Does Secretin-stimulated MRCP Predict Exocrine Pancreatic Insufficiency?

A Comparison With Noninvasive Exocrine Pancreatic Function Tests

Arne R. J. Schneider, MD,* Renate Hammerstingl, MD,† Matthias Heller, MD,† Nada Povse,* Lydia Murzynski,* Thomas J. Vogl, MD,† Wolfgang F. Caspary, MD,* and Juergen Stein, MD*

Background: Data on magnetic resonance cholangiopancreatography with secretin stimulation (S-MRCP) for the assessment of exocrine pancreatic insufficiency (EPI) are limited. We compared pancreatic function tests with the findings of S-MRCP in patients with chronic pancreatitis (CP) and disease controls.

Methods: S-MRCP was performed in 23 patients (18 CP, 5 disease controls). MRCP images were analyzed for secretin-induced duodenal liquid filling (0 = no filling; 1 = duodenal bulb; 2 = up to lower flexure; 3 = beyond lower flexure). EPI was evaluated by fecal elastase, fecal fat concentration, and a 13C mixed chain triglyceride breath test. Clinically relevant EPI was stated if 2 of 3 tests were pathologic.

Results: EPI was diagnosed in 10 of 18 patients with CP. Patients without EPI showed either grade 2 (n = 4) or grade 3 (n = 9) duodenal filling, whereas only 1/10 patients with EPI showed grade 3 duodenal filling. Sensitivity and specificity of S-MRCP for the diagnosis of EPI were 69% and 90%, respectively.

Conclusions: Assessment of duodenal filling should be performed in patients who undergo S-MRCP for the evaluation of pancreatic morphology. However, minor degrees of duodenal filling are equivocal and require further diagnostic evaluation.

Key Words: chronic pancreatitis, exocrine pancreatic insufficiency, MRCP, secretin

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P ancreatic exocrine insufficiency is a common sequel of chronic pancreatitis (CP) or pancreatic resection. Therapeutic consequences of exocrine pancreatic insufficiency (EPI) imply alimentary modifications and the

initiation of an oral pancreatic enzyme supplementation. In clinical routine, fecal elastase 1 concentration is used for the noninvasive screening of EPI.[1–3] Fecal elastase concentration (FEC) predicts severe pancreatic insufficiency with 95% sensitivity and 85% specificity. On the other hand, the method detects mild or moderate degrees of pancreatic insufficiency with relatively low sensitivity (60% to 70%). A number of other diagnostic tests may further increase sensitivity, but these are time-consuming and require considerable patient cooperation. "Direct" assessment of pancreatic function after intravenous application of secretin and caerulein is still considered the gold-standard. However, a lack of standardization and the unpleasant placement of a nasoduodenal tube are considerable disadvantages of the test. The sensitivity and specificity of this method range from 67% to 97% and 85% to 98%, respectively.[1,4,5] With respect to noninvasive diagnostic tests, the assessment of stool weight and fecal fat excretion (42%, 92%) and the ^{13}C mixed triglyceride breath test (46% to 100%, 76% to 81%) are alternative methods with varying degrees of accuracy.[1,6–9]

On the other hand, magnetic resonance imaging (MRI) is increasingly recognized as a noninvasive imaging method for the evaluation of pancreatic parenchymal and ductal morphology. Sensitivity of MR cholangiopancreatography (MRCP) for the diagnosis of CP is about 75% and can be further increased to 90% by intravenous application of secretin to enhance the quality of ductal (side branch) imaging.[10,11] Secretin is a gastrointestinal peptide hormone that stimulates the secretion of a bicarbonate-rich pancreatic fluid. The latter can be visualized by T2-weighted sequences during MRI. Only few studies have addressed the question of whether secretin-enhanced MRCP (S-MRCP) may also predict EPI. In this regard, semiquantitative assessement of secretin-induced duodenal filling during MRCP has been considered the major surrogate parameter of exocrine pancreatic function. The limited number of patients and the fact that EPI was either suspected[12] or diagnosed on the basis of a single pancreatic function test, for example, the *N*-benzoyl-L-tyrosyl para-amino-benzoic acid,[13] Lundh test,[14] endoscopic secretin test,[15] and fecal fat concentration[16] remain major drawbacks of these trials. Secretin-induced duodenal filling showed varying

degrees of sensitivity (72% to 92%) and specificity (71% to 87%) for the prediction of pancreatic insufficiency or correlation with pancreatic function tests. Secretin solely induces the secretion of a bicarbonate-rich pancreatic fluid, but does not stimulate the production of digestive enzymes. For this reason, we aimed to combine different noninvasive pancreatic function test to further improve the diagnosis of advanced EPI for a reliable comparison with the findings of secretin-stimulated MRCP.

PATIENTS AND METHODS

Twenty-three patients [17 male; median age 48 years (range 18 to 79 y)] underwent S-MRCP and pancreatic function tests. Eighteen patients suffered from known CP (based on ERCP findings), whereas 5 persons underwent MRI for the further evaluation of unspecific abdominal symptoms without known pancreatic disease (disease-controls). ERCP morphology of the pancreatic duct was assessed according to the criteria of the Cambridge-classification.[17] One patient with CP had a known pancreas divisum. Pancreatic tail resection without biliopancreatic diversion had been performed in 1 patient with chronic idiopathic pancreatitis 20 years before, because of acute necrotizing pancreatitis of unknown origin. The remaining patients neither reported diseases of the small bowel (eg, celiac disease, Whipple disease) nor previous pancreatic or small bowel surgery. Eight of 18 patients with CP had a history of temporary endoscopic stenting for symptomatic pancreatic duct or biliary stenoses, but none had stenting during the performance of the diagnostic study procedures. Demographic and laboratory data of the patients and disease-controls are outlined in Table 1. All disease controls and the majority of patients with CP had a sufficient nutritional status, as reflected by the body mass index (BMI) and serum albumin concentration.

Imaging Technique

S-MRCP was performed with a clinical 1.5-T imager (Magnetom Sonata, Siemens, Erlangen, Germany)

TABLE 1. Demographic and Clinical Data of Study Patients (Median and Range)

Male/female	17/6
Age	48 (18-79)
CP	18/23
Alcoholic	12
Idiopathic	6
Duration of CP (y)	7 (1-35)
Pancreatic duct morphology (ERCP)	
in patients with CP	
Cambridge I	5
Cambridge II	5
Cambridge III	8
Diabetes mellitus in patients with CP	8/18
BMI (kg/mL)	
CP	20.3 (14.4-26.6)
Disease controls	24.9 (19.4-29.6)
Albumin (g/dL)	
CP	4.3 (3.0-4.7)
Disease controls	4.5 (4.1-4.7)

after a minimum of 8 hours fasting. The scanner was equipped with a phased-array body coil. The patient was placed in the supine position for imaging. MR pancreatography was performed within one breath hold by using a single-shot HASTE T2-weighted sequence (4500 ms repetition time, 983 ms effective echo, 313 ms inversion time) a section thickness of 80 mm, matrix size of 356×512, field of view of 350, and an acquisition time of 4.5 seconds before and after stimulation of secretin. Patients were asked to hold their breath from just before the acquisition of each dynamic image until immediately after the acquisition. The actual breath hold duration was close to 5 seconds. To reduce the blurring fat saturation mode and presaturation bands (thickness, 80 mm) were applied anteriorly and posteriorly to reduce artefacts. The projections were oriented in the coronal plane and included the entire main pancreatic duct up to its emergence at the papilla of Vater. No further postprocessing of image was needed. Thirty minutes before the beginning of imaging, patients received 300 mL of a negative superparamagnetic contrast agent orally (Lumirem, Guerbet, France) to achieve a complete endoluminal signal extinction in the stomach and the small bowel. Antiperistaltic agents were not administered. A set of images was acquired before secretin stimulation, which enabled optimal positioning of the imaged section. Subsequently, 1 CU secretin per kg body weight (Secrelux, Sanochemia, Germany) was applied intravenously and image acquisition was repeated every 30 seconds for 10 minutes.

Image Analysis

MRCP images were analyzed for general image quality, duodenal signal extinction, and duodeno-jejunal filling. The latter was graded according to the following scheme: grade 1 corresponded to secretin-induced filling confined to the duodenal bulb, duodenal filling grade 2 meant a signal increase up to the caudal flexure and a liquid filling beyond was labeled grade 3 (Fig. 1). Cases of no duodenal filling after secretin were graded "0". Both the beginning and the period until maximum duodenal filling were documented. Additionally, pancreatic duct morphology was evaluated for the presence of pseudo-cysts and stenoses. Stenoses were considered relevant if the prestenotic part of the duct was dilated.

All MRI images were analyzed by 2 radiologists (R.H., M.H.) and a gastroenterologist (A.S.) without knowledge on the results of exocrine pancreatic function tests. Interpretational discrepancies were resolved by consensus.

Assessment of Exocrine Pancreatic Function

All patients underwent 3 noninvasive tests for the assessment of exocrine pancreatic function:
- FEC was assessed with a monoclonal enzyme-linked immunosorbent assay (Pancreatic elastase 1, Schebo Biotech, Giessen, Germany). The assay was performed according to the guidelines of the manufacturer. An
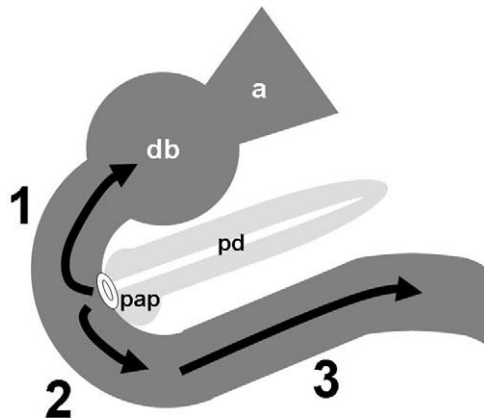
FIGURE 1. Scheme showing the grading of duodenal filling by MRI (a indicates antrum; db, duodenal bulb; pd, pancreatic duct; pap, papilla of Vater).

elastase concentration of $< 200 \, \mu g/g$ was considered pathologic.

- Patients were asked to collect the stools completely during 3 consecutive days after a period of 5 days on a diet containing 80 to 100 g of fat daily. Oral pancreatic enzyme substitution was paused 3 days before the beginning of stool collection. Fecal fat content (FAT) was assessed with near infrared spectrometric analysis.[18] A fat content of more than 7 g/d indicated pathologically increased fat excretion.

- All patients underwent a ^{13}C-mixed chain triglyceride breath test (MCT-BT) as previously published.[8] After an overnight fast (> 10 h), patients received 250 mg of 1,3-distaryl,2[^{13}C]octanoylglycerol mixed in 30 g of chocolate cream. The chocolate cream was spread on 2 slices of toast (50 g) and the patient asked to eat the toast within 5 minutes together with 200 mL of water. Breath samples were taken before and every 30 minutes after the application of the tracer for the following 6 hours. Patients were requested to remain at rest during the test period and were not allowed to smoke. Breath samples were analyzed by nondispersive infrared spectrometry (IRIS, Wagner Analysentechnik, Bremen, Germany) as previously published. A cumulative ^{13}C-dose recovery (cPDR) after 6 hours of less than 23% was considered pathologic. Advanced EPI was diagnosed if 2 tests showed pathologic results.

The study was performed in accordance with the Declaration of Helsinki.

Statistical Analysis

Spearman-correlation and the Mann-Whitney test were used for the comparison of continuous data. Sensitivity and specificity of S-MRCP were assessed in a contingency table with Fisher exact test. A $P \leq 0.05$ was considered significant.

RESULTS

All diagnostic tests were well tolerated. Patients did not report any worsening of symptoms, which could be

attributed to the application of secretin during MRCP or the test meal during the MCT-BT. MR images could be sufficiently evaluated with respect to the assessment of secretin-induced duodenal filling. Ten of 18 patients with CP (56%) showed EPI with at least 2 pathologic exocrine pancreatic function tests (6 pathologic FEC, FAT, and MCT-BT; 2 pathologic FEC and MCT-BT; 1 pathologic FEC and FAT; 1 pathologic FAT and MCT-BT). Although 1 patient with CP had normal FEC, pathologically increased FAT and decreased cPDR together with clinical signs of malnutrition and malabsorption clearly indicated severely compromised exocrine pancreatic function. The BMI of patients with EPI was significantly lower compared with persons without insufficiency (19.0 ± 3.2 vs. $23.0 \pm 3.3 \, \mathrm{kg/m^2}$; $P = 0.02$). Secretin-induced duodenal filling ranged up to the caudal flexure (grade 2) in 4 (31%) and beyond (grade 3) in 9 of 13 patients (69%) without EPI (Figs. 2, 3). On the contrary, only 1 of 10 persons with EPI demonstrated grade 3 duodenal filling. Among the rest of the patients with EPI, duodenal filling showed heterogeneous results. Accordingly, a duodenal filling not beyond the caudal flexure yielded a sensitivity of 69% and a specificity of 90% for the prediction of exocrine pancreatic insufficiency ($P = 0.01$). Results of the MCT-BT and FEC decreased as duodenal filling diminished (Fig. 4). Compared with patients who showed grade 3 duodenal filling, cPDR after 6 hours of sampling significantly differed in patients with grade $0/1$ and grade 2 duodenal filling. All patients with grade 0 or 1 filling showed elastase concentrations below $100 \, \mu g/g$ and a cPDR below 23%, indicating severely compromised exocrine pancreatic function. In patients with EPI, the interval between secretin application and the beginning of duodenal filling did not differ from patients without EPI (124 ± 19 vs. $170 \pm 27 \, \mathrm{s}$, $P = 0.17$). The same applied to the time of maximum duodenal filling (420 ± 63 vs. $404 \pm 47 \, \mathrm{s}$, $P = 0.79$).

MRI detected stenoses of the pancreatic duct in 9 of 18 patients with CP (50%), which corresponded well with ERCP findings. Single stenoses were located in the pancreatic head in 4 and in the body in 2 cases, whereas
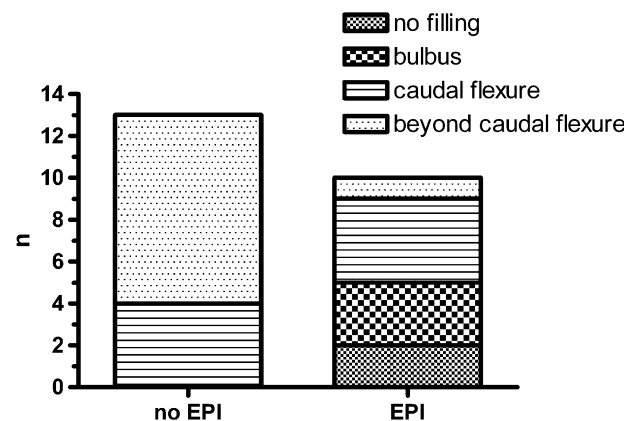

FIGURE 2. Distribution of duodenal filling in patients with and without EPI.
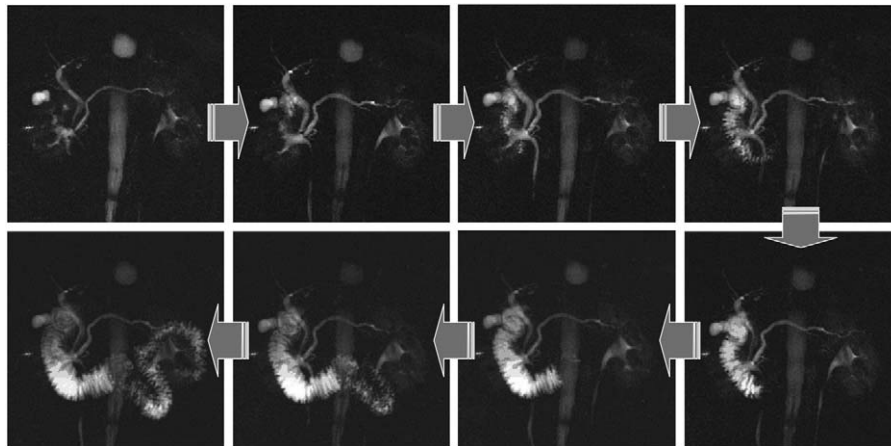
FIGURE 3. Example of sequential S-MRCP images (arrows) showing duodenal filling far beyond the caudal duodenal flexure in a patient with normal exocrine pancreatic function.

3 patients displayed multiple stenoses. Though stenoses were considered relevant in 6 patients due to prestenotic dilation of the duct, 4 of these patients achieved at least grade 2 duodenal filling.

DISCUSSION

MRCP has been accepted as a reliable noninvasive method for the diagnosis of both pancreatic and biliary disease.[19,20] With respect to tumor staging, MRCP with concomitant MRI of the abdomen provides considerable information which has been referred to as a "one stop shopping" for the planning of therapeutic endoscopic and surgical procedures.[21] If secretin-MRCP provided additional information on exocrine pancreatic function, this would further support the conceptual extent of the method. In recent years, a number of publications have addressed the value of S-MRCP for the estimation of

exocrine pancreatic function.[12–16] Studies mainly focused on the assessment of secretin-induced duodenal filling, which reflects pancreatic fluid and bicarbonate production. However, EPI was diagnosed by different methods that either imply limited sensitivity and specificity or poor standardization. For this reason, a combination of different tests has been proposed to improve diagnostic accuracy.[22]

We performed S-MRCP in patients who had neither undergone surgery with a disruption of the pancreatico-duodenal junction nor had endoscopic pancreatic duct stenting. This premises guaranteed pancreaticocibal synchrony and an adequate performance of indirect pancreatic function tests.

The results of duodenal filling were compared with a combination of noninvasive exocrine pancreatic function tests. We can proceed from the fact that the claim of at least 2 pathologic pancreatic function tests improved the accuracy of the diagnosis of clinically relevant EPI. This statement is further confirmed by the fact that patients diagnosed with EPI showed a significantly lowered BMI. However, we refrained from a classification of mild, moderate, and severe pancreatic insufficiency, because minor degrees of pancreatic insufficiency do not call for therapeutic consequences and because indirect function tests are not suitable for a grading of exocrine deficiency.

S-MRCP predicted EPI with moderate sensitivity (69%) and considerable specificity (90%). Cappeliez et al[15] reported similar results (sensitivity 72%, specificity 87%) by comparing of S-MRCP with the findings of an intraductal secretin test. What could account for the limited sensitivity of S-MRCP? With respect to duodenal filling and exocrine pancreatic function, secretin-induced MRCP implies 2 conceptual drawbacks: firstly, minor or moderate degrees of EPI primarily cause a reduction of digestive enzymes whose concentration and function are assessed by FEC and the MCT-ST. On the other hand, a decrease of secretin-induced pancreatic bicarbonate concentration and fluid volume indicates advanced stages of
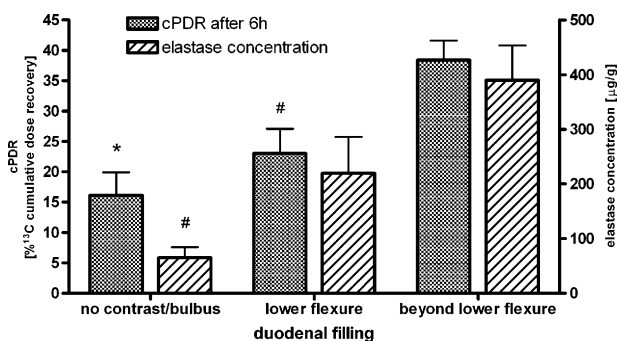

FIGURE 4. FEC and cPDR after 6 hours according to the degree of duodenal filling (mean with standard error; #$P<0.05$ vs. filling beyond lower flexure; *$P<0.01$ vs. filling beyond lower flexure). Elastase concentration: $P=0.17$ for grade 0/1 vs. grade 2; $P=0.1$ for grade 2 vs. 3; $P=0.02$ for duodenal filling grade 0/1 vs. 3. cPDR after 6 hours: $P=0.18$ for grade 0/1 versus grade 2; $P=0.01$ for grade 2 versus 3; $P=0.0007$ for grade 0/1 versus 3.

pancreatic insufficiency.[23,24] For this reason, S-MRCP neglects less severely compromised pancreatic exocrine function. Additionally, we perceived duodenogastric reflux in some patients, which might have caused an underestimation of duodenal filling. This problem is also encountered in classic invasive pancreatic function tests that require nasoduodenal tubes for the collection of pancreatic juice. However, insufficient collection or underestimation of pancreatic secretion would have caused false negative results and decreasing specificity. A recent study by Monill et al[16] reported higher sensitivity (92%) but lower specificity (71%) for the prediction of EPI compared with our study and the trial by Cappeliez et al.[15] In this study, pancreatic insufficiency was diagnosed solely by fecal fat quantification. Accordingly, only patients with severely compromised exocrine pancreatic function and considerably reduced pancreatic secretion were identified and may have accounted for an improved sensitivity of S-MRCP. Although 50% of our study patients with CP exhibited pancreatic duct stenoses, this did not seem to interfere with the degree of duodenal filling. The fact that patients were asymptomatic despite potentially relevant stenoses also reflects the well-known discrepancies between duct morphology and pain perception.[25,26]

In conclusion, duodenal filling should be assessed in patients who undergo S-MRCP for the evaluation of pancreatic pathology, because dynamic filling beyond the lower duodenal flexure virtually excludes clinically relevant EPI. However, minor degrees of duodenal filling require additional diagnostic tests and a clinical estimation of the nutritional status to correctly define the need for therapeutic measures. Recently developed experimental methods for an MR-based quantification of secretin-enhanced pancreatic outflow may improve accuracy, but remain to be validated.[27,28]

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