# Biliary Scintigraphy Versus Sphincter of Oddi Manometry in Patients with Post-cholecystectomy Pain: Is It Time to Disregard the Scan?

*James Toouli, MBBS, PhD, FRACS*

**Address**
Flinders University, Flinders Medical Centre, Bedford Park, South Australia 5042, Australia.
E-mail: jim.toouli@flinders.edu.au

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Sphincter of Oddi (SO) dysfunction is diagnosed using manometry, and patients with an abnormal SO basal pressure respond well to division of the SO. However, manometry is invasive and is associated with a low, yet significant, incidence of complications. Scintigraphy techniques have been developed with the aim of providing a noninvasive means of assessing SO motility. However, when compared with SO manometry these techniques fall short in sensitivity and specificity for diagnosing SO dysfunction. Furthermore, they do not select patients who will respond to treatment. Consequently, the quest for development of a noninvasive investigation for diagnosis of SO dysfunction continues. In the mean time, improved manometric techniques that enhance reproducibility and reduce complications have been developed.

## Introduction

Sphincter of Oddi (SO) manometry has been used for over two decades to assess SO function in patients with suspected SO dysfunction [1]. In patients with an abnormally elevated basal pressure, endoscopic sphincterotomy is effective therapy [2,3]. However, manometry is invasive and carries a significant risk of pancreatitis that has been reported to be as high as 8% to 17% of patients [4,5]. Hence, noninvasive techniques that can diagnose SO dysfunction have been sought.

## Scintigraphy Versus Manometry

Scintigraphy has been used to assess anatomic or functional obstruction of bile flow. The parameters used to assess obstruction are many and include the time taken to the maximal count over the biliary tract ($T_{max}$), the time taken for 50% of tracer to accumulate over the biliary tract ($T_{1/2}$), the time taken for tracer to enter the duodenum, prolonged excretion of tracer from the biliary tract, and the transit time of tracer from the hepatic hilum to the duodenum. Early studies were encouraging and suggested that this investigation may replace manometry in the diagnosis of SO dysfunction [6–11]. Sostre *et al.* [12] developed a scoring system using six scintigraphic variables to enhance the accuracy and reproducibility of scintigraphy in patients with suspected SO dysfunction. Using this scoring system (Table 1), which incorporates quantitative and qualitative measures, these authors found 100% sensitivity and specificity in 26 patients studied when compared against manometry.

Cicala *et al.* [13] independently developed a separate group of measures and found that the hepatic hilum to duodenum transit time (HDTT) was the best predictor of delayed bile flow into the duodenum. This variable was compared against SO manometry in patients with suspected SO dysfunction after cholecystectomy and found to have a sensitivity of 83% and a 100% specificity when the HDTT was longer than 9 minutes [14]. Other groups have also evaluated the scintigraphic HDTT against a manometric diagnosis of SO dysfunction with variable results [15,16]. In addition, a separate measure used by all groups has been the time of appearance of nucleotide activity in the duodenum (DAT). Similar to the HDTT, it has a variable correlation with abnormal SO manometry [17].

Of particular concern was a report by Pineau *et al.* [18••], who evaluated the specificity of cholecystokinin scintigraphy in 20 asymptomatic patients following cholecystectomy. The evaluation was done according to the parameters set out by Sostre *et al.* [12]. There was good agreement between three observers reading the same scan but poor agreement between repeat scans on the same patient. The authors concluded that scintigraphy was of questionable value in the diagnosis of SO dysfunction.

A further clinically practical issue regarding scintigraphy is its role in predicting outcome after treatment. Unlike patients with manometric diagnosis of SO dysfunction,

**Table 1. Sostre criteria for scoring scans**

| Criterion | Score |
|---|---|
| Peak time | |
| Less than 10 minutes | 0 |
| 10 or more minutes | 1 |
| Time of biliary visualization | |
| Less than 15 minutes | 0 |
| 15 or more minutes | 1 |
| Prominence of biliary tract | |
| Not prominent | 0 |
| Prominent major intrahepatic ducts | 1 |
| Prominent small intrahepatic ducts | 2 |
| Bowel visualization | |
| Less than 15 minutes | 0 |
| 15–30 minutes | 1 |
| More than 30 minutes | 2 |
| CBD emptying | |
| By more than 50% | 0 |
| Less than 50% | 1 |
| No change | 2 |
| Increasing activity | 3 |
| CBD to liver ratio | |
| $CBD^{60} < liver^{60}$ | 0 |
| $CBD^{60} > liver^{60}$ but $< liver^{15}$ | 1 |
| $CBD^{60} > liver^{60}$ and $= liver^{15}$ | 2 |
| $CBD^{60} > liver^{60}$ and $liver^{15}$ | 3 |

CBD—common bile duct.

patients with scintigraphic diagnosis of SO dysfunction have not been subjected to randomized trials of treatment. Consequently, treatment outcome cannot serve as a measure for the usefulness of scintigraphy, and comparison with manometry remains the only means for evaluating its efficacy. Our research group reported in 2002 the results of a study that prospectively set out to compare the Sostre scoring system, the HDTT, and DAT in post-cholecystectomy patients with suspected SO dysfunction, using SO manometry as the objective standard [19••].

## Methods

Patients with a history of cholecystectomy who are aged 18 to 80 years and have suspected biliary SO dysfunction as defined by the Rome II criteria were studied [1]. The Rome II criteria include the presence of at least one episode of biliary pain over the previous 12 months in the absence of any structural abnormality in the biliary tract. Biliary pain was defined as intermittent episodes of severe pain well localized to the epigastrium or right upper quadrant. All patients had undergone endoscopic retrograde cholangiopancreatography (ERCP) within 12 months of study enrollment to rule out common bile duct (CBD) stones. The classification system devised by Hogan and Geenen [20] is based on ERCP findings of a dilated CBD greater than 12 mm and liver function test abnormalities.

### Scintigraphy technique

Patients underwent scintigraphy within 1 month before manometry, the majority within a week. Following a 4-hour fast, patients were administered with an infusion of cholecystokinin–octapeptide (CCK-OP), 20 ng/kg (Kinevac; Bracco Diagnostics, Mississauga, Ontario, Canada) over 45 minutes. Fifteen minutes after the commencement of the CCK-OP infusion, 50 megabecquerels of $^{99m}$Tc-DIDA (diethyl iminodiacetic acid) was injected intravenously. Digital images were obtained in the anterior projection with the patient supine at one frame per minute for 60 minutes using a gamma camera, and the data were stored on computer.

Regions of interest were placed over the right lobe of the liver (excluding visible bile ducts) and CBD to generate time–activity curves. Three-minute composite static images were recorded on film for subsequent visual assessment.

### Reporting of scintigraphy

The Sostre score was assessed by two independent observers, as described by Sostre *et al.* [12]. Both observers had no knowledge of the clinical scenario. This scoring system has six parameters (Table 1):

1. Time of peak hepatic activity obtained from the liver time–activity curve
2. Time at which the intrahepatic biliary tract was first visualized using the static images
3. Prominence or dilation of the biliary tract
4. Time at which the "bowel" was first visualized using static images; this was interpreted as when the duodenum or jejunum was clearly seen
5. Percentage of CBD emptying as determined from the time–activity curve
6. CBD-to-liver ratio; this was determined by visually comparing CBD at 60 minutes with the liver parenchyma at 15 and 60 minutes from the static images

The maximum score is 12. Sostre *et al.* [12] defined a score of 6 or higher as abnormal and a score of 4 or lower as normal, with a score of 5 regarded as an equivocal result.

Another independent observer determined the HDTT and DAT from the 1-minute static digital images. Preliminary studies found no difference when determining these values between the static images and time–activity curves determined from regions of interest at the hepatic hilum and duodenum with subtraction of hepatic activity.

### Manometry

Patients underwent endoscopic SO manometry with a standard triple-lumen catheter (Wilson-Cook, Winston-Salem, NC) with each lumen perfused at 0.13 mL/min, as has been previously described [21]. The assembly was withdrawn through the SO of the biliary duct. Patients in whom cannulation failed or for whom it was only possible from the pancreatic duct were excluded from data analysis.

**Table 2. Mean Sostre score for both observers**

| | SOBP >40 mm Hg (*n*=8)* | SOBP <40 mm Hg (*n*=21)* |
|---|---|---|
| Sostre score | 3.8 (± 0.56) | 2.95 (± 0.29) |
| HDTT, *min* | 5.38 (± 0.93) | 4.62 (± 0.46) |
| DAT, *min* | 10.63 (± 1.11) | 10.0 (± 0.72). |

*Plus or minus standard error of the mean.
DAT—duodenal appearance time; HDTT—hepatic hilum to duodenum transit time; SOBP—sphincter of Oddi basal pressure.

The manometry was assessed by two observers who were aware of the clinical scenario but were blinded as to the scintigraphy results. The basal pressure in the SO was taken as the mean of the lowest pressure points between SO pressure waves within a sustained high pressure zone seen in at least two of the three recording channels on two pull-throughs. The duodenal pressure was used for the zero reference point; recordings were taken for at least 23 minutes. A basal pressure of greater than 40 mm Hg was considered abnormal [22].

Manometric tracings were also assessed for evidence of SO dyskinesia [22], which is seen manometrically as an incoordinate sphincter with several abnormalities, including the following: rapid phasic wave frequency (>7 phasic waves/min) often called tachyoddia; excessive retrograde phasic wave propagation (>50% of phasic waves); high-amplitude phasic waves (>300 mm Hg); intermittent elevations of the sphincter basal pressure that relaxes with smooth muscle relaxants, often termed "SO spasm"; and a paradoxic response to CCK-OP administration (failure to inhibit phasic wave activity). An additional analysis included patients with SO dyskinesia as abnormal, but the main focus of the study defined abnormal as an elevated basal pressure.

### Statistics

Sostre scores, HDTT, and DAT values were compared against manometry and the Hogan and Geenen classification using one-way analysis of variance (ANOVA). Two-by-two tables were constructed to determine sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) for the Sostre scores, HDTT, and DAT with various values defined as abnormal and manometry as the gold standard. Interobserver variation for the scintigraphic score was assessed using correlation coefficient. Correlation coefficient was also used to assess whether there was any relationship between the basal pressure and the scintigraphic variables.

## Results

Thirty-two patients (30 female) entered the study. Fifteen patients were classified as Hogan and Geenen type II, with the remainder type III.

Sphincter of Oddi manometry from the bile duct was successfully performed in 29 of the 32 patients. The three remaining patients were excluded from the analysis. Eight of the remaining 29 patients had an elevated basal pressure (SO stenosis), and a further five patients had evidence of SO dyskinesia.

The mean Sostre scores, HDTT, and DAT were marginally higher in the group with an elevated basal pressure (Table 2), but these differences were not statistically significant ($P$=0.556, 0.491, and 0.779 respectively). For patients with an elevated basal pressure, the sensitivity, specificity, PPV, and NPV for the Sostre score and HDTT are shown in Tables 3 and 4. The results generally showed a low sensitivity, and any adjustments in definitions of abnormal for the scintigraphic measures to improve the sensitivity resulted in a worsening in the specificity.

When the "cut-off" values were applied for the Sostre score as originally defined (*ie*, score ≥6 abnormal, score ≤ 4 normal, score 5 equivocal) [12], the results for observer A and B respectively showed a sensitivity of 38% (PPV, 43%) and specificity of 76% (NPV, 72%), with three of six patients having equivocal scores (only one patient with abnormal manometry). Although in 17 of the 29 scans the observers for the Sostre score differed in their scores, the correlation coefficient ($r$=0.722) showed that the interobserver variability was not marked and mirrored the poor sensitivity and specificity results found from both observers.

The results for the HDTT when a time of 9 minutes or more was defined as abnormal, as defined by Sand *et al.* [15], showed a sensitivity of 13% (PPV, 50%) and a specificity of 95% (NPV, 74%). DAT results mirrored the HDTT findings and are not shown. Inclusion of patients with SO manometric evidence of SO dyskinesia as abnormal did not improve the results for either the Sostre score (taken as the highest value from both observers) or the HDTT (Table 5).

A dilated CBD may increase the capacitance of the biliary tract with alterations of the time–activity curve for the CBD without there necessarily being a sphincter abnormality. When the six patients with a CBD dilated to 12 mm or more were excluded from analysis, the Sostre score specificity improved to 100%, but the sensitivity remained poor at 17% with corresponding PPV (PPV, 50%; NPV, 71%).

There was no correlation between SO basal pressure and HDTT or DAT ($r$<0.01). Also, there was no association between the Hogan and Geenen classification with type II or III patients and the Sostre score and DAT ($P$=0.126, 0.782 respectively). For the HDTT, type II patients had a significantly longer time compared with the type III patients (5.1 ± 0.6 minutes vs 3.0 ± 0.4 minutes, $P$=0.005).

More recently, Rosenblatt *et al.* [23] reported the results from a larger series of patients with suspected SO dysfunction where comparisons were made between

**Table 3. Sensitivity, specificity, positive predictive values, and negative predictive values for Sostre scores for observer A and B with sphincter of Oddi basal pressure greater than 40 mm Hg defined as abnormal**

| | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) |
|---|---|---|---|---|
| Observer A | | | | |
| Score ≥6 | 38% (10 – 74) | 90% (68 – 98) | 60% (17 – 93) | 79% (57 – 92) |
| Score ≥5 | 38% (10 – 74) | 76% (52 – 91) | 38% (10 – 74) | 76% (52 – 91) |
| Score ≥4 | 50% (17 – 83) | 76% (52 – 91) | 44% (15 – 77) | 80% (56 – 93) |
| Observer B | | | | |
| Score ≥6 | 25% (4 – 64) | 86% (63 – 96) | 40% (7 – 83) | 75% (53 – 89) |
| Score ≥5 | 38% (10 – 74) | 62% (39 – 81) | 27% (7 – 61) | 72% (46 – 89) |
| Score ≥4 | 38% (10 – 74) | 52% (30 – 74) | 23% (6 – 54) | 69% (41 – 88) |

NPV—negative predictive value; PPV—positive predictive value.

**Table 4. Sensitivity, specificity, postive predictive values, and negative predictive values for hepatic hilum to duodenum transit time with sphincter of Oddi basal pressure greater than 40 mm Hg defined as abnormal**

| | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) |
|---|---|---|---|---|
| HDTT ≥9 | 13% (1 – 53) | 95% (74 – 100) | 50% (3 – 97) | 74% (53 – 88) |
| HDTT ≥8 | 25% (4 – 64) | 90% (68 – 98) | 50% (9 – 91) | 76% (54 – 90) |
| HDTT ≥7 | 25% (4 – 64) | 81% (57 – 94) | 33% (6 – 76) | 74% (51 – 89) |
| HDTT ≥6 | 38% (10 – 74) | 76% (52 – 91) | 38% (10 – 74) | 76% (52 – 91) |
| HDTT ≥5 | 63% (26 – 90) | 57% (34 – 77) | 36% (14 – 64) | 80% (51 – 95) |

HDTT—hepatic hilum to duodenum transit time; NPV—negative predictive value; PPV—positive predictive value.

**Table 5. Sensitivity, positive predictive values, and negative predictive values for Sostre scores (defined as highest value for both observers) and hepatic hilum to duodenum transit times: results with sphincter of Oddi basal pressure greater than 40 mm Hg and sphincter of Oddi dyskinesia defined as abnormal**

| | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) |
|---|---|---|---|---|
| Score ≥6 | 31% (10 – 61) | 81% (54 – 95) | 57% (20 – 88) | 59% (37 – 79) |
| Score ≥5 | 38% (15 – 68) | 63% (36 – 84) | 45% (18 – 75) | 56% (31 – 78) |
| Score ≥4 | 46% (20 – 74) | 50% (26 – 74) | 43% (19 – 70) | 53% (27 – 78) |
| HDTT ≥9 | 8% (0 – 38) | 94% (68 – 100) | 50% (3 – 97) | 56% (36 – 74) |
| HDTT ≥8 | 15% (3 – 46) | 88% (60 – 98) | 50% (9 – 91) | 56% (35 – 75) |
| HDTT ≥7 | 19% (5 – 46) | 81% (54 – 95) | 50% (14 – 86) | 50% (30 – 70) |
| HDTT ≥6 | 38% (15 – 68) | 81% (54 – 95) | 63% (26 – 90) | 62% (39 – 81) |
| HDTT ≥5 | 54% (26 – 80) | 56% (31 – 79) | 50% (24 – 76) | 60% (33 – 83) |

HDTT—hepatic hilum to duodenum transit time; NPV—negative predictive value; PPV—positive predictive value.

SO manometry, fatty meal sonography, and hepatobiliary scintigraphy. Manometry and scintigraphy were done as described previously, and three measures were used: time to peak of the radionuclide in the bile ducts, halftime, and downslope. Normal values had been determined in prior studies. Fatty meal sonography measured bile duct diameter 45 minutes after ingestion of a fatty meal, and the result was considered abnormal if ductal dilation was seen at this time. Three hundred four consecutive patients with a provisional diagnosis of SO dysfunction were studied. A diagnosis of SO dysfunction was made in 73 patients (24%) using manometry; with scintigraphy, 86 patients were abnormal; and with fatty meal sonography there were 22 abnormal readings. Taking manometry as the standard, a true positive result was obtained in 15 patients using fatty meal sonography and 36 with scintigraphy. Fatty meal sonography gave false-positive results in seven patients and scintigraphy in 50 patients. The sensitivity of fatty meal sonography was 21%, and for scintigraphy it was 49%, whereas specificities were 97% and 78%, respectively. Of the 73 patients with manometric SO dysfunction who underwent sphincterotomy, 40 had a good long-term result with symptom resolution. Of these results, scintigraphy and sonography predicted 85%.

The authors concluded that there is a poor correlation between scintigraphy, sonography, and sphincter manometry. Whereas the noninvasive investigation may predict up to 85% of those that manometry selects, these investigations should not at this stage replace manometry.

A scintigraphic study that used intravenous injection of morphine to stimulate the SO and hence enhance any abnormality has also been reported [24]. The specificity and sensitivity in this study, when compared with manometry, were 81% and 83%, respectively. These results are similar to those of Rosenblatt *et al.* [23] and similarly fall short of the results achieved by manometry.

## Discussion

The potential for noninvasive evaluation of patients with suspected biliary SO dysfunction is attractive, especially with the advent of magnetic resonance cholangiopancreatography, which can reliably image the biliary tract to exclude retained CBD stones, avoiding the need for ERCP [25]. If scintigraphy and any other noninvasive technique were to prove sensitive and specific, they could be used either as screening tests, with SO manometry performed on patients in whom the scintigraphic findings were equivocal, or as the test that leads to treatment. However, in current practice, there appears to be poor correlation between scintigraphy and manometry and, more importantly, scintigraphy appears to undercall patients who, on manometry, have been shown to have SO dysfunction. Few or no data are available on other noninvasive techniques.

The scintigraphy study by Corazziari *et al.* [14] reported excellent results using the HDTT, but neither our study [19••] nor the study by Rosenblatt *et al.* [23] reproduced their results. Our protocol differed from the Italian study in two ways. We used static images to determine the HDTT by visually assessing when the tracer first reaches the hepatic hilum and subsequently the duodenum, which has been reported by others as a technique to assess the transit time [16]. Our preliminary studies showed no differences between time–activity curves or the use of static images to determine the HDTT or DAT. The Italian group used a subtraction technique to remove background tracer from the region of interest involving the right ventricle of the heart that requires 15-second scans. They believe that the static images detect duodenal activity much later than using this subtraction technique. Other groups who describe good results with the HDTT used time–activity curves but not the subtraction technique employed by the Italian investigators [16].

An additional difference between the studies is the way SO manometry is done and reported. In our study [19••] and that of Rosenblatt *et al.* [23], SO basal pressure is taken as the mean pressure in at least two recording channels over a finite period—usually a minimum of 30 seconds. In the Italian study [14], a value labeled as the "maximum basal pressure reading" has been used. This value has not been used in any of the studies that characterized the manometric features of SO motility. It may introduce errors and account for some of the discrepancies.

## Conclusions

Biliary scintigraphy versus manometry; is it time to disregard the scan? Based on the evidence in the published literature and results of our comparative study, the answer would have to be in the affirmative. A noninvasive investigation of SO motility is a desirable objective. However, an investigation that is not reproducible and also at best selects only 85% of patients who may have SO dysfunction is not very useful. Only SO manometry has been tested prospectively in its ability to diagnose patients who are then successfully treated by division of the SO. Studies assessing scintigraphy have only compared it with manometry; hence, we have no way of evaluating whether scintigraphy on its own might select a different population of patients who might respond to treatment. Although manometry is not perfect, is invasive, and is associated with complications, it is the best means at our disposal for diagnosing SO dysfunction. Our unit's activities are focused on improving the safety of manometry by the development of a new manometric device. Preliminary studies with a sleeve assembly show that it provides accurate and reproducible recordings with minimal complications [26••]. This is not to say that the quest for a noninvasive investigation should cease. Ideally, a noninvasive scintigraphic or magnetic resonance investigation that selects patients with SO dysfunction who will respond to treatment is preferable to invasive endoscopic manometry. However, to date, no such investigation exists and manometry remains the best investigation for the diagnosis of SO dysfunction.

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