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Original Article

Sphincter of Oddi Manometry: Reproducibility of Measurements and Effect of Sphincterotomy in the EPISOD Study

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Background/Aims

The reproducibility of sphincter of Oddi manometry (SOM) measurements and results of SOM after sphincterotomy has not been studied sufficiently. The aim of our study is to evaluate the reproducibility of SOM and completeness of sphincter ablation.

Methods

The recently published Evaluating Predictors and Interventions in sphincter of Oddi dysfunction (EPISOD) study included 214 subjects with post-cholecystectomy pain, and fit the criteria of sphincter of Oddi dysfunction type III. They were randomized into 3 arms, irrespective of manometric findings: sham (no sphincterotomy), biliary sphincterotomy, and dual (biliary and pancreatic). Thirty-eight subjects had both biliary and pancreatic manometries performed twice, at baseline and at repeat endoscopic retrograde cholangiopancreatography after 1-11 months. Sham arm was examined to assess the reproducibility of manometry, and the treatment arms to assess whether the sphincterotomies were complete (elevated pressures were normalized).

Results

Biliary and pancreatic measurements were reproduced in 7/14 (50%) untreated subjects. All 12 patients with initially elevated biliary pressures in biliary and dual sphincterotomy groups normalized after biliary sphincterotomy. However, 2 of 8 subjects with elevated pancreatic pressures in the dual sphincterotomy group remained abnormal after pancreatic sphincterotomy. Paradoxically, normal biliary pressures became abnormal in 1 of 15 subjects after biliary sphincterotomy, and normal pancreatic pressures became abnormal in 5 of 15 patients after biliary sphincterotomy, and in 1 of 9 after pancreatic sphincterotomy.

Conclusions

Our data suggest that SOM measurements are poorly reproducible, and question whether we could adequately perform pancreatic sphincterotomy.

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Key Words

Endoscopic retrograde cholangiopancreatography; Sphincter of Oddi dysfunction; Sphincter of Oddi manometry; Endoscopic sphincterotomy

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Introduction

Sphincter of Oddi dysfunction (SOD) can cause pain by impeding pancreatic and bile flow, and is often considered in patients with otherwise unexplained pancreaticobiliary-type pain after cholecystectomy. The diagnosis gained widespread acceptance following the landmark publication by Geenen and colleagues,[1] which introduced the Hogan-Geenen Milwaukee classification system. This system defines 3 types of SOD. Type I refer to patients presenting with elevated liver function tests and dilated common bile ducts. Type II contains one of those criteria, but not both, and type III has none.

Sphincter of Oddi manometry (SOM) is performed during endoscopic retrograde cholangiopancreatography (ERCP) to assess elevated sphincter pressures and has become popular in many referral centers as a guide to therapeutic intervention, because several cohort studies and 3 small randomized trials showed that the results of biliary manometry predicted the outcome of biliary sphincterotomy.[2] No such validation of pancreatic manometry has been reported. The manometry technique itself has been criticized as it provides recordings only for a few minutes in patients who are heavily sedated or anesthetized.

Whether or not manometric readings are reproducible is an important question since the results are used to decide whether or not to perform sphincterotomies. Another key question is whether biliary and pancreatic sphincterotomies, as currently practiced, actually ablate the sphincters effectively. Despite the overwhelming amount of sphincterotomies described in the literature, there is little data reporting repeat manometry status after spincterotomy. One would assume that normalizing the elevated sphincter pressure after sphincterotomy correlates with improved clinical outcomes. Therefore, we aimed to provide data from a recent stringent clinical trial to address these questions of reproducibility and the completeness of sphincter ablation.

Materials and Methods

The Evaluating Predictors and Interventions in SOD (EPISOD) study was an institutional review board approved sham-controlled randomized trial, which enrolled 214 patients in 7 US centers registered on clinicaltrials.gov (NCT00688662).[3] They were aged 18 to 65 years, had burdensome pain more than 3 months after cholecystectomy, and fit the criteria of SOD type III. Patients underwent ERCP by experienced endoscopists, under conscious sedation, modified or full anesthesia, based on local practice. Anesthesiologists were instructed not to use agents of high-dose prescription analgesics (ie, > 1 mg/kg meperidene, > 1 μg/kg fentanyl), anti-cholinergics, smooth muscle relaxants, or glucagon.

SOM was performed by the standard water-perfusion method, using a basal pressure of more than 40 mmHg in both leads to define abnormality in the biliary and pancreatic sphincters. Patients were randomized into 3 arms, irrespective of the manometric findings. Seventy-three were assigned to the sham (no sphincterotomy) group and 141 to sphincterotomy group; 94 of these underwent biliary sphincterotomy and 47 had both biliary and pancreatic (dual) sphincterotomies. Thirty-eight subjects returned to the treating center within a year because of persistent or recurrent symptoms, and underwent repeat ERCP, with both biliary and pancreatic manometries. Results in the sham arm were examined to assess the reproducibility of manometry, and those in the treatment arms to assess whether the sphincterotomies were complete (ie, elevated pressures were normalized).

SAS software version 9.2 (SAS Institute Inc, Cary, NC, USA) was used to perform descriptive statistics and statistical analysis. Variables were described using counts and percentages for categorical data, or means, standard deviations (SD) and medians, interquantile ranges for continuous data.

Results

Data on both the initial and repeat manometries were available from 38 subjects; 14 in the sham arm, 15 after biliary sphincterotomy, and 9 after both biliary and pancreatic sphincterotomy.

Sham Arm: Subjects Without Sphincterotomy

The 14 subjects had a mean age of 32.5 (SD: 11.4) years and all were female. The average time to repeat study was 156.9 (SD: 90.8) days. Of the biliary pressures, 2 remained normal, 5 became abnormal and 7 remained abnormal. Of the pancreatic pressures, 7 remained abnormal, 2 became abnormal, 3 remained normal and 2 became normal (Fig. 1). Thus, 9/14 (64%) biliary pressures and 10/14 (71%) pancreatic pressures were reproducible. Overall, both biliary and pancreatic measurements were reproduced in 7/14 (50%) subjects. The time interval between the initial and repeat manometries was not a predictor of reproducibility.

Subjects with Sphincterotomy

The 15 subjects treated by biliary sphincterotomy had a mean age of 34.1 (SD: 7.1) years, and 14 (93%) were female. Of the
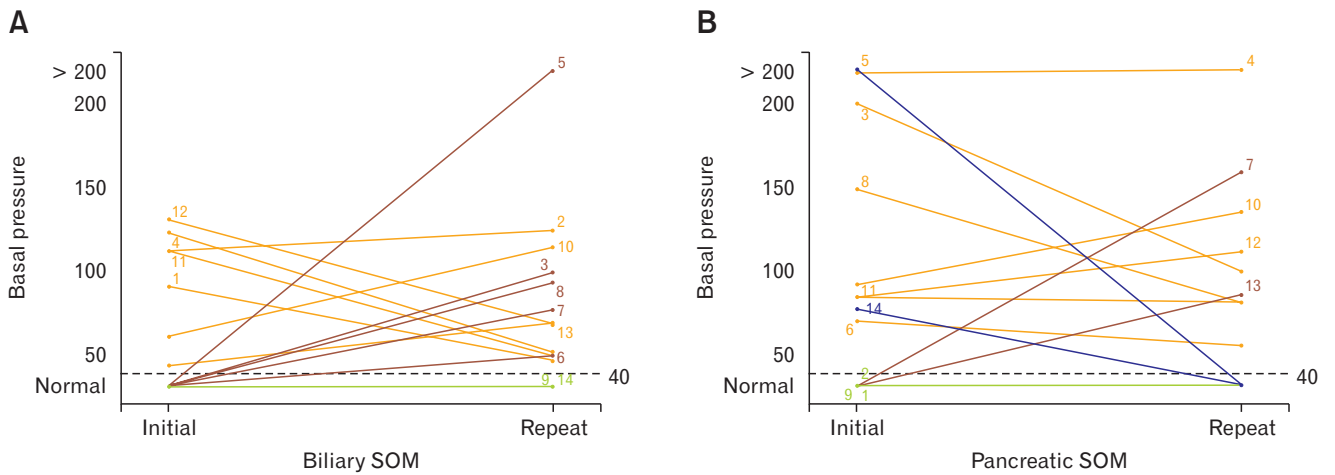
Figure 1. Sham: biliary (A) and pancreatic (B) pressures. Figures represent biliary or pancreatic basal pressure readings during initial and repeat sphincter of Oddi manometry (SOM). A basal pressure > 40 mmHg is defined as abnormal. For clarity, any values over 200 mmHg have been graphed at > 200 mmHg, and all reports of "normal manometry" without actual numbers are recorded as normal.
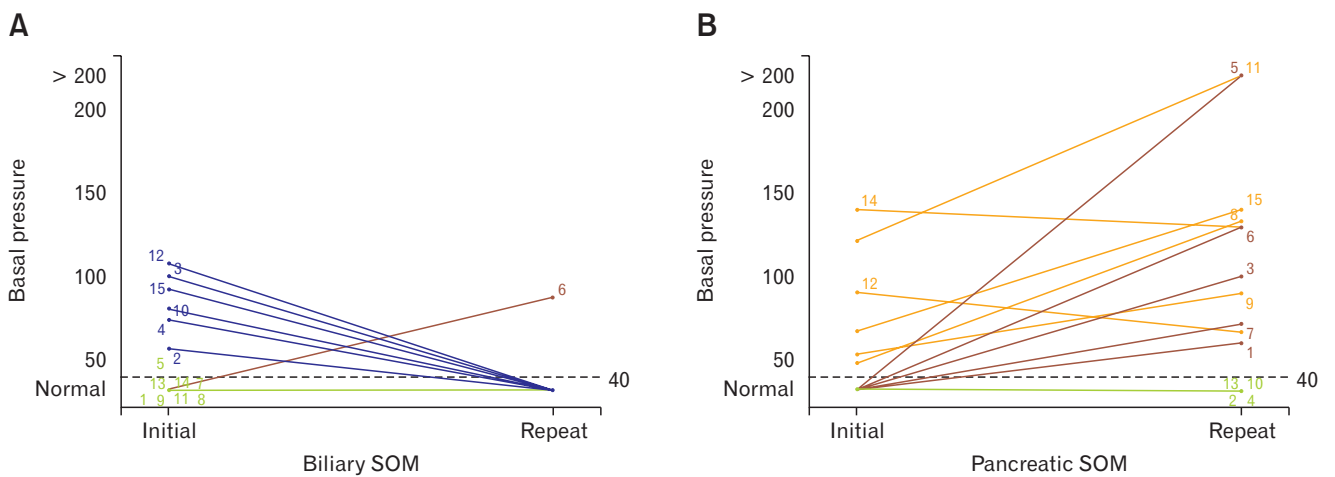

Figure 2. After biliary sphincterotomy: biliary (A) and pancreatic (B) pressures. Figures represent biliary or pancreatic basal pressure readings during initial and repeat sphincter of Oddi manometry (SOM). A basal pressure > 40 mmHg is defined as abnormal. For clarity, any values over 200 mmHg have been graphed at > 200 mmHg, and all reports of "normal manometry" without actual numbers are recorded as normal.

biliary pressures, 8 remained normal, 6 normalized, and 1 became abnormal. Of the pancreatic pressures, 4 remained normal, 6 remained abnormal, and 5 became abnormal (Fig. 2).

The 9 subjects treated by both biliary and pancreatic sphincterotomy had a mean age of 42.3 (SD: 10.8) years, and 8 (88%) were female. Of the biliary pressures, 3 remained normal and 6 normalized. Of the pancreatic pressures, 6 normalized, 2 remained abnormal, and 1 became abnormal (Fig. 3).

Thus, overall, the 12 patients with initially elevated biliary pressures in the biliary and dual sphincterotomy groups all normalized after biliary sphincterotomy. However, 2 of 8 subjects with elevated

pancreatic pressures in the dual sphincterotomy group remained abnormal after pancreatic sphincterotomy. Paradoxically, biliary pressures were reported to become abnormal in 1 of 15 subjects in the biliary sphincterotomy group after biliary sphincterotomy. Similarly, pancreatic pressures became abnormal in 5 of 15 subjects in the biliary sphincterotomy group after biliary sphincterotomy, and in 1 of 9 after pancreatic sphincterotomy.

Discussion

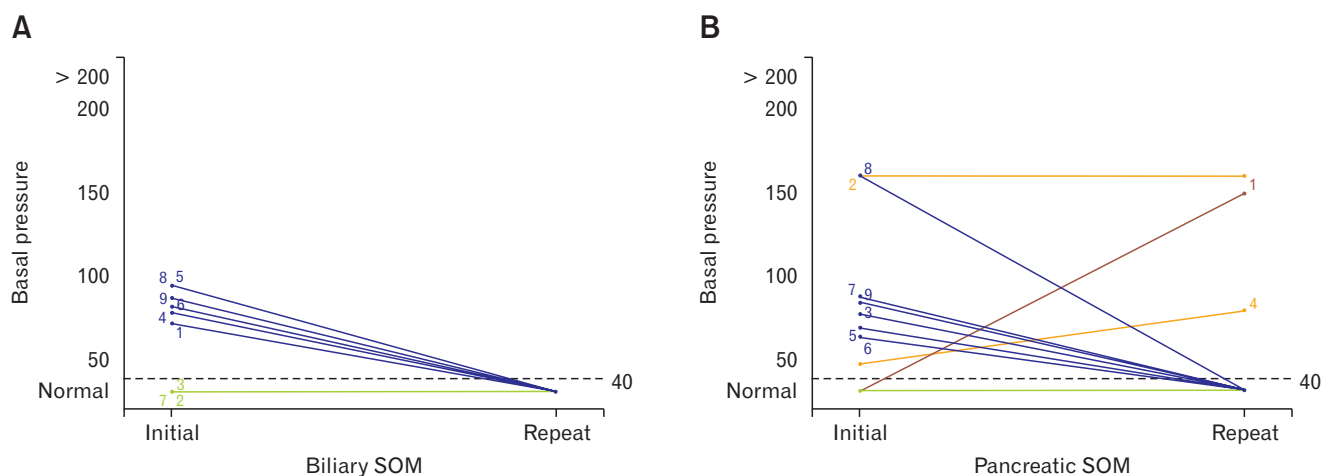Because of the lack of any other diagnostic tool for SOD,

Figure 3. After pancreatic and biliary sphincterotomy: biliary (A) and pancreatic (B) pressures. Figures represent biliary or pancreatic basal pressure readings during initial and repeat sphincter of Oddi manometry (SOM). A basal pressure > 40 mmHg is defined as abnormal. For clarity, any values over 200 mmHg have been graphed at > 200 mmHg, and all reports of "normal manometry" without actual numbers are recorded as normal.

Table. Reported Results of Repeat Sphincter Manometry

	No. of Subjects	SOD type	Sphincter studied	Interval, days (mean)	No. of Reproducible
Geenen et al, 1989[1]	24	II (100%)	Biliary	356	24 (100%)
Guelrud et al, 1990[7]	10	Healthy volunteers	Biliary	7	10 (100%)
Thune et al, 1991[8]	12	I, II (N/A)	Biliary	98 (median)	11 (92%)
Varadarajulu et al, 2003[9]	12	II (42%), III (58%)	Biliary and pancreatic	337	7 (58%)
Khashab et al, 2010[10]	30	I (3%), II (57%), III (40%)	Biliary and pancreatic	493 (median)	12 (40%)
Present study	14	III (100%)	Biliary and pancreatic	157	7 (50%)

SOD, sphincter of Oddi dysfunction.

manometry became accepted by many clinicians as a "gold standard", reinforced by the results of the early randomized studies that showed that the results of biliary manometry correlated with the outcome of biliary sphincterotomy.[1,4,5] That evidence may be less convincing, now that we know that pancreatic pressure abnormalities are equally common, and presumably would need therapeutic attention to provide optimal outcomes.[7] The only study evaluating the value of both biliary and pancreatic manometry (in patients mostly classified as SOD type III) showed that neither were predictive of the outcome of sphincterotomies.[3] It would be helpful to have similarly stringent studies of dual manometry in patients with SOD type II. The putative gold standard loses even more credibility when we examine reproducibility. In this study we showed that basal sphincter pressure results were the same, when repeated, in only 7/14 (50%) of our study subjects. This finding is consistent with 2 other studies in the last decade which involved both sphincters,

but contrasts with the almost 100% reproducibility in earlier studies looking only at the biliary sphincter (Table).[1,7-10] Significant lack of reproducibility is not surprising, since the measurements span only a few minutes and sphincter pressures are known to vary with the migratory motor complex.[11,12] Furthermore, there may be subtle differences in medication use in sedation/anesthesia, confounding the interpretation of sphincter measurements, as opiates are known to cause sphincter of Oddi spasm.[13] However, we were unable to detect any large differences in the opiate doses used between the cases with reproducible manometries and those without. Longer duration ambulatory measurements akin to those used in esophageal testing would be ideal, but have not been attempted because of the likely increased risk of causing pancreatitis.

One assumes that endoscopic sphincterotomy can be helpful only if it eliminates the sphincter pressure. There are few data on this point, despite the huge numbers that have been performed.

Biliary sphincterotomy is easier to perform than pancreatic sphincterotomy, or at least, that the end point is clearer. That fact is supported by our results, which showed normalization of the biliary pressures in all 12 cases. However, that applied to only 6 of 8 on the pancreatic side. Several studies have reported their findings when manometry is repeated on a return visit. Park et al[14] performed dual manometry in 69 patients (out of 313) who returned to their site with residual symptoms after undergoing dual sphincterotomies. Their data also support the idea that biliary sphincterotomy is more effective. Residual hypertension after sphincterotomy was found on the biliary side in only 1 (1%) of patients, but in 35 (51%) on the pancreatic side. Data published in abstract by Catalano et al[15] and colleagues also showed a high proportion of residual sphincter hypertension—69 of 85 (82%)—with most of them (59) on the biliary side. However, the data are difficult to interpret since an entry criterion for the studies was an abnormality in only one or other sphincter, so that we do not have precise comparisons.

A striking and unique finding in our study is that normal manometry actually became abnormal in some patients when retested after sphincterotomy. Biliary pressures become abnormal in 1 of 15 subjects after biliary sphincterotomy. Furthermore, pancreatic pressures became abnormal in 5 of 15 subjects after biliary sphincterotomy, and in 1 of 9 after pancreatic sphincterotomy. Whilst these findings may simply again reflect the demonstrated lack of reproducibility, they at least suggest that scarring may occur with important clinical consequences, as in one report that described patients who developed recurrent attacks of pancreatitis after biliary sphincterotomy for stones.[16]

This study has several limitations. Since it is a nested cohort design, it was not powered a priori. However, the data originate from a well-executed, stringent, randomized controlled trial as opposed to previous retrospective studies, which have substantially more potential for bias. A further point is that, like other similar studies, the repeat manometries were not necessarily performed by the same endoscopist. The main limitation is that the only patients being restudied were those with residual or recurrent symptoms. The results might be different in those responding to sphincterotomy. There is only one report where patients were brought back for repeat manometry irrespective of their clinical status. Toouli et al[4] found residual biliary abnormalities in 19 of 37 patients 3 months after biliary sphincterotomy.

In conclusion, the results of this study adds to the literature undermining confidence in the value of SOM as currently practiced, as the measured sphincter pressure is only a small duration of physiologic active sphincter. Therefore, improvement may be possible if ambulatory measurement methods are developed as for the esophageal motility experience. Lastly, our results also question our ability to perform pancreatic sphincterotomies adequately.

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