measured and interpreted (7, 8). Much like particle physics, the deeper you delve into SOD, the more fantastic it gets.

### RISK, REALITY, AND CLASSIFICATION ABUSE

Most of us who perform SOM recognize that it is the “high risk” end of our “business.” The “Holy Grail” of SOD is a sensitive and specific, noninvasive test that will identify patients likely to benefit from ES. Thus far, such a test has not materialized. Thankfully, the morphine-prostigmine provocative test (Nardi Test) is extinct. Biliary ultrasound following secretory stimulation and quantitative hepatobiliary scintigraphy have low sensitivity and specificity (9, 10). So, for now we are stuck with a quite invasive test (ERCP with SOM) that carries significant risk of PEP. Pancreatic duct (PD) stenting after SOM appears to protect against severe PEP (11). In my practice, the placement of long (6–8 cm), unflanged, single pigtail, three French (Fr) gauge PD stents has become routine after SOM, *whether or not sphincterotomy is performed*. Although it would make me a happy man to see our manometry equipment consigned to the scrap heap, the reality of current HBP practice is that a subset of patients meet the Milwaukee Criteria for SOD, and merit study. However, I spend a lot of time in my clinic talking patients out of having SOM performed. This is more easily said than done, as many travel long distances to our referral center, bringing with them unrealistic expectations of what ERCP, SOM, and ES can do for them. Too often these expectations are built on the unfounded optimism of their referring physicians. Patients with chronic functional abdominal pain are often abandoned by their doctors, and they get little sympathy—or help—from pain clinics. We need to do better by these often difficult and challenging individuals. In the case of SOD, we can start by better patient selection for SOM. According to the Milwaukee Criteria for evaluating postcholecystectomy pain, SOD requires “typical biliary pain” with or without: elevation of aspartate aminotransferase

**Table 1.** Milwaukee Classification of Sphincter of Oddi Dysfunction

Type	Type of SOD		
	I	II	III
Typical pain	+	+	+
LFTs $>1.5 N \times 2$	+	+	—
Bile duct $>12$ mm	+	—	—

(AST) or alkaline phosphatase (alk phos) to  $\geq$ two times the upper limit of normal on two separate occasions with normalization within 24–48 h, and dilatation of the extrahepatic bile duct to  $\geq 12$  mm diameter (Table 1). (The liver function test (LFT) abnormality requirement was subsequently diluted to either transaminase (alanine aminotransferase (ALT), AST) or alk phos  $\geq 1.5$  times normal (12)). The original classification included bile duct drainage time after cholangiography. This has been shown to be inconsistent and unreliable (13); most investigators have dropped drainage time as a criterion for SOD. To me, “typical” biliary pain is clearly misunderstood. It is not lancinating pain lasting seconds, neither is it constant pain lasting all day, with or without exacerbations. It is not exacerbated by eating, relieved by defecation, or accompanied by diarrhea. In my experience, biliary pain rarely crosses the midline and is never a purely left-sided discomfort. Typical biliary pain does not respond to anticholinergic antispasmodics (*e.g.*, dicyclomine, hyoscyamine), antacids, H<sub>2</sub>-blockers, or proton pump inhibitors (PPIs). In the Rome II classification of SOD, the typical pain is said to last from 30 min to several hours, with pain-free intervals between attacks (14). (In fairness, I must state here that some experts in the field consider the nature of the pain—intermittent *versus* constant—irrelevant to the diagnosis of SOD). The Milwaukee Criteria require that LFTs normalize between attacks. However, patients are frequently labeled as having type II SOD on the basis of a pain syndrome plus mildly elevated serum transaminases or alk phos, which never normalize. Many of these patients are obese and have a fatty liver (steatosis or steatohepatitis). Twelve millimeters is an impressively dilated bile duct: the upper limit of normal for common bile duct diameter is 7 mm (15). Under the original Milwaukee Criteria, a bile duct of 8 mm or 10 mm does not “make the cut” as abnormal. We used to accept a few millimeters of bile duct enlargement as inevitable after cholecystectomy. However, this was probably an “urban legend.” A 1999 study from England showed no difference between pre- and postlaparoscopic cholecystectomy bile duct diameter in a large cohort of patients (16). Most ERCP endoscopists would consider a 10 mm bile duct “generous” and have a low threshold to performing ES, knowing that the risk of PEP is low in this setting. Indeed, ES is often justified for access to “trawl” the duct for small stones and sludge. This is where we start down the slippery slope of changing our diagnosis in mid-work-up from SOD to papillary stenosis or biliary microlithiasis.

## A CLASSIFICATION IN TROUBLE: THE LEANING TOWER OF SOD

Type I is not an episodic sphincter disturbance: it is a mechanical obstruction to biliary outflow (papillary stenosis). We rarely see type I SOD at referral centers because it is managed effectively in the community by ES without SOM. That leaves type II and type III SOD. The best data available (17) suggest that patients with true type II SOD have an 85% chance of pain relief by ES if their manometry is abnormal, but only 35% if the sphincter pressures are normal. SOM is “highly recommended” in type II patients. Type III patients—those with “typical biliary pain” alone—comprise 90% of our SOD workload in the Duke HBP Disorders Clinic. As the trite—but nonetheless true—saying goes, “No one ever died of type III SOD.” Unfortunately, some patients *have* died from necrotizing pancreatitis complicating ERCP done as part of the investigation of obscure abdominal pain. Type III SOD patients are a high-risk, low-yield group when it comes to ERCP. Fewer than half of type III patients investigated at Duke University Medical Center have abnormal manometry, and even those have only (at best) a 50:50 chance of sustained benefit from ES. The likelihood of benefit if their pressures are normal is abysmal,  $<15\%$  (*i.e.*, worse than placebo). To add to the misery, type III SOD patients have the highest risk of complications of ERCP, principally pancreatitis (18). There are huge differences in success rates for managing type III SOD between specialist centers. For example, Sherman *et al.* (19), in an admittedly small study comparing ES and surgical biliary sphincteroplasty to sham ES (Sham), found that during a 3-yr follow-up, 69% of manometrically proven type II and type III patients undergoing ES or surgical biliary sphincter ablation improved compared to only 24% in the Sham group. Eleven of 19 type III patients (58%) had sustained benefit, which is remarkable. Using a modified classification that considers both biliary and pancreatic sphincter pressures, the same investigators found the frequency of SOD was similar in both their type II and type III patients (59% vs 67%) (20). Several studies have shown that there is nothing “magical” about the 1.5 times normal “cutoff” for abnormal LFTs. Silverman *et al.* (21) found no difference in the frequency of elevated basal sphincter pressures in type II “hybrid” patients (those with pain and marginal LT elevations  $<1.5$  times normal) when compared to those with “true” type II SOD, and recommended that they be considered as identical. Sustained benefit is the desired outcome of sphincterotomy for SOD. Undoubtedly, ERCP followed by a night or two (or longer) in the hospital with abdominal pain has a huge placebo effect. Too many of the published studies on SOD therapy have had depressingly short follow-up. Wehrmann *et al.* (22) found that 70% of patients with type II SOD and 39% of those with type III reported symptomatic improvement 4–6 wk after sphincterotomy. However, at a median 2.5 yr follow-up, the sustained benefit for type II was 60% but only 8% for type III ( $p < 0.01$ ). These investigators found no statistical

difference in abnormal sphincter pressures between type II and type III patients (62.5% vs 50%).

### TYPE III: THE (VISCERAL HYPERALGESIA) TWILIGHT ZONE OF SOD

Two explanations have been offered for the poor correlation between the results of SOM and response to ES in type III SOD: (i) SOD may be a marker for—but not a cause of—pain in type III SOD patients, or (ii) SOD has a causative role in a subset of type III patients, but SOM cannot accurately detect this. Personally, I believe that many patients labeled as having type III SOD have a diffuse gastrointestinal motility disturbance, characterized by visceral hyperalgesia and intolerance of gaseous distention. Desautels *et al.* (23) have shown that patients with type III SOD exhibit duodenal-specific visceral hyperalgesia, with duodenal distension reproducing their symptoms. In an unpublished, retrospective review of hospitalization of type II and type III SOD patients at our institution for severe abdominal pain immediately following ERCP  $\pm$  SOM  $\pm$  ES, one-third had complete resolution of their pain and normal serum amylase and lipase levels the next morning: these individuals behave like they are developing PEP, but they don't. I believe that air insufflation of the gut during endoscopy triggers a "motility storm" in these patients. Their pain is genuine and frequently requires large doses of narcotic analgesics to control. It is hard to believe that cutting the biliary sphincter will cure these individuals of their chronic pain syndromes. The best hope for them may be pharmacologic manipulation of visceral pain sensation, a science that is in its infancy but already making some impressive strides. In those whose pain truly arises from the biliary sphincter, nonablative endoscopic therapy may be feasible. Intrasphincteric nitric oxide injection has been shown to reduce sphincter of Oddi motility in an endoscopic porcine model (24), and a number of investigators have reported encouraging results from injections of botulinum toxin (BoTox<sup>TM</sup>) in dogs (25) and humans (26, 27). As the biliary sphincter cannot be easily defined, "blind" (four quadrant) BoTox<sup>TM</sup> injections into the papillary fold have been tried, with lasting benefit in some type III SOD patients (RA Kozarek, personal communication). However, concerns have been raised about inflammatory reaction provoked by BoTox<sup>TM</sup> injection and the risk of "late" papillary stenosis.

ES has many benefits, but in type III SOD "to cut is (not guaranteed) to cure." As Sherman states in a 2001 review article (17), "The (published) results clearly indicate that the response rate and enthusiasm for sphincter ablation must be correlated with patient presentation and balanced against the high complication rates reported for endoscopic therapy of SOD. Most studies indicate that patients undergoing ES for SOD have complication rates 2–5 times higher than (those) undergoing ES for bile duct stones." Admittedly, PD stenting after SOM  $\pm$  ES appears to reduce the risk, especially

of severe (necrotizing) pancreatitis. The first NIH-funded, multicenter, randomized, prospective controlled trial of endoscopic therapy for SOD is about to start, coordinated from the Medical University of South Carolina. I wish the investigators success: their results just might start to clear the muddy waters of SOD.

### IS THERE LIFE BEYOND SOD?

What happens to type III SOD patients who don't get ERCP? Surprisingly, no one knows. Some of them become "bouncing balls," seeking second and subsequent opinions from multiple referral centers. Others return to their referring physicians, never to be seen by us again. Do their pain syndromes eventually resolve, or do they learn to live with them, like most patients with chronic pancreatitis? No one knows. Following these patients for years is difficult, especially in the United States, with its highly mobile population. Well-constructed, long-term, prospective studies are needed to answer the question. Serious SOD researchers should read Bret Petersen's outstanding evidence-based reviews of the subject (28, 29) before setting forth. To paraphrase Sir Winston Churchill, SOD is "a riddle in a mystery, wrapped inside an enigma." It's time to reshuffle the SOD "deck." Anyone for a Consensus Conference?

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