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Pancreatic duct compliance following secretin stimulation: A novel EUS diagnostic tool for chronic pancreatitis

Timothy B. Gardner, MD¹, Edward D. Purich, PhD², and Stuart R. Gordon, MD¹

¹Section of Gastroenterology & Hepatology, Dartmouth-Hitchcock Medical Center, Lebanon, NH

²ChiRhoClin, Inc., Burtonsville, MD

Abstract

OBJECTIVES—Endoscopic Ultrasound (EUS) evaluation of pancreatic duct compliance following secretin-stimulation (sEUS) along with EUS morphologic examination (EUS) and duodenal fluid [HCO₃⁻] measurement (ePFT) in one endoscopic session has not been reported as a means of evaluating for chronic pancreatitis (CP). We evaluated the feasibility of the combined examination and compare EUS measurements of pancreatic ductal compliance with duodenal [HCO₃⁻] for diagnosing CP.

METHODS—Prospective case series of patients with suspected CP who underwent combined EUS, sEUS and ePFT examination in one endoscopic session. The main outcome measures were the feasibility of performing the combination examination and the correlation between ductal compliance and duodenal fluid [HCO₃⁻] measurement.

RESULTS—All examinations were completed in one endoscopic session and there were no complications in 35 patients. Although there was a trend toward less change from baseline head and body ductal diameter in patients with CP, only the percent change from baseline in the tail was significant (CP 144.3% vs. normal 240.9%, $p < 0.01$). Regression analysis demonstrated fair correlation between maximum change in ductal diameter and duodenal [HCO₃⁻] ($r^2 = 0.27$).

CONCLUSIONS—Combined EUS, sEUS, and ePFTs is feasible and safe, with preliminary results demonstrating positive correlation between pancreatic ductal compliance and duodenal fluid [HCO₃⁻].

Keywords

Chronic pancreatitis; Secretin stimulation; Endoscopic Ultrasound; Ductal compliance

INTRODUCTION

Endoscopic ultrasonography (EUS) has increasingly been used as single modality to diagnose chronic pancreatitis (CP).¹⁻³ While the morphologic changes seen on EUS have been well characterized, there is disagreement about whether morphologic EUS examination alone should be used as the gold standard for diagnosis, especially in patients with early or “minimal change” disease.^{4,5} Poor inter-rate reliability, disagreement about which features

Corresponding Author: Timothy B. Gardner, MD Section of Gastroenterology & Hepatology Dartmouth-Hitchcock Medical Center One Medical Center Drive Lebanon, NH 03756 (603) 650-6472 – telephone (603) 650-5225 – fax timothy.b.gardner@hitchcock.org.

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are physiologic vs. pathologic, and lack of consensus as to which morphologic features should receive more relative weight in diagnosis have led to concerns over the accuracy of EUS to diagnosis CP.⁶⁻⁸

More recently, the development of the endoscopic pancreatic function test (ePFT) using secretin stimulation has made direct pancreatic function testing more accessible, allowing clinicians the opportunity to easily perform a functional assessment of the pancreas.⁹⁻¹¹ While the ePFT is being used more often in diagnosis, it does have the drawback of being time-intensive and available at only specialized centers.

Main pancreatic ductal compliance measurements following secretin stimulation have been reported as a useful surrogate marker for pancreatic function in patients undergoing secretin-enhanced MRCP (sMRCP).¹² The rationale is that secretin stimulation of the pancreatic ductal cells should cause a transient increase in the intra-ductal fluid volume. By measuring the change in the main pancreatic duct diameter from baseline, inferences can be made about the exocrine function of the pancreas - i.e. the greater change in diameter from baseline, the more likely the exocrine pancreas is functioning normally.

The purpose of this study was 1) to evaluate the feasibility of performing EUS morphologic evaluation, EUS secretin-enhanced ductal compliance measurements and secretin-enhanced duodenal fluid [HCO_3^-] measurement in one endoscopic session and 2) to evaluate the correlation between pancreatic ductal compliance and duodenal fluid [HCO_3^-] following secretin stimulation as a measurement of pancreatic exocrine function. We hypothesized that the combined examination would be feasible without any adverse events and that there would be at least fair correlation between ductal compliance measurement and duodenal fluid [HCO_3^-] following secretin stimulation

METHODS

Study Design and Patient Population

The study was approved by the Dartmouth Medical School Institutional Review Board protocol #17287. In 2008, our center began performing EUS and ePFTs during the same endoscopic session as a means of streamlining patient evaluation and limiting the inherent risks of a second endoscopic procedure. As part of the procedure, main pancreatic duct diameter measurements following secretin stimulation (see “combined examination “below) were taken. All patients had provided informed written consent in the endoscopy suite prior to undergoing the combined procedures. Included patients were those referred to the investigators for EUS evaluation of possible CP – including those with “large duct” and “small duct” disease. All patients had chronic (>3 months) abdominal pain. Patients were excluded if they were referred for sphincter of oddi (SOD) dysfunction or acute pancreatitis. All of the included subjects had been evaluated by one of the investigators in the Dartmouth Pancreas Clinic prior to referral for the procedure.

Combined Examination

Patient sedation was accomplished via standard conscious (Midazolam, Fentanyl and/or Meperidine) or monitored (Propofol) sedation as per the endoscopists and American Society of Gastrointestinal Endoscopy (ASGE) and American Society of Anesthesiology (ASA) guidelines. A radial EUS echoendoscope with color Doppler assessment capability was then passed via standard technique and the pancreas examined from the gastric and duodenal stations. The echoendoscope measured standard parenchymal (hyperechoic foci, hyperechoic strands, lobular contour, cysts, calculi) and ductal (main duct dilatation, irregularity, hyperechoic margins, stones and the presence of visible side branches) abnormalities.

Next, the echoendoscope was used to aspirate the gastric and duodenal lumens dry and the samples discarded. Once the gastric and duodenal lumens have been aspirated dry, patients were given a test dose of human secretin at 0.2 mcg IV to assess for a possible allergic response. If after one minute there was no evidence of an allergic reaction, the remaining full dose of secretin 0.2 mcg/kg IV was given over one minute. Beginning at time 2 minutes after the completion of secretin intravenous infusion, the pancreatic duct diameter was measured in the head, body, and tail using endosonographic calipers during the procedure. Hard copies of endoscopic films were not subsequently reviewed. Measurements of the pancreatic duct then occurred sequentially every two minutes until time ten minutes following the conclusion of secretin administration. Careful attention was made to performing the serial measurements from the same location in the head (1 cm proximal to the ampulla), body (at the confluence of the splenic vein and SMV) and tail (mid tail per endosonographer's discretion) respectively,.

The ePFT portion of the examination then commenced. The echoendoscope was removed and a forward-viewing gastroscope placed into the stomach. Stomach contents were then aspirated dry. The forward-viewing gastroscope was then placed across the pylorus into the distal duodenum. Beginning time 15 minutes following the completion of the secretin infusion, duodenal fluid samples (5-10 ml) were collected through the suction channel of the gastroscope. The samples were collected in a standard endoscopic collection container and placed on ice. At time 30 minutes after the completion of secretin infusion and at time 45 minutes after the completion of secretin infusion, samples were obtained in a similar fashion and placed in separate containers on ice.

At the conclusion of the procedure, the duodenal fluid samples were brought immediately to the chemistry laboratory where the bicarbonate concentration using the hospital autoanalyzer was obtained. Using the autoanalyzer for this technique required at least two-three fold dilution of the fluid contents. The highest bicarbonate concentration from the 3 samples was considered the peak concentration. See Figure 1. All patients had been contacted by phone within 10 days following the procedure.

Statistical Analysis

As this represented primarily a feasibility study, it was not powered to provide a definitive measurement of effect. To compare groups, CP was defined as having duodenal fluid [HCO_3^-] measurement at 15, 30 and 45 minutes all ≤ 80 mEq/L. The first outcome of interest was the feasibility of performing the combined EUS examination. This was evaluated by 1) the percent completion of all three examinations in one endoscopic session 2) the development of any adverse events with the three procedures. The second primary outcome was the determination of the correlation between the change in ductal diameter following secretin-enhancement and the duodenal fluid [HCO_3^-].

Descriptive statistics were used to characterize the population with means and 95% confidence intervals. The two-tailed student's t-test was used to assess for differences between continuous means of the two populations. The two-tailed Fisher exact and chi-square tests were used to compare categorical variables. A p value ≤ 0.05 was set for statistical significance. Multivariable and logistic regression models were then built using the diagnosis of CP as the dependent variable and potentially significant independent variables (time from baseline to maximum ductal diameter, number of EUS parenchymal features, number of EUS ductal features, percent change from baseline ductal diameter to peak diameter). All statistical analysis was performed using Microsoft EXCEL (Microsoft Corporation, Redmond, WA) and SAS v. 8.2 (SAS Institute, Inc., Cary, NC).

RESULTS

35 patients underwent the combined procedure and patients were categorized into those with CP (duodenal fluid $[\text{HCO}_3^-]$ all ≤ 80 mEq/L) and those without CP. Their baseline characteristics are displayed in Table 1. The groups were similar except for patients with CP were more likely to have EUS MST parenchymal features present on EUS. There was no difference in results among patients who received conscious (29 patients) vs. monitored (6) sedation. All 35 patients completed the combined examination per the standard reported in the Methods section. There were no adverse events reported periprocedurally or in the immediate post-operative period including reactions to secretin, development of pancreatitis, or inability to safely be sedated during the procedure.

Specific characteristics in regard to ductal compliance are shown in Table 2. Although there was a trend toward less change from baseline ductal diameter in patients with CP, only the percent change from baseline in the tail was significant. The median time to maximum ductal dilation from baseline ductal diameter (Tmax) was not different between CP and normal patients (based on duodenal fluid $[\text{HCO}_3^-]$ measurement) in the head (6 minutes vs. 4 minutes, $p=0.76$), body (6 minutes vs. 4 minutes, $p=0.87$) or tail (4 minutes vs. 4 minutes, $p=0.53$), although there was a trend toward a longer response in CP patients.

The correlation between the time to maximum ductal diameter and the duodenal fluid bicarbonate level at 15, 30, and 45 minutes is demonstrated in Figure 2. Correlation calculations indicated an r^2 of 0.26. Correlation was poor when comparing the rate of change to maximum ductal diameter from baseline in the head, body and tail. Figure 3. Table 3 demonstrates the ORs for important diagnostic variables related to CP. The number of parenchymal changes seen on EUS appeared to have the strongest correlation for diagnosing CP based on the duodenal bicarbonate concentration.

DISCUSSION

In this report, we describe the first use of combined EUS morphologic examination, dynamic EUS evaluation of main duct compliance following secretin stimulation (sEUS) and duodenal fluid $[\text{HCO}_3^-]$ measurement (ePFT) in one endoscopic session. Although not a definitive evaluation of its test characteristics, our results demonstrate that combining these procedures is feasible, safe and may provide a simple means of combining a structural and functional evaluation of the pancreas.

The EUS diagnosis of CP has relied on MST, as defined by the International Working Group, since these guidelines were published in 1998.¹³ While there have been new EUS classification schema proposed, using morphologic EUS examination as the diagnostic gold standard for CP is limited by inter-observer variability, lack of consensus about which EUS features are most important for diagnosis and which features are truly pathologic.¹⁴⁻¹⁶ The limitations of EUS morphologic examination are especially apparent when diagnosing minimal change disease.

Direct pancreatic function testing, developed nearly 50 years ago, is generally considered an accurate means of evaluating pancreatic function.^{17,18} However, its use has been limited in recent years to specialized centers due to laborious technical requirements, transient lack of available stimulating medications (i.e. secretin) and lack of interest. More recently endoscopic pancreatic function tests have been developed which are simple to perform, reproducible and becoming more widely available.^{19,20} ePFTs provide a functional assessment of the pancreas without requiring specialized technical expertise. However, ePFTs in their current form are time-intensive, and do not allow for a morphologic examination of the pancreas to be performed concomitantly.

The value of the combined procedure described in this report is it allows for both a functional *and* structural evaluation of the pancreas to be performed simultaneously. Furthermore, because the ductal compliance value (maximum change from baseline diameter) does appear to provide at least fair correlation with the duodenal fluid $[\text{HCO}_3^-]$ measured at 15, 30 and 45 minutes, it potentially could be used as a surrogate marker for pancreatic function. This may allow for increased access to pancreatic functional evaluation for centers not able to perform conventional ePFTs.

As primarily a feasibility study, this report does not have sufficient power to answer several important questions in regard to test characteristics. For example, we cannot draw conclusions about the true correlation between ductal compliance and duodenal fluid $[\text{HCO}_3^-]$ given the small number of patients. In addition, it is not possible to determine which region of the pancreatic duct (head, body, tail) is most representative of the degree of gland fibrosis and to what degree regional variation in gland fibrosis affects ductal changes. We also cannot determine which time from baseline is most representative of maximum ductal diameter change or even if 10 minutes following secretin stimulation is enough time to demonstrate maximum compliance. Further, prospective study, which is being planned across multiple centers, will be necessary to definitively answer these questions. Until its test characteristics are better validated, we do not recommend using EUS ductal compliance measurement as the sole means of diagnosing CP. Furthermore, ductal compliance measurements should not be used as a surrogate for standard ePFTs.

There are several limitations to this study beyond its small sample size. We did not evaluate either the inter- or intra-rater reliability of this technique as patients did not undergo repeat procedures by the same endoscopist, the procedure was not performed on the same patient by different endoscopists, and there was only one endoscopist who reviewed the EUS images at the time of the procedure. In addition, although every effort was made to ensure measurements were made from the same position, it is possible that ductal measurements were taken from slightly different locations at each time point. This raises the concern about reproducibility of the data. We also did not compare the results with other techniques – such as secretin-enhanced MRCP. Finally, we did not consider the issue of sphincter of oddi dysfunction, which potentially could skew the compliance results, and did not perform sphincter manometry. However, none of our patients clinically were considered to be suffering from SOD Type I-III.

Nevertheless, this study does demonstrate the potential for a simple, safe, novel means of characterizing pancreatic structure and function in one endoscopic session. The combined procedure does not require any additional time and offers a means to significantly reduce the cost of the procedures done separately. As the diagnosis of CP can sometimes be challenging, especially in minimal-change disease, this study demonstrates that there may be a role for EUS ductal compliance measurement as a future diagnostic tool. Multi-center study of this technique to further evaluate its test characteristics is planned.

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Figure 1.
Combined EUS, e-PFT and sEUS Testing Study Schema

Figure 2.

Scatterplot demonstrating the percent change in pancreatic diameter from baseline based on duodenal $[HCO_3^-]$. Each dot on the figure represents one patient measurement post-Secretin stimulation (generally three per patient at 15, 30 and 45 minutes) performed during ePFT. Ductal compliance is defined as the percent change from baseline of the maximum ductal diameter following secretin stimulation (log transformed).

Figure 3. Scatterplot demonstrating the rate of change from baseline to maximum dilation in the main pancreatic duct. Each dot on the figure represents one patient measurement post-Secretin stimulation (generally three per patient at 15, 30 and 45 minutes) performed during ePFT.

Table 1

Baseline Patient Characteristics

Characteristic	CP [*]	No CP	p-value
Number	15	20	
Age (years)	41.5 (35.2 -47.8)	44.6 (39.1 thru 50.01)	0.46
Female	47%	75%	0.16
Narcotic Use	67%	35%	0.07
Suspected Etiology			
Idiopathic	20%	20%	0.33
Toxin	27%	5%	
Hereditary	53%	75%	
EUS Features [†]			
Parenchymal	2.2 (1.6 - 2.9)	0.7 (0.14 - 1.3)	0.001
Ductal	1.1 (0.6 - 1.5)	0.5 (0.1 - 0.9)	0.06

^{*} CP defined as duodenal fluid [HCO₃⁻] measurement at 15, 30 and 45 minutes all ≤80 mEq/L

[†] Based on the 9 EUS Minimum Standard Technology criteria

Table 2

Characteristics of Ductal Compliance Measurements

Characteristic	CP *	No CP	p-value
Mean baseline ductal diameter (mm)			
Head	2.33 (1.13)	1.94 (0.75)	0.24
Body	1.49 (0.77)	1.36 (0.63)	0.29
Tail	1.21 (0.72)	0.91 (0.48)	0.61
Mean peak ductal diameter (mm)			
Head	3.11 (1.13)	3.15 (1.19)	0.35
Body	2.34 (0.95)	2.53 (0.93)	0.66
Tail	1.56 (0.52)	1.84 (0.54)	0.55
Percent change from baseline ductal diameter to peak diameter			
Head	143.4	172.2	0.17
Body	178.9	208.1	0.33
Tail	144.3	240.9	0.01

* Standard deviations are in parentheses

Table 3Odds Ratios for Diagnosing CP based on Duodenal [HCO₃⁻] Measurement)

Characteristic	Odds Ratio	95% Confidence Interval
T(max) *		
Head	1.00	(0.64-1.57)
Body	0.92	(0.61-1.38)
Tail	0.71	(0.43-1.17)
Percent change from baseline ductal diameter to peak diameter		
Head	0.99	(0.97-1.01)
Body	0.99	(0.97-1.00)
Tail	0.97	(0.94-1.00)
Number of parenchymal features		
Head	3.20	(1.14-9.02)
Body	3.21	(1.1-9.35)
Tail	3.81	(0.96-15.09)
Number of ductal features		
Head	0.52	(0.12-2.29)
Body	0.88	(0.18-4.20)
Tail	0.80	(0.16-4.01)

* T_{max}= The median time to maximum ductal dilation from baseline ductal diameter