Turn On the Pancreas!

ChiRhoStim® (Human Secretin for Injection)

**Functional EUS**
*Pancreatic Function Testing (PFT) with EUS Imaging*
- Studies have shown that you can combine an EUS with PFT to perform visual and functional pancreatic tests.
- Secretin is the Gold Standard for pancreatic function testing.
- Most accurate method for diagnosing chronic pancreatitis.

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*Facilitating Successful Cannulation*
- Save time and money with ChiRhoStim®.
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- Reduces cannulation time by 32%.
- Opens pancreatic duct orifices within one minute.

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*Visually Clarify & Sharpen Images*
- Improve your MRCP images with ChiRhoStim®.
- Turn Static MRCP’s into dynamic images with pancreatic stimulation.
- Observe pancreatic function and fluid flow in a fasted patient.

References:
1. Stevens T. Endoscopy 2009;41:836-841
2. CRC 98-4 amendment study to NDA 21-256

*The ChiRhoStim® Advantage*
- ChiRhoStim® is reimbursable with J-Code 2850
- ChiRhoStim® is a synthetic peptide not manufactured by a recombinant process.
- Less chance of an allergic reaction.
- Superior Stability.

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For highlighted prescribing information using ChiRhoStim® (Human Secretin for Injection) please see reverse side.
Combined EUS and ePFT Procedure (EUS-ePFT)

Purpose of the combined procedure:
To evaluate pancreas function with the highly flexible imaging by endoscopic ultrasound (EUS) procedure, increases early detection of chronic pancreatitis, provide better patient care and reduce procedure cost.

The combined procedure provides for:
A. Imaging of the pancreas resting prior to stimulation.
B. Dynamic imaging of the pancreas after Secretin stimulation.
C. Direct monitoring of pancreatic fluid flow directly to evaluate ductal compliance.
D. Opportunity to collect pancreatic fluid.

Benefits:
1. Shorter procedure times (20 min EUS and 45 min ePFT).
2. Combine two billable procedures into one procedure time and bill for an increased profit margin.
3. Both procedures are currently the standard medical practice for the evaluation of CP.
4. Eliminate redundant portions of the procedures, reduce total recovery time for the patient, and decrease the cost of separate procedures.

Supporting Research:
1. Combined EUS/ePFT are feasible and safe, with preliminary results demonstrating a positive correlation between pancreatic ductal compliance and duodenal fluid [HCO3-].
2. Combined EUS/ePFT are useful in the diagnosis of CP and may improve the sensitivity for detection of early fibrosis.
3. Combined EUS/ePFT is both feasible and safe and produce complimentary functional and structural information for evaluation of CP.
4. Evidence suggests that low duodenal HCO3 values are among the first measurable abnormalities in CP.

Coding:
Human Secretin J-code 2850, Pancreatic function test CPT codes 43757, EUS CPT Code for upper GI exams is 43259. The general CPT code (Radiological Supervision and Interpretation Code) is 76376, and FNA CPT Code is 88172, 96374

Combined EUS, ePFT, and EUS evaluation of main duct compliance after secretin stimulation testing

<table>
<thead>
<tr>
<th>Radial EUS Morphologic Exam (10 Minutes)</th>
<th>Aspiration of Gastric Contents (One minute)</th>
<th>Test Dose of Secretin (One minute)</th>
<th>Secretin Stimulation (One Minute)</th>
<th>sEUS and ePFT evaluation (45 minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Measurement of baseline MPD diameter in head, uncinate, body and tail</td>
<td>2. Measurement of Specific parenchymal (hyperechoic foci with shadowing, lobular contour, cysts) and ductal (main duct dilatation, irregularity, hyperchoic margins, stones and the presence of visible side branches abnormalities.</td>
<td>1. Measurement of MPD at 2,4,6,8, 10 minutes following completion of secretin stimulation</td>
<td>2. Collection of duodenal fluid at 15, 30, and 45 minutes following conclusion of secretin stimulation.</td>
<td></td>
</tr>
</tbody>
</table>

Time of Combined Test
EUS 0-------------------10   EUS-EPFT 15 ------------------55

References:
Combined Endoscopic Ultrasound and Pancreatic Function Test Method (EUS-PFT) Protocol

1. After patient is under conscious sedation and assessed, a radial EUS echoendoscope is passed and used to evaluate for standard parenchymal and ductal abnormalities.

2. Aspirate the gastric and duodenal lumens dry and discard the samples.

3. Administer an IV test dose of ChiRhoStim® 0.2 mcg if using the 16 mcg vial (0.1 mL) or 0.4 mcg if using the 40 mcg vial (0.1 mL) to test for possible allergies, as per the package insert.

4. After one minute, if there are no signs of allergic reaction, administer ChiRhoStim® at a dose of 0.2 mcg/kg body weight over 1 minute, as per the package insert.

5. The ePFT portion of the examination is then commenced as per above with samples collected at 0 (baseline), 15, 30, 45 and 60 minutes after secretin injection using the echoendoscope.

6. Beginning at time 2 minutes after the completion of secretin intravenous infusion, the pancreatic duct diameter is measured 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), using endosonographic calipers during the procedure.

7. Measure the pancreatic duct sequentially every two minutes until time 12 minutes following the conclusion of secretin administration.

8. Perform the serial measurements from the same location in the head, body, and tail, as described in step 6. The percent change from ductal diameter at baseline can be used as surrogate marker of pancreatic fibrosis – i.e. the greater the change in diameter, the less likely fibrosis.
ChiRhoStim®

第一节 一般信息
ChiRhoStim® injectables are indicated for:

1. **Stimulation of Exocrine Pancreas:**
   - **Diagnosis:**
     - **Assessment:**
       - To facilitate the identification of the ampulla of Vater and accessory papilla during endoscopic retrograde cholangiopancreatography (ERCP)

2. **Use in Various Procedures:**
   - **Administration via Intravenous Injection:**
     - 0.2 mcg/kg body weight by intravenous injection over 1 minute
     - CT scan
     - Endoscopic retrograde cholangiopancreatography (ERCP)
     - Duodenal intubation

3. **Supplied:**
   - **Concentration:**
     - 4 mcg/mL
     - **Stability:**
       - Stored at -20°C
       - Lyophilized sterile powder

4. **Dosage Forms and Strengths:**
   - ChiRhoStim® single dose 16 mcg/10 mL vial
   - ChiRhoStim® single dose 40 mcg/10 mL vial

5. **Adverse Reactions:**
   - **Incidence:**
     - Nausea, flushing, abdominal pain

6. **Contraindications:**
   - **Relative:**
     - History of allergic reaction

7. **Warnings and Precautions:**
   - **Monitoring:**
     - Routine monitoring

8. **Dosage and Administration:**
   - **Injection Site:**
     - Intravenous injection

9. **References:**
   - **Materials:**
     - Scientific articles

10. **Full Prescribing Information:**
    - **Access:**
      - Online resource

11. **Table of Adverse Reactions:**
    - **Reactions:**
      - Nausea, flushing, abdominal pain

**Analysis of Exocrine Pancreas Function:**
- **Indications for Test:**
  - Diagnosis of pancreatic exocrine dysfunction

**Acute Pancreatitis:**
- **Evaluation:**
  - Identification of the ampulla of Vater and accessory papilla

**Gastrinomas:**
- **Identification:**
  - Secretin-stimulated endoscopic pancreatic function test

**Secretin-stimulated Endoscopic Pancreatic Function Test (ePFT):**
- **Bicarbonate Concentration:**
  - Determined

**Human Secretin:**
- **Characteristics:**
  - Concentration: 4 mcg/mL

**ChiRhoStim®: A registered trademark of ChiRhoClin, Inc.**

**Manufactured for:**
- ChiRhoClin, Inc.
- Burlington, MD 20815-6129

**DataNP06**
Pancreatic Duct Compliance After Secretin Stimulation

A Novel Endoscopic Ultrasound Diagnostic Tool for Chronic Pancreatitis

Timothy B. Gardner, MD,* Edward D. Purich, PhD,† and Stuart R. Gordon, MD*

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The authors declare no conflict of interest.

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Objectives: Endoscopic ultrasound (EUS) evaluation of pancreatic duct compliance after secretin stimulation (sEUS) along with EUS morphologic examination (EUS) and duodenal fluid [HCO₃⁻] measurement (endoscopic pancreatic function test, ePFT) in 1 endoscopic session has not been reported as a means of evaluating for chronic pancreatitis (CP). We evaluated the feasibility of the combined examination and compared EUS measurements of pancreatic ductal compliance with duodenal fluid [HCO₃⁻] for diagnosing CP.

Methods: The study is a prospective case series of patients with suspected CP who underwent a combined EUS, sEUS, and ePFT examination in 1 endoscopic session. The main outcome measures were the feasibility of performing the combination examination and the correlation between ductal compliance and ePFT.

Results: All examinations were completed in 1 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 healthy patients 240.9%, P < 0.01). Regression analysis demonstrated fair correlation between maximum change in ductal diameter and duodenal fluid [HCO₃⁻] (r² = 0.27).

Conclusions: Combined EUS, sEUS, and ePFTs are feasible and safe, with preliminary results demonstrating a positive correlation between pancreatic ductal compliance and duodenal fluid [HCO₃⁻].

Key Words: chronic pancreatitis, secretin stimulation, endoscopic ultrasound, ductal compliance

(Pancreas 2012;41: 290–294)

Endoscopic ultrasonography (EUS) has increasingly been used as a single modality to diagnose chronic pancreatitis (CP). Although the morphologic changes seen on EUS have been well characterized, there is a disagreement about whether morphologic EUS examination alone should be used as the criterion standard for diagnosis, especially in patients with early or “minimal change” disease. Poor interrater reliability, disagreement about which features are physiologic versus 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 diagnose CP.

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. Although the ePFT is being used more often in diagnosis, it does have the drawback of being time intensive and available only at specialized centers.

Main pancreatic duct compliance measurements after secretin stimulation have been reported as a useful surrogate marker for pancreatic function in patients undergoing secretin-enhanced magnetic resonance cholangiopancreatography. The rationale is that secretin stimulation of the pancreatic ductal cells should cause a transient increase in the intraductal 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—that is, the greater the change in diameter from baseline, the more likely the exocrine pancreas is functioning normally.

The purposes of this study were (1) to evaluate the feasibility of performing EUS morphologic evaluation, EUS secretin-enhanced ductal compliance measurements, and secretin-enhanced duodenal fluid [HCO₃⁻] measurement in 1 endoscopic session and (2) to evaluate the correlation between pancreatic ductal compliance and duodenal fluid [HCO₃⁻] after 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 a fair correlation between ductal compliance measurement and duodenal fluid [HCO₃⁻] after secretin stimulation.

MATERIALS AND METHODS

Study Design and Patient Population

The study was approved by the Dartmouth Medical School institutional review board (protocol no. 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 after secretin stimulation (see “Combined Examination” later) were taken. All patients had provided informed written consent in the endoscopy suite before 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 before 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 the American Society of Gastrointestinal Endoscopy and American Society of Anesthesiology guidelines. A radial EUS echoendoscope with color Doppler echocardiographic assessment capability was then
passed via a standard technique, and the pancreas was examined from the gastric and duodenal stations. The echoendoscope measured standard parenchymal (hyperechoic foci, hyperechoic strands, lobular contour, cysts, and 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 were discarded. Once the gastric and duodenal lumens have been aspirated dry, patients were given a test dose of human secretin at 0.2 mg/kg intravenously to assess for a possible allergic response. If after 1 minute there was no evidence of an allergic reaction, the remaining full dose of secretin 0.2 mg/kg intravenously was given during 1 minute.

Beginning at 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 2 minutes until 10 minutes after the conclusion of secretin administration. Careful attention was made in 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 superior mesenteric vein), and tail (midtail as per endosonographer’s discretion).

The ePFT portion of the examination then commenced. The echoendoscope was removed, and a forward-viewing gastroscope was placed in the stomach. Stomach contents were then aspirated dry. The forward-viewing gastroscope was then placed across the pylorus into the distal duodenum. Beginning at 15 minutes after 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 30 and 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 2- to 3-fold dilution of the fluid contents. The highest bicarbonate concentration from the 3 samples was considered the peak concentration (Fig. 1). All patients had been contacted by telephone within 10 days after the procedure.

**Statistical Analysis**

Because 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 [HCO₃⁻] measurement at 15, 30, and 45 minutes all 80 mEq/L or less. The first outcome of interest was the feasibility of performing the combined EUS examination. This was evaluated by (1) the percent completion of all 3 examinations in 1 endoscopic session and (2) the development of any adverse events with the 3 procedures. The second primary outcome was the determination of the correlation between the change in ductal diameter after secretin enhancement and the duodenal fluid [HCO₃⁻].

Descriptive statistics were used to characterize the population with means and 95% confidence intervals. The 2-tailed Student t test was used to assess for differences between continuous means of the 2 populations. The 2-tailed Fisher exact and

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Narcotic use</td>
</tr>
<tr>
<td>Suspected etiology</td>
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<tr>
<td>Idiopathic</td>
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<td>Toxin</td>
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<tr>
<td>Hereditary</td>
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<tr>
<td>EUS features*</td>
</tr>
<tr>
<td>Parenchymal</td>
</tr>
<tr>
<td>Ductal</td>
</tr>
</tbody>
</table>

*Chronic pancreatitis is defined as duodenal fluid [HCO₃⁻] measurement at 15, 30, and 45 minutes all 80 mEq/L or less.

†Based on the 9 EUS Minimum Standard Terminology criteria.
χ² tests were used to compare categorical variables. \( P \leq 0.05 \) 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 analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, Wash) and SAS v. 8.2 (SAS Institute, Inc, Cary, NC).

### RESULTS

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

Specific characteristics about 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 was not different between CP and healthy patients (based on duodenal fluid \([\text{HCO}_3^-]\) measurement) in the head (6 vs 4 minutes, \( P = 0.76 \)), body (6 vs 4 minutes, \( P = 0.87 \)), or tail (4 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. The correlation was poor when comparing the rate of change to maximum ductal diameter from baseline in the head, body, and tail (Fig. 3).

Table 3 demonstrates the odds ratios for important diagnostic variables related to CP. The number of parenchymal changes seen on EUS seemed 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 after secretin stimulation, and duodenal fluid \([\text{HCO}_3^-]\) measurement (ePFT) in 1 endoscopic session. Although not a definitive evaluation of its test characteristics, our results demonstrate that combining these procedures is feasible and 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,\(^{13}\) because these guidelines were published in 1998. Although there have been new EUS classification schemata proposed, using morphologic EUS examination as the diagnostic criterion standard for CP is limited by interobserver variability and lack of consensus about which EUS features are most important for diagnosis and which features are truly pathologic.\(^{14-16}\) Limitations of EUS morphologic examination are especially apparent when diagnosing minimal-change disease.

---

**TABLE 2. Characteristics of Ductal Compliance Measurements**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CP</th>
<th>No CP</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ductal diameter, mean (SD), mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>2.33 (1.13)</td>
<td>1.94 (0.75)</td>
<td>0.24</td>
</tr>
<tr>
<td>Body</td>
<td>1.49 (0.77)</td>
<td>1.36 (0.63)</td>
<td>0.29</td>
</tr>
<tr>
<td>Tail</td>
<td>1.21 (0.72)</td>
<td>0.91 (0.48)</td>
<td>0.61</td>
</tr>
<tr>
<td>Peak ductal diameter, mean (SD), mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>3.11 (1.13)</td>
<td>3.15 (1.19)</td>
<td>0.35</td>
</tr>
<tr>
<td>Body</td>
<td>2.34 (0.95)</td>
<td>2.53 (0.93)</td>
<td>0.66</td>
</tr>
<tr>
<td>Tail</td>
<td>1.56 (0.52)</td>
<td>1.84 (0.54)</td>
<td>0.55</td>
</tr>
<tr>
<td>Percent change from baseline ductal diameter to peak diameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>143.4</td>
<td>172.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Body</td>
<td>178.9</td>
<td>208.1</td>
<td>0.33</td>
</tr>
<tr>
<td>Tail</td>
<td>144.3</td>
<td>240.9</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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**FIGURE 2.** Scatterplot demonstrating the percent change in pancreatic diameter from baseline based on duodenal fluid \([\text{HCO}_3^-]\). Each dot on the figure represents 1 patient measurement after secretin stimulation (generally 3 measurements 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 after secretin stimulation (log transformed).
Direct pancreatic function testing, developed nearly 50 years ago, is generally considered an accurate means of evaluating pancreatic function. However, its use has been limited in recent years to specialized centers because of laborious technical requirements, transient lack of available stimulating medications (ie, secretin), and lack of interest. More recently, ePFTs have been developed, which are simple to perform, reproducible, and becoming more widely available. Endoscopic pancreatic function tests 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 a structural evaluation of the pancreas to be performed simultaneously. Furthermore, because the ductal compliance value (maximum change from baseline diameter) does seem to provide at least a fair correlation with the duodenal fluid [HCO₃⁻] measured at 15, 30, and 45 minutes, it can potentially 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.

Because it is primarily a feasibility study, this report does not have sufficient power to answer several important questions about test characteristics. For example, we cannot draw conclusions about the true correlation between ductal compliance and duodenal fluid [HCO₃⁻] given the small number of patients. In addition, it is not possible to determine which region of the pancreatic duct (head, body, or 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 after secretin stimulation is enough time to demonstrate maximum compliance. Furthermore, a 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 interrater or the intrarater reliability of this technique because 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 1 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_{\text{max}} )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>1.00</td>
<td>0.64–1.57</td>
</tr>
<tr>
<td>Body</td>
<td>0.92</td>
<td>0.61–1.38</td>
</tr>
<tr>
<td>Tail</td>
<td>0.71</td>
<td>0.43–1.17</td>
</tr>
<tr>
<td>Percent change from baseline ductal diameter to peak diameter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>0.99</td>
<td>0.97–1.01</td>
</tr>
<tr>
<td>Body</td>
<td>0.99</td>
<td>0.97–1.00</td>
</tr>
<tr>
<td>Tail</td>
<td>0.97</td>
<td>0.94–1.00</td>
</tr>
<tr>
<td>No. parenchymal features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>3.20</td>
<td>1.14–9.02</td>
</tr>
<tr>
<td>Body</td>
<td>3.21</td>
<td>1.1–9.35</td>
</tr>
<tr>
<td>Tail</td>
<td>3.81</td>
<td>0.96–15.09</td>
</tr>
<tr>
<td>No. ductal features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>0.52</td>
<td>0.12–2.29</td>
</tr>
<tr>
<td>Body</td>
<td>0.88</td>
<td>0.18–4.20</td>
</tr>
<tr>
<td>Tail</td>
<td>0.80</td>
<td>0.16–4.01</td>
</tr>
</tbody>
</table>

\( T_{\text{max}} \) indicates the median time to maximum ductal dilation from baseline ductal diameter.

FIGURE 3. Scatterplot demonstrating the rate of change from baseline to maximum dilation in the main pancreatic duct. Each dot on the figure represents 1 patient measurement after secretin stimulation (generally 3 measurements per patient at 15, 30, and 45 minutes) performed during ePFT.
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 magnetic resonance cholangiopancreatography. Finally, we did not consider the issue of SOD dysfunction, which potentially could skew the compliance results, and did not perform sphincter manometry. However, none of our patients were clinically considered to be experiencing SOD type I to III.

Nevertheless, this study demonstrates the potential for a simple, safe, novel means of characterizing pancreatic structure and function in 1 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. Because the diagnosis of CP can sometimes be challenging, especially in minimal-change disease, this study demonstrates that there may be a role for EUS duical compliance measurement as a future diagnostic tool. A multicenter study of this technique to further evaluate its test characteristics is planned.

REFERENCES
Endoscopic Ultrasound, Secretin Endoscopic Pancreatic Function Test, and Histology: Correlation in Chronic Pancreatitis

Swar Albashir, MD¹, Mary P. Bronner, MD², Mansour A. Parsi, MD³, R. Matthew Walsh, MD¹ and Tyler Stevens, MD³

OBJECTIVES: Endoscopic ultrasound (EUS) and hormone-stimulated pancreatic function tests are considered useful, and possibly complementary, in the diagnosis of early chronic pancreatitis (CP). Few past studies have compared either methods with a histological gold standard. The aims were to assess correlations of EUS score and endoscopic pancreatic function test (ePFT) results with the degree of histological fibrosis, as well as the sensitivity of each method for detecting fibrosis.

METHODS: This was a retrospective study of patients who underwent EUS, ePFT, or both within 12 months of pancreatic resection or wedge biopsy. EUS scoring was performed using 9 standard criteria, with ≥4 considered abnormal. An ePFT peak bicarbonate concentration < 80 mM was considered abnormal. Surgical specimens were reviewed in a blinded manner by an expert pancreatic pathologist and assigned a fibrosis score from 0 to 12. Correlations of the EUS score and ePFT peak bicarbonate with the fibrosis score are reported using the Spearman correlation coefficient. Sensitivity and specificity was calculated for each method against the histological gold standard (fibrosis score ≥2).

RESULTS: Twenty-five patients were included. The fibrosis score significantly correlated with the EUS score (r = 0.72; 95% confidence interval (CI) = 0.43, 0.87; P < 0.001) and the ePFT peak bicarbonate (r = −0.57; 95% CI = −0.81, −0.10; P = 0.016). EUS had a sensitivity of 84% (95% CI = 69, 100) and specificity of 100% (95% CI = 40, 100) compared with histology. The ePFT had a sensitivity of 86% (95% CI = 67, 100) and specificity of 67% (95% CI = 13, 100). When both modalities were combined, the sensitivity increased to 100% (95% CI = 63, 100).

CONCLUSIONS: Both EUS and ePFT are useful tests in the diagnosis of CP. Combining EUS with ePFT may improve the sensitivity for detection of early fibrosis.

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INTRODUCTION
Endoscopic ultrasound (EUS) and hormone-stimulated pancreatic function testing (PFT) are potentially useful diagnostic tests for early, “minimal change,” chronic pancreatitis (CP). EUS detects structural abnormalities of the pancreatic duct and parenchyma indicative of fibrosis (1,2). PFTs are an independent, complementary marker for fibrosis, as they assess the degree of pancreatic exocrine insufficiency. Both EUS structural abnormalities and exocrine insufficiency may be present in patients who do not have obvious structural changes (e.g., calcifications) on conventional imaging (3). However, the results of EUS and PFT are also frequently discordant in the early phase of CP (4). This may imply that some patients develop structural changes before functional abnormalities, or vice versa.

PFTs are infrequently performed because of the difficulty of gastroduodenal-tube placement, requirement for fluoroscopy, and need for complicated laboratory techniques. To overcome these limitations, our group (5,6) and others (7,8) have developed endoscopic pancreatic function tests (ePFTs) that use standard hospital autoanalyzers for fluid analysis. These tests ease the performance
of PFT and have been validated against traditional Dreiling-tube PFTs, thus potentially increasing the availability of functional testing to patients.

It is not clear whether EUS or PFT is more accurate for diagnosis of early CP. Most studies of new tests for CP have used non-histological radiographic or composite reference standards. Few studies have compared EUS (9,10) or PFT (11,12) using a histological gold standard. Furthermore, the ePFT has never been compared with histology. The primary aim of this study was to assess the correlations of EUS and ePFT results with the degree of histological fibrosis. We also sought to determine the sensitivity of both methods for detecting pancreatic fibrosis. We hypothesized that combined EUS and ePFT would optimize the sensitivity for fibrosis.

METHODS

Study design

This is a single-center institutional review board (IRB)-approved cross-sectional study of the accuracy of ePFT and EUS for the diagnosis of CP (IRB #09–202). The electronic medical record was queried for all patients who underwent a pancreatic resection or open biopsy for CP, and who underwent EUS or ePFT within 12 months before surgery. Exclusion criteria included patients with pancreatic cancer or a history of pancreatic surgery.

Endoscopic ultrasound

All EUS procedures were performed by experienced endoscopists. The presence or absence of nine ductal and parenchymal criteria was routinely assessed in a prospective manner: hyperechoic foci, hyperechoic strands, cysts, lobularity, calcifications, hyperechoic duct margins, visible side branches, main pancreatic duct dilation, and main pancreatic duct irregularity (score 0–9) (13). The presence of four or more features was considered abnormal (10).

Secretin ePFT

The secretin ePFT was performed as described earlier (5,6). After sedation, an endoscope is passed into the stomach. Intravenous secretin is administered at a dose of 0.2 mcg/kg. The residual gastric fluid is thoroughly suctioned to prevent gastric contamination of the duodenal samples. Duodenal aspirates are collected at 15-min intervals for 1 h. The aspirates are analyzed for bicarbonate concentration using a hospital autoanalyzer. A peak bicarbonate concentration <80 mM (millimolar) is considered abnormal.

Histological grading

The original slides for each surgery were retrieved from the pathology archives. An expert pancreatic pathologist (M.B.) blinded to the EUS and ePFT results reviewed and scored the pathological specimens based on the system proposed by Ammann et al. (14). The pancreatic parenchyma is comprised of grouped lobules of acini (functional unit of the exocrine pancreas) emptying into an intralobular duct. Pancreatic fibrosis in CP is found both within lobules and surrounding lobules. The Ammann system quantifies the amount of intralobular and perilobular fibrosis in the pancreatic parenchyma. The grade (mild, moderate, or severe) and distribution (focal or diffuse) of intralobular and perilobular fibrosis is quantified based on a 0–12 point score. A fibrosis score of 2 or more was considered abnormal (9).

Statistical analysis

Means, s.d., and percentages are reported for descriptive statistics. The strengths of relationships of continuous variables are reported as Spearman correlation coefficients with 95% confidence intervals (CIs). Contingency tables were constructed to analyze the test performance of EUS and ePFT compared with the histological reference standard. The sensitivity and specificity were determined for each test with 95% CI.

RESULTS

Patients

Between 2001 and 2009, 25 patients underwent EUS, ePFT, or both within 1 year before pancreatic surgery (Table 1). The mean time before surgery (s.d.) was 0.40 (0.35) years for EUS and 0.39 (0.35) years for ePFT. All patients were debilitated with chronic upper abdominal pain because of suspected CP, and had failed to respond to conventional medical management. Eighteen patients (72%) lacked calcifications and were classified as minimal change CP. None of the patients had suspicion of pancreatic cancer, or were eventually found to have pancreatic cancer.

The pathological specimen consisted of a resection in 9 patients and open surgical biopsy in 16 patients. The patients underwent the following operations: three patients with suspicion of minimal change CP underwent exploratory laparotomy with random wedge pancreatic biopsy; eight patients with suspicion of minimal change CP underwent a total pancreatectomy with autoislet cell transplantation with random wedge biopsy; one patient with calcifications on CT underwent a total pancreatectomy with autoislet cell transplantation with random wedge biopsy; four patients with an obstructed main pancreatic duct underwent a lateral pancreatecojejunostomy drainage surgery (Puestow) with random wedge biopsy; nine patients with abdominal pain and suspected focal CP underwent a partial pancreatectomy (Whipple or Frey in six; distal pancreatectomy in three). Random wedge biopsies were obtained from the periductal pancreas in drainage procedures, or a peripheral portion of the gland in total pancreatectomy with autoislet cell transplantation as not to mar the dissolution process.

Twenty-one patients (84%) had a histological fibrosis score ≥2, consistent with CP. The initial pathological diagnosis obtained from the medical record was “chronic pancreatitis” in 19 patients (2 with features of autoimmune pancreatitis) and “normal parenchyma” in 6 patients. The initial pathological diagnosis was concordant with the fibrosis scoring (either both positive or both negative) in 23 of 25 patients. In the two discordant cases, the pathological diagnosis was “normal,” whereas the fibrosis scores were 2 and 5.
EUS vs. histopathology

Twenty-three patients underwent a preoperative EUS (15 combined EUS/ePFT, 8 EUS alone). Patients with EUS criteria frequently had histological changes of fibrosis (Figure 1). A significant positive correlation was observed between the number of EUS criteria and histopathological fibrosis score ($r_s = 0.72; 95\%\ CI = 0.43, 0.87; P < 0.001$) (Figure 2). EUS ($\geq 4$ criteria) had a sensitivity of 84\% (16 / 19 patients; $95\%\ CI = 69, 100$) and specificity of 100\% (4 / 4 patients; $95\%\ CI = 40, 100$) compared with the histopathological reference standard ($\text{fibrosis score} \geq 2$) (Figure 3). In the subset with suspected minimal change CP, EUS had a sensitivity of 75\% (9 / 12 patients; $95\%\ CI = 51, 100$) and specificity of 100\% (4 / 4 patients; $95\%\ CI = 40, 100$).

Secretin ePFT vs. histopathology

Seventeen patients underwent a preoperative ePFT (15 combined EUS/ePFT, 2 ePFT alone). A significant negative correlation was observed between the ePFT peak bicarbonate concentration and the histopathological fibrosis score ($r_s = -0.57; 95\%\ CI = -0.81, -0.10; P = 0.016$) (Figure 2). The ePFT (peak bicarbonate <80 mM) had a sensitivity of 86\% (12/14 patients; $95\%\ CI = 67, 100$) and specificity of 67\% (2/3 patients; $95\%\ CI = 13, 100$) compared with the histopathological reference standard (Figure 3). In the subset with suspected minimal change CP, the ePFT had a sensitivity of 80\% (8/10 patients; $95\%\ CI = 55, 100$) and specificity of 67\% (2/3 patients; $95\%\ CI = 13, 100$).

Combined EUS/ePFT vs. histopathology

Fifteen patients underwent combined EUS/ePFT. The combined EUS/ePFT (either EUS $\geq 4$ criteria or peak bicarbonate <80 mM) had a sensitivity of 100\% (12/12 patients; $95\%\ CI = 74, 100$) and specificity of 67\% (2/3 patients; $95\%\ CI = 63, 100$) compared with the histopathological reference standard (Figure 3). In the subset with suspected minimal change CP, the EUS/ePFT had a sensitivity of 100\% (8/8 patients; $95\%\ CI = 63, 100$) and specificity of 67\% (2/3 patients; $95\%\ CI = 13, 100$).

### Table 1. Patient characteristics

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AP, history of acute pancreatitis; ePFT, endoscopic pancreatic function test; EUS, endoscopic ultrasound; SOD, sphincter of Oddi dysfunction; TP/AIT, total pancreatectomy with autoislet cell transplantation.

*Calcifications on computed tomography scan.
Figure 1. Examples of correlated endoscopic ultrasound (EUS) and histological findings. (a) EUS shows a normal “salt and pepper” echotexture of the pancreatic parenchyma. (b) In the same patient, histology reveals normal ductal and islet tissues without fibrosis (hematoxylin and eosin stain). (c) EUS shows stranding and contiguous lobulations (arrows) in a patient with suspected minimal change chronic pancreatitis (CP). (d) In the same patient, histology reveals well-developed perilobular fibrosis (arrow) (hematoxylin and eosin stain). (e) EUS shows a mildly dilated main pancreatic duct with an echogenic duct wall (arrow). (f) In the same patient, histology reveals a dilated main duct with prominent periductal fibrosis (hematoxylin and eosin stain). (g) EUS shows a dilated duct with a shadowing intraductal calculus in a patient with calcific CP. (h) Histological examination reveals eosinophilic stone material within the duct (arrow) (hematoxylin and eosin stain).

Figure 2. (a) Scatter plots of the histological fibrosis score vs. endoscopic ultrasound (EUS) score and (b) endoscopic pancreatic function test (ePFT) peak bicarbonate concentration.

\[ r = 0.72, P < 0.001 \]

\[ r = -0.57, P = 0.016 \]
Sensitivity and specificity for EUS (84%) and secretin ePFT (86%) for the detection of early CP. Our data show comparable test performance in the subset with minimal change (non-calcific) chronic pancreatitis (CP) is also depicted.

**DISCUSSION**

Controversy exists over whether EUS or functional testing is most accurate for the diagnosis of early CP. Our data show comparable sensitivities for EUS (84%) and secretin ePFT (86%) for the detection of histologically confirmed pancreatic fibrosis. Both EUS and ePFT results significantly correlated with the degree of histologic fibrosis ($r = 0.72$ and $-0.57$, respectively). The combined EUS/ePFT procedure produced 100% sensitivity for CP.

Histological comparison is often considered the best reference standard for defining a test’s performance. Our results are consistent with two previously published studies (9,10) and one abstract (15) comparing EUS with histology. In one study, 42 patients underwent EUS within 2 months of pancreatic resection (10). The presence of ≥4 EUS criteria provided 91% sensitivity and 86% specificity for detecting histologic fibrosis. A high correlation was observed between the EUS score and fibrosis score ($r = 0.85$, $P < 0.0001$). Ductal changes had a higher correlation with histology than parenchymal features. A limitation of that study was that most patients underwent resection for pancreatic cancer, making it difficult to apply the results to patients evaluated for abdominal pain in the setting of benign CP. In another study of 41 patients lacking calcifications, three or more EUS criteria had 83% sensitivity and 80% specificity for detecting CP (9). A significant correlation was observed between histology and EUS score ($r = 0.40$, $P = 0.01$). Each EUS criterion produced an average 0.81 increase in the fibrosis score.

Two earlier studies have compared a traditional (Dreiling tube) secretin PFT to histology. Both studies found significant correlations of PFT parameters (e.g., bicarbonate, amylase output) with histological severity (11,12). Our study is the first to compare the ePFT with histology. We have previously shown the secretin ePFT to yield equivalent results as the Dreiling-tube method (6). The endoscopic method is easier to perform than traditional methods and can be performed by any gastroenterologist.

It is attractive to propose that structural and functional tests are complementary in the diagnosis of early CP (16,17). What is unclear with this approach is how to interpret discordant results. Earlier studies have shown suboptimal concordance of EUS and PFT in patients with suspected CP (18). Our data shed light on the significance of discordant results by providing histological comparison in patients who underwent both modalities. There were 12 patients with histologically proven CP who underwent both EUS and ePFT. Of these, nine patients had an abnormal EUS and ePFT (75% concordance). Results were discordant in the remaining three patients (two patients with EUS+/ePFT−, one patient with EUS−/ePFT+). All three patients had mild fibrosis (fibrosis scores 2, 2, and 5, respectively). These preliminary results suggest that either test can become abnormal in the earliest stages of fibrosis, and that performance of both tests may optimize detection of mild fibrosis. They also indicate that either test may have a false negative result and miss patients with early stages of CP. We have previously shown that the ePFT can be performed during the same endoscopic session as EUS allowing a comprehensive functional and structural assessment of the pancreas (19).

There are some limitations of our study. First, the small sample size limits the precision of our sensitivity and specificity estimates. The limited sample size reflects the fact that our study contains a highly selected sample of patients who went to surgery. All had severe pain and in some cases pronounced structural features of CP. Spectrum bias occurs when there is an increased prevalence of severe disease in the study sample compared with a consecutively selected sample, and may artifically increase sensitivity. Less than one fourth our patients had calcifications suggestive of advanced CP. However, patients with calcifications do not require an endoscopic test for diagnosis of CP and may contribute to spectrum bias. To surmount this limitation, we calculated ancillary sensitivity and specificity estimates in the subset without calcifications. As expected, sensitivity in the minimal change subset was slightly lower for both EUS and ePFT. However, the combined EUS/ePFT maintained 100% sensitivity in the suspected minimal change cohort, albeit in a small sample of eight patients with proven fibrosis. Another limitation is that only four patients had normal histology in the limited tissue available for analysis, which limits our ability to measure specificity. In this small sample, the EUS showed 100% specificity. However, ePFT had 67% specificity because of one patient with a borderline abnormal ePFT result (peak bicarbonate 78 mM). This may suggest that the ePFT result was a false positive, or the possibility of sampling bias based on the patchy nature of mild CP. Many of the patients had a wedge biopsy, which may not represent the pathological state of the entire gland. Despite these limitations, we believe our study sheds light on the
dilemma of diagnosis of early CP. Future larger multicenter histological studies of minimal change CP are needed to confirm our findings. This may be possible in the future because of the increasing performance of total pancreatectomy with autoislet cell transplantation (15). The Rosemont classification is a new system for EUS CP scoring, which incorporates weighted criteria and a four-level diagnostic stratification (20). This new system may improve diagnosis and should be validated compared with a histological gold standard. Endosonographers have only recently begun using the Rosemont classification, so the validity of this scoring method could not be assessed in this study.

In conclusion, both EUS and ePFT can detect early histological changes of CP. Each test independently predicts fibrosis, and the results may be interpreted in a complementary manner. We believe the combined EUS and ePFT optimizes the early and accurate diagnosis of CP, ultimately providing useful management options to patients.

CONFLICT OF INTEREST
Guarantor of the article: Tyler Stevens, MD.
Specific author contributions: Acquisition of data and drafting of the manuscript: Siwar Albashir; critical revision of the manuscript for important intellectual content: Mansour Parsi; critical revision of the manuscript for important intellectual content: R. Matthew Walsh; histological interpretation of tissue specimens and critical revision of the manuscript for important intellectual content: Mary Bronner; study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, study supervision, and final approval of the manuscript: Tyler Stevens.
Financial support: None.
Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE
- Both endoscopic ultrasound (EUS) and endoscopic pancreatic function test (ePFT) may be useful tests for diagnosing early and advanced chronic pancreatitis (CP); however, there are few studies that have compared either or both methods with histology.

WHAT IS NEW HERE
- The number of EUS features, indicating structural changes of CP, correlates with the histological fibrosis score.
- The secretin ePFT peak bicarbonate also correlated with histological fibrosis score, indicating a relationship between mild fibrosis and exocrine insufficiency.
- Both EUS and ePFT showed good (~80%) sensitivity for CP as single tests; however, sensitivity was 100% when the tests were combined.

REFERENCES
Prospective comparison of radial and linear endoscopic ultrasound for diagnosis of chronic pancreatitis

Background and study aims: Linear endoscopic ultrasonography (EUS) is currently favored by many endosonographers for the evaluation of pancreatic pathology. However, radial EUS was used in early studies validating EUS for chronic pancreatitis. Radial and linear EUS have never been compared for the diagnosis of chronic pancreatitis. The aim of this study was to compare radial and linear EUS for the diagnosis of chronic pancreatitis using the secretin-stimulated endoscopic pancreatic function test (ePFT) as the reference standard.

Patients and methods: One hundred consecutive patients evaluated for pain of possible pancreatic origin underwent combined radial EUS, linear EUS, and secretin ePFT during a single endoscopic session. EUS images were acquired on videotape and blindly scored by three reviewers. The main outcome measure was diagnostic accuracy.

Results: The accuracy of radial EUS and linear EUS (cutpoint ≥ 4 criteria) was 84% and 74%, respectively. The statistical test for noninferiority was significant (P < 0.001) suggesting that the accuracy of radial EUS is as good as or superior to linear EUS. The ratio of accuracy (πradial/πlinear) was 1.14 (95% confidence interval [CI] 0.99 to 1.28). No statistically significant differences were found between radial and linear EUS in terms of sensitivity, specificity, or overall discriminative ability (area under receiver operating characteristic curve 0.84 vs. 0.76, P = 0.10). Interobserver variability was similar for radial (Fleiss’ κ = 0.61, 95%CI 0.43 to 0.79) and linear EUS (κ = 0.50, 95% CI 0.28 to 0.72).

Conclusions: The accuracy of radial EUS is as good as linear EUS for the diagnosis of chronic pancreatitis.

Introduction

Endoscopic ultrasonography (EUS) is increasingly used as a diagnostic test for early chronic pancreatitis in patients with abdominal pain. EUS allows a close inspection of the head, body, and tail of the pancreas from gastric and duodenal stations, and detects ductal and parenchymal features thought to correlate with fibrosis [1]. Radial EUS scopes provide a 360° sonographic view, which is perpendicular to the tip of the endoscope. Linear EUS scopes provide a 150° sector view, which is parallel to the long axis of the endoscope.

Pancreatic ultrasound was first performed by radiologists who used linear ultrasound technology to characterize many of the same criteria of ductal and parenchymal abnormalities of chronic pancreatitis currently used by today’s endosonographers [2]. Linear EUS is currently favored by endosonographers for evaluating pancreatic and biliary diseases, including the staging of pancreatic cancer, imaging, and sampling of cysts, and diagnosis of pancreas divisum [3–7]. However, some endosonographers prefer radial EUS for diagnostic purposes when fine-needle aspiration (FNA) is not anticipated. Furthermore, the early studies that validated EUS for the diagnosis of chronic pancreatitis used radial EUS [8–10]. To the best of our knowledge, no prior studies have compared radial and linear EUS technology for the diagnosis of chronic pancreatitis. A persistent challenge in studying tests for chronic pancreatitis is the lack of a histological gold standard. Hormone-stimulated pancreatic function tests (PFT) have been called a nonhistological reference standard because they detect mild exocrine insufficiency as a surrogate for early fibrosis [11,12].

The primary aim of this study was to compare the results of radial and linear EUS in patients evaluated for chronic pancreatitis using the secretin PFT as the reference standard. We hypothesized that the accuracy of radial EUS is as good as linear
EUS for the diagnosis of chronic pancreatitis. Radial EUS was considered at least as good as linear EUS if the correct diagnosis was achieved in at least 90% of cases diagnosed by linear EUS.

Methods

Study design

This was a single-center prospective cross-sectional study to compare radial and linear EUS technology for the diagnosis of chronic pancreatitis using the secretin-stimulated ePFT as the reference standard. The institutional review board at the Cleveland Clinic approved this research protocol (IRB #8549). Each patient gave informed consent to allow passage of a linear scope in addition to the combined radial EUS and secretin ePFT planned for their clinical evaluation. All patients who consented to the study were able to tolerate the entire procedure.

Study population

Consecutive patients undergoing an evaluation for abdominal pain possibly due to chronic pancreatitis were screened for eligibility. The inclusion criteria included: age >18 years and ability to sign the written informed consent document. The exclusion criteria included: pregnancy, ongoing alcohol or drug abuse within the past 2 months, severe cardiac, pulmonary, or renal comorbidity, recent use of anticholinergic medications, recent acute pancreatitis (more than a threefold increase in amylase and lipase in the past 2 months), or a history of medical conditions that affect pancreatic function (vagotomy, gastrectomy, pancreatic surgery, inflammatory bowel disease, celiac disease, cirrhosis).

Combined EUS and secretin ePFT

The endoscopic procedures for this study were performed by a single endoscopist (TS). The combined EUS and secretin ePFT procedure took approximately 60 minutes to complete (Fig. 1). After sedation, radial (GF UM-130 or GF UE-160; Olympus, Melville, New York, USA) then linear (GF UC-160P-OL5; Olympus) echoendoscopes were passed in sequence. Representative portions of the pancreatic head, body, and tail were recorded on digital videotape (Fig. 2). During the EUS examination, the standard dose of synthetic secretin (0.2 µg/kg i.v.) was administered. Duodenal samples (5–10 mL each) were collected at 15, 30, and 45 minutes after secretin administration through the suction channel of the scope as previously described [13, 14]. After completion of the EUS examination, the echoendoscope was usually removed and the standard upper endoscope was inserted for collection of duodenal samples. In some cases the echoendoscope was used to collect the first or subsequent samples. All samples were transported on ice to the laboratory for immediate analysis of bicarbonate concentration by a hospital autoanalyzer. The highest concentration from the three samples was considered the peak concentration. A peak bicarbonate concentration of less than 80mmol/L was considered abnormal [15].

EUS consensus scoring

Radial and linear EUS videotapes were edited and labeled in a random fashion onto separate videotapes. EUS tapes were interpreted by three blinded expert endoscopists (JD, JV, and GZ). Each expert had performed more than 1000 pancreatic EUS examinations. All three experts had expertise in both radial and linear EUS. However, two experts expressed a preference for radial EUS for pancreatic diagnosis; the third expressed a preference for linear EUS. Each interpreter reviewed the tapes privately and completed a score sheet. The presence or absence of nine criteria was recorded and a score assigned for the patient’s clinical evaluation. The nine criteria included: lobularity, hyperechoic foci, hyperechoic strands, cysts, main duct dilatation, main duct irregularity, hyperechoic duct walls, visible side-branches, and calcifications [10]. Each criterion was considered present based on its identifi-
cation by at least two of the three interpreters. The possible range of scores was 0 to 9. Each interpreter also assigned a quality score (1 = poor; 2 = fair; 3 = good) for each examination.

Statistical methods and sample size

The primary outcome for comparison of radial and linear EUS was diagnostic accuracy (true positives + true negatives)/total). The reference standard was defined as an abnormal secretin PFT (peak bicarbonate < 80 mmol/L). The difference in accuracy of radial and linear EUS was assessed using a noninferiority test [16]. The alternative hypothesis was that the accuracy of radial EUS was as good as or better than linear EUS, accepting a ratio of accuracy greater than 90% (HA: \( \frac{\pi_{\text{radial}}}{\pi_{\text{linear}}} > 0.90 \)). The null hypothesis was that linear EUS had superior accuracy to radial EUS (HA: \( \frac{\pi_{\text{radial}}}{\pi_{\text{linear}}} < 0.90 \)). We retrospectively calculated our statistical power for assessing noninferiority based on our sample size of 100 patients and the observed discordance rate of 18% (4% linear correct/radial incorrect, 14% radial correct/linear incorrect). Given these parameters and Tang’s formula [17], we had 91% power to demonstrate noninferiority of radial EUS compared with linear EUS.

Contingency tables were constructed to calculate the sensitivity and specificity at each cutoffpoint. Receiver operating characteristic (ROC) curves were plotted to determine overall discriminative abilities of radial and linear EUS, and were compared using a non-parametric approach [18]. The strength of relationships between continuous variables is reported using the Pearson correlation coefficient. The Cohen’s kappa \( \kappa \) statistic was used to assess agreement of radial and linear EUS [19]. Fleiss’ kappa \( \kappa \) was used to assess agreement between multiple raterst [20]. Kappa statistics \( \kappa \) were interpreted based on the convention by Landis and Koch [21]: < 0: no agreement; 0 – 0.20: slight agreement; 0.21 – 0.40: fair agreement; 0.41 – 0.60: moderate agreement; 0.61 – 0.80: substantial agreement; 0.81 – 1.0: almost perfect agreement. SAS version 9.1 (SAS, Inc. Cary, North Carolina, USA) was used for all statistical analyses. The power calculation was programmed using R statistical software version 2.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 100 patients were recruited. Exocrine insufficiency (peak bicarbonate < 80 mmol/L) was found in 41 patients (41%). Eighteen patients had advanced chronic pancreatitis detectable by computed tomography (CT) scan. Seventeen of these 18 patients (94%) with advanced chronic pancreatitis had exocrine insufficiency. The demographic and clinical characteristics of the group are shown in Table 1.

A total of 83 patients had conscious sedation administered by a gastroenterologist. Seventeen patients had deep sedation administered by an anesthesiologist. There was no significant difference in the quality scores of the radial and linear videotaped examinations (Wilcoxon signed rank \( P = 0.46 \)).

The diagnostic abilities of radial and linear EUS consensus scoring were compared using the secretin PFT reference standard. The sensitivity, specificity, and accuracy of radial and linear EUS consensus score were determined at each diagnostic threshold (Table 2).

The area under the ROC curve was 0.84 (95%CI 0.75 to 0.93) for radial EUS versus 0.76 (95%CI 0.66 to 0.87) for linear EUS (\( P = 0.10 \)). A cutoff of \( \geq 4 \) criteria resulted in the highest accuracy for both radial and linear EUS.

The accuracy of radial EUS and linear EUS (cutoff \( \geq 4 \) criteria) was 84% and 74%, respectively. The statistical test for noninferiority was significant (\( P < 0.001 \)), suggesting that the accuracy of radial EUS is as good as linear EUS. The ratio of accuracy (\( \frac{\pi_{\text{radial}}}{\pi_{\text{linear}}} \))

### Table 1 Clinical characteristics.

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>n and %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>38</td>
</tr>
<tr>
<td>Female</td>
<td>62</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>20</td>
</tr>
<tr>
<td>30 – 39</td>
<td>13</td>
</tr>
<tr>
<td>40 – 49</td>
<td>27</td>
</tr>
<tr>
<td>50 – 59</td>
<td>19</td>
</tr>
<tr>
<td>≥ 60</td>
<td>21</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>9</td>
</tr>
<tr>
<td>Caucasian</td>
<td>91</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
</tr>
<tr>
<td>&lt; 24</td>
<td>21</td>
</tr>
<tr>
<td>24 – 26</td>
<td>24</td>
</tr>
<tr>
<td>27 – 31</td>
<td>17</td>
</tr>
<tr>
<td>≥ 32</td>
<td>20</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td>Never/light</td>
<td>72</td>
</tr>
<tr>
<td>Moderate/heavy (former or recent)</td>
<td>28</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Never/former</td>
<td>63</td>
</tr>
<tr>
<td>Current</td>
<td>37</td>
</tr>
<tr>
<td>History of acute pancreatitis</td>
<td>27</td>
</tr>
<tr>
<td>Cross-sectional imaging</td>
<td></td>
</tr>
<tr>
<td>Normal pancreas</td>
<td>68</td>
</tr>
<tr>
<td>Abnormal pancreas</td>
<td>18</td>
</tr>
<tr>
<td>Imaging unavailable</td>
<td>14</td>
</tr>
</tbody>
</table>

### Table 2 Test performance of radial and linear endoscopic ultrasonography (EUS) consensus scoring.

<table>
<thead>
<tr>
<th>Cut-point</th>
<th>Radial EUS, % (95%CI)</th>
<th>Linear EUS, % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>≥ 2</td>
<td>80 (68 to 93)</td>
<td>64 (52 to 77)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>76 (62 to 89)</td>
<td>78 (67 to 89)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>68 (54 to 83)</td>
<td>95 (89 to 100)</td>
</tr>
<tr>
<td>≥ 5</td>
<td>59 (43 to 74)</td>
<td>100 (94 to 100)</td>
</tr>
<tr>
<td>≥ 6</td>
<td>41 (26 to 57)</td>
<td>100 (94 to 100)</td>
</tr>
</tbody>
</table>

CI, confidence interval.
Both radial and linear EUS consensus scores exhibited a strong negative correlation with peak bicarbonate concentration (Fig. 4).

**Table 3** shows the concordance of radial and linear EUS for individual features and overall diagnosis. Concordance for individual features ranged from 58% (hyperechoic duct walls) to 97% (cysts). After adjustment for multiple comparisons (Bonferroni’s method), there was no statistically significant difference between linear and radial EUS for detection of any of the individual features.

Fleiss’ kappa (κ) scores were calculated to evaluate interobserver variability among the three expert interpreters (Table 4). Agreement beyond chance for overall chronic pancreatitis diagnosis was moderate for both radial (Fleiss κ = 0.61, 95%CI 0.43 to 0.79) and linear EUS (κ = 0.50, 95%CI 0.28 to 0.72). Agreement beyond chance was moderate or substantial (κ ≥ 0.41) for main duct dilation and calcifications, but slight or fair for the other criteria.

**Discussion**

We have shown that the accuracy of radial EUS is as good as linear EUS for the diagnosis of exocrine insufficiency, a marker of chronic pancreatitis (noninferiority test P < 0.001). No statistically significant differences were found in the sensitivity, specificity, overall discrimination (ROC area under curve), or interobserver variability of radial and linear EUS.

Many endosonographers prefer linear EUS for evaluating pancreatic diseases. Some endosonographers also believe that linear EUS produces higher quality and more complete imaging of the pancreas. Potential advantages of linear EUS include color-flow Doppler capability, enhanced tissue resolution, and the ability to perform fine-needle aspiration. These characteristics make linear EUS ideal for the evaluation and staging of pancreatic masses and cysts. Of course, newer electronic radial EUS scopes also offer color-flow Doppler and similar tissue resolution as linear scopes.

Seminial studies of EUS for diagnosis of chronic pancreatitis have utilized radial EUS technology, as linear EUS instruments were not widely available [8 – 10]. We often use radial EUS for the evaluation of patients with pain of possible pancreatic origin. In these patients, it is very unlikely that FNA will be required. This study validates the use of radial EUS imaging for diagnosis of chronic pancreatitis because radial was found to be noninferior to linear. We did not have adequate power to demonstrate the superiority of radial EUS. However, trends for improved accuracy, sensitivity, and interobserver variability were observed for radial EUS. The reason for these observed differences is not clear. Poor-quality linear EUS acquisition or taping is unlikely to explain the disparity given the absence of significant difference in quality scores. Radial EUS provides a cross-sectional image similar to a CT scan, which may make anatomical distinction and evaluation of structures including the pancreatic duct easier.

There are several strengths of the current study. First, testing was applied to a large consecutive sample of patients evaluated for chronic pancreatitis. Consecutive recruitment prevents the sampling and verification biases encountered in recent histological correlate studies. Second, blinded consensus scoring was used to obtain a fair comparison of radial versus linear EUS and to minimize the effect of operator dependence. Our own study confirms a high level of interobserver variability for EUS criteria observed in past studies [22]. Third, our sample was mostly comprised of patients with normal CT scans (suspected “minimal change”
chronic pancreatitis), the patients most likely to benefit from EUS. The presence of few patients with advanced structural abnormalities on CT scan decreases spectrum bias found in some past studies.

Some limitations should also be mentioned. First, the true accuracy of the PFT reference standard is not known. Based on limited histological comparison studies, direct PFTs are thought to have approximately 85% sensitivity and specificity for diagnosis of chronic pancreatitis [23, 24]. However, false-positive results may be due to procedural factors or chronic narcotic use, and false-negative results may be due to preserved exocrine function despite the presence of chronic pancreatitis. Second, EUS and PFT were performed during the same endoscopic session, which may theoretically confound the results of EUS. Specifically, secretin might alter the appearance of EUS ductal criteria. Two prior studies using transabdominal ultrasound [25, 26] and another using EUS [27] have measured main pancreatic duct diameters after secretin administration is minimal and most significant in patients with ductal obstruction (e.g., stricture, stone, and ampullary stenosis). Our study did not include serial and timed measurements of the pancreatic duct after secretin administration. Finally, we included a subset of patients with established chronic pancreatitis based on CT imaging. It is true that EUS is a second-line test for diagnosis of chronic pancreatitis, when the cross-sectional imaging tests are negative. We chose to include some patients with severe structural changes to allow a comparison between radial and linear EUS to detect “major” structural features (e.g., calcifications, main duct dilatation). However, we showed no significant difference in accuracy in the subset with normal CT scan.

This study also confirms the feasibility of performing EUS and secretin PFT as a comprehensive evaluation of pancreatic structure and function. We have previously demonstrated the validity of the endoscopic secretin PFT compared with the traditional Dreiling method [13, 14]. Both structural and functional testing may be useful in diagnosing the earliest stages of chronic pancreatitis [28]. Long-term follow-up studies are needed to better understand the predictive value of this endoscopic approach to diagnosis.

**Acknowledgment**

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A poster summary of this study was presented at the American Society of Gastrointestinal Endoscopy meeting, Digestive Disease Week 2008, San Diego, California, USA.

**Competing interests:** None

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Combined Endoscopic Ultrasound and Secretin Endoscopic Pancreatic Function Test in Patients Evaluated for Chronic Pancreatitis

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Abstract

Background Endoscopic ultrasound and endoscopic secretin pancreatic function test may be combined in a single endoscopic session (EUS/ePFT) to diagnose chronic pancreatitis (CP).

Aims Our primary aim was to assess the correlation and concordance of combined EUS and secretin ePFT bicarbonate results in suspected minimal change CP.

Methods Radial EUS included scoring for nine criteria (normal <4 criteria) with endoscopic collection of duodenal samples at 15, 30, and 45 min after secretin stimulation (normal peak bicarbonate ≥80 mmol/l).

Results Three hundred and two patients completed the EUS/ePFT (252 for suspected minimal change CP, 38 for established CP, 12 for painless steatorrhea). In patients evaluated for suspected minimal change CP, a moderate negative correlation was observed between endoscopic ultrasound score and peak bicarbonate ($r = -0.38$, $P < 0.001$). The EUS and ePFT results were 76% concordant and 24% discordant. The ePFT was 85% sensitive and EUS was 100% sensitive for detecting patients with established calcific CP. The EUS/ePFT diagnosed CP in two of 12 of patients evaluated for painless steatorrhea or diarrhea with weight loss.

Conclusions The combined EUS/ePFT is feasible and safe. There is only moderate correlation and concordance of endoscopic ultrasound and endoscopic pancreatic function test results in patients with suspected minimal change CP. The EUS and ePFT results produce complimentary functional and structural information for the evaluation of CP.

Keywords Chronic pancreatitis · Pancreatic function testing · Endoscopic ultrasound

Abbreviations

CI Confidence interval
CP Chronic pancreatitis
CT Computed tomography
EUS Endoscopic ultrasound
ePFT Endoscopic pancreatic function test
mmol/l Millimoles per liter
NPV Negative predictive value
PFT Pancreatic function test
PPV Positive predictive value

Introduction

The diagnosis of early or “minimal-change” chronic pancreatitis (CP) is difficult due to the lack of readily identifiable structural features on computed tomography (CT) scan [1]. Endoscopic ultrasound (EUS) detects subtle and severe abnormalities of the duct and parenchyma and is now considered a structural reference standard [2, 3]. Hormone-stimulated pancreatic function tests detect exocrine insufficiency that may accompany early and late
stages of pancreatic fibrosis. We have validated an endoscopic version of the secretin pancreatic function test (ePFT) that consists of endoscopic collection of duodenal fluid for bicarbonate analysis and yields equivalent results as the traditional Dreiling tube method in crossover studies [4, 5].

Neither EUS nor ePFT are gold standards. EUS has high interobserver variability [6]. Minimal EUS features lack specificity, which may lead to over-diagnosis of CP, particularly if a lower number of criteria is used to establish the diagnosis [7, 8]. Exocrine insufficiency detected with ePFT is a likewise imperfect predictor of CP. Although many patients develop functional abnormalities with early fibrosis, there is a subset of patients with calcific pancreatitis that have preserved exocrine function [9]. Since there is no single perfect test, some experts have proposed that combining structural and functional testing may optimize the diagnosis of CP [10–12].

In the past 3 years, we have combined EUS and secretin ePFT during the same endoscopic session to provide a simultaneous assessment of pancreatic structure and function. The relationship of EUS with duct-cell and acinar-cell function was examined in 50 patients with mild and severe CP who underwent secretin EUS/ePFT and cholecystokinin ePFT [13]. The EUS score was significantly correlated with both the secretin ePFT peak bicarbonate \( r = -0.71 \) and CCK ePFT peak lipase \( r = -0.54 \). However, the test results were concordant in only 72% of patients with suspected minimal change CP.

In this study, we report the outcomes of our clinical experience with the combined secretin EUS/ePFT in a large consecutive sample composed primarily of patients with suspected minimal change CP. Our primary aim was to better define the relationship between EUS and secretin ePFT results in patients with suspected early CP. We hypothesized that EUS and PFT results would have a modest correlation and concordance in this group. As a secondary aim, we examined the results of EUS/PFT in patients with established severe CP. We also assessed the relative diagnostic importance of EUS features based on their ability to predict exocrine insufficiency.

Materials and Methods

Study Design

This is a retrospective cohort study, approved by the Cleveland Clinic Institutional Review Board (IRB 08-421). The pancreas database was queried for all consecutive patients who had undergone a combined EUS/ePFT for suspected or established CP. The demographic and etiologic characteristics, EUS/ePFT test results, diagnoses, and treatment recommendations were extracted from the electronic medical record using a standardized data-collection form.

Combined EUS and ePFT

The combined EUS and secretin ePFT procedure takes 50–60 min to perform. Under moderate or deep sedation, an electronic radial echoendoscope was passed for imaging of the head, body, and tail of the pancreas. EUS scoring routinely included nine criteria: hyperechoic foci, hyperechoic strands, cysts, parenchymal lobularity, main duct dilation, main duct irregularity, visible side-branches, hyperechoic duct walls, and calcifications. The presence of ≥4 criteria was considered abnormal [3]. During the EUS examination, a standardized intravenous dose of synthetic secretin (0.2 mcg/kg) was administered. Following the EUS examination, the echoendoscope was usually removed and the standard upper endoscope inserted for collection of duodenal samples. The stomach was cleared to prevent subsequent acid contamination of the duodenal samples. Duodenal samples were collected at 15, 30, and 45 min after secretin stimulation through the suction channel of the endoscope. In some cases the echoendoscope was used to collect the first or subsequent samples. Samples were transported on ice and analyzed for bicarbonate concentration on a hospital auto-analyzer. The highest concentration from the three samples was considered the peak concentration. A peak bicarbonate concentration of less than 80 mmol/l was considered abnormal [14].

Statistical Methods

Percentages are reported for clinical characteristics and test results. Two-by-two contingency tables were constructed to calculate sensitivity, specificity, concordance, and predictive values. The test characteristics are reported with 95% confidence intervals. The Spearman method was used to measure the correlation of continuous EUS and ePFT results. A \( P \)-value < 0.05 was considered statistically significant. SAS version 9.1 software was used for all analyses (The SAS Institute, Cary, NC).

Results

A total of 302 patients completed the EUS/ePFT between April 2006 and July 2009 for one of three clinical indications:

1. Suspected minimal change CP \( n = 252 \): EUS/ePFT performed for abdominal pain of suspected pancreatic
origin after cross-sectional imaging (CT or MRCP) was non-diagnostic.

2. Established CP \( (n = 38) \): EUS/ePFT performed for further evaluation of abdominal pain and CP diagnosed by cross-sectional imaging (CT or MRCP). All patients had pancreatic calcifications, combined with atrophy, main pancreatic duct dilation, or both.

3. Painless steatorrhea \( (n = 12) \): EUS/ePFT performed for evaluation of painless steatorrhea or diarrhea with weight loss after non-diagnostic cross-sectional imaging.

The demographic and clinical characteristics for each group are shown in Table 1.

**Table 1** Demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Suspected minimal change CP ( n(%) )</th>
<th>Established CP ( n(%) )</th>
<th>Painless steatorrhea or diarrhea ( n(%) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ( (n = 302) )</td>
<td>252</td>
<td>38</td>
<td>12</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;30)</td>
<td>47 (18.7)</td>
<td>4 (10.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>(30–39)</td>
<td>53 (21.0)</td>
<td>8 (21.1)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>(40–49)</td>
<td>59 (23.4)</td>
<td>8 (21.1)</td>
<td>6 (50.0)</td>
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<tr>
<td>(50–59)</td>
<td>52 (20.6)</td>
<td>13 (34.2)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>(\geq60)</td>
<td>41 (16.3)</td>
<td>5 (13.2)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>84 (33.3)</td>
<td>22 (57.9)</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td>Female</td>
<td>168 (66.7)</td>
<td>16 (42.1)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Race</td>
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<tr>
<td>Caucasian</td>
<td>234 (92.9)</td>
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<td>11 (91.7)</td>
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<tr>
<td>African American</td>
<td>16 (6.3)</td>
<td>2 (5.3)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (0.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
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<td>Diabetes</td>
<td>23 (9.1)</td>
<td>17 (44.7)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>60 (23.8)</td>
<td>5 (13.2)</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td>At least one risk factor</td>
<td>192 (76.2)</td>
<td>33 (86.8)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Multiple risk factors</td>
<td>93 (36.9)</td>
<td>29 (76.3)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Specific risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of acute pancreatitis</td>
<td>88 (34.9)</td>
<td>18 (47.4)</td>
<td>1 (8.5)</td>
</tr>
<tr>
<td>Heavy alcohol (remote or current)</td>
<td>31 (12.3)</td>
<td>22 (57.9)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Active cigarette smoking</td>
<td>75 (29.8)</td>
<td>23 (60.5)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Pancreas divisum</td>
<td>20 (7.9)</td>
<td>2 (5.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sphincter of Oddi dysfunction</td>
<td>26 (10.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>High triglycerides</td>
<td>15 (6.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<td>CFTR mutations</td>
<td>11 (4.4)</td>
<td>4 (10.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>End stage renal disease</td>
<td>3 (1.2)</td>
<td>2 (5.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Necrotizing acute pancreatitis</td>
<td>1 (0.4)</td>
<td>2 (5.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1.2)</td>
<td>3 (7.9)</td>
<td>0 (0)</td>
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<tr>
<td>EUS/ePFT results</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Concordant normal</td>
<td>160 (63.5)</td>
<td>0 (0)</td>
<td>10 (83.3)</td>
</tr>
<tr>
<td>Discordant: EUS+/PFT−</td>
<td>20 (7.9)</td>
<td>5 (13.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Discordant: EUS−/PFT+</td>
<td>40 (15.9)</td>
<td>2 (5.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Concordant abnormal</td>
<td>32 (12.7)</td>
<td>31 (81.6)</td>
<td>2 (16.7)</td>
</tr>
</tbody>
</table>

Minimal Change Chronic Pancreatitis

There were 252 patients evaluated for suspected minimal change CP. In this subset, a moderate negative correlation was observed between EUS score and peak bicarbonate concentration \( r = -0.38, \) CI \(-0.48, -0.27\) (Fig. 1). This correlation was significantly lower than that observed in the entire sample of 302 patients, which included both mild and severe CP (Spearman \( r = -0.59, \) CI \(-0.65, -0.50\)). The concordance of dichotomized EUS and ePFT results in suspected minimal change CP was 76.2\% (192/252). There were 160 patients (63.5\%) that had concordant normal EUS/ePFT results (<4 criteria, peak bicarbonate ≥80 mmol/l).
There were 32 patients (12.7%) that had concordant abnormal EUS/ePFT results (≥4 criteria, peak bicarbonate <80 mmol/l). In 60 patients (23.8%), discordant results were observed: There were 20 patients with abnormal EUS and normal ePFT (≥4 criteria, peak bicarbonate ≥80 mmol/l). There were 40 patients with normal EUS and abnormal ePFT (<4 criteria, peak bicarbonate <80 mmol/l).

Established Chronic Pancreatitis

Thirty-eight patients underwent the EUS/ePFT for the staging of established CP. The primary rationale for EUS/ePFT was to rule out occult neoplasm, measure exocrine function, and assess for main pancreatic duct obstruction. Four patients were found to have pancreatic masses. Fine needle aspiration was positive for adenocarcinoma in all 4 patients.

In the 34 patients with established calcific CP and no pancreatic adenocarcinoma, the sensitivity of ePFT (peak bicarbonate <80 mmol/l) was 85.3% (CI 73, 97). There were five patients (14.7%) that had a normal ePFT, suggestive of preserved exocrine function. Only one of these five patients described loose or oily bowel movements. The sensitivity of EUS (≥4 criteria) for detecting established calcific CP was 100% (CI 90, 100). Thirty-one patients had a dilated pancreatic duct on EUS suggestive of main duct obstruction.

Painless Steatorrhea

Twelve patients underwent EUS/ePFT for evaluation of painless steatorrhea (n = 6) or diarrhea with weight loss (n = 6). Two patients had concordant abnormal EUS/ePFT results and were diagnosed with CP and exocrine insufficiency. Ten patients had concordant normal EUS/ePFT. In these ten patients, the follow-up diagnosis was celiac disease in one patient, small intestinal bacterial overgrowth in three patients, post-infectious irritable bowel syndrome in two patients, and dietary intolerance in one patient. The remaining three patients with concordant normal EUS/ePFT had diarrhea or steatorrhea of undetermined etiology.

EUS Criteria for Prediction of Exocrine Insufficiency

The test characteristics of EUS criteria using secretin ePFT as reference standard are shown in Table 2. The EUS criteria are ranked in order of their positive predictive value (PPV). The highest PPVs were observed for calcifications

![Image of graph showing EUS score versus secretin ePFT peak bicarbonate concentration in 302 patients undergoing EUS/ePFT. The results are stratified based on group: suspected minimal change CP (and painless steatorrhea) versus established CP. The horizontal and vertical dashed reference lines represent typical diagnostic cutpoints used for ePFT (80 mmol/l) and EUS (≥4 criteria).](image-url)

**Table 2** Test performance characteristics for EUS criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>n</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>Mean peak bicarbonate mmol/l (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcifications</td>
<td>29</td>
<td>25% (17,33)</td>
<td>98% (97,100)</td>
<td>90% (79,100)</td>
<td>71% (65,76)</td>
<td>46.7 (20.4)</td>
</tr>
<tr>
<td>Visible side branches</td>
<td>66</td>
<td>47% (37,56)</td>
<td>92% (88,96)</td>
<td>76% (65,86)</td>
<td>76% (70,81)</td>
<td>60.4 (24.3)</td>
</tr>
<tr>
<td>Cysts</td>
<td>20</td>
<td>14% (8,21)</td>
<td>97% (95,100)</td>
<td>75% (56,94)</td>
<td>68% (62,73)</td>
<td>65.0 (25.9)</td>
</tr>
<tr>
<td>MPD irregularity</td>
<td>82</td>
<td>50% (41,60)</td>
<td>86% (81,91)</td>
<td>66% (56,76)</td>
<td>76% (70,81)</td>
<td>65.4 (24.3)</td>
</tr>
<tr>
<td>MPD dilation</td>
<td>72</td>
<td>44% (35,53)</td>
<td>87% (82,92)</td>
<td>65% (54,76)</td>
<td>74% (68,80)</td>
<td>63.9 (24.5)</td>
</tr>
<tr>
<td>Lobularity</td>
<td>114</td>
<td>62% (52,71)</td>
<td>75% (69,81)</td>
<td>58% (49,67)</td>
<td>78% (72,84)</td>
<td>71.9 (24.8)</td>
</tr>
<tr>
<td>Hyperechoic foci</td>
<td>145</td>
<td>69% (60,78)</td>
<td>64% (57,70)</td>
<td>51% (43,59)</td>
<td>79% (73,85)</td>
<td>76.1 (23.9)</td>
</tr>
<tr>
<td>Hyperechoic strands</td>
<td>154</td>
<td>73% (64,81)</td>
<td>61% (54,68)</td>
<td>51% (43,59)</td>
<td>80% (74,87)</td>
<td>76.6 (23.7)</td>
</tr>
<tr>
<td>Hyperechoic duct wall</td>
<td>98</td>
<td>43% (33,53)</td>
<td>73% (67,79)</td>
<td>47% (37,57)</td>
<td>70% (64,76)</td>
<td>79.1 (25.4)</td>
</tr>
<tr>
<td>EUS (≥4) in complete sample</td>
<td>90</td>
<td>61% (52,70)</td>
<td>87% (82,9)</td>
<td>72% (63,81)</td>
<td>80% (75,85)</td>
<td>65.3 (23.6)</td>
</tr>
<tr>
<td>EUS (≥4) in minimal-change CP</td>
<td>50</td>
<td>46% (34,59)</td>
<td>90% (85,94)</td>
<td>64% (51,77)</td>
<td>81% (76,86)</td>
<td>74.5 (18.8)</td>
</tr>
</tbody>
</table>

The individual criteria are ranked in order of positive predictive value. n number of patients with the criterion, 95% CI 95% confidence interval, SD standard deviation

a The four patients found to have pancreatic cancer were excluded from this analysis
(90%), visible side-branches (76%), and cysts (75%). Main pancreatic duct dilation, irregularity, and parenchymal luctarity had intermediate PPV (58–66%). Hyperechoic foci, strands, and duct wall had relatively poor PPV (47–51%). Using secretin ePFT as the reference standard, EUS was 61% sensitive (CI 52, 70) and 87% specific (CI 82, 92) for detecting exocrine insufficiency. In the subset with suspected minimal change CP, the sensitivity was 46% (CI 34, 59) and specificity was 90% (85, 94).

Procedural Factors and Safety

In 213 patients (70.5%), the EUS/ePFT was completed using moderate sedation. In the remaining 89 patients (29.5%), EUS/ePFT was completed using deep sedation provided by an anesthesiologist. Three patients were unable to complete the procedure under moderate sedation. Two of these underwent a repeat procedure with anesthesia. The other did not undergo EUS/ePFT and is not included in the analysis.

No major procedure-related or sedation-related complications were observed with the EUS/ePFT procedures. One female patient had typical pancreatic pain following the procedure. Laboratory testing and plain films were entirely normal. Another female patient developed pancreatic pain and an associated rise in lipase from 45 U/l on the day before procedure to 202 U/l a few hours following the procedure. She was admitted for observation and had complete resolution of the pain the next day with decrease in lipase (36 U/l). This patient did not have pancreas divisum or other ductal obstructive pathology. No allergic reactions were observed related to secretin administration.

Discussion

This study demonstrates the feasibility and utility of combined EUS and secretin ePFT for the diagnosis of chronic pancreatitis. Our primary aim was to evaluate the correlation of EUS features and secretin ePFT bicarbonate results in patients evaluated for minimal change CP. We found that the EUS score and secretin ePFT peak bicarbonate concentration were only moderately correlated in patients evaluated for minimal change CP (Spearman \( r = -0.38 \)). Likewise, the concordance of EUS and ePFT was only 76.2% in this group. Chowdhury et al. [15] also observed suboptimal agreement of EUS and Dreiling-tube secretin PFT in patients with abdominal pain and negative CT. In that study, results were concordant in only 13 of 21 patients (62%). The lack of concordance in suspected minimal change CP patients suggests that either test may become abnormal in the earliest stages of fibrosis.

It has been suggested that structural and function testing can be used synergistically to diagnose early CP [10–12]. This is one of few studies demonstrating this approach in a large consecutive sample. In our experience, discordant abnormal results frequently resulted in a diagnosis of CP and referral for pancreas-directed therapy. Concordant normal results (especially with 0 or 1 EUS criteria) generally ruled out CP. We acknowledge that our study is descriptive and does not include a histological criterion to measure the accuracy of the combined EUS/ePFT results. It is possible that some patients assigned a diagnosis of CP after the EUS/ePFT results may have been misclassified since no gold-standard exists. The interpretation of discordant results is especially problematic and several issues must be considered: First, either structural or functional abnormalities may occur first in CP [13]. Second, a subset of patients with moderate or even advanced structural abnormalities has preserved exocrine function [9, 13]. Third, neither EUS nor PFT are completely specific, as alcohol, age, and recent acute pancreatitis may influence either test [16, 17]. The ePFT collects duodenal aspirates rather than pure pancreatic juice. Therefore, contamination with gastric acid, bile, or duodenal secretions may theoretically confound the bicarbonate results and produce false-positive or false-negative results. Because both tests are imperfect, long-term follow-up may sometimes be required to ascertain the presence or absence of CP. Clinical judgment must be used to interpret the results in the context of the history to arrive at a diagnosis.

The EUS/ePFT useful may also be useful in evaluating patients with established CP. In a patient with established CP who lacks steatorrhea, the ePFT may help direct enzyme supplementation therapy. A normal PFT may spare some of these patients the cost and nuisance of exogenous enzymes. Patients without steatorrhea who have an abnormal ePFT may have sub-clinical exocrine insufficiency and benefit from enzymes to prevent nutritional deficiencies and bone loss [18, 19]. Chronic pancreatitis is a known risk factor for pancreatic cancer and the risk increases with disease severity [20]. In our study, the EUS revealed occult pancreatic neoplasm in four patients with established CP (9.5%), none of whom had a definite mass on CT. These patients had worsening pain or weight loss that prompted concern for malignancy. Differentiating benign from malignant masses may be difficult with EUS and new adjunctive imaging techniques are being investigated [21–23]. EUS also helped detect main duct obstruction due to intraductal calcifications or strictures which benefit from endoscopic or surgical decompression.

A limitation of the combined EUS/ePFT is the lack of widespread availability and acceptance of endoscopic PFT methods. At our center, crossover studies comparing endoscopic and Dreiling collection yielded very similar...
bicarbonate results [4, 5]. A frequent criticism of endoscopic PFT methods is the need for prolonged endoscopy [24]. However, the current study supports the feasibility and safety of the technique. EUS/ePFT may not be feasible for all centers, particularly if anesthesia support is not easily available or if schedules are unable to accommodate a 1-h endoscopy. However, combining EUS with ePFT spares the need for two separate procedures as now performed at some centers. Multicenter validation of the EUS/ePFT is needed before it can be widely recommended.

The traditional method of EUS CP scoring is non-weighted. Each criterion is counted equally, and the number of criteria is compared against a diagnostic cutpoint. However, experts recognize that EUS criteria have different levels of diagnostic value. The Rosemont classification is a weighted system of EUS CP scoring that was recently proposed after an expert consensus conference [25]. In the Rosemont classification, the main pancreatic duct and parenchymal calcifications are considered “major A” features, lobularity with honeycombing is considered a “major B” feature, and the remaining criteria are considered “minor features”. As a secondary aim, we used our data set to investigate the relative diagnostic value of individual EUS criteria. We found that calcifications had the highest PPV (90%) for exocrine insufficiency, which supports this as a “major feature” in the Rosemont classification. Lobularity had only moderate PPV (58%). However, we did not distinguish lobularity with honeycombing (major B by Rosemont) and without honeycombing (minor by Rosemont). Rosemont considers MPD dilation, MPD irregularity, and visible side-branches as minor features. We found these ductal features highly predictive of exocrine insufficiency. Of course, the secretin ePFT assesses duct-cell bicarbonate secretion. As such, a greater correlation with ductal than parenchymal features is expected.

It is interesting that one patient developed mild acute pancreatitis following the EUS/ePFT procedure. Secretin-induced pancreatitis is not well described in the literature, and seems most plausible if there is an outflow obstruction (e.g., pancreas divisum). In this case, the patient had no ductal obstructive pathology. It may be reasonable to include a remote possibility of acute pancreatitis in the discussion of the risks and benefits prior to the EUS/ePFT.

Chronic pancreatitis is a continuum of disease starting with the first attack of acute pancreatitis [26]. The combined EUS/ePFT allows the gastroenterologist to provide a comprehensive pancreatic examination in a single endoscopic session that characterizes the structural and functional state of the gland. This method provides multifaceted information that can be used to diagnose and manage patients with suspected early and well-established chronic pancreatitis.

References


Endoscopic ultrasonography (EUS) is firmly established as a useful imaging modality for the diagnosis and evaluation of a variety of gastrointestinal disorders including cancer staging, submucosal tumors, portal hypertension, and other intrinsic gastrointestinal tract disease. The investigation of pancreaticobiliary disease on the other hand has been generally more difficult because of the retroperitoneal location of the involved organs and structures. Nonetheless, the pancreas, pancreatic duct, and biliary tree can be fully evaluated by experienced endosonographers.

The pancreas and biliary tract have secretory functions that could allow for dynamic imaging. Currently available dynamic studies of the biliary tract include hepatobiliary scintigraphy, fatty-meal transabdominal ultrasonography, and...
ERCP with sphincter of Oddi manometry (SOM). In contrast, dynamic imaging of the pancreas has not been readily available. Warshaw et al in a 1985 study described the use of transabdominal ultrasonography with pancreatic stimulation using secretin in the evaluation of ampullary stenosis. In theory, intravenous administration of secretin causes prompt, transient stimulation of pancreatic exocrine flow. Flow occurs into the main pancreatic duct and through the major or minor papilla. Any obstruction in pancreatic flow may cause a sustained dilation of the main pancreatic duct. This has been described by many investigators but the concept has not gained wide acceptance because of the inherent difficulty in evaluating the pancreas with extracorporeal ultrasound. EUS allows for improved imaging of retroperitoneal structures (including pancreas and pancreatic duct) because of the proximity of the transducer to the target organ/structure, thereby bypassing skin, subcutaneous tissues, and bowel as well as the usual interference by intestinal gas. Because of the improved resolution (using higher frequencies), visualization of the pancreatic duct and its side branches is considerably easier compared with extracorporeal ultrasonography. The pancreas can be seen by means of conventional ultrasonography in 70% to 90% of control subjects and patients with suspected pancreatic disease. In acute pancreatitis the success rate drops to 62%. The main pancreatic duct is demonstrated by conventional ultrasound in 55% to 90% of cases.

The aim of the current study was to evaluate changes in the main pancreatic duct by EUS during secretin stimulation of the pancreas and to diagnose obstructive disorders of the pancreas including sphincter of Oddi dysfunction (SOD), stenotic minor papilla, pancreatic duct stricture, and pancreatic duct stones.

**PATIENTS AND METHODS**

During a 36-month period, 120 patients (74 men, 46 women, age range 26 to 62 years, mean 56 years) with suspected pancreatic disorders underwent dynamic real-time EUS imaging of the pancreas using secretin stimulation (SSEUS). Of the 120 study patients, 40 had documented chronic pancreatitis (abnormal secretin test, pancreatography and/or pancreatic calcifications), 40 had symptomatic pancreas divisum, 20 were suspected of having SOD, and 20 were suspected of having occlusion of pancreatic duct stents. Twenty control subjects (no pancreatic disorder by clinical history and prior radiographic study) initially underwent SSEUS to assess the behavior of the main pancreatic duct during active secretion in healthy individuals. The control subjects were undergoing EUS for non-pancreatic disease (i.e., non-pancreatic tumor staging, submucosal tumors, and portal hypertension). The current study design was approved by our institutional review board without modification and all patients gave informed written consent before each procedure.

EUS was performed using the Olympus EU-M3 or EU-
M20 echoendoscopes (Olympus America, Inc., Melville, N.Y.). The pancreas and pancreatic duct were imaged by placing the echoendoscope in the duodenum (head of pancreas) and the water-filled stomach (body and tail of the pancreas). Pancreatic duct diameter was measured at the level of the splenic vein and superior mesenteric vein confluence. Duct diameters were initially measured at baseline (time = 0). Subsequent measurements were performed every minute after administration of secretin 1 IU/kg at 1 minute intervals for a total of 15 minutes. Sedation was accomplished with intravenous administration of midazolam, 2 to 10 mg. Narcotics such as meperidine were avoided because of their positive effects on the sphincter of Oddi.

The control group was evaluated to define a normal response and to develop criteria for judging an abnormal response in other patient groups. It consisted of 20 consecutive patients undergoing EUS for the evaluation of submucosal tumor of the stomach and esophagus, thickened gastric folds, esophageal cancer staging, lung cancer staging, and gastric ulcer. Of the 20 control patients studied by SSEUS, 16 had no ductal change, whereas 4 patients had ductal dilation of 1 mm within 2 to 3 minutes of secretin injection but this was not sustained (< 10 minutes) throughout the 15 minute testing interval (Fig. 1). These results defined a normal response to secretin stimulation.

An abnormal result was considered to be a duct diameter that increased by 1 mm or greater and remained widened by at least 1 mm throughout the 15-minute testing interval. If dilation of the duct occurred but was transient (less than 15 minutes), it was considered a normal response and negative study.

All study patients subsequently underwent ERCP.

EUS and ERCP examinations were performed by separate endoscopists unaware of the results of the other study. Sphincter of Oddi manometry (SOM) was performed using an Arndorfer triple-lumen perfusing catheter (Arndorfer Inc., Greenfield, Wis.) and Synectics Medical Software (Synectics, Irving, Tex.). Two station pull-through maneuvers were performed and basal sphincter of Oddi pressures recorded. Patients with pancreatic duct stents had these removed and they were sectioned to evaluate for obstruction at the time of ERCP.

Kappa statistics, a measure of observed agreement beyond that due to chance alone, were used to assess accuracy of SSEUS to diagnose an obstructed pancreatic duct. A kappa value of greater than 0.75 represents excellent agreement, 0.50 to 0.75 good agreement, and 0.25 to 0.49 fair agreement.

RESULTS

Chronic pancreatitis

Forty patients (22 men, 18 women, age 32 to 72 years) with chronic pancreatitis (abnormal secretin test, pancreatic calcifications, and clinical presentation) underwent SSEUS (Fig. 2). The etiology of the chronic pancreatitis was as follows: 14 pancreas divisum, 10 alcohol, 11 idiopathic, 4 papillary stenosis, and 1 familial pancreatitis. Twenty-seven patients had a normal response to secretin stimulation and 13 had an abnormal response (Table 1). Pancreatograms in the 13 patients with an abnormal result revealed significant ductal and papillary abnormalities in 12 patients (7 strictures, 3 ductal stones, 2 papillary stenosis). Of the 27 patients with...
normal results, 24 had no evidence of ductal obstruction; the remaining 3 patients had significant ductal obstruction (2 strictures, 1 a stone). There was excellent agreement between SSEUS and ERCP in the diagnosis of ductal obstruction (kappa = 0.78, p = 0.001). Three patients with an abnormal SSEUS underwent the study again 3 months after stone removal (1) and stricture dilation (2) and had normal responses, suggesting that SSEUS can predict a successful outcome of treatment.

**Pancreas divisum**

Forty patients (24 men, 16 women, age 27 to 63 years) with history of pancreatitis secondary to pancreas divisum were studied by SSEUS (Fig. 3). Of these, 22 were subsequently treated by stent insertion with or without sphincterotomy because of delayed drainage with a relatively normal pancreatogram at ERCP. The remaining 18 patients had moderate to severe chronic pancreatitis (Cambridge class III = 11 and IV = 7) and did not undergo stent insertion because of existing protocols (no treatment in patients with advanced disease) for endoscopic treatment of pancreas divisum patients. Of the 22 treated patients, 16 had relief of pain and pancreatitis, whereas 6 had little benefit. Of the 16 patients in whom stent therapy was beneficial, 13 (81%) had an abnormal SSEUS; only 1 of 6 (17%) of the patients who experienced no benefit from stent therapy had an abnormal SSEUS (p = 0.02). Hence, SSEUS accurately predicted which patients would respond to endoscopic treatment (Table 2).

---

### Table 1.
**Response of the pancreatic duct to secretin stimulation in patients with chronic pancreatitis (n = 40): evaluation of EUS (SSEUS)**

<table>
<thead>
<tr>
<th>Chronic pancreatitis</th>
<th>SSEUS results</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic duct obstruction</td>
<td>Duct dilation</td>
<td>SEN</td>
</tr>
<tr>
<td>Yes (n = 15)</td>
<td>12*</td>
<td>3</td>
</tr>
<tr>
<td>No (n = 25)</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Total = 40</td>
<td>13</td>
<td>27</td>
</tr>
</tbody>
</table>

*7 strictures, 3 stones, 2 papillary stenoses.

### Table 2.
**Response of the pancreatic duct to secretin stimulation in patients with symptomatic pancreas divisum treated with stenting (n = 20): evaluation by EUS (SSEUS)**

<table>
<thead>
<tr>
<th>Pancreas divisum</th>
<th>SSEUS results</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to stent therapy</td>
<td>Duct dilation</td>
<td>SEN</td>
</tr>
<tr>
<td>Yes (n = 16)</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>No (n = 6)</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Total = 22</td>
<td>14</td>
<td>8</td>
</tr>
</tbody>
</table>

*Statistics reflect SSEUS as a predictor of response to stent therapy of pancreas divisum.

### Table 3.
**Response of the pancreatic duct to secretin stimulation in patients with suspected Sphincter of Oddi Dysfunction (SOD) or papillary stenosis (n = 20): evaluation by EUS (SSEUS)**

<table>
<thead>
<tr>
<th>SOD</th>
<th>SSEUS results</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOM</td>
<td>Duct dilation</td>
<td>SEN</td>
</tr>
<tr>
<td>Normal (n = 13)</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Abnormal (n = 7)</td>
<td>4*</td>
<td>3†</td>
</tr>
<tr>
<td>Total = 20</td>
<td>5</td>
<td>15</td>
</tr>
</tbody>
</table>

*Three had SOD of PD sphincter.
†Three had SOD of CBD sphincter only.
Sphincter of Oddi dysfunction

Twenty patients (15 women, 5 men, age 42 to 72 years) with suspected SOD were referred for ERCP and SOM. A basal sphincter of Oddi pressure of 40 mm Hg or less was considered normal. All patients underwent pre-ERCP SSEUS (Fig. 4). Thirteen patients had a normal SOM and 7 patients had an abnormal SOM (Table 3). Of the 13 patients with a normal SOM, SSEUS results included 12 normal and 1 abnormal ductal response. Of the 7 patients with an abnormal SOM, SSEUS identified 4 with abnormal responses (3 with SOD of the pancreatic duct, 1 with SOD of the common bile duct) and 3 with normal responses (all diagnosed with SOD of the common bile duct). These results suggest excellent negative and positive predictive values but poor overall sensitivity for the SSEUS diagnosis of SOD (kappa = 0.53, p = 0.05).

Pancreatic duct stent occlusion

Lastly, 20 patients (13 men, 7 women, age range 38 to 61 years) with in situ pancreatic duct stents (13 dorsal duct, 7 ventral duct) presented with recurrent symptoms (pain, nausea, vomiting) or pancreatitis and suspected premature stent occlusion. Stent occlusion was assessed after removal at ERCP (Table 4). Of the 14 stents found to be occluded, 12 had an abnormal SSEUS (sustained, 1 mm or more ductal dilation from baseline). Among the 6 patients whose stents were found to be patent, there was only one abnormal SSEUS demonstrating ductal dilation with secretin (p = 0.01).

DISCUSSION

Intravenous administration of secretin causes increased pancreatic duct secretory flow within the first minutes of administration. Initial studies by Warshaw et al.12 concluded that such increased flow might result in abnormal dilation of the pancreatic duct, detectable with ultrasound, if an obstruction to flow was present. Thirty patients with suspected papillary stenosis and 22 patients with symptomatic pancreas divisum were studied. These investigators found that a positive test (pancreatic ductal dilation of 1 mm or greater) was a good predictor of papillary stenosis (major or minor papilla) and clinical response to surgical sphincteroplasty. Repeat secretin ultrasound testing after surgical treatment showed no further dilation in the majority of patients suggesting that the obstruction to pancreatic outflow had been corrected. Other investigators have not been able to reproduce these positive results.15-18

Technical difficulties associated with conventional ultrasonography (such as the ability to routinely image the pancreas and particularly the pancreatic duct because of its retroperitoneal location, interference from bowel gas, and measurement of small changes in duct caliber) limit the accuracy and reproducibility of the test and thus may explain the

Figure 3. SSEUS in a patient with symptomatic pancreas divisum. A, Pancreatic duct diameter (6 mm) before secretin stimulation (frequency 7.5 MHz, range 6 cm). B, Pancreatic duct dilatation (12 mm) at 11 minutes after secretin stimulation (frequency 7.5 MHz, range 6 cm).
differences in results obtained by different investigators. Alternatively, EUS, because of the close proximity of the transducer to the target organ, allows for improved resolution and imaging of both the pancreatic parenchyma and duct. Contrary to the conclusion of Warshaw et al.\textsuperscript{12} that an abnormal response to secretin is dilation of the pancreatic duct by 1 mm or more, Glaser\textsuperscript{30} and Bolondi\textsuperscript{31} and their associates reported that many normal subjects exhibit transient pancreatic ductal dilation of 1 mm or more. Dilation may simply be the response of a distensible duct to increased flow rates and may also be due to the effect of secretin on the sphincter of Oddi. Thus, relative obstruction of pancreatic outflow, accompanied by some dilation of the pancreatic duct, may represent a physiologic phenomenon after pancreatic stimulation. In fact, failure of the duct to dilate transiently may reflect underlying exocrine insufficiency or pancreatic fibrosis.\textsuperscript{30}

Cavallini et al.\textsuperscript{14} evaluated the response of the main pancreatic duct to secretin using ultrasound with respect to the degree of dilation as well as its duration. They noted that dilation was occasionally seen in normal subjects but was more prolonged in patients with acute pancreatitis. These investigators concluded that prolonged ductal dilation might thus indicate either a persistent impediment to pancreatic outflow or an exaggerated pancreatic secretory response to secretin.

The advantages of EUS over conventional ultrasound in imaging the pancreatic duct are considerable. Small incremental changes in ductal diameter can be more accurately assessed. The current study evaluated the role of secretin stimulated EUS in a variety of conditions. To determine a normal response, 20 consecutive patients with no pancreatic or biliary disorder underwent SSEUS. In this group, 16 of 20 had no ductal change, whereas the

<table>
<thead>
<tr>
<th>Suspected PD stent occlusion</th>
<th>Duct dilation</th>
<th>SSEUS results</th>
<th>Statistics</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>SEN</td>
<td>SPEC</td>
</tr>
<tr>
<td>Patent (n = 6)</td>
<td></td>
<td></td>
<td></td>
<td>86%</td>
</tr>
<tr>
<td>Occluded (n = 14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total = 20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4. SSEUS in a patient with SOD of the pancreatic segment of the sphincter of Oddi. A, Pancreatic duct diameter (5 mm) before secretin stimulation (frequency 7.5 MHz, range 6 cm). B, Pancreatic duct dilatation (7 mm) at 9 minutes after secretin stimulation (frequency 7.5 MHz, range 6 cm).
remaining 4 patients had a transient increase in ductal diameter of 1 mm (less than 10 minutes). Therefore, an abnormal study was defined as a sustained pancreatic ductal dilation of 1 mm or more for at least 15 minutes. This normal response to secretin has been previously established by others in 92% to 95% of control subjects.

Treatment of obstructive disorders of the pancreas including strictures, stones, SOD and certain patients with pancreas divisum has included both endoscopic therapy (sphincterotomy, dilation and stent placement) and surgical therapy (surgical sphincteroplasty and pancreaticojunostomy). Success rates for endoscopic therapy have been reported to be as high as 90%. The identification of patients who will respond to surgical or endoscopic therapy is difficult and currently unreliable using conventional imaging modalities.

Four distinct, symptomatic groups underwent SSEUS examination to assess ductal response to secretin. Obstruction of pancreatic secretory flow was suspected in all groups. In each case, the result of SSEUS was compared with ERCP with and without SOM. SSEUS was shown to be accurate in assessing ductal obstruction in all groups except patients with SOD of the bile duct segment of the sphincter of Oddi. It also showed excellent positive predictive value of response to stent therapy in patients with pancreas divisum. In this latter group, 81% of patients (13 of 16) with a clinical response to sphincterotomy and or stent therapy of the minor papilla had an abnormal SSEUS before treatment.

The current study demonstrates the usefulness of dynamic imaging of the pancreatic duct by secretin-stimulated EUS in the evaluation of a variety of obstructive pancreatic diseases. It may allow us to predict those patients who are likely to benefit from therapeutic pancreatic endoscopy. We believe that the improved resolution of endoscopic versus transabdominal ultrasonography allows for a more accurate and complete examination of the pancreas without the inherent deficiencies of the latter modality. The encouraging results obtained with this new technique warrant its further evaluation in randomized clinical trials.

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