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TOPIC HIGHLIGHT

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Pancreatic function testing: Here to stay for the 21st century

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Abstract

The diagnosis of Chronic Pancreatitis (CP) is based on the detection of abnormal structure or function of the diseased pancreas. The pancreatic function tests more accurately determine the presence of CP than tests of structure, especially for early stage disease. The function tests can be divided into two categories: non-invasive and invasive. The invasive "tube" tests can reliably detect mild, early CP, but are only available at a few referral centers and tend to be poorly tolerated by patients. The non-invasive tests are easy to obtain, but tend to perform poorly in patients with early, mild disease. Therefore, no one test is useful in all clinical situations, and a detailed understanding of the rational, pathophysiologic basis, strengths, and limitations of various tests is needed. This review highlights the role of various pancreatic function tests in the diagnosis of CP including fecal fat analysis, fecal elastase, fecal chymotrypsin, serum trypsin, the secretin stimulation test, the cholecystokinin (CCK) stimulation test, the combined secretin-CCK stimulation test, the intraductal and endoscopic secretin stimulation tests, and the functional magnetic resonance imaging of the pancreas after secretin stimulation.

Key words: Pancreatic function testing; Secretin stimulation test; CCK stimulation test; Fecal elastase; Endoscopic secretin stimulation test; Chronic pancreatitis

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INTRODUCTION

Gastroenterologists frequently encounter patients with Chronic Pancreatitis (CP), which is responsible for 86 000 annual admissions in the United States alone[1]. Even more frequently encountered is the patient with chronic abdominal pain and suspected CP based on equivocal imaging or laboratory findings. Although defined by irreversible histologic damage to the pancreas, histologic specimens are difficult and morbid to obtain. Therefore, in practice, the diagnosis of CP is based on the detection of abnormal structure or function (endocrine and exocrine) of the diseased pancreas. However, gross radiographic and endoscopic structural changes are insensitive and can be nonspecific - especially for early stage disease. Therefore, gastroenterologists are often forced to rely on tests of pancreatic function, the so-called, pancreatic function tests (PFT's), to diagnose CP. Arguably, these more accurately determine the presence of CP than tests of structure. Unfortunately, many of these PFT's themselves have significant drawbacks.

Several new PFT's have been introduced in the last 5-10 years, such as fecal elastase, Secretin-stimulated Magnetic Resonance Cholangio-pancreatography (S-MRCP), and endoscopic Pancreatic Function Testing (ePFT).

A few key points in using and interpreting PFT's are: first, they can be falsely positive for at least a few months after an attack of acute pancreatitis; second, negative PFT's do not exclude acute relapsing pancreatitis in patients who do not yet have structural or functional pancreas damage; third, although the best PFT's, especially the secretin-based stimulation tests, are more sensitive in the detection of CP than nonfunctional tests, rarely they still can miss early stage CP.

NORMAL PANCREATIC PHYSIOLOGY

In order to appreciate the utility of pancreatic function

testing, one has to understand the normal functioning of the pancreas. In the basal or fasting state, the pancreas excretes small amounts of protein - rich and mildly alkaline fluid. During a meal, gastric distension and acid production stimulate the duodenal S cells to release secretin into the blood, which signals the ductal cells of the small ducts of the pancreas to secrete a large volume of bicarbonate-rich, clear, watery fluid (so called *hydraulic secretion*). Similarly, the postprandial increase in amino acids and fatty acids in the duodenal fluid stimulates the I cells of the duodenum to secrete cholecystokinin (CCK, aka pancreozymin). CCK, in turn, signals the acinar cells of the pancreas to release enzyme-rich fluid into the pancreatic duct. This is so called *echolic secretion*[2]. For completeness, vago-vagal pathways also stimulate pancreatic secretion and modulate hormone release. These are primarily responsible for an increase in pancreatic secretion during the cephalic phase of digestion. The effects of these two hormonal systems (Secretin and CCK) are measurable and are abnormal in CP. For example, CCK levels are elevated in patients with early CP compared to controls, and these levels are often low in advanced disease[3]. In general terms, the chronically damaged pancreas produces decreased volume, bicarbonate, and enzymes in pancreatic juice in response to a stimulus than the normal pancreas. These decrements can be exploited during pancreatic function testing.

NATURAL HISTORY OF CP

Pancreatic function testing is clinically important for a number of reasons. First, CP is a heterogenous disease. Patients lie on a spectrum ranging from early, painful disease (so called minimal change, or small duct CP) with relatively preserved physiology to end stage disease with very little endocrine or exocrine function. Patients with early stage CP are very difficult to diagnose and distinguish from other causes of chronic abdominal pain. For example, conventional testing, such as pancreas-protocol computed tomography (CT) scans, Magnetic Resonance Imaging (MRI), and Magnetic Resonance Cholangio-Pancreatography (MRCP), generally detects patients with late stage CP, typically when 50% or more of the gland is fibrotic and has been essentially destroyed. Some experts suggest that the traditional pancreatic function tests may detect patients with as little as 30% damage to the pancreas[4].

Another reason that PFT's are useful is that clinical assessment of steatorrhea (exocrine dysfunction) is unreliable. Many patients can have steatorrhea with only a single formed bowel movement a day. Further complicating the prediction of steatorrhea is the often long course of acute pain relapses or early CP that occurs for many years before the development of steatorrhea. In natural history studies, the time to the development of steatorrhea is quite long, about 20 years. Part of this lag time is explained by the pancreas' extensive reserve of lipase secreting capacity. The pancreas has to lose ninety percent of its lipase production before steatorrhea is measurable by fecal fat testing. Yet, lipase depletion occurs earlier and is more profound than protease and amylase deficiency[5]. This fact can be exploited during pancreatic function testing. Part of lipase's vulnerability is its dependence on bicarbonate secretion by the pancreas to ensure a high duodenal pH - up to 7.5-9.0 for optimum activity. Endocrine dysfunction may occur at, or slightly after, the development of steatorrhea[6]. Certainly, the time course of exocrine and endocrine dysfunction varies depending on the etiology of the CP. As an extreme example, cystic fibrosis patients can present in infancy with failure to thrive due to exocrine failure[7].

PROBLEMS WITH STRUCTURAL (NONFUNCTIONAL) TESTS FOR CP

Besides the subtle progression of the natural history of CP as a reason for the utility of pancreatic function testing, many of the conventional tests in the detection of CP have a number of drawbacks.

CT

CT is fairly sensitive for the detection of advanced CP with calcification, atrophy, fat replacement, and ductal dilation. In some studies as high as 75%[8] to 80%[9]. However, others have found that when compared to better tests such as ERCP and Secretin-CCK function testing, CT is only 47% sensitive in the diagnosis of CP. The specificity of CT is considerably higher than the sensitivity, around 90%[10]. CT carries the additional benefit of evaluating the pancreas for other pathology (e.g. pancreatic cancer), and the whole abdomen for alternative explanation of the patient symptoms.

MRCP

MRCP is a fairly good test for the detection of advanced CP. However, even compared to the relatively insensitive endoscopic retrograde cholangiopancreatography (ERCP), MRCP is only about 75% sensitive for advanced disease and 25% for small duct CP[11]. Generally, MRCP detects many of the same changes that are seen on CT. An added benefit of MRCP is improved detection and characterization of biliary and pancreatic strictures compared to other noninvasive imaging tests. However, the visualization of the pancreatic duct (PD) can be difficult by MRCP, which depends on volume and flow in the pancreatic duct that is already quite low in CP. Non-occluding strictures can make visualization of the PD difficult. Generally, conventional MRCP, like CT, does not detect subtle side branch abnormalities of minimal change CP[12].

ERCP

This test involves cannulation of the pancreatic and biliary ducts. ERCP is generally considered the gold standard in the diagnosis of structural pancreatic duct diseases. In several studies, ERCP can even detect a very small number of patients with negative PFT's[13].

However, these changes can be seen in the normally aging pancreas, and, overall, the sensitivity of ERCP for small duct CP is significantly less than that of the best pancreatic function tests, even at the quarternary centers most proficient at ERCP[14,15]. Overall, ERCP has sensitivity of 66% for detecting minimal change CP and is 93% sensitive for late stage CP, compared to secretin stimulation testing[5]. In addition, ERCP is highly operator dependent. Furthermore, it is fairly invasive and carries a risk of up to 20% of acute post-ERCP pancreatitis which is greatest in the patients suspected of having minimal change CP (with non-dilated ducts). Recent preliminary data suggest that even a relatively mild episode of acute post ERCP pancreatitis may lead to CP when evaluated several years after the episode of post-ERCP pancreatitis[16].

Endoscopic ultrasound (EUS)

EUS is an excellent initial test of choice in the diagnosis of minimal change CP. It has relatively few risks, even if fine needle aspiration is used, and is as sensitive as MRCP in the detection of occult choledocholithiasis[17], and is superior to MRCP and transabdominal ultrasound in detecting cholecystolithiasis. However, it does have several drawbacks. It still requires sedation so a full day of work is missed - not only by the patient, but by a driver/chaperone - making it relatively expensive. EUS is highly operator dependent. In addition, even more than ERCP, EUS can be falsely positive due to the echotexture changes of the normal aging pancreas or in diabetics. Therefore, EUS is better at "ruling out" CP than it is at "ruling in" CP. Sensitivities and specificities of EUS vary from 90% and 85% *versus* histology for advanced disease[18] to 97% and 60%, respectively for EUS-FNA compared to ERCP[19], to 57% and 64%, respectively for plain EUS compared to secretin stimulation testing[20], to 83% and 80%, respectively in a mixed population of early and advanced disease compared to histology[21]. Much controversy surrounds the endosonographic definition of CP, with some groups still using 3 EUS criteria for CP, while most agreeing that 5 or more criteria must be present diffusely[22]. Unfortunately, to date no consensus exists on the exact EUS diagnostic criteria for CP.

PANCREATIC FUNCTION TESTS FOR CP

Noninvasive "tubeless" pancreatic function tests

In an effort to discover a sensitive and specific function test for CP that avoids risk and invasive procedures and that can be performed on outpatient basis, several tests have been developed, all of which suffer several severe shortcomings, but may be useful in diagnosing CP in a patient with a long alcohol history or with equivocal imaging findings. Generally, these tests only detect advanced CP with steatorrhea, but are fairly cheap and reliable.

Seventy-two hour fecal fat: The 72 h fecal fat collection was once a routine part of the workup for malabsorption, and it remains the gold standard for quantification of steatorrhea. However, it suffers from many drawbacks, including its nonspecificity for pancreatic disease. For example, bacterial overgrowth, short bowel syndrome, and small bowel mucosal disease (e.g. celiac disease and Crohn's disease) can present with steatorrhea. However, the diarrhea of CP tends to be less voluminous yet fattier than other diarrheal illnesses. In addition, the 72 h fecal fat is inaccurate when performed in the outpatient setting for several reasons. First, it is unrealistic to expect the patient to refrigerate 72 h worth of stool. Second, adherence to a standardized 100 g/24 h fat diet per day for a total of 6 d (the 3 d preceding the test and then the test itself) is difficult. Achieving at least 100 g/d, typical for a large fast food lunch of double cheeseburger and French fries with milkshake, is relatively easy (of course, false negatives can occur in the patient unable to consume that much fat due to pain, though, these are typically early CP patients, who do not yet have steatorrhea). However, quantification of daily fat intake with food diaries as an outpatient is unreliable, making calculation of the coefficient of fat absorption similarly unreliable. Third, for this test, the patient must be off of oral pancreatic enzymes supplements for about a week prior to collection. As a result, some patients have bloating, abdominal discomfort, and gas from malabsorption or are otherwise unwilling to stop the enzymes.

In our institution, for the above reasons, we reserve the 72 h stool collection for research purposes, during which time the patient is admitted to a metabolic ward with a dietician familiar with the protocol to monitor consumption and adjust later meals to account for what has not been consumed. A 72 h stool collection during a high fat diet showing more than 7 g/d fat in the stool is abnormal[23]. The levels of steatorrhea seen in CP tend to be much higher (often > 20 g/d). For practicality, most pancreatologists have abandoned this test. However, a modified 24 h protocol can be used for clinical purposes to monitor response to enzyme therapy in patients experiencing an unexplained increase in steatorrhea, especially in growing children with cystic fibrosis, despite alleged compliance with enzymes.

Spot fecal fat: Sudan staining of a random stool sample for fecal fat is relatively insensitive for fat malabsorption. Generally, it detects steatorrhea only at 25 g/d or more. As a stool collection, it suffers many of the drawbacks of the 72 h fecal fat, including patient embarrassment, need to stop pancreatic enzyme supplements, need to be on a high fat diet for several days before the collection, *etc.* Greater than 6 droplets of fat per high power field are indicative of steatorrhea. As in the case of the 72 h fecal fat analysis, fat substitutes in foods such as Olestra©/Olean© or drugs such as orlistat or ezetimibe can give false positive results.

Fecal chymotrypsin: In advanced CP, lower concentrations of pancreatic proteases reach the stool than in controls. Trypsin is the principal protease secreted by the

pancreas, however, it undergoes degradation in the distal small bowel so is not a good fecal marker for pancreas enzyme output[24]. On the other hand, several other proteases made by the pancreas, such as chymotrypsin are useful stool markers. As with all fecal protease assays, the fecal chymotrypsin should be thought of as a surrogate for the 72 h fecal fat rather than for the conventional, "tube," pancreatic function tests. Chymotrypsin evades degradation in stool by binding to insoluble debris in stool and is stable for several days at room temperature, enabling a sample to be shipped to a reference lab. A fecal chymotrypsin below 3 U/g of stool suggests advanced CP. This test is altered by exogenous pancreatic enzyme supplementation so is useful to monitor for compliance, but is not available in the United States[25]. The fecal chymotrypsin assay is of little clinical value to detect early stage CP, but it has a reasonable sensitivity for advanced disease of from 50% to 80%, increasing to 80%-90% in cystic fibrosis[26], with a specificity of 50%-100%[27-29]. As in all fecal protease assays, watery diarrhea, such as from short bowel syndrome, can give false positive results (low fecal chymotrypsin) by diluting the sample.

Fecal elastase (FE): Pancreatic elastase-1 is a pancreas-specific protease that is minimally degraded during intestinal transit. In fact, it is concentrated 6-fold in stool compared to duodenal juice[30,31]. The concentration of fecal elastase in stool measured by Enzyme Linked Immunosorbant Assay (ELISA) correlates well with duodenal amylase, lipase, and trypsin in both CP patients and controls[32]. Typically, a fecal elastase less than 100 mcg/g of stool indicates severe pancreatic insufficiency. A value between 100-200 mcg is indeterminant, but in the face of other evidence, is suggestive of CP. Values over 200 mcg are normal.

FE suffers from many of the same limitations of the fecal chymotrypsin assay, notably that it only detects patients with steatorrhea and severe CP that likely could have been detected by other means. In various studies, compared to conventional pancreatic function testing and ERCP, the sensitivity of FE varies from between 0%-65% for mild disease to 33%-100% for severe CP, with generally good specificity (from 29% to 95%)[33-37]. FE may be superior to fecal chymotrypsin. For example, in one small study the FE had a sensitivity of 64% for detecting CP compared to 25% for fecal chymotrypsin[38]. Also, like fecal chymotrypsin only a spot stool sample is required rather than a 24 h or 72 h collection. FE also does not cross react to exogenous porcine enzymes so patients can remain on therapy for the test. However, FE is more expensive than fecal chymotrypsin.

Serum trypsin: The serum trypsinogen (a.k.a. trypsin) assay is unique among pancreatic function tests in being a serum sample, making it convenient and relatively cheap. Low levels, less than 20 ng/mL, are specific for CP, but are sensitive only for advanced disease. Levels from 20-29 are indeterminant, but sometimes represent early CP[39]. Sensitivities for mild to severe CP patients combined range from 33%-65%, but specificity is quite high[40]. Sensitivity for exocrine dysfunction is quite high, at about 95%[39]. One added benefit is that trypsin levels over 150 ng/mL are indicative of pancreatic inflammation. For example, the trypsin can be positive for a relapse of CP even when amylase and lipase levels are normal. Conversely, it can help differentiate benign, chronically elevated amylase and lipase from pancreatic inflammation[41]. The test used in our institution is a Radio-Immune Assay (RIA), so it has the disadvantage of requiring several days to obtain a result. We typically obtain this test along with the fecal elastase and pancreatic protocol CT as an initial battery in all patients suspected of having CP referred to our clinic. However, like the fecal assays, it is basically a marker of advanced disease and steatorrhea.

Invasive, traditional, "tube" pancreatic function tests

Since first described in the 1930s and 1940s, several techniques have been developed to measure pancreatic function after physiologic or supraphysiologic stimuli[42,43]. The central theme of these tests is to collect and quantitate the quality of pancreatic secretions to determine pancreatic secretory capacity.

Secretin stimulation test (SST): In a technique more widely publicized by Dreiling[44], a double lumen, 26 Fr, oro-duodenal tube with both gastric and duodenal ports is introduced fluoroscopically, stiffened with a guidewire, with only topical anesthesia (benzocaine spray and viscous lidocaine) applied to the posterior pharynx. The weighted tip should be advanced close to the ligament of Treitz and the tapered radiopaque portion of the tube should be positioned at the pylorus. Placement can be hampered by multiple factors including patient discomfort, nausea, gastroparesis, and pyloric stenosis.

We place both the gastric and duodenal ports to low constant suction by an electric flywheel pump whose gauge measures 2-5 inches Hg (51-127 mmHg). However, the suction produced by these pumps may be lower than the gauge suggests: our lab has found that standard wall units are too strong and inconsistent and may result in adherence of the tube to the duodenal wall with clogging of the ports. Constant vigilance is required to prevent clogging of ports which decreases yield of duodenal fluid. During experiments with Polyethylene Glycol (PEG) labeled with carbon 14 (^{14}C), 85% or more of duodenal fluid can be collected with this double lumen "Dreiling" tube with relatively little reflux of duodenal contents into the stomach[45,46]. We then measure basal duodenal and basal gastric pH and volume over 15 min. Next, we give a bolus of intravenous (IV) secretin, because bolus administration has been shown to be equivalent[47] or superior[48] to continuous infusion. The typical dose of porcine secretin is a 1 U/kg IV bolus. This is a supraphysiologic dose, but is usually well tolerated other than some flushing. However, the cost of secretin is fairly high. One study showed that an even higher dose of secretin (4-5 U/kg) might be more sensitive[49]. We now use synthetic human secretin at

dose 0.2 mg/kg which has been shown to be equivalent to porcine secretin[50]. We then measure three parameters of the duodenal fluid collected over one hour in four 15 min aliquots: volume, pH, and bicarbonate concentration in mEq/L measured by back titration with hydrochloric acid. Others have found that automated analyzers are almost as good as the standard labor intense back titration[51]. The gastric pH and volume at the end of the study are also recorded. The highest concentration of bicarbonate obtained among the four 15 min aliquots is the peak bicarbonate concentration. For completeness, a microscopic exam is performed on the duodenal aspirate for Giardia, Gram stain, and Crystals. Then, the bicarbonate output (the product of bicarbonate concentration and volume) for that hour long post-stimulation period is calculated. The tube is then removed and the patient can resume normal activities and can drive home. Standardized ranges are 80-130 mEq/L for the peak bicarbonate, 1.5-5.7 mL/kg for the volume/kg of patient weight, and 10.1 to 37.0 mEq/h for the bicarbonate output. If the peak bicarbonate is less than 80 mEq/L, the patient is very likely to have CP. If the volume is low and proper position of the collecting tube is reconfirmed, we typically state that the patient should be evaluated further for a pancreatic duct obstruction.

The SST is arguably the most sensitive test for CP. Classically, bicarbonate is thought to be produced by small pancreatic ducts[2]. Consequently, one might anticipate that the SST would be the most sensitive test to diagnose small duct, minimal change CP. This hypothesis was upheld in several studies. The SST, when compared with histology, is 75% sensitive in detecting early stage CP, and up to 97% for late stage disease with a specificity of 90%[52,53]. Compared to SST, ERCP has about a 66% sensitivity for early disease, though it comes close to SST for late stage disease[4,54].

In addition, several histologic studies suggest bicarbonate production may be the best way to diagnose early CP. A study in dogs indicates that the maximal bicarbonate output is closely related to functional pancreatic mass[55]. In addition, an early study by Dr. Dreiling found an excellent correlation between findings on histology and findings of the SST. The SST picked up 20/24 patients (83%) who had CP by pathology whereas ERCP was only 17/24 (71%) sensitive. All underwent SST first, followed by ERCP, and 24 went on to exploratory laparotomy[54].

However, the SST does have some shortcomings, notably difficulty with tube placement and that false positives can be seen for several months after an attack of acute pancreatitis. This is the reason we delay EUS, S-MRCP, fecal elastase testing, fecal fat testing, and SST for several months after an attack of acute pancreatitis.

CCK stimulation testing: In use almost as long as the SST, the classical CCK stimulation test is a useful test, developed and used primarily at the Mayo Clinic in Rochester, Minnesota. Because this test measures ecbolic (enzyme) output, it is, in theory, a measure of the processes that lead to steatorrhea, and could be less sensitive than SST. However, it is still one of the most sensitive tests for the presence of CP. One study of normal controls in Japan found no differences between the SST and the CCK stimulation test[56]. The CCK stimulation test has a number of drawbacks including the need for placement of two specialized 2-lumen tubes with simultaneous gastric and duodenal aspiration and duodenal perfusion of a solution containing mannitol and PEG. CCK is also administered under constant infusion at 40 ng/kg per hour, but it can be given as a bolus[57,58]. Caerulein, which is found on the skin of tree frogs and can be produced synthetically, can substitute for CCK. Caerulein is, in fact, many times more potent a secretogogue than CCK[59]. Bombesin can also substitute for CCK[60].

In the classical CCK stimulation test, as in most tube tests, the basal 20 min aspiration of duodenal and gastric contents is discarded. The gastric and duodenal ports are continually withdrawn under low intermittent suctioning and duodenal fluid is collected over 80 min into four 20 min aliquots. Also during the first 20-40 min, the contraction of the gallbladder by CCK (and resultant flow of bile into the duodenum) affects the measurement of pancreatic output. In addition, as CCK can delay gastric emptying[61], and is thought to cross the blood brain barrier and mediate central pain mechanisms[62], symptoms of nausea and vomiting are common during infusion and more common than symptoms from secretin infusion[63]. The classic CCK stimulation test also requires measurement, and constant intestinal perfusion, of a nonabsorbable marker, and recovery rates vary significantly[64]. If the illustration in the *Gastroenterology* article which first described it is still in use today, it has fewer aspiration ports in the duodenum than the conventional Dreiling tube, and uses pressure suctioning of 40 mmHg[65] which, as mentioned above, may be somewhat different than the suction used at University of Florida with the conventional Dreiling tube.

A modified version of this test using a conventional Dreiling tube, placed under light sedation, and measuring only lipase by a hospital based lab assay was found to be very sensitive in patients with both early (Cambridge 2) and late stage CP by ERCP (Cambridge 3 and 4)[66]. However, no one has compared this test directly to the SST. In addition, as we shall discuss later in the section on endoscopic secretin stimulation testing, use of sedation may affect recovery of secretions and cost.

Combined secretin-CCK (secretin-pancreozymin) stimulation testing: This test is used mostly in Europe and Japan and allows measurement of both bicarbonate and enzyme production by the pancreas. In theory, the simultaneous administration of Secretin with CCK has the potential to dilute the measurement of enzyme activity by watery, bicarbonate solution. However, CCK can also be given before[67] or after[57] Secretin. It also shares one of the drawbacks of the CCK stimulation test: increased bile secretion into the duodenum.

In one study of the Secretin-CCK test, the peak bicarbonate - rather than CCK-related parameters - was correlated nearly linearly to the severity of histologic changes in CP. Also in this study, the second and third best measures of histologic damage were the amylase activity and the total volume, respectively. In that study, the secretin-CCK test was 67% sensitive for various stages of CP, which is somewhat less than other studies of the SST. However, this study used stringent requirements for the diagnosis of CP. All 3 parameters (peak bicarbonate, volume of duodenal secretions, and amylase output) had to be decreased in order to qualify as CP. Applying our cutoffs for peak bicarbonate, only, to this data would give greater sensitivity with only some loss of specificity[4,68].

Another study found that the trypsin activity in pancreatic fluid was not as sensitive a measure of CP as the peak bicarbonate during Secretin-CCK testing[69]. A recent, and probably the largest, study of Secretin-CCK stimulation testing supported this finding, mostly in cystic fibrosis patients. In this study, 336 CCK-Secretin tests were reviewed. Using enzyme (trypsin) activity alone (cutoff < 50 U/kg per hour) would have had 25% false positives if enzyme recovery were not corrected for losses (if a marker had not been used); i.e. 25% of patients with good enzyme activity would have been falsely classified as pancreas-insufficient[70].

A third study of 19 alcoholic CP patients and 6 patients with idiopathic CP who underwent CCK-secretin testing and went on to surgery for refractory symptoms, 18/18 of whom had an abnormal ERCP, found that the peak bicarbonate concentration and output were the best measures of small duct dilation seen on histology. In addition, peak bicarbonate output was the best measure of acinar atrophy with a Spearman correlation coefficient of -0.71 (P between 0.001 and 0.01) and the chymotrypsin output was also significantly correlated (Spearman, -0.57), but with a higher P of between 0.01 and 0.02. Peak volume also correlated fairly well with acinar atrophy (Spearman -0.44, P between 0.02 and 0.05), but peak bicarbonate concentration was weaker (Spearman -0.17, $P > 0.05$). In summary, this study found that the hydraulic parameters (volume, peak bicarbonate concentration, peak bicarbonate output) were overall better predictors of abnormal histology than the ecbolic parameters (chymotrypsin)[2].

These studies indicate that the CCK portion of the Secretin-CCK stimulation test adds little information in the diagnosis of CP that the secretin stimulation portion alone (or perhaps the classic SST) already provides. However, the Secretin-CCK test is certainly a more sensitive measure of pancreatic enzyme production than the bentiromide test, which tests primarily protease production by the pancreas[71].

Perfusion testing: Researchers in the Gastroenterology Division at the University of Florida in Gainesville over the last 25 years have developed and implemented a method of measuring endogenous and exogenous pancreatic enzyme activity in the duodenum of patients with CP analogous to the Mayo clinic CCK methodology. This "perfusion test" enables quantification of delivery of exogenous pancreatic enzymes to the duodenum. Some notable differences between this perfusion test and the CCK stimulation test include use of a standardized meal rather than CCK to stimulate the pancreas, use of a modified Dreiling tube attached to a 7 Fr Dobhoff tube, placed without sedation under fluoroscopy, and the perfusion of radiolabeled Carbon-14 Polyethylene Glycol (PEG) to enhance assessments of recovery. This perfusion test measures endogenous enzyme production in the fasted and fed states with a standardized Ensure® meal. Volume of both gastric and duodenal collections, pH, and enzyme activity are recorded over a 3 h period. The test is then repeated immediately after intake of an exogenous pancreatic enzyme[72]. The inconvenience and time required for this test render it useful only for the research setting.

Intraductal SST: In the intraductal secretin stimulation test, typically the main pancreatic duct is cannulated using ERCP techniques and then pancreatic fluid is collected, after the administration of secretin alone, or secretin followed by CCK. The patient is sedated without anticholinergic medications such as diphenhydramine (Benadryl®) or opiates, usually with benzodiazepines. Typically, the pancreatic fluid collected in this manner has a higher bicarbonate concentration than in the classical SST, around 130 mEq/L for controls, and less then 105 mEq/L for CP patients, owing to lack of contamination by bile and duodenal content. Some of the disadvantages of this test include the complication rate of ERCP, the need for sedation, and the relatively short time periods of collection (usually 15 min, as limited by sedation and fluoroscopy room time). An advantage of the intraductal test is that pure pancreatic juice is collected without contamination with bile or duodeno-gastric contents and that it can be used in patients with Billroth I and Ⅱ gastric resections.

One group showed that the intraductal test could not reliably differentiate between 19 CP patients, 14 "early CP" patients, and 14 controls[73], despite a long intraductal collection period of 60 min. The investigators used extra CCK with secretin after the initial secretin boluses in 15 patients. They used only 70 U maximum of secretin and did not adjust for weight of the patients. In addition, their aspiration catheter was prefilled with a dye to assist in identifying the start of the collection, which may have been problematic due to mixing. Also their "early CP" patients had only acute relapsing pancreatitis with no evidence of chronicity by imaging or conventional pancreatic function testing.

For the analyses, it appears they combined the patients with "early CP" and those with CP. They found that this combined group of CP patients produced significantly less volume of pancreatic secretions than controls after stimulation with 1 CU of secretin and 70 CU of secretin but not after 4 CU of secretin. CP patients also had significantly less bicarbonate concentrations only after 4 CU of secretin compared to

controls. Bicarbonate output was decreased significantly at all time points for CP patients compared to controls. Interestingly, at only the first minute time point, in patients with CP, the protein content of fluid was higher but not significantly so, than controls, perhaps due to concretions of inspissated enzymes in this group from PD stasis. However, after 70 CU of secretin, the protein output of CP patients was significantly less than controls.

A second, larger study of 12 patients with CP and 33 controls (22 normals and 11 with other nonpancreatic GI disorders), which used only a 20 min collection time, found that the sensitivity of the intraductal test peak bicarbonate compared to SST was 100% with a specificity of only 66%. Volume had an 88% sensitivity and a 91% specificity for CP by SST[74].

The most recent study of the intraductal secretin stimulation test was less favorable. In this comparison of the intraductal secretin stimulation test and SST, in which 19 patients served as their own control, the sensitivity of the intraductal secretin stimulation test compared to the conventional SST was only 80%, with a very poor specificity of 20%. Against pancreatogram, the intraductal test was 100% sensitive but only 55% specific[75]. This group used three 5-min collections (as is customary for most intraductal secretin stimulation tests) and the first was discarded. Based on these results, we do not recommend the use of the intraductal secretin stimulation test for routine diagnostic or research purposes.

Endoscopic secretin stimulation testing (eSST): An alternative to traditional pancreatic function testing is to sedate the patient, and collect duodenal juice under endoscopic guidance from a polyethylene tube passed through the biopsy channel of a standard upper endoscope after stimulation with secretin[51,76] or the combination of secretin-CCK[77]. This offers the advantage of patient comfort and sedation. The eSST has been extensively studied by a group of investigators from the Cleveland Clinic. The overall impression is that the eSST has the potential to yield results similar to the conventional SST. This comes to no surprise since the two tests are very similar with the main differences being the use of sedation in the eSST and the use of the endoscope to collect duodenal secretions rather than a Dreiling tube for the conventional SST. However, it should be noted that the eSST and the SST have only been directly compared in one small cross over study of healthy controls only, without any CP patients, in which the SST group also received sedation, which we do not do and could have confounded the results in favor of the eSST[78].

Unfortunately, the eSST has several disadvantages. Although the eSST is technically easy to perform, it is impractical, and to date it has not gained acceptance. The main problem appears to be that occupying an endoscopy room and keeping the patient sedated for more than one hour are cost-prohibitive. Although the Cleveland Clinic group has shown that a 45 min endoscopic collection is reasonable with good sensitivity with some loss of specificity[79], we have shown that a full 60 min is necessary for full sensitivity and specificity of the classical secretin stimulation test[80]. Furthermore, patients and their escorts will also have to miss a whole day of work. In addition, medications used for sedation may have effects on pancreatic secretions[81]. Opiates may constrict the sphincter of Oddi, and propofol contains 5% triglyceride which may have effects on pancreatic secretion. Although one small study of normal subjects did not find an effect of light sedation on secretion during endoscopic secretin stimulation testing, it used fairly low doses - 2.5 mg of midazolam and 62.5 mg of meperidine[82]. However, we have found that greater amounts of sedatives are required in most patients with chronic abdominal pain who are referred for evaluation of possible CP.

"Enhanced imaging" pancreatic function tests (S-MRCP): Because of some of the shortcomings of conventional MRCP in the diagnosis of pancreatic disorders, some have investigated the use of MRI with secretin stimulation to increase the flow and volume in the pancreatic duct. The filling of the duodenum can be semi-quantitated to assess for CP. One possible problem with this technique is that it measures volume of pancreatic flow rather than bicarbonate concentration. In theory, obstructive lesions, or sphincter of Oddi spasm could give positive results in the absence of true CP[83]. In addition, MR images are acquired over at most 30 min, which is often an insufficient length of time during secretin stimulation and which may lead to reduced sensitivity.

One German study of 18 CP patients, defined by ERCP, many of whom had previously undergone pancreatic duct stenting and removal, and 5 diseased controls exemplified some of these issues with S-MRCP. This study, even on these patients with obviously advanced CP, showed a 69% sensitivity of S-MRCP with 1 CU/kg of secretin and 90% specificity as compared to relatively insensitive pancreatic function tests, such as the fecal elastase and ^{13}C Mixed Chain Triglyceride Breath Test (MCT-BT)[83].

Another method that S-MRCP uses to assess for CP is parenchymal enhancement during gadolinium infusion (also used during conventional MRI, but which is not used during conventional MRCP). To assess for parenchymal enhancement, T1-weighted sequences with fat suppression are crucial. Also important is the pattern of gadolinium enhancement of the parenchyma: CP patients show decreased enhancement in the arterial phase and increased enhancement in the early venous phase, which are thought to be due to decreased pancreatic blood flow. On T2 imaging, enhancement is seen in CP patients compared to controls, indicating fatty or fibrous replacement of the parenchyma. After 0.5 IU/kg of secretin, the reduced T2 signal changes showed a good correlation with the Lundh test, a pancreatic function test using meal based stimulation. This study also showed a good correlation between

duodenal diameter after S-MRCP and the Lundh test. Patients with severe CP had an average increase in duodenal diameter of 1.7 mm. In mild CP the increase was 4.7 mm, and in controls, 14 mm. However, in this study, the patient population was not well defined. They did have a cohort with mild pancreatitis but again we do not know the criteria used to establish this[84].

Another group, this time from Japan, has distinguished S-MRCP, which they reserve to look for duct changes, from "Secretin-Stimulated, Diffusion Weighted MRI" which focuses on secretin-induced changes within the parenchyma of the gland. This new type of MRI calculates the Apparent Diffusion Coefficient (ADC) which measures diffusion of water molecules in the microcirculation. They claim that this type of MRI is even more sensitive than S-MRCP and that it evaluates local and regional pancreatic exocrine function. They also measured changes in alcoholic patients, known not to have structural pancreatic disease by conventional CT. Notably these patients did not undergo pancreatic function testing or ERCP[11].

CONCLUSION

Most pancreatic function tests have high sensitivity and specificity to accurately diagnose patients with advanced CP. The noninvasive tests tend to perform poorly in patients with early, mild disease. Some specialized invasive "tube" tests can reliably detect mild, early CP but are only available at a few quarternary referral centers. S-MRCP and Diffusion Weighted, Secretin Stimulated MR are promising technologies but, for the near future, are not likely to provide the same discriminating power as the best "tube" tests. The quest for a simple, noninvasive, cheap, and accurate pancreatic function test continues.

REFERENCES

1 **Kozak LJ**, Owings MF, Hall MJ. National Hospital Discharge Survey: 2002 annual summary with detailed diagnosis and procedure data. *Vital Health Stat 13* 2005; 1-199
2 **Heij HA**, Obertop H, van Blankenstein M, ten Kate FW, Westbroek DL. Relationship between functional and histological changes in chronic pancreatitis. *Dig Dis Sci* 1986; **31**: 1009-1013
3 **Slaff JI**, Wolfe MM, Toskes PP. Elevated fasting cholecystokinin levels in pancreatic exocrine impairment: evidence to support feedback regulation. *J Lab Clin Med* 1985; **105**: 282-285
4 **Chowdhury RS**, Forsmark CE. Review article: Pancreatic function testing. *Aliment Pharmacol Ther* 2003; **17**: 733-750
5 **Forsmark CE**. Chronic pancreatitis. In Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 7th ed. Philadelphia: Saunders, 2002: 949
6 **Layer P**, Yamamoto H, Kalthoff L, Clain JE, Bakken LJ, DiMagno EP. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. *Gastroenterology* 1994; **107**: 1481-1487
7 **Durie PR**. Pancreatic aspects of cystic fibrosis and other inherited causes of pancreatic dysfunction. *Med Clin North Am* 2000; **84**: 609-620, ix
8 **Manfredi R**, Brizi MG, Masselli G, Gui B, Vecchioli A, Marano P. Imaging of chronic pancreatitis. *Rays* 2001; **26**: 143-149
9 **Luetmer PH**, Stephens DH, Ward EM. Chronic pancreatitis: reassessment with current CT. *Radiology* 1989; **171**: 353-357
10 **Malfertheiner P**, Buchler M, Stanescu A, Ditschuneit H. Exocrine pancreatic function in correlation to ductal and parenchymal morphology in chronic pancreatitis. *Hepatogastroenterology* 1986; **33**: 110-114
11 **Sugiyama M**, Haradome H, Atomi Y. Magnetic resonance imaging for diagnosing chronic pancreatitis. *J Gastroenterol* 2007; **42** Suppl 17: 108-112
12 **Akisik MF**, Sandrasegaran K, Aisen AA, Maglinte DD, Sherman S, Lehman GA. Dynamic secretin-enhanced MR cholangiopancreatography. *Radiographics* 2006; **26**: 665-677
13 **Gupta V**, Toskes PP. Diagnosis and management of chronic pancreatitis. *Postgrad Med J* 2005; **81**: 491-497
14 **Forsmark CE**, Toskes PP. What does an abnormal pancreatogram mean? *Gastrointest Endosc Clin N Am* 1995; **5**: 105-123
15 **Toskes PP**. Update on diagnosis and management of chronic pancreatitis. *Curr Gastroenterol Rep* 1999; **1**: 145-153
16 **Symersky T**, van Hoorn B, Masclee AA. The outcome of a long-term follow-up of pancreatic function after recovery from acute pancreatitis. *JOP* 2006; **7**: 447-453
17 **Ledro-Cano D**. Suspected choledocholithiasis: endoscopic ultrasound or magnetic resonance cholangio-pancreatography? A systematic review. *Eur J Gastroenterol Hepatol* 2007; **19**: 1007-1011
18 **Varadarajulu S**, Eltoum I, Tamhane A, Eloubeidi MA. Histopathologic correlates of noncalcific chronic pancreatitis by EUS: a prospective tissue characterization study. *Gastrointest Endosc* 2007; **66**: 501-509
19 **Hollerbach S**, Klamann A, Topalidis T, Schmiegel WH. Endoscopic ultrasonography (EUS) and fine-needle aspiration (FNA) cytology for diagnosis of chronic pancreatitis. *Endoscopy* 2001; **33**: 824-831
20 **Chowdhury RS**, Bhutani MS, Mishra G, Toskes PP, Forsmark CE. Comparative analysis of pancreatic function testing versus morphologic assessment (by EUS) for the evaluation of chronic unexplained abdominal pain. *Gastroenterology* 2001; **120**: A647
21 **Chong AK**, Hawes RH, Hoffman BJ, Adams DB, Lewin DN, Romagnuolo J. Diagnostic performance of EUS for chronic pancreatitis: a comparison with histopathology. *Gastrointest Endosc* 2007; **65**: 808-814
22 **Raimondo M**, Wallace MB. Diagnosis of early chronic pancreatitis by endoscopic ultrasound. Are we there yet? *JOP* 2004; **5**: 1-7
23 **Safdi M**, Bekal PK, Martin S, Saeed ZA, Burton F, Toskes PP. The effects of oral pancreatic enzymes (Creon 10 capsule) on steatorrhea: a multicenter, placebo-controlled, parallel group trial in subjects with chronic pancreatitis. *Pancreas* 2006; **33**: 156-162
24 **Adham NF**, Dyce BJ, Geokas MC, Haverback BJ. Stool chymotrypsin and trypsin determinations. *Am J Dig Dis* 1967; **12**: 1272-1276
25 **Goldberg DM**. Proteases in the evaluation of pancreatic function and pancreatic disease. *Clin Chim Acta* 2000; **291**: 201-221
26 **Scotta MS**, Marzani MD, Maggiore G, De Giacomo C, Melzi D'Eril GV, Moratti R. Fecal chymotrypsin: a new diagnostic test for exocrine pancreatic insufficiency in children with cystic fibrosis. *Clin Biochem* 1985; **18**: 233-234
27 **Dominguez-Munoz JE**, Hieronymus C, Sauerbruch T, Malfertheiner P. Fecal elastase test: evaluation of a new noninvasive pancreatic function test. *Am J Gastroenterol* 1995; **90**: 1834-1837
28 **Loser C**, Mollgaard A, Folsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. *Gut* 1996; **39**: 580-586
29 **Durr HK**, Otte M, Forell MM, Bode JC. Fecal chymotroypsin: a study on its diagnostic value by comparison with the secretin-cholecystokinin test. *Digestion* 1978; **17**: 404-409
30 **Sziegoleit A**, Krause E, Klor HU, Kanacher L, Linder D.

Elastase 1 and chymotrypsin B in pancreatic juice and feces. *Clin Biochem* 1989; **22**: 85-89
31 **Sziegoleit A**, Linder D. Studies on the sterol-binding capacity of human pancreatic elastase 1. *Gastroenterology* 1991; **100**: 768-774
32 **Stein J**, Jung M, Sziegoleit A, Zeuzem S, Caspary WF, Lembcke B. Immunoreactive elastase I: clinical evaluation of a new noninvasive test of pancreatic function. *Clin Chem* 1996; **42**: 222-226
33 **Dominguez-Munoz JE**, Hieronymus C, Sauerbruch T, Malfertheiner P. Fecal elastase test: evaluation of a new noninvasive pancreatic function test. *Am J Gastroenterol* 1995; **90**: 1834-1837
34 **Gullo L**, Ventrucci M, Tomassetti P, Migliori M, Pezzilli R. Fecal elastase 1 determination in chronic pancreatitis. *Dig Dis Sci* 1999; **44**: 210-213
35 **Lankisch PG**, Schmidt I, Konig H, Lehnick D, Knollmann R, Lohr M, Liebe S. Faecal elastase 1: not helpful in diagnosing chronic pancreatitis associated with mild to moderate exocrine pancreatic insufficiency. *Gut* 1998; **42**: 551-554
36 **Loser C**, Mollgaard A, Folsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. *Gut* 1996; **39**: 580-586
37 **Amann ST**, Bishop M, Curington C, Toskes PP. Fecal pancreatic elastase 1 is inaccurate in the diagnosis of chronic pancreatitis. *Pancreas* 1996; **13**: 226-230
38 **Katschinski M**, Schirra J, Bross A, Goke B, Arnold R. Duodenal secretion and fecal excretion of pancreatic elastase-1 in healthy humans and patients with chronic pancreatitis. *Pancreas* 1997; **15**: 191-200
39 **Jacobson DG**, Curington C, Connery K, Toskes PP. Trypsin-like immunoreactivity as a test for pancreatic insufficiency. *N Engl J Med* 1984; **310**: 1307-1309
40 **Borgstrom A**, Wehlin L. Correlation between serum concentrations of three specific exocrine pancreatic proteins and pancreatic duct morphology at ERCP examinations. *Scand J Gastroenterol* 1984; **19**: 220-227
41 **Lake-Bakaar G**, McKavanagh S, Gatus B, Summerfield JA. The relative values of serum immuno-reactive trypsin concentration and total amylase activity in the diagnosis of mumps, chronic renal failure, and pancreatic disease. *Scand J Gastroenterol* 1980; **15**: 97-101
42 **Chiray M**, Jeandel A, Salmon A. L'exploration clinique du pancreas et l'injection intraveneuse de secretine purifiee. *Presse Med* 1930; **38**: 977
43 **Lagerlof HO**. Pancreatic function and pancreatic disease: studied by means of secretin. *Acta Med Scand* 1942; **128**: 1
44 **Dreiling DA**, Hollander F. Studies in pancreatic function; preliminary series of clinical studies with the secretin test. *Gastroenterology* 1948; **11**: 714-729
45 **Go VL**, Hofmann AF, Summerskill WH. Simultaneous measurements of total pancreatic, biliary, and gastric outputs in man using a perfusion technique. *Gastroenterology* 1970; **58**: 321-328
46 **Lagerlof HO**, Schutz HB, Holmer S. A secretin test with high doses of secretin and correction for incomplete recovery of duodenal juice. *Gastroenterology* 1967; **52**: 67-77
47 **Takebe T**, Koike D, Yokoyama Y. Modern trends in biochemical tests of the pancreas: CS test and S test. *Biliary Tract Pancreas* 1986; **7**: 583-588
48 **Farini R**, Del Favero G, Adorati M, Pedrazzoli S, Fabris G, Giordano P, D'Angelo A, Zotti E, Lise M, Chiaramonte M, Salvagnini M, Naccarato R. Comparison between bolus injection and infusion of secretin and pancreozymin in the diagnosis of chronic pancreatic disease (one hour test). *Acta Hepatogastroenterol* (Stuttg) 1977; **24**: 462-468
49 **Bordalo O**, Noronha M, Lamy J, Dreiling D. The secretin test with the standard dose and high dose in chronic pancreatitis. *Minerva Med* 1976; **67**: 3599-3606
50 **Somogyi L**, Ross SO, Cintron M, Toskes PP. Comparison of biologic porcine secretin, synthetic porcine secretin, and synthetic human secretin in pancreatic function testing. *Pancreas* 2003; **27**: 230-234
51 **Ceryak S**, Steinberg WM, Marks ZH, Ruiz A. Feasibility of an endoscopic secretin test: preliminary results. *Pancreas* 2001; **23**: 216-218
52 **Steer ML**, Waxman I, Freedman S. Chronic pancreatitis. *N Engl J Med* 1995; **332**: 1482-1490
53 **Kitagawa M**, Naruse S, Ishiguro H, Nakae Y, Kondo T, Hayakawa T. Evaluating exocrine function tests for diagnosing chronic pancreatitis. *Pancreas* 1997; **15**: 402-408
54 **Waye JD**, Adler M, Dreiling DA. The pancreas: a correlation of function and structure. *Am J Gastroenterol* 1978; **69**: 176-181
55 **Hansky J**, Tiscornia OM, Dreiling DA, Janowitz HD. Relationship between maximal secretory output and weight of the pancreas in the dog. *Proc Soc Exp Biol Med* 1963; **114**: 654-656
56 **Suzuki T**, Suzuki K, Kobayashi E, Ogawa Y, Kawamura Y, Nakai T, Suzuki S, Hayakawa T, Noda A, Kondo T. Comparative study of the secretin test and pancreozymin secretin test in chronic pancreatitis. *Nippon Shokakibyo Gakkai Zasshi* 1986; **83**: 2209-2215
57 **Bank S**, Marks IN, Moshal MG, Efron G, Silber R. The pancreatic-function test--method and normal values. *S Afr Med J* 1963; **37**: 1061-1066
58 **Zieve L**, Silvis SE, Mulford B, Blackwood WD. Secretion of pancreatic enzymes. I. Response to secretin and pancreozymin. *Am J Dig Dis* 1966; **11**: 671-684
59 **Gullo L**, Costa PL, Fontana G, Labo G. Investigation of exocrine pancreatic function by continuous infusion of caerulein and secretin in normal subjects and in chronic pancreatitis. *Digestion* 1976; **14**: 97-107
60 **Basso N**, Giri S, Improta G, Lezoche E, Melchiorri P, Percoco M, Speranza V. External pancreatic secretion after bombesin infusion in man. *Gut* 1975; **16**: 994-998
61 **Liddle RA**, Morita ET, Conrad CK, Williams JA. Regulation of gastric emptying in humans by cholecystokinin. *J Clin Invest* 1986; **77**: 992-996
62 **Xie JY**, Herman DS, Stiller CO, Gardell LR, Ossipov MH, Lai J, Porreca F, Vanderah TW. Cholecystokinin in the rostral ventromedial medulla mediates opioid-induced hyperalgesia and antinociceptive tolerance. *J Neurosci* 2005; **25**: 409-416
63 **Akisik MF**, Sandrasegaran K, Aisen AA, Maglinte DD, Sherman S, Lehman GA. Dynamic secretin-enhanced MR cholangiopancreatography. *Radiographics* 2006; **26**: 665-677
64 **Conwell DL**, Zuccaro G, Morrow JB, Van Lente F, O'Laughlin C, Vargo JJ, Dumot JA. Analysis of duodenal drainage fluid after cholecystokinin (CCK) stimulation in healthy volunteers. *Pancreas* 2002; **25**: 350-354
65 **Go VL**, Hofmann AF, Summerskill WH. Simultaneous measurements of total pancreatic, biliary, and gastric outputs in man using a perfusion technique. *Gastroenterology* 1970; **58**: 321-328
66 **Conwell DL**, Zuccaro G, Morrow JB, Van Lente F, Obuchowski N, Vargo JJ, Dumot JA, Trolli P, Shay SS. Cholecystokinin-stimulated peak lipase concentration in duodenal drainage fluid: a new pancreatic function test. *Am J Gastroenterol* 2002; **97**: 1392-1397
67 **Sun DC**. Normal values for pancreozymin-secretin test. *Gastroenterology* 1963; **44**: 602-606
68 **Hayakawa T**, Kondo T, Shibata T, Noda A, Suzuki T, Nakano S. Relationship between pancreatic exocrine function and histological changes in chronic pancreatitis. *Am J Gastroenterol* 1992; **87**: 1170-1174
69 **Rolny P**, Jagenburg R. The secretin-CCK test and a modified Lundh test. A comparative study. *Scand J Gastroenterol* 1978; **13**: 927-931
70 **Schibli S**, Corey M, Gaskin KJ, Ellis L, Durie PR. Towards the ideal quantitative pancreatic function test: analysis of test variables that influence validity. *Clin Gastroenterol Hepatol* 2006; **4**: 90-97
71 **Lankisch PG**, Schreiber A, Otto J. Pancreolauryl test.

Evaluation of a tubeless pancreatic function test in comparison with other indirect and direct tests for exocrine pancreatic function. *Dig Dis Sci* 1983; **28**: 490-493

72 **Slaff J**, Jacobson D, Tillman CR, Curington C, Toskes P. Protease-specific suppression of pancreatic exocrine secretion. *Gastroenterology* 1984; **87**: 44-52

73 **Denyer ME**, Cotton PB. Pure pancreatic juice studies in normal subjects and patients with chronic pancreatitis. *Gut* 1979; **20**: 89-97

74 **Ochi K**, Harada H, Mizushima T, Tanaka J, Matsumoto S. Intraductal secretin test is as useful as duodenal secretin test in assessing exocrine pancreatic function. *Dig Dis Sci* 1997; **42**: 492-496

75 **Draganov P**, Patel A, Fazel A, Toskes P, Forsmark C. Prospective evaluation of the accuracy of the intraductal secretin stimulation test in the diagnosis of chronic pancreatitis. *Clin Gastroenterol Hepatol* 2005; **3**: 695-699

76 **Conwell DL**, Zuccaro G Jr, Vargo JJ, Trolli PA, Vanlente F, Obuchowski N, Dumot JA, O'laughlin C. An endoscopic pancreatic function test with synthetic porcine secretin for the evaluation of chronic abdominal pain and suspected chronic pancreatitis. *Gastrointest Endosc* 2003; **57**: 37-40

77 **Bornschein W**. A fast endoscopic test of pancreatic secretion (endoscopic secretin-caerulein-test) (author's transl). *Z Gastroenterol* 1978; **16**: 582-592

78 **Stevens T**, Conwell DL, Zuccaro G Jr, Van Lente F, Purich E, Khandwala F, Fein S. A randomized crossover study of secretin-stimulated endoscopic and dreiling tube pancreatic function test methods in healthy subjects. *Am J Gastroenterol* 2006; **101**: 351-355

79 **Stevens T**, Conwell DL, Zuccaro G Jr, Lewis SA, Love TE. The efficiency of endoscopic pancreatic function testing is optimized using duodenal aspirates at 30 and 45 minutes after intravenous secretin. *Am J Gastroenterol* 2007; **102**: 297-301

80 **Draganov P**, George S, Toskes PP, Forsmark CE. Is a 15-minute collection of duodenal secretions after secretin stimulation sufficient to diagnose chronic pancreatitis? *Pancreas* 2004; **28**: 89-92

81 **Konturek SJ**. Opiates and the gastrointestinal tract. *Am J Gastroenterol* 1980; **74**: 285-291

82 **Conwell DL**, Zuccaro G, Purich E, Fein S, Vanlente F, Vargo J, Dumot J, O'laughlin C, Trolli P. The effect of moderate sedation on exocrine pancreas function in normal healthy subjects: a prospective, randomized, cross-over trial using the synthetic porcine secretin stimulated Endoscopic Pancreatic Function Test (ePFT). *Am J Gastroenterol* 2005; **100**: 1161-1166

83 **Schneider AR**, Hammerstingl R, Heller M, Povse N, Murzynski L, Vogl TJ, Caspary WF, Stein J. Does secretin-stimulated MRCP predict exocrine pancreatic insufficiency?: A comparison with noninvasive exocrine pancreatic function tests. *J Clin Gastroenterol* 2006; **40**: 851-855

84 **Czako L**. Diagnosis of early-stage chronic pancreatitis by secretin-enhanced magnetic resonance cholangiopancreatography. *J Gastroenterol* 2007; **42** Suppl 17: 113-117

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