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A Randomized Crossover Study of Secretin-Stimulated Endoscopic and Dreiling Tube Pancreatic Function Test Methods in Healthy Subjects

Tyler Stevens, M.D.,[1] Darwin L. Conwell, M.D.,[1] Gregory Zuccaro Jr., M.D.,[1] Frederick Van Lente, Ph.D.,[2] Edward Purich, Ph.D.,[4] Farah Khandwala, M.S.,[3] and Seymour Fein, M.D.[4]
[1]*Department of Gastroenterology and Hepatology;* [2]*Department of Clinical and Laboratory Medicine;* [3]*Department of Biostatistics and Epidemiology, Cleveland Clinic Foundation, Cleveland, Ohio; and* [4]*ChiRhoClin, Inc., Burtonsville, Maryland*

OBJECTIVES: We have developed an endoscopic method of secretin endoscopic pancreatic function testing (ePFT) to simplify duodenal fluid collection. Validation of the ePFT requires a direct comparison to the traditional PFT using a Dreiling tube (DT). Our aim was to compare bicarbonate concentrations [HCO_3^-] obtained by the ePFT and DT methods in healthy subjects (HS).

METHODS: HS were randomized to either DT or ePFT, then crossed over to the other test after a minimum 1-wk washout. An age/weight-based sedation bolus was used for each test. *DT protocol*: Endoscopic placement of a DT was confirmed by fluoroscopy. After a baseline 15-min collection and administration of IV synthetic secretin, fluid was continuously collected in 15-min aliquots for an hour. *ePFT protocol*: Endoscopy was performed using a 6-mm endoscope. After gastric aspiration and discard and IV secretin, duodenal aspirates were obtained every 15-min for an hour. Fluid specimens were auto-analyzed for [HCO_3^-].

RESULTS: Twelve HS were enrolled (6F, mean age 37 yr). The difference in [HCO_3^-] between the two methods was not significant at the 0-, 30-, 45-, or 60-min collections. An excellent correlation in peak [HCO_3^-] was observed ($R^2 = 0.84$, $p < 0.001$). Using a peak [HCO_3^-] cutpoint 80 mEq/L, there was 100% agreement between the methods; using cutpoint 90 mEq/L, there was 83% agreement.

CONCLUSIONS: The accuracy of the ePFT is similar to DT: There were minimal differences in [HCO_3^-] at each of the timed collections and at peak. There is an excellent correlation in peak [HCO_3^-] and high level of diagnostic agreement between the tests.

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INTRODUCTION

Direct pancreatic function tests (PFT) utilizing double lumen gastro-duodenal tubes for timed collection of duodenal fluid are considered the most sensitive diagnostic tests for pancreatic exocrine insufficiency and early chronic pancreatitis (CP) (1, 2). Although direct PFTs represent the standard reference method for measuring pancreatic function, placement of gastro-duodenal (Dreiling) tubes is difficult, cumbersome, and time-consuming; therefore, direct PFTs have, in large part, been relegated to academic centers.

We have recently developed a direct, secretin endoscopic pancreatic function test (ePFT). This method uses standard endoscopy for the timed aspiration of duodenal fluid for bicarbonate analysis. The secretin ePFT successfully differentiates patients with and without established CP (3). Additionally, our test reproduces the well-understood electrolyte secretory curves observed in classic studies of pancreatic physiology employing gastroduodenal collection tubes (4). The use of sedation and anagesia in doses typically employed in upper endoscopy does not appear to have a significant effect on bicarbonate secretion (5). The ePFT offers several potential advantages over the Dreiling tube (DT) method, including widespread availability, ease of performance, and decreased cost (6).

In spite of these potential benefits and encouraging preliminary data, a rigorous comparative study of the two collection methods has not been performed. The aim of the present study was to directly compare the results of secretin testing using endoscopic and DT collection methods in healthy subjects (HS). We hypothesized that the endoscopic collection method would demonstrate similar test performance characteristics as the DT method.

This research was accepted as an oral presentation at the American Pancreatic Association meeting, 2004 in Chicago, IL.

METHODS

Study Population

Healthy adult subjects capable of informed consent were recruited into this institutional review board-approved research protocol. Female subjects underwent a urine pregnancy test prior to each study procedure. An equal number of men and women were recruited. Exclusion criteria included: pregnancy, allergy or sensitivity to secretin, history of alcohol or drug abuse, recent use of narcotic analgesics or anticholinergic medications, history of acute or chronic pancreatitis, or other diseases known to effect pancreatic secretion (vagotomy, gastrectomy, inflammatory bowel disease, malnutrion, or liver disease).

Study Design

A single-center, randomized, two-way crossover study was performed. Subjects were randomized by computer to receive either the secretin ePFT or Dreiling tube pancreatic function test (D-PFT) for period 1. After a minimum 1-wk washout, subjects were crossed over to the alternate test method for period 2.

At the onset of each procedure, a test dose (0.2 μg) of synthetic secretin was administered followed by a 5-min observation period. A single-dose of IV sedation and analgesia was administered according to an age- and weight-based nomogram (7).

D-PFT Method

A double-lumen collection tube (Dreiling gastroduodenal tube, CR Bard, Covington, GA) was placed endoscopically using a guidewire (8). Fluoroscopy was used to confirm placement of the tip at the ligament of Treitz. The gastric and duodenal aspiration ports were connected to low intermittent suction at 20–60 mmHg pressure. A baseline 15-min collection (Bottle A) was obtained (time –15 to 0 min). At time 0, a full dose of IV synthetic porcine secretin (0.2 μg/kg) was administered. Pancreatic fluid was continuously collected in four 15-min aliquots over a period of 60 min (Bottles B–E).

ePFT Method

Our method of secretin ePFT has been previously described (3, 4). An Olympus GIF-XP 160 ultrathin endoscope (Olympus America Corp., Melville, NY) was used to maximize patient comfort. After topical lidocaine spray and placement of a bite block, the endoscope was passed into the stomach. All gastric secretions were aspirated and discarded. The endoscope was passed through the pylorus into the duodenum. After aspirating duodenal fluid for several seconds to rinse residual gastric acid from the suction channel, a baseline duodenal sample (3–5 cc) was obtained from the postbulbar duodenum. The full dose of synthetic porcine secretin (0.2 μg/kg) was administered at time 0. Duodenal fluid aspirates were obtained intermittently every 15-min for 60 min (Bottles B–E). Approximately 3–5 cc of duodenal fluid was aspirated at each timed-collection because this amount is sufficient for analysis. In most cases, the tip of the scope remained in the duodenum for the entire procedure. Between collections, the scope was allowed to rest on the bed in a secure position to minimize scope motion. Fluid was usually easily aspirated because of the large volume of pancreatic fluid secretion following secretin administration. In these cases, individual samples were collected in a matter of seconds. Occasionally, fluid secretion was less voluminous and required 2–3 min of endoscopic manipulation for collection of an adequate sample.

Bicarbonate Analysis

All fluid specimens were sent on ice to our clinical laboratory for measurement of bicarbonate concentration (12). Bicarbonate concentrations were determined as total carbon dioxide by a rate pH measurement using reagents and an auto-analyzer (CX3 Delta, Beckman-Coulter, Brea, CA). After acidification of the specimen, bicarbonate forms carbon dioxide gas, which passes through a silicone membrane and results in a rate of pH change between the membrane and a pH electrode. The rate of pH change is related to the initial [HCO_3^-] in the fluid sample.

Statistical Methods

Twelve subjects were required to demonstrate a [HCO_3^-] difference of 10 mEq/L (SD 12 mEq/L), based on an alpha of 0.05 and power of 0.8 for a paired study design. The following statistical techniques for nonparametric analysis of paired data were used: median differences and interquartile ranges for descriptive statistics, Wilcoxon signed rank test for quantitative comparisons and the Spearman rank method for correlation assessment.

RESULTS

Demographics

Twelve HS were recruited (6 females). The mean age was 37 years (range 31–54 yr). All subjects tolerated the full duration of both procedures. Three subjects had to repeat the D-PFT method because gastric fluid contamination was suspected on the basis of a very low [HCO_3^-] ($<$10 mEq/L). The median volume of duodenal drainage fluid obtained during the Dreiling test was 205 mL (range 111–332 mL).

Timed Duodenal Fluid Bicarbonate Concentrations

The timed individual [HCO_3^-] and median bicarbonate curves for both test methods are displayed in Figure 1. In the majority of subjects, the secretory curves were closely similar (Fig. 2). The median differences in [HCO_3^-] were determined for each collection time point (Table 1). The differences are calculated as the difference between D-PFT and ePFT; therefore, negative values imply lower [HCO_3^-] for the D-PFT method. Comparisons were only possible for seven subjects at the baseline (time 0) collection because no fluid was aspirated using the DT method at that time point. The

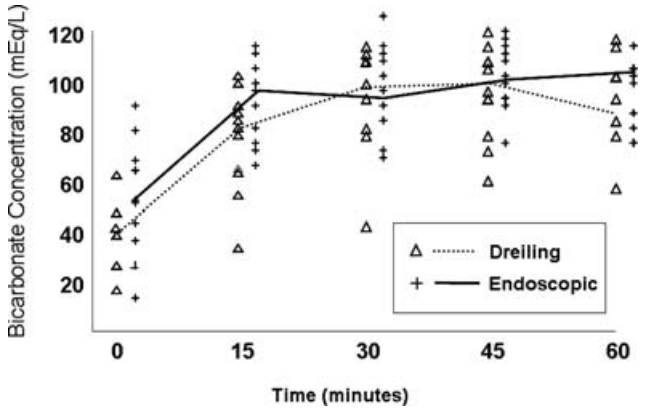

Figure 1. Timed bicarbonate concentrations for ePFT and D-PFT methods of secretin testing.

$[HCO_3^-]$ difference was statistically significant only at the 15-min collection.

Peak Duodenal Fluid Bicarbonate Concentrations

Eleven of 12 HS achieved a peak $[HCO_3^-]$ greater than the historical cutpoint, 80 mEq/L. The peak $[HCO_3^-]$ for the remaining patient was 78 mEq/L for both tests. The median difference in peak $[HCO_3^-]$ (D-PFT − ePFT) was −9.0 mEq/L (IQR −13.5,−1.5, $p = 0.01$) (Fig. 3). An excellent correlation in peak $[HCO_3^-]$ was observed for the two methods ($R^2 = 0.84$, $p < 0.001$) (Fig. 4).

Agreement between the two test methods was determined using the previously cited normal cutpoints for peak bicarbonate, 80 mEq/L (9) and 90 mEq/L (10, 11). These cutpoints were used to convert the continuous test measure (peak bicarbonate) to a binary result (positive/negative). When determining agreement, the same cutpoint for peak bicarbonate (either 80 or 90 mEq/L) was applied to both tests. Using a cutpoint of 80 mEq/L, there was 100% agreement between the tests. Using a cutpoint of 90 mEq/L, agreement was observed in 9/12 (83%) of subjects. Of the three patients who had discordant results using the cutpoint 90 mEq/L, two had a positive D-PFT and negative ePFT and 1 had a positive ePFT and negative D-PFT.

Time of Procedure

The median time of procedure from entrance into the endoscopy suite to transport to the recovery area was determined for each test method. The median time was 106 min (range 91–138 min) for the Dreiling test and 72 min (range 65–86 min) for the ePFT ($p < 0.001$).

Safety

No procedure- or medication-related complications were noted throughout the study. Specifically, no episodes of pancreatitis were encountered.

DISCUSSION

We have shown that the secretin-stimulated ePFT compares favorably with the DT method. There were minimal differences in the duodenal fluid $[HCO_3^-]$ at each of the timed collections. An excellent correlation in peak $[HCO_3^-]$ and high level of agreement was observed between the methods.

Interestingly, the difference in $[HCO_3^-]$ between the methods was larger at the 0 and 15 min collections compared with the 30-, 45-, and 60-min collections. This may result from early variability in bicarbonate secretion after secretin. The lower $[HCO_3^-]$ observed for the Dreiling method at those time points may occur because the fluid is collected *continuously* rather than intermittently (as with the ePFT); therefore, the $[HCO_3^-]$ obtained by the DT method represents an average of bicarbonate secretion across the collection period.

One potential drawback of the endoscopic method is the lack of continuous collection of gastric fluid to avoid

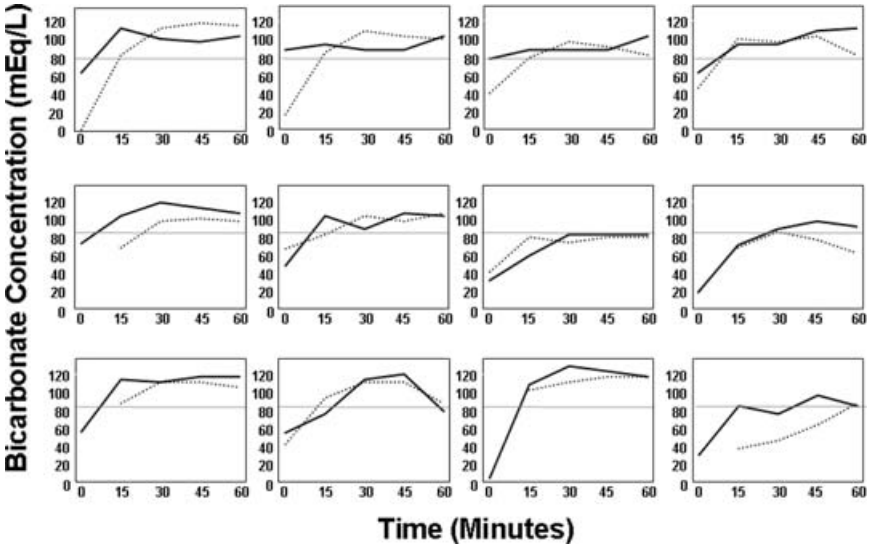

Figure 2. Bicarbonate secretory curves for ePFT (solid line) and D-PFT (dashed line) methods for each subject.

Table 1. Differences in Bicarbonate Concentration

Time (min)	N	Mean*	Median*	25th*	75th*	*p* Value
0	7	−28.14	−17.00	−64.00	−10.00	0.1094
15	12	−15.50	−15.00	−28.50	−4.50	0.0137
30	12	−0.50	1.50	−10.50	10.50	0.9824
45	12	−5.00	−6.00	−10.50	3.00	0.2207
60	12	−6.25	−1.50	−16.50	3.00	0.2861

*Median, mean, and IQR for *differences* in [HCO_3^-] (mEq/L, Dreiling minus ePFT).

acidification of the duodenal contents. However, the results of our study do not suggest significant acid contamination. To minimize the chance of gastric acid entering the duodenum, patients were kept in the left lateral decubitus position throughout the duration of the procedure. At the conclusion of the ePFT procedures, we did not observe large volumes of gastric fluid to reaccumulate in the fundus; however, a recognized weakness of our study was that we did not aspirate and quantify the amount of gastric fluid. The best evidence against significant gastric acid contamination is that the [HCO_3^-] values for endoscopic test were generally higher than for the Dreiling test, further diminishing the likelihood of gastric fluid contamination. A potential explanation is that there is *more* gastric acid contamination with the DT method. We hypothesize that the visually targeted aspiration and discard of gastric fluid at the onset of the ePFT is more effective than the "continuous" collection of gastric fluid by the DT. This is because the gastric port of the DT may not always be properly situated in the dependent areas of the stomach for optimal collection of fluid.

In contrast to the early phase of secretion, there was less variability and smaller [HCO_3^-] differences observed between the methods at the 30-, 45-, and 60-min collections. Most likely this is because these aspirates were obtained during the peak phase of bicarbonate secretion. In a previous

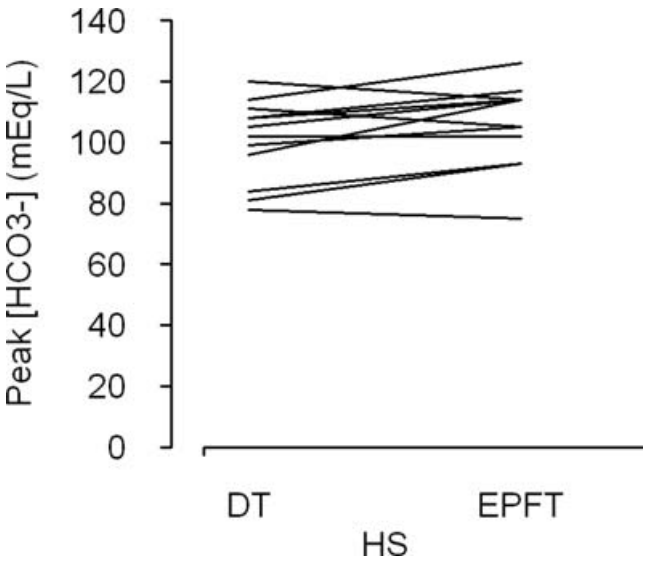

Figure 3. Individual peak [HCO_3^-] for ePFT and DT collection methods.

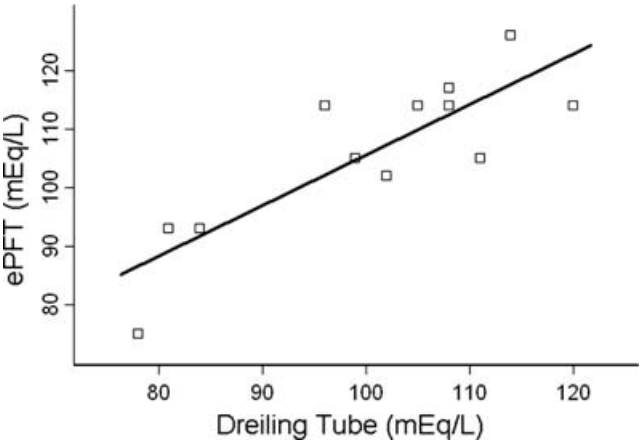

Figure 4. Scatterplot of peak [HCO_3^-] obtained by the ePFT and DT methods. An excellent correlation was observed between the two methods ($R^2 = 0.84$, $p < 0.001$).

study, we demonstrated that the ePFT method reproduces the well-described patterns of electrolyte secretion observed with gastroduodenal collection tubes (4). The present study provides further evidence that the secretin ePFT provides equivalent information to the Dreiling method.

Although the Dreiling method resulted in statistically lower peak [HCO_3^-] compared with the endoscopic method, the magnitude of the differences was small (median −9.0 mEq/L, IQR −13.5, −1.5 mEq/L). There was excellent agreement between the methods using the traditional cutpoints 80 and 90 mEq/L, preserving the diagnostic integrity of the endoscopic test. Because of minor methodological differences between the tests, the diagnostic thresholds for the ePFT may need to be adapted from those used in traditional secretin testing. Further study is underway to better define appropriate normal cutpoints for the ePFT.

Perhaps the most compelling evidence of the equivalency of the endoscopic and Dreiling secretin tests is found in Figure 2. With one exception (subject 12), the bicarbonate curves are highly similar for both test methods within individual subjects. We suspect that gastric acid contamination resulted in the low [HCO_3^-] seen in the D-PFT for subject 12. Notably, we had to repeat the D-PFT in three other patients because of gastric fluid contamination. It is likely that the tube fell back into the stomach in these patients, another practical problem with the old method.

The use of gastroduodenal collection tubes for pancreatic function testing does not take advantage of the major recent advances in endoscopic technology. In addition to previously cited advantages of endoscopic function testing, including simultaneous luminal examination, greater ease, and lack of fluoroscopy (3, 4), the current study demonstrates that the time of procedure is substantially less for the ePFT. The endoscopic test has been shown to minimize endoscopy costs because of decreased procedure time, lack or requirement of fluoroscopy, lack of need for purchase, and processing of DTs (10). Perhaps the most beneficial aspect of the ePFT

will be the widespread availability of the test to all practicing gastroenterologists. Traditional direct PFT are currently available only at a few centers and may soon become "extinct" because gastroduodenal tubes are no longer manufactured. An accurate and widely available pancreatic function test may have an important future role in the diagnostic algorithm for patients with dyspepsia. The ePFT is relatively safe and less invasive than other costly and risky tests (*e.g.*, ERCP) often performed for ruling out chronic pancreatitis in patients with abdominal pain.

In conclusion, this crossover study demonstrates that the endoscopic collection method yields equivalent bicarbonate results to the DT method of direct secretin PFT. Further investigations are needed to compare the endoscopic and Dreiling methods in patients with chronic pancreatitis.

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STUDY HIGHLIGHTS

What Is Current Knowledge

- Pancreatic function testing may help in the diagnosis of patients with abdominal pain.
- Direct, hormone-stimulated pancreatic function tests (PFT) are highly sensitive for the diagnosis of pancreatic exocrine insufficiency.
- If validated, an endoscopic PFT offers several potential advantages over traditional PFT methods that require passage of Dreiling tubes.

What Is New Here

- This prospective, crossover study demonstrated that a secretin *endoscopic* PFT (ePFT) provided similar results to those obtained using the Dreiling tube method in healthy subjects.
- The ePFT may increase accessibility of function testing to gastroenterologists.

Reprint requests and correspondence: Darwin L. Conwell, M.D., Department of Gastroenterology and Hepatology, Cleveland Clinic Foundation, 9500 Euclid Avenue, Desk A31, Cleveland, OH 44195.
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