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Human Sphincter of Oddi Motility and Cholecystokinin Response Following Liver Transplantation

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The reported incidence of sphincter of Oddi dysfunction following orthotopic liver transplantation has ranged from 3% to 7%. If sphincteric dysfunction is unrecognized, therapy may be inappropriate; when recognized, extensive surgery may be required. To prospectively identify patients with sphincteric dysfunction, we performed sphincter of Oddi motility studies through the t-tube tract three months after transplantation. Baseline sphincter motility and response to intravenous cholecystokinin were evaluated. The results of 10 subjects are reported; nine had normal basal sphincter pressure (16 ± 5.8 mm Hg), and all had normal frequency (3.6 ± 1/min), amplitude (86 ± 31 mm Hg), and duration (4.5 ± 1 sec) of phasic contractions. One subject had an elevated basal pressure (47 mm Hg). All, including the subject with elevated basal pressure, demonstrated a normal response to intravenous cholecystokinin with significant inhibition of phasic contraction frequency and amplitude. We demonstrate that simultaneous studies of the sphincter and duodenum can be obtained via the t-tube tract, providing the opportunity for prospective evaluation of sphincteric function. We conclude that sphincter of Oddi function usually remains normal following liver transplantation with choledochocholedochostomy.

KEY WORDS: sphincter of Oddi; motility; cholecystokinin; liver transplantation.

Orthotopic liver transplantation typically includes end to end anastomosis of the donor bile duct to recipient bile duct, choledochocholedochostomy (CDCD). Following this surgery, 16–19% of patients have a postoperative biliary tract complication, of which 13–20% are reportedly due to sphincter of Oddi (SO) dysfunction (1–3). The diagnosis of SO dysfunction has been based upon finding nonobstructive dilatation of both donor and recipient segments of the bile duct by ultrasonography, percutaneous cholangiography, or endoscopic retrograde cholangiopancreatography (ERCP). Stieber et al (1) reported that 23 of 441 liver transplantation patients with CDCD developed this complication, manifested as elevation of serum bilirubin and hepatic enzymes. This often prompts treatment for presumed rejection before the diagnosis of SO dysfunction is made (1). Most post transplantation patients diagnosed with SO dyskinesia or stenosis undergo Roux-en-Y choledochojejunostomy (1, 2) although Stratta et al (3) reported successful treatment with endoscopic sphincterotomy in three patients. Manometric SO motility studies were not used in these reports to help confirm SO dysfunction and have not been previously reported following liver transplantation.

ERCP manometric studies of normal subjects provide reference values for SO basal pressure and

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phasic contractile activity (4–6). ERCP manometric studies also provide criteria for SO stenosis and dyskinesia and their correlation with clinical manifestations (7–11).

When given as an intravenous bolus, cholecystokinin (CCK) typically inhibits phasic contractions of the SO and decreases basal pressure (4, 12, 13). Some patients with biliary dyskinesia have a paradoxical increase in SO basal pressure or phasic contractions following intravenous CCK. This abnormal response is thought to be due to denervation of the SO and may be useful in differentiating patients with biliary dyskinesia from normals (9, 14, 15).

Previous t-tube tract SO manometric studies following cholecystectomy have allowed simultaneous recordings from the SO and duodenum, establishing the relationship of SO motility to the fasting gastrointestinal migrating motor complex (16–18).

Our purpose in this study was to determine if sphincter of Oddi motility and response to intravenous cholecystokinin remain normal following orthotopic liver transplantation with choledochocholedochostomy.

MATERIALS AND METHODS

Subjects. All patients undergoing orthotopic liver transplantation with CDCD were contacted in the postoperative period and asked to participate in an experimental study. All participants signed an informed consent that was approved by the Human Investigations Committee of the University of Virginia Health Sciences Center. During the interval of this study, 23 patients were eligible; 14 agreed to participate.

Manometry. Manometric studies were performed three months after liver transplantation, which is our standard time for removal of the t tube. The manometry catheter (Wilson-Cook Medical Inc., Winston-Salem, North Carolina) used for this study was made to our specifications and was modeled after that used by Worthley et al (18). The catheter was 40 cm in length, 6 French in diameter, with four lumens each 0.018-in. in diameter. The catheter was designed to advance over a 0.018-in. guide wire (Wilson-Cook Medical), which exited through a lumen terminating at the distal catheter tip; the remaining three lumens terminated as sideholes located 5, 20, and 22 mm from the catheter's distal end.

During manometric studies each of the three sideholes were perfused with sterile, bubble-free water at a rate of 0.25 ml/min by a minimally compliant hydraulic–capillary infusion system (Arndorfer Medical Specialities, Greendale, Wisconsin) with maintenance of a constant reservoir pressure of 7 psi (19). Each sidehole was connected to a pressure transducer (type 4-327-I, Beckman, Anaheim, California) and a recording was made on a polygraph (Dynograph R511A, Beckman) using a paper speed

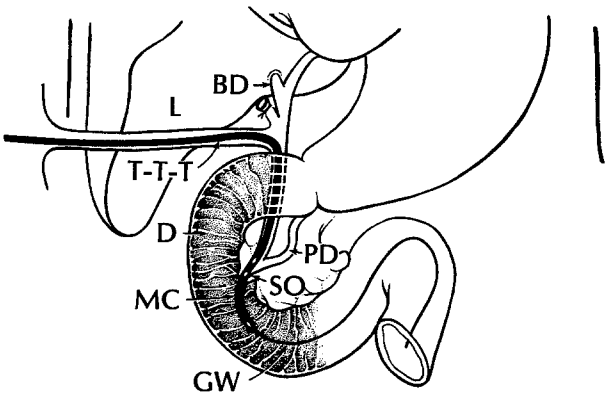

Fig 1. Schematic representation of the motility catheter (MC) placed through the t-tube tract (T-T-T). The proximal two sideholes are positioned in the sphincter of Oddi (SO) and the distal sidehole in the duodenum (D). Liver (L), bile duct (BD), guidewire (GW) and pancreatic duct (PD) are labeled. [Modified from Worthley et al (18)]

of 10 cm/min. Occlusion of a sidehole recorded a pressure rise in excess of 100 mm Hg/sec.

Use of nitrates, anticholinergics, and calcium channel blockers was prohibited 24 hr prior to the study. Motility studies were performed following a 6-hr fast. A light breakfast (coffee and toast) before 8:00 AM was allowed the day of the study. Intravenous ampicillin and gentamicin were infused 30 min prior to t-tube manipulation. Vancomycin was substituted for those allergic to ampicillin.

Studies were performed with subjects supine on a fluoroscopy table. The t-tube site was prepped and draped in a sterile fashion. A t-tube cholangiogram was then performed with a nonionic contrast (Omnipaque 300, Winthrop Pharmaceuticals, NY) agent. Following review of the cholangiogram, a 0.038-in. movable-core 15-mm J guidewire (Cook Co., Bloomington, Indiana) was advanced under fluoroscopic guidance through the t tube into either the common bile duct (CBD) or through the SO into the duodenum. The t tube was then removed leaving the guidewire in place. A 7 French angiographic catheter was then advanced over the guidewire into the biliary tree. Using this catheter, the 0.038-in. guidewire was exchanged for a 0.018-in. wire that was advanced into the duodenum. The angiographic catheter was then removed, and the motility catheter advanced over the 0.018-in. guidewire with placement of all sideholes in the duodenum (Figure 1). Fluoroscopy was used as necessary to assess catheter position; no additional contrast was used after the initial cholangiogram.

Duodenal pressure was used as the zero reference pressure and established for each of the three sensitivity scales (80, 200, and 400 mm Hg maximum pen deflection) at the beginning and end of each study. After establishing a duodenal baseline, a slow station pull-through was performed to determine the basal pressure profile of the SO. The catheter was then readvanced over the guidewire into the duodenum. The catheter was then slowly pulled back until the proximal two sideholes were repositioned in the high-pressure zone of the sphincter, where it was then held stationary (Figure 2a and b). After 7 min of

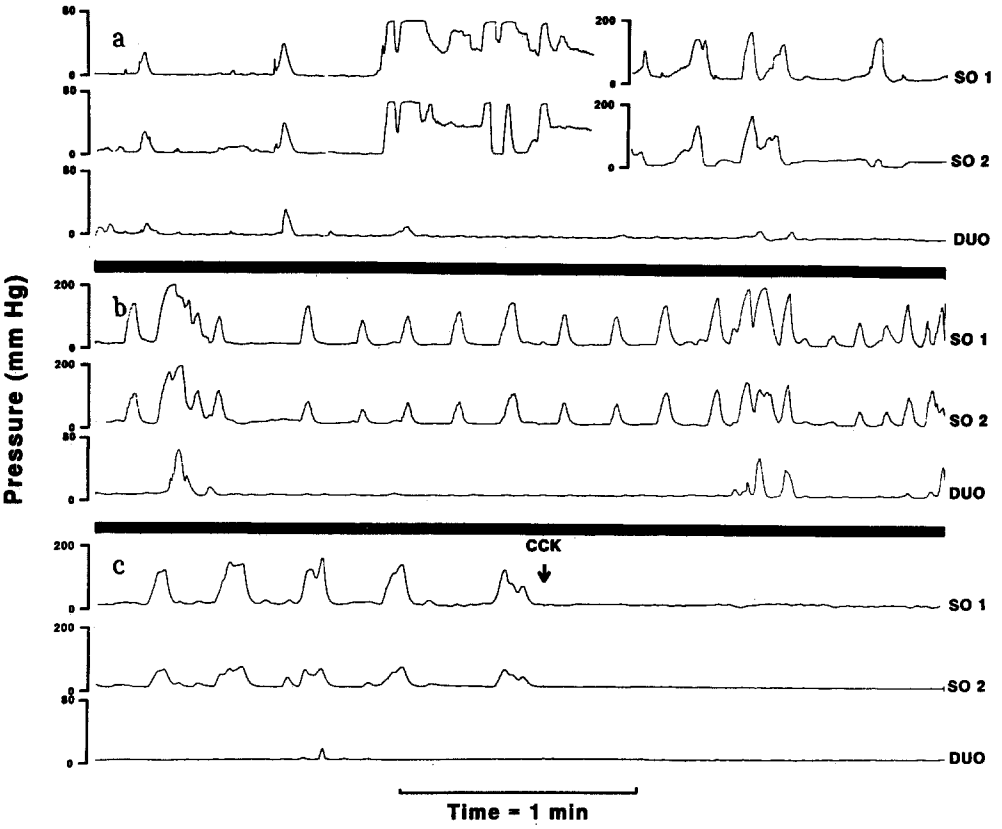

Fig 2. Manometric tracings from the proximal (SO 1) and distal (SO 2) sphincter of Oddi and duodenum (DUO). (a) The motility catheter is being pulled back from the duodenum with the proximal two sideholes entering the high-pressure zone of the sphincter. Note that the sensitivity scale for maximal pen deflection is changed from 0–80 to 0–200 mm Hg to capture the peaks of phasic sphincter of Oddi contractions. (b) Duodenal contractions superimposed on the sphincter of Oddi. (c) Response to an intravenous bolus of cholecystokinin.

recording, all sideholes were again advanced into the duodenum. This procedure was repeated three separate times. The sensitivity for maximal pen deflection was changed as needed to capture peak amplitudes of all phasic contractions.

Following the third 7-min recording period, with the two proximal sideholes in the high-pressure zone of the sphincter, subjects were administered 0.02 μg/kg CCK (Kinevac, Squibb Diagnostics, Princeton, New Jersey) as an intravenous bolus injection. Catheter position was held stationary for an additional 10 min of recording, and then the motility study was terminated.

Before catheter removal, subjects were administered sublingual nifedepine, 10 mg or 20 mg as tolerated by blood pressure response, to reduce sphincteric resistance to bile flow and theoretically the risk of bile leak and peritonitis. The catheter was then withdrawn into the CBD and bile aspirated. Ciprofloxacin, 500 mg *per os* twice a day, was administered for five days following completion of the study.

Scoring of Manometric Tracings. Each tracing was read by two of the authors (R.D.R. and P.Y.). The initial station pull-through was used to define the basal pressure profile of the SO and determine CBD pressure. Since CBD pressure tended to be stable, an average value over 30 sec was determined. No other data are reported from this pull-through.

Of the three separate 7-min recordings from the high-pressure zone, the tracing with the highest average basal pressure was used for evaluation of baseline manometric data. To minimize artifact induced by catheter movement, the first 2 min were discarded (20). During the remaining 5-min recording period, basal pressure was averaged from the lowest pressure recorded from consecutive 10-sec intervals.

Basal SO pressure would vary up to 10 mm Hg without clear evidence of a contraction; therefore a 20 mm Hg rise in pressure was required to identify a contraction. Frequency, amplitude, and duration of phasic SO contractions were determined during the 5-min recording interval. Peak amplitude of phasic contractions was measured relative to the average basal pressure. Duration was measured from the beginning of the rapid upstroke to the end of the rapid downstroke of each contraction. SO contractions were also subdivided by the presence or absence of a temporally associated duodenal contraction; average amplitude and duration were calculated for each group.

From the distal sidehole, frequency and amplitude of

TABLE 1. SPHINCTER OF ODDI MOTILITY DATA

	Baseline		*Following CCK*	
	Mean	*Standard deviation*	*Mean*	*Standard deviation*
Basal pressure (mm Hg)	16.2*	5.8*	13.8	5.2
Phasic frequency (*N*/min)	3.6	1.0	1.7†	2.3
Phasic amplitude (mm Hg)	86.3	30.6	27.2‡	9.2
Phasic duration (sec)	4.5	1.0	2.3‡	0.4

*$N = 9$ (subject with elevated basal pressure excluded).
†$P < 0.05$ vs baseline.
‡$P < 0.01$ vs baseline.

duodenal contractions were measured during this same 5-min period. The duodenal baseline tended to fluctuate less than 4 mm Hg; a rise of 10 mm Hg was used to identify duodenal contractions. The amplitude of duodenal contractions occurring with and without temporally associated SO contractions were analyzed separately.

Following CCK injection, 30 sec of motility tracing were discarded to allow for circulation time to the gut. The subsequent 3 min were analyzed as described above.

Statistical Analysis. Data are presented as mean (± standard deviation) unless otherwise stated. Two-sample and paired *t* tests were used as appropriate to compare normally distributed data sets. For data sets that did not pass the Wilk-Shapiro test of normality, the Wilcoxon rank sum test was used to test for significance in unpaired samples, and the Wilcoxon signed rank test was used for paired samples; $P < 0.05$ was required for significance.

RESULTS

Data from the first two subjects studied were not included in the results due to differences in study technique while the protocol and equipment were being developed and standardized. The motility catheter could not be positioned in the CBD in two of the remaining 12 study subjects.

Baseline Motility Data and CCK Response. The mean CBD pressure was 11.3 (± 5.7) mm Hg with a range of 4–20 mm Hg. Mean values for SO basal pressure and phasic contraction frequency, amplitude, and duration at baseline and following intravenous CCK are presented in Table 1.

One subject had a basal SO pressure of 47.0 mm Hg, which was significantly (>3 SD) higher than the rest of the subjects. Including this subject to determine mean basal SO pressure results in an increase from 16.2 (± 5.8) to 19.3 (± 11.2) mm Hg, a value that remains similar to that reported elsewhere in normal subjects (5, 6). This subject was considered to have abnormally elevated basal SO pressure.

TABLE 2. COMPARISON OF SPHINCTER OF ODDI CONTRACTIONS WITH AND WITHOUT SUPERIMPOSED DUODENAL CONTRACTION

Sphincter of Oddi	*With duodenal contraction*	*Without duodenal contraction*
% SO contractions	24.3 ± 14	75.7 ± 14
Phasic frequency (*N*/min)	1.0 ± 0.6*	2.6 ± 0.6
Phasic amplitude (mm Hg)	118 ± 35†	78 ± 32
Phasic duration (sec)	5.4 ± 1.8	4.2 ± 0.9

*$P < 0.01$ versus without duodenal contraction.
†$P < 0.05$ versus without duodenal contraction.

Frequency, amplitude, and duration of phasic contractions were similar to those reported by others measuring SO motility via a t-tube tract (16–18) and not markedly different from normal ERCP manometric data (5, 6).

Following CCK injection, there was rapid inhibition of SO activity in all subjects with a significant decrease in frequency, amplitude, and duration of phasic contractions (Figure 2c). The frequency and amplitude of SO contractions gradually returned to normal over 2–12 min. No subject demonstrated a "paradoxical" response to CCK (14, 15). In the subject identified as abnormal, basal SO pressure fell from 47 mm Hg to 16.2 mm Hg following intravenous CCK. Among the nine subjects with normal basal SO pressure, CCK resulted in a downward trend in basal pressure from 16.2 (± 5.8) mm Hg to 13.5 (± 5.4) mm Hg ($P = 0.09$).

Duodenal contractions occurred at a rate of 1.2 (± 1.0)/min. No phase III activity of the duodenal migrating motor complex was observed during the recording periods. Following intravenous CCK, one subject demonstrated a brief burst of duodenal contractions, but duodenal inhibition was typically noted. In the 3-min study interval following CCK, the duodenal contraction rate was 1.4 (± 2.4, range 0–16) with five subjects having no contractions.

Sphincter of Oddi Contractions with and Without Temporally Associated Duodenal Contractions. Phasic contractions of the SO occurred continuously at a mean rate of 3.6 (± 1.0)/min. Duodenal contractions occurred intermittently, either with or without a simultaneous SO contraction. When a duodenal contraction was temporally associated with a SO contraction, the amplitude of the SO contraction was significantly higher than when no duodenal contraction occurred simultaneously (Table 2 and Figure 2b). Duodenal contractions occurring simultaneously with a SO contraction had a significantly

higher amplitude than those that occurred without a SO contraction: 28.4 (± 6.5) mm Hg versus 12.8 (± 2.6) mm Hg, respectively ($P < 0.001$).

Complications. Two subjects developed transient bile leak and peritonitis. The fourth subject studied developed abdominal pain as the angiographic catheter was being manipulated over the 0.038-in. guidewire, and the procedure was terminated. The sixth subject developed pain immediately following catheter removal at the completion of an uneventful motility study. Both subjects were briefly hospitalized for intravenous antibiotics and narcotics. Measures previously described to reduce the possibility of bile leak were subsequently introduced. The remaining eight subjects were without evidence of bile leak, including one whose study was aborted because of obvious t-tube tract disruption.

DISCUSSION

Postoperative complications involving the biliary tract are not uncommon following orthotopic liver transplantation. Complications include anastomotic stricture, bile leak, and diffuse dilation of the biliary tree without apparent obstruction, which is thought to be caused by sphincter of Oddi dyskinesia or stenosis.

Possible etiologies of SO stenosis and dyskinesia are poorly understood. Stenosis may be caused by inflammation, muscular hypertrophy, or fibrosis of the sphincter zone (8). Most investigators agree that an elevated SO basal pressure or a paradoxical response to intravenous CCK are findings compatible with SO dyskinesia (6–11, 14, 15, 20). The paradoxical CCK response is thought to be caused by denervation of the SO with loss of CCK responsive inhibitory neurons (9, 14, 21, 22). Following liver transplantation with CDCD, Stieber et al have suggested that SO dysfunction may be due to "either devascularization or denervation of the papilla of Vater during the recipient hepatectomy" (1). Our data support the thesis that CCK-sensitive inhibitory neurons of the SO are usually intact following liver transplantation.

Our values for phasic contraction frequency, amplitude, and duration are similar to those reported by other authors performing t-tube SO motility studies in other populations (17, 18). The mean amplitude of phasic contractions in some of our subjects was lower than those reported from ERCP manometric studies, but overall the ranges were similar (5, 6). Torsoli et al (17) also noted lower amplitude of phasic contractions when t-tube studies were compared to ERCP manometric studies. The reason for this is unknown. The results from t-tube tract studies may be different due to the prior surgery or to the motility catheter remaining stationary in the SO for longer periods than is possible with brief ERCP manometric studies. It remains undetermined which technique most accurately represents normal physiologic function.

We have demonstrated that temporally associated duodenal and SO contractions result in a significant increase in the contraction amplitude of both components. The increase in SO contraction amplitude in the presence of a duodenal contraction might be explained by summation of the contractions of the two separate muscle groups since the majority of the SO muscle fibers are located in the duodenal intramural segment of the choledochoduodenal junction (20, 23). This explanation has been suggested from ERCP manometric studies (4, 24), previous t-tube SO motility studies (17), and animal model recordings of simultaneous SO and duodenal motility (25). Duodenal contractions may, however, occur without a concomitant increase in SO contraction amplitude, indicating a degree of isolation between the two muscle groups. An alternate explanation for the observed increase in contraction amplitude is that it may result from electrical coupling between the two muscle groups. The SO and duodenal smooth muscle have different embryologic origins (20, 26), but whether they share electrical control potentials is controversial and variation exists among species (7, 25, 27–30). In the common environment of the choledochoduodenal junction, strong duodenal action potentials might influence temporally associated SO depolarization, enhancing SO contraction amplitude. Our data cannot resolve this question; studies obtaining simultaneous electromyographic and manometric data will be required.

We have established that t-tube SO manometry is feasible and relatively safe. Steroids and immunosuppressive medications conceivably interfere with strong t-tube tract formation and manipulation of the t-tube tract possibly increases the risk of bile leak. Bile leaks occur in this patient population when the t tube is removed, but the incidence of this complication has not been reported. Two subjects studied early in our protocol experienced bile leak and peritonitis. After we initiated procedures to decrease CBD pressure, this complication did not occur even though one later subject had t-tube tract disruption. We have not observed any other com-

plications during these studies including cholangitis or pancreatitis.

In conclusion, sphincter of Oddi motility and the response to intravenous cholecystokinin remain intact following liver transplantation with choledochocholedochostomy. The normal CCK response suggests that the neural pathways to the SO usually survive the extensive surgery. Excellent SO manometric studies can be obtained in these patients via the t-tube tract with acceptable risk. These data will permit prospective evaluation for SO dysfunction, possibly prevent unnecessary and potentially harmful treatment, and allow a trial of nonsurgical therapy. The technique of t-tube manometry also provides a method for prolonged, high-quality manometric studies that should increase our understanding of the physiology and pharmacology of the choledochoduodenal junction.

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