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Quantification of pancreatic exocrine function with secretin-enhanced magnetic resonance cholangiopancreatography: normal values and short-term effects of pancreatic duct drainage procedures in chronic pancreatitis. Initial results

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Abstract The aim of this study was to quantify pancreatic exocrine function in normal subjects

and in patients with chronic pancreatitis (CP) before and after pancreatic duct drainage procedures (PDDP) with dynamic secretin-enhanced magnetic resonance (MR) cholangiopancreatography (S-MRCP). Pancreatic exocrine secretions [quantified by pancreatic flow output (PFO) and total excreted volume (TEV)] were quantified twice in ten healthy volunteers and before and after treatment in 20 CP patients (18 classified as severe, one as moderate, and one as mild according to the Cambridge classification). PFO and TEV were derived from a linear regression between MR-calculated volumes and time. In all subjects, pancreatic exocrine fluid volume initially increased linearly with time during secretin stimulation. In controls, the mean PFO and TEV were 6.8 ml/min and 97 ml; intra-individual deviations were 0.8 ml/min and 16 ml. In 10/20 patients with impaired exocrine secretions before treatment, a significant increase of PFO and TEV was observed after treatment ($P < 0.05$); 3/20 patients presented post-procedural acute pancreatitis and a reduced PFO. The S-MRCP quantification method used in the present study is reproducible and provides normal values for PFO and TEV in the range of those obtained from previous published intubation studies. The initial results in CP patients have demonstrated non-invasively a significant short-term improvement of PFO and TEV after PDDP.

Keywords MR cholangiopancreatography - MR quantification - Chronic pancreatitis

Introduction

Chronic pancreatitis (CP) is an inflammatory and fibrotic process leading to the gradual destruction of pancreatic parenchyma. Impairment of pancreatic exocrine outflow due to stones and/or strictures is associated with pain and further functional loss, probably due to an ischemic process [1-3]. In this setting, endoscopic pancreatic duct drainage procedures (PDDP), which are similar in principle to derivation surgery, are increasingly used to relieve pain and improve pancreatic secretions drainage into the duodenum [4-6]. These procedures consist of sphincterotomy, stone extraction and stricture dilation followed by stent placement, and they are combined in some cases with extracorporeal shock-wave lithotripsy (ESWL) of pancreatic duct obstructive stones. The results of pure pancreatic juice (PPJ) studies already suggested that even if drainage procedures cannot change the maximal exocrine capacity of the pancreas, they significantly increase the outflow of pancreatic juice into the duodenum [7] and may improve fat digestion [8]. Whether these endoscopic treatments delay exocrine function impairment is not yet known [4].

Current diagnostic methods for the assessment of exocrine pancreatic function are either invasive, requiring duodenal juice or PPJ collections, or lack sensitivity and specificity, as shown by indirect function tests such as the faecal elastase test [9, 10]. Secretin-enhanced magnetic resonance (MR) cholangiopancreatography (S-MRCP) is a non-invasive imaging technique that allows the depiction of morphologic changes in pancreatic ducts and a qualitative assessment of exocrine function by monitoring duodenal filling after exocrine stimulation [11-14]. Furthermore, recent developments in S-MRCP techniques have shown the feasibility of a quantitative assessment of the pancreatic exocrine function [15-17]. These quantification methods have demonstrated a linear relationship between MR signal intensity and fluid volume, and both require a calibration procedure.

In the present study we propose a similar quantification method using S-MRCP to assess pancreatic exocrine function during secretin stimulation by measuring pancreatic flow output (PFO) and total excreted volume (TEV). Our study has a primary and secondary purpose: (1) to obtain reference values for PFO and TEV in a control group of healthy volunteers; (2) to quantitatively assess short-term effects of PDDP on pancreatic exocrine secretions in patients with CP.

Materials and methods

The study was approved by our hospital review board, and a written informed consent was obtained from all subjects after the examination procedure was explained.

Study design

This study was conducted as a prospective trial performed in a single centre. Pancreatic exocrine function was estimated at S-MRCP by quantifying PFO and TEV during secretin stimulation. Prior to patient study, we performed the S-MRCP quantification technique twice in ten healthy volunteers to assess the reproducibility of the method and to define reference values for PFO and TEV. The method was then applied in patients with CP to assess short-term effects of PDDP on pancreatic exocrine secretions.

Study population

The study population was comprised of 30 individuals in two groups. Group 1 was the control group and was comprised of ten healthy volunteers (three men, seven women; age range 22-34 years; mean age \pm standard deviation, 26.5 ± 4.9 years) within 20% of ideal body weight and without medical history of pancreatic disease. The alcohol intake per day was inferior to 10 g and abstinence for 2 weeks before the beginning of the study was required. No prior or concomitant medication was permitted. After a fasting period of at least 6 h, each volunteer underwent two S-MRCP examinations performed at 1-week intervals with the same dose of secretin. Group 2 was comprised of 20 consecutive patients with CP (15 men, five women; age range 32-71 years; mean age \pm standard deviation, 51 ± 10.5 years). They had no previous endoscopic or surgical treatment and had been referred to our institution for PDDP. The diagnosis of CP was based on the presence of pancreatic calcifications shown by plain film and/or computed tomography (CT) and by duct lesions revealed at diagnostic endoscopic retrograde cholangiopancreatography (ERCP). The severity of the disease was classified according to the morphologic changes in the pancreatic ducts shown by ERCP [18]. According to this classification, CP was graded as severe in 18 patients, who exhibited severe main pancreatic duct irregularity, intraductal filling defects, calculi, main pancreatic duct obstruction and strictures; as moderate in one patient with main pancreatic duct dilatation and irregularity, side branch changes and cysts smaller than 10 mm; and as mild in one patient with a normal main pancreatic duct 2-4 mm in diameter but more than 3 abnormal side branches. Endoscopic treatment was performed for pain management. The pain pattern of each patient was classified as type A or type B [19]. Type A is characterised by short relapsing pain episodes (<10 days) separated by long pain-free intervals. This pattern was recorded in 11 patients. Type B pattern is

characterised by prolonged periods of either daily persistent pain or clusters of recurrent severe pain episodes and was observed in nine patients. All patients underwent S-MRCP prior to treatment, which included endoscopic pancreatic sphincterotomy, stone extraction, and/or stenting in case of duct stricture; and pseudo cyst drainage, if necessary; 17 patients had ESWL for obstructive stones in the main pancreatic duct just before ERCP. Table 1 shows clinical characteristics, biological findings and treatment for all CP patients. Complete treatment required more than one endoscopic procedure in five patients. Clinical surveillance and biological tests, including level of serum pancreatic amylase and lipase, were done during the 24 h after treatment. MR examinations were performed after a fasting period of at least 6 h. MR acquisitions were repeated 24 h after the end of treatment.

Table 1 Clinical characteristics, biologic findings and treatment of patients with chronic pancreatitis

Patient no./age (y)/gender	Aetiology	Duration disease (months)	Pain pattern	Cholestasis	Cambridge classification	ESWL	ERCP
1/48/F	Idiopathic	72	B	No	Severe	Yes	EPS
							Stone extraction
							Stricture dilation
							Stent
2/60/M	Alcohol	5	A	No	Severe	Yes	EPS
							Stone extraction
							Stricture dilation
							Stent
3/66/M	Idiopathic	n.d.	A	Yes	Severe	No	EPS
4/46/M	Alcohol	1	B	No	Severe	Yes	EPS
							Stone extraction
							Stricture dilation
							Pcyst drainage
5/48/M	Alcohol	6	B	No	Severe	Yes	EPS
							Stone extraction
							Stricture dilation
							Stent

6/55/M	Alcohol	108	A	Yes	Severe	Yes	EPS
							Pcyst drainage
							Stricture dilation
							Stone extraction
							Stent
7/34/M	Idiopathic	72	B	No	Moderate	No	EPS
							Stent
8/48/M	Alcohol	24	A	No	Severe	Yes	EPS
							Stone extraction
							Stricture dilation
							Stent
9/35/M	Idiopathic	96	A	No	Mild	No	EPS
10/61/F	Idiopathic	168	B	Yes	Severe	Yes	EPS
							Stone extraction
11/59/M	Alcohol	9	A	No	Severe	Yes	EPS
							Stone extraction
12/51/M	Alcohol	204	A	Yes	Severe	Yes	EPS
							Stone extraction
							Pcyst drainage
							Stent
13/49/M	Alcohol	7	B	No	Severe	Yes	EPS
							Stone extraction
14/58/M	Alcohol	24	A	Yes	Severe	Yes	EPS
							Stone extraction
							Stent
15/61/M	Alcohol	6	B	No	Severe	Yes	EPS
							Stone extraction

16/32/F	Idiopathic	4	A	No	Severe	Yes	EPS Stone extraction
17/45/M	Alcohol	8	B	No	Severe	Yes	EPS Stone extraction Stent
18/50/M	Alcohol	48	B	No	Severe	Yes	EPS Stone extraction Pcyst drainage
19/71/F	Alcohol	48	A	Yes	Severe	Yes	EPS Stone extraction
20/44/F	Alcohol	60	A	No	Severe	Yes	EPS Stone extraction

ESWL Extracorporeal shock wave lithotripsy, ERCP endoscopic retrograde cholangiopancreatography, EPS endoscopic pancreatic sphincterotomy, Pcyst pseudocyst

MR imaging protocol

All investigations were performed with a fixed imaging protocol on a 1.5 Tesla super-conducting magnet [Gyrosan Intera (maximum amplitude of the gradients, 30 mT/m; maximum slew rate, 150 T/m/s); Philips Medical Systems, Best, The Netherlands] equipped with a phased array surface coil (Synergy body coil; Philips Medical System, Best, The Netherlands) and with parallel imaging capabilities (sensitivity encoding) [20]. All subjects were placed in the supine position.

The pancreatic MR examination protocol consisted of: (1) coronal T2-weighted single-shot turbo spin-echo, respiratory triggered, covering the upper abdominal region (effective single shot acquisition duration 650 msec, effective echo time 80 ms, echo train length 72, sense factor 2 in the left-right direction, 25 slices 4-5 mm thick with a 0.4 mm slice gap, field of view 400-450 mm with a rectangular field of view depending on the body habitus and matrix 226x400); (2) transverse 3D T1-weighted fast field echo with fat saturation in a single breath hold (TR/TE: 3.9/1.9 ms, flip angle 10°, sense factor 2 in the anterior-posterior direction, 40 slices acquired and after interpolation, 80 slices reconstructed with a thickness of 2 mm, field of view 400 mm with a rectangular field of view, depending on the body habitus and matrix 192x256, acquisition time 18 s); and (3) S-MRCP, coronal multi-slice turbo spin-echo, heavily T2-weighted, with fat-suppression (TE 850 ms, echo train of 198 echoes 75% Half Fourier, slice thickness 15-17 mm, six slices without gap, field of view 350 mm and matrix 264x512). The acquisition time for each dynamic was 12.5 s within a single breath hold. This sequence allows maximal intensity

projections (MIP) in the coronal plane. After the first dynamic acquisition, 20 mg of an anti-peristaltic drug (hyoscine butylbromide, Boehringer Ingelheim, Germany) was injected intravenously followed by a bolus of secretin injected at a dose of 1 clinical unit per kilogram of body weight (Secrelux, Sanochemia, Neuss, Germany). MRCP dynamic acquisitions were then repeated at intervals of 30-45 s for 15 min. For the calibration procedure, six additional acquisitions were performed in the same scan after individuals had ingested 120 ml of water in six increments of 20 ml. Each increment was administered to the subject remaining in the magnet in the supine position by a technician via a plastic cup and the use of a straw. Between each drink, an interval of 45-60 s was observed to ensure that all quantity of water ingested arrived in the stomach.

Image analysis and quantification

After elimination of the name and examination date, an MR technician transferred all images to an independent diagnostic workstation (View Forum, Philips, Best, The Netherlands) for analysis. All images were analysed individually by two radiologists experienced in pancreatic imaging. Qualitative image analysis included overall evaluation of image quality graded as follows: good, when no artefacts at all were observed; adequate, when minimal artefacts were present with little perturbations on interpretation; and inadequate, when important artefacts with difficulties on interpretation were present.

To quantify PFO and TEV during secretin stimulation, a large rectangular region of interest (ROI), including all fluid content of the stomach, duodenum, bowel and pancreas, was drawn on each slice for all dynamic acquisitions. The ROI did not include the fluid content of the bladder. The reason for drawing a large ROI was to avoid any signal loss from out-flowing fluid during secretin stimulation. Mean ROI signal intensity $\langle S \rangle$ was measured electronically. Before starting the quantification measurements, and because of possible diaphragmatic-level irregularities throughout successive breath holds, we verified that the targeted fluid volume remained inside the volume encompassed by the six slices throughout all dynamic acquisitions; mean ROI signal intensity was measured in the outer slices (slices 1 and 6), where a signal variation greater than 10% within these slices constituted an exclusion criterion.

An individual signal calibration procedure was performed for each case. During the additional six dynamic acquisitions, the mean signal intensity in the ROI was measured in each of the six slices and summed. The baseline value (obtained just before the administration of the first known volume of water) was subtracted to provide the reference signal intensities S^{ref} . These six values were plotted against the known water volume V (120 ml) given *per os* in increments of 20 ml. Assuming that there is a linear relationship between signal intensity and fluid volume, a linear regression was computed. The slope of this regression line provided the reference quantity designated by dS^{ref}/dV , representing the increase in total signal intensity per millilitre of water added. The pancreatic exocrine volume secreted at time t after secretin administration was then calculated with the following equation:

$$\frac{\sum_j \langle S \rangle_j (t) - \sum_j \langle S \rangle_j (t_0)}{dS^{\text{ref}}/dV}$$

where:

Σ_j = sum of all six slices

$\langle S \rangle_j(t)$ = mean signal intensity in the ROI in slice j at time t after secretin administration

$\langle S \rangle_j(t_0)$ = mean signal intensity in the ROI in slice j at time t_0 before secretin administration.

The calculated volumes were plotted against time. A regression line was computed. It included excreted volume values from the first detectable excreted volume up to the maximum excreted volume. The latter volume corresponded to the first plateau value when the plateau phase was present, or to the last value measured corresponding to the end of acquisition. The slope of the regression line gave the estimation of PFO (in millilitres per minute). The interval between secretin administration and the beginning of a detectable excreted volume as well as the duration of excretion were recorded. TEV throughout the experiment was calculated as the product of PFO and duration of the excretion.

In patients, coronal MIPs were analysed to measure main pancreatic duct diameters in all dynamic series of images in order to monitor variations in duct diameter during secretin stimulation. Main pancreatic duct diameters were measured on the screen display at the body site with an electronic caliper at the same location before and after secretin injection. The baseline, maximum and final diameter (15 min after secretin injection) of the main pancreatic duct were recorded.

Statistical analysis

In order to assess the reproducibility of the quantification method, intra-individual differences between PFO and TEV obtained from the two S-MRCP examinations performed in each of the healthy volunteers were calculated, and the mean absolute difference was computed. A Wilcoxon signed rank test was used to assess possible significant differences between the two S-MRCP sessions. The same statistical test was used in the patient study to analyse differences before and after treatment of the following parameters: PFO, interval between secretin administration and the beginning of pancreatic volume excretion, duration of excretion, TEV, diameter of the main pancreatic duct at baseline (before secretin stimulation), and maximum value of the diameter and diameter at 15 min after secretin. P values <0.05 were considered significant. Linear regression analysis was used to compare the measurements obtained by the two readers, and a scatter diagram of differences between readers and mean reader observations (Bland-Altman) was plotted [21].

Results

Clinical study

All MR examinations were completed and well-tolerated by all individuals. Both readers estimated all MR images to be of good quality. No signal variations larger than 10% were depicted in the outer slices of S-MRCP dynamic acquisitions. Concerning the individual signal calibration procedure (Fig. 1), the linear regression between mean MR increase in signal intensity and volumes of water administered during the last six acquisitions was very good (R^2 ranging from 0.95 to 0.99; median 0.97).

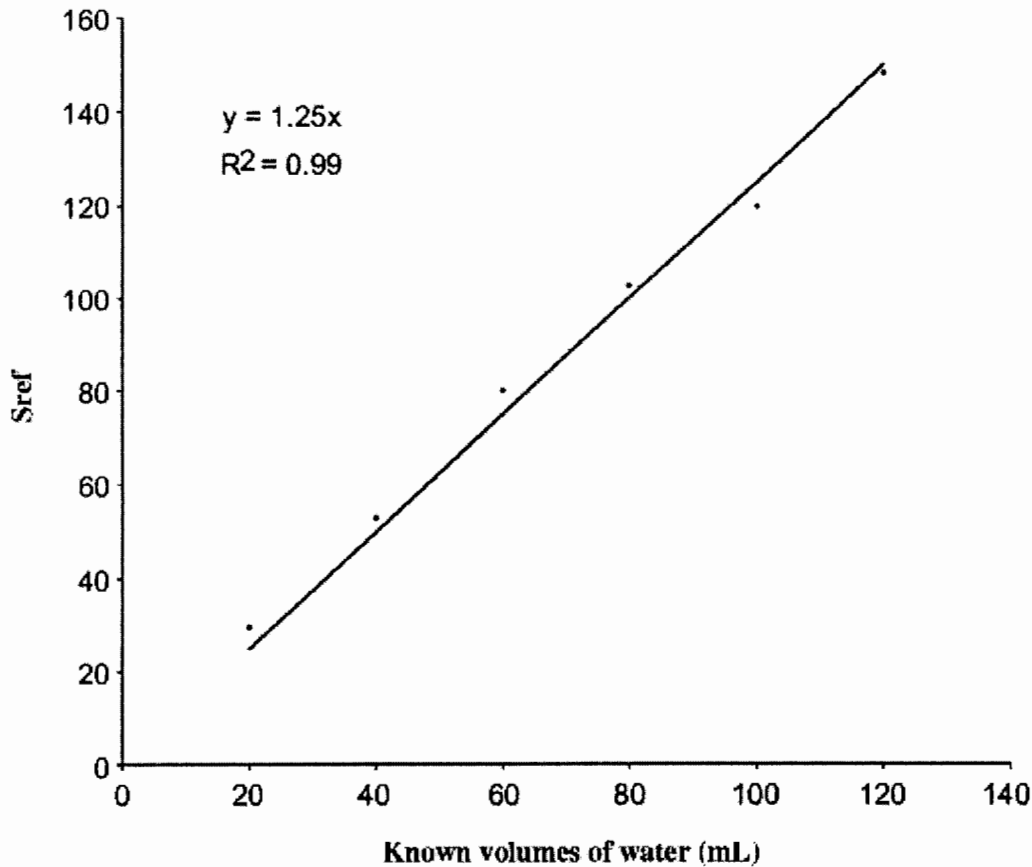


Fig. 1 Graph shows the individual calibration procedure in one patient (patient 15 in Table 1) obtained from reader 1. Reference signal intensities [Sref (y)] were plotted against the known volumes of water (x) administered *per os* in increments of 20 ml during the additional last six acquisitions. The slope of the linear regression provided the reference quantity ($d S^{ref}/dV$). In this patient, the reference quantity is 1.25

Group 1: control group

During secretin stimulation in all healthy volunteers, the pancreatic fluid volume increased linearly with time (R^2 ranging from 0.90 to 0.97; median 0.95). In three volunteers, a plateau phase was observed at the end of the two sessions [30% (6/20)]. The beginning of a detectable excreted volume was observed 30-45 s after secretin administration; the mean excretion duration was 14 min (SD 1 min 20 s). The mean PFO was 6.8 ml/min (SD 1.4 ml/min), with a mean TEV of 97 ml (SD 22 ml). The reproducibility of the technique was characterised by a mean intra-

individual difference between sessions of 0.8 ml/min for PFO and 16 ml for TEV (Table 2), with no statistically significant difference between sessions ($P=0.38$).

Table 2 Pancreatic flow output and total excreted volume in control group (group 1)

Subject no./age(y)/gender	PFO (ml/min)		TEV (ml)	
	Session I	Session II	Session I	Session II
1/34/F	8.6	8.4	124	110
2/32/M	6.8	6	102	93
3/24/F	5.4	7.6	81	114
4/23/F	8.3	7.1	125	84
5/22/M	6.5	6.4	86	73
6/23/M	7.8	8.1	117	120
7/24/F	8.8	8.4	132	126
8/34/F	5.4	5.1	81	76
9/24/F	5.6	4.2	84	63
10/23/F	5.4	6.4	81	70

Data values obtained from reader 1. *PFO* pancreatic flow output, *TEV* total excreted volume

Group 2: patient study

During the first 24 h of surveillance after treatment, three patients presented pain associated with biologic changes (3× normal values of serum pancreatic amylase and lipase) related to mild post-procedural acute pancreatitis. No other post-procedural complications were observed. In all patients, the pancreatic fluid volume secreted under secretin stimulation increased linearly with time (R^2 ranging from 0.75 to 0.99; median 0.89) (Fig. 2). Table 3 shows the results obtained in the patient group.

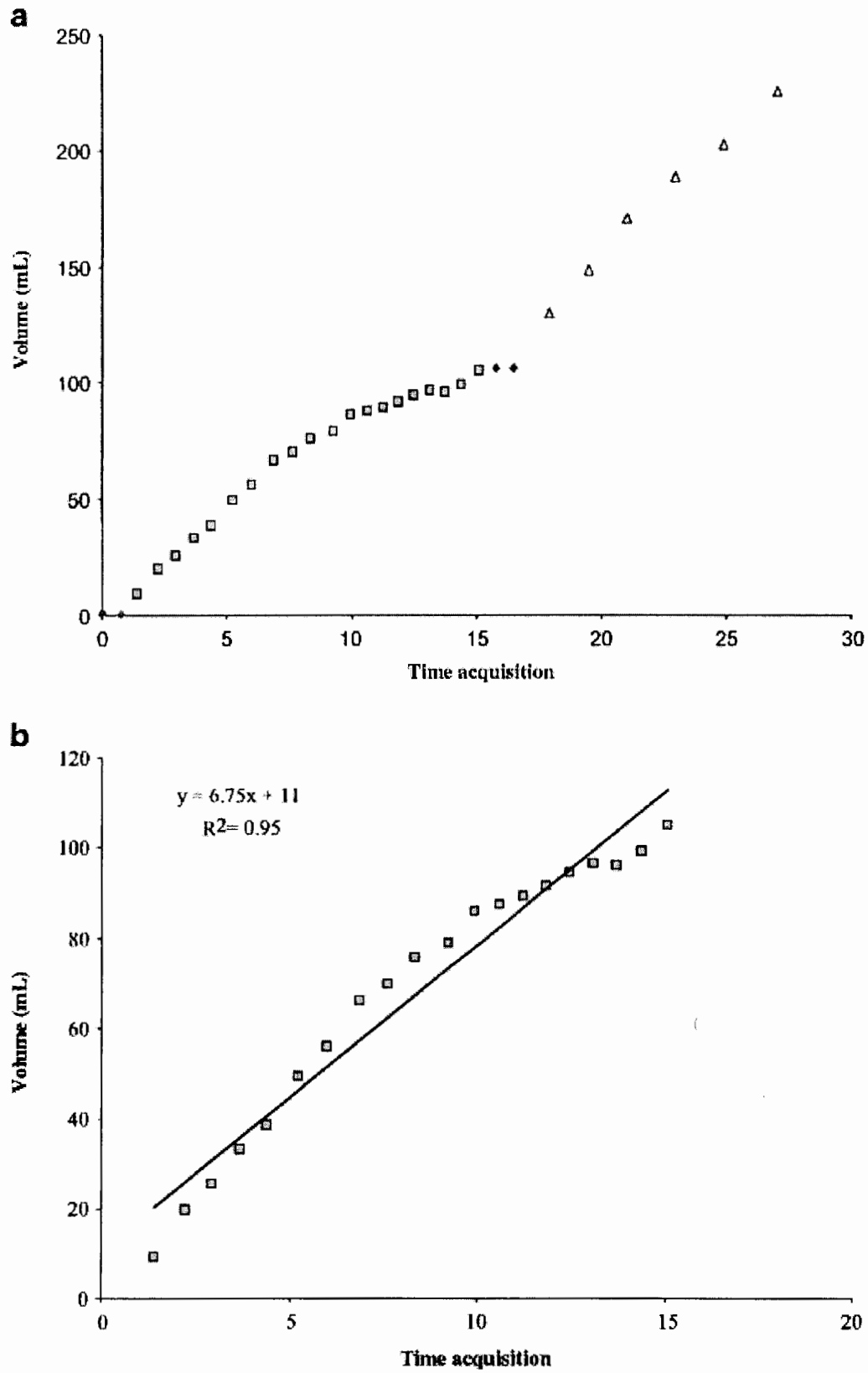


Fig. 2 Same patient as in Fig. 1. **a** Graph shows a linear increase of pancreatic fluid volume during

secretin stimulation. Pancreatic fluid volumes calculated for each dynamic acquisition after secretin administration were plotted against time. The last six points (*open triangles*) are the measurements for calibration procedure as shown in **a** (*filled diamonds*). Points discarded from the analysis. **b** Plot of excreted pancreatic exocrine volumes included between the first detectable excreted volume after secretin administration and the first plateau (*open squares* in **a**). The slope of the linear regression gives a pancreatic flow output of 6.75 ml min^{-1} . The total excreted volume was 92.3 ml

Table 3 Pancreatic flow output and total excreted volume in patient group (group 2) after exclusion of patients with mild post-procedural acute pancreatitis

	Patients with impaired exocrine function ($n=8$)		Patients with preserved exocrine function ($n=9$)	
	PFO (ml/min) mean \pm SD	TEV (ml) mean \pm SD	TEV (ml) mean \pm SD	PFO (ml/min) mean \pm SD
Before treatment	3.5 \pm 1.8	42 \pm 28	8.3 \pm 0.6	108 \pm 13
After treatment	5.6 \pm 2.7	72 \pm 44	8.9 \pm 3.2	113 \pm 37
<i>P</i> value*	0.007	0.006	0.30	0.35

PFO pancreatic flow output, TEV total excreted volume

*Wilcoxon rank test

Data are mean values from both readers

Before PDDP, a reduced PFO (defined as less than the mean level of PFO in normal subjects minus 1 standard deviation: 5.4 ml/min) was found in 10/20 patients; 6/10 presented a pain pattern type A. A plateau phase was observed before and after treatment in one patient and just after treatment in another patient [15% (3/20)]. The mean PFO and the mean TEV were 3.6 ml/min \pm standard deviation: 1.7 ml/min and 41 ml/min \pm standard deviation: 25 ml, respectively. After treatment, excluding the two patients in this group who presented mild post-procedural acute pancreatitis, a statistically significant increase of PFO and TEV was recorded by both readers in eight patients ($P=0.012$ for PFO and TEV). In the remaining ten patients, normal values of PFO ($>5.4 \text{ ml/min}$) were measured before treatment. Among these patients, 5/10 presented a pain pattern type A. In six patients, a plateau phase was found before and after treatment while in two patients the plateau phase was observed only after treatment [70% (14/20)]. The mean PFO and the mean TEV were 8.6 ml/min \pm standard deviation: 1.1 ml/min and 112 ml \pm standard deviation: 16 ml, respectively. After excluding one patient for having mild post-procedural acute pancreatitis, the PFO and TEV did not increase significantly after treatment (Fig. 3) in the nine remaining patients ($P=0.85$ for PFO and $P=1$ for TEV).

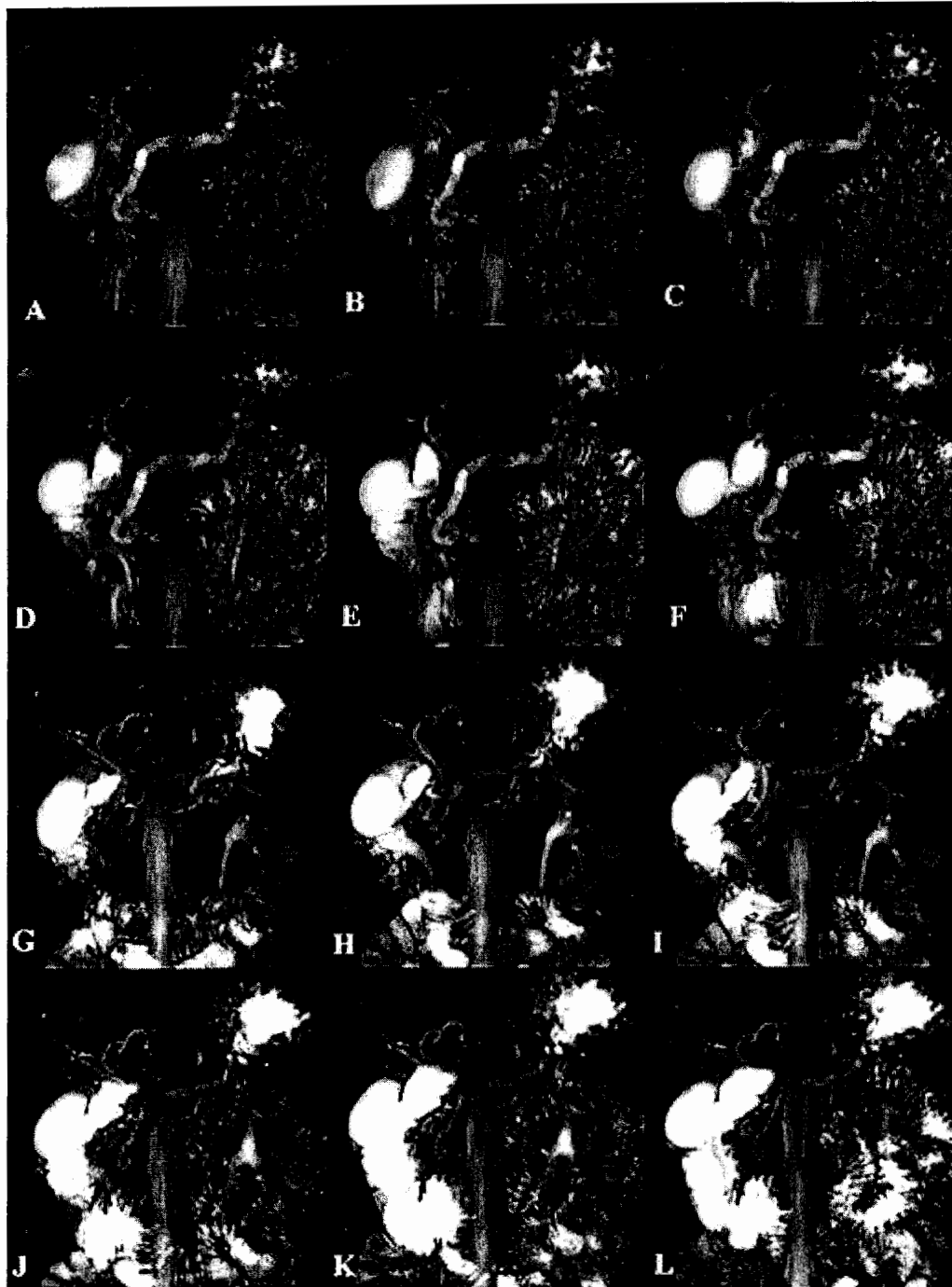


Fig. 3 Coronal maximum intensity projections (MIP) of dynamic S-MRCP ($\infty/850$) obtained before (a-f) and after (g-l) treatment in a 32-year-old woman (patient 16 in Table 1). Images were acquired before (a, g) and, respectively, at 30 s (b, h), 2 min (c, i), 5 min (d, j), 10 min (e, k) and 15 min (f, l) after secretin administration. Images before treatment show a dilated main pancreatic duct with an "ansa pancreatica". After treatment, the diameter of the main pancreatic duct decreased. The pancreatic flow output (total excreted volume) was 7.1 ml/min (111 ml) before treatment and 8.6 ml/min (146 ml) after treatment

Comparing the two pain pattern groups, the morphologic and functional evolution after PDDP was not different. The three patients with mild post-procedural acute pancreatitis showed a decrease in PFO and TEV at the 24-h S-MRCP control. Moreover, in accordance with the results published in a previous study [22], in these three patients, no clinical and biologic side effects due to secretin administration were observed. Interestingly, two of these three patients accepted a follow-up study to be conducted 1 month later, which showed an increase in PFO well above the initial level (Table 4).

Table 4 Pancreatic flow output (millilitres per minute) in patients with mild post-procedural acute pancreatitis^a

Patient no/age(y)/gender ^b	Before treatment	After treatment	After recovery
7/34/M	4.6	2.8	9.6
9/35/M	3.1	1.1	8.3
5/48/M	11.2	6.7	n.d.

^aValues are means of those measured by the two readers

^bNumbers correspond to patients in Table 1

The interval between secretin administration and the beginning of pancreatic fluid volume excretion (range, 30-120 s) and flow duration of excretion (range, 5-15 min) was not statistically different before and after treatment ($P=0.35$ and $P=0.19$, respectively). Changes in mean main pancreatic duct diameter during secretin stimulation are shown in Fig. 4. A statistically significant decrease in main pancreatic duct diameter was observed after treatment ($P<0.05$). However, the variation from baseline to maximum values of main pancreatic duct diameter during secretin stimulation was not statistically different either before or after treatment ($P=0.07$).

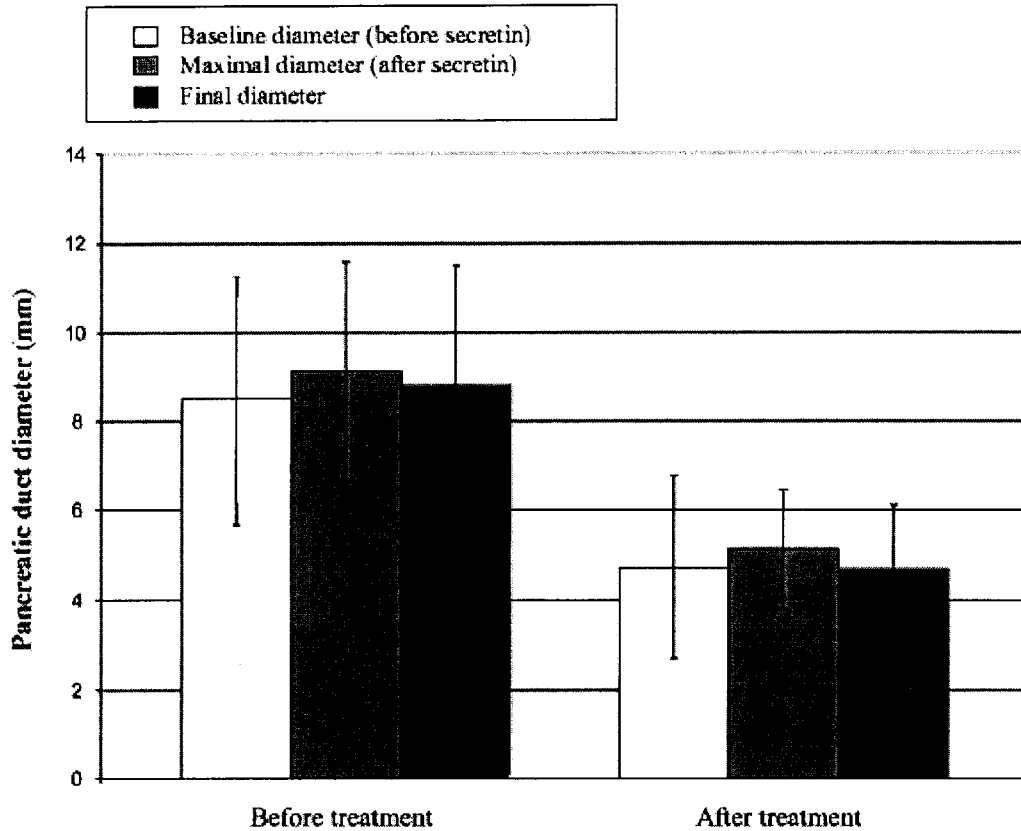


Fig. 4 Mean main pancreatic duct diameters measured before and after treatment during secretin stimulation. Statistically significant decrease of main pancreatic duct diameter was observed after treatment ($P<0.05$) while variation of the main pancreatic duct diameter during secretin stimulation did not differ significantly before and after treatment ($P=0.07$). Data reported are the mean values from both readers' measurements performed in all patients ($n=20$)

Figure 5 shows the inter-observer agreement. Measurement of the PFO from both readers correlated linearly ($R^2=0.88$). The linear regression was given by $x=0.97 y+0.20$ where x and y are the respective readers' measurements for PFO. The mean absolute value of the difference between readers was 0.8 ml/min for PFO and 13 ml for TEV.

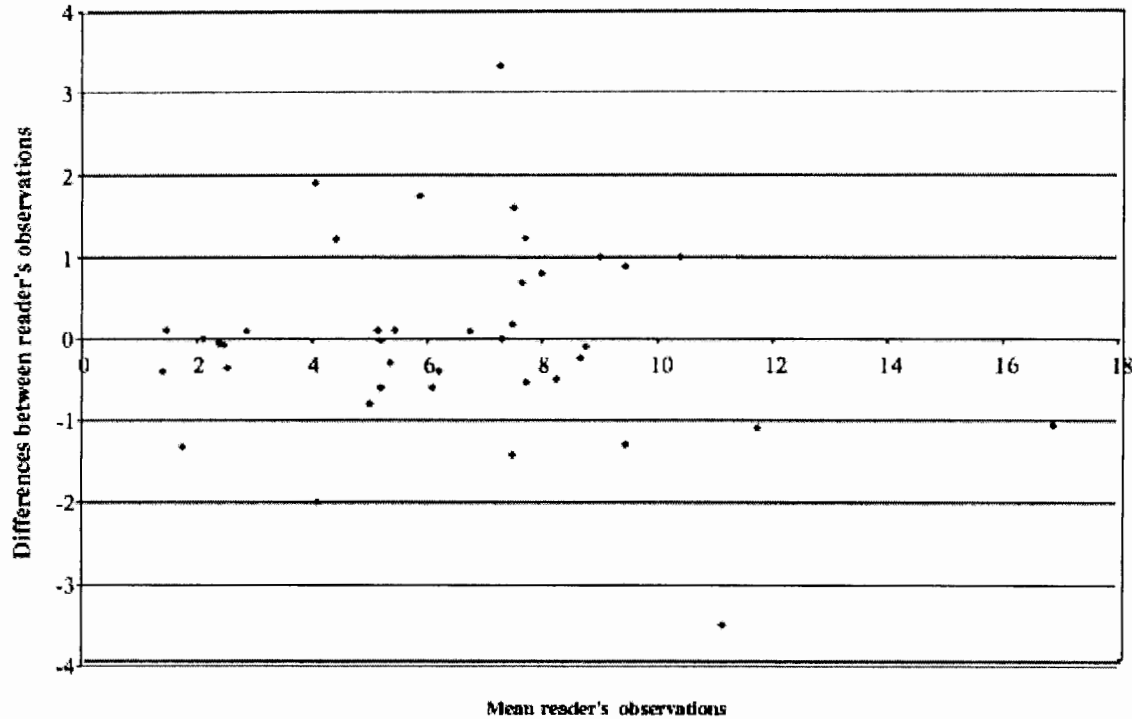


Fig. 5 Bland-Altman scatter plot for pancreatic flow output measurements (millilitres per minute) before and after treatment from both readers

Discussion

Many attempts have been made in the aim to develop a non-invasive, indirect method to evaluate pancreatic exocrine function. Previous studies have suggested the great potential of S-MRCP in such an attempt [11, 12, 15-17]. The present study has demonstrated that S-MRCP allows quantification of pancreatic exocrine secretions during secretin stimulation and, although these initials results were obtained in a limited number of patients, suggests that it could be of major usefulness for diagnosis and follow-up of acute and chronic pancreatitis.

The method used here to quantify pancreatic exocrine secretions using S-MRCP is based on a linear relationship between signal intensity and fluid volume, as it has already been verified by previous published studies [15-17]. During the dynamic S-MRCP acquisitions, peristalsis and variable breath-hold levels may result in fluid repositioning that could lead to fluid loss out of the ROI. Therefore, multi-slice acquisition and a large ROI were designed in order to cover a volume large enough to contain all fluid movement inside the gastrointestinal tract. We verified that the signal intensity in the outer slices did not change either during secretin stimulation or during the last six dynamic acquisitions. In addition, an anti-peristaltic drug was given just before secretin administration.

To derive the volume of pancreatic exocrine secretions following secretin stimulation, we performed an individual calibration procedure based on a linear regression between the known quantities of water administered *per os* and the increased signal intensity. With this individual calibration procedure, the effects on signal intensity of the amplification factors, coil positioning and patient corpulence are neutralised, making comparison between patients independent of these confounding factors. Furthermore, the same ROI was used for both calibration and measurements, which rendered the whole procedure less operator-dependent and avoided the use of a specific reference ROI that would have been more affected by factors such as surface coil distance. The individual internal reference value and the choice of the same ROI for both calibration and measurements constitute the main differences between the present and previous studies as the latter were based either on the calculation of a common external reference value from a group of healthy volunteers [15, 17] or on the choice of a separate ROI for the reference value containing 100% of water and located in the stomach [16]. A possible limitation of our calibration procedure is that it was performed 15 min after the administration of secretin. In some of the investigations, a signal plateau had not been reached by this time, and we cannot therefore assume that the pancreas stopped secreting when calibration measurements were made. Thus, continuing pancreatic exocrine secretions might confound our calibration, leading to possible overestimation of the reference quantity and underestimation of TEV volume. This problem could be overcome by performing the calibration procedure before secretin stimulation. However the fluid filling the stomach would mask the main pancreatic duct, making morphologic assessment difficult on MIP images.

In our series, all the investigated individuals underwent the complete procedure without discomfort or any adverse effect. Under secretin stimulation, the increase of the pancreatic exocrine volumes over time was linear for all subjects, followed by a plateau phase in 30% of the examinations in the control group, in 15% in patients with impaired pancreatic exocrine function and in 70% in patients with preserved pancreatic exocrine function. According to our results, the observation of a plateau phase at the end of the experiment does not correlate to a reduced secretory capacity of the exocrine pancreas [17]. Rather, it may correlate to the achievement of the maximal excretory capacity before the end of the acquisition.

The pancreatic flow output was determined as the slope of the regression line bounded in between the first detectable volume and the maximum volume excreted after secretin stimulation. The choice of these cut-off points was left to the readers and was the major source of inter-observer variability, which, however, remained acceptable (Fig. 5), and the linear regression did not reveal a systematic over-estimation by either reader.

The first purpose of this study was to obtain reference values for PFO and TEV. The intra-individual differences between PFO and TEV obtained for the two S-MRCP sessions showed a good reproducibility of the technique. The results obtained in the control group have not been compared with a gold standard technique, such as intubation procedures with sampling of duodenal juice or PPJ collections after secretin administration. However, the values calculated in this study are in the range of those reported in previous endoscopic studies. Devière et al. [23], using PPJ collections, reported a mean output value of 6.5 ml/min (standard deviation: 1.6 ml/min), and Bozkurt et al. [24], using duodenal juice collections, reported 6.9 ml/min (standard deviation: 1.4 ml/min). Furthermore, Cappelliez et al. [12] observed a correlation between PPJ collection parameters, principally bicarbonate concentration, and different grades of duodenal filling evaluated at S-MRCP in patients with CP.

The second purpose was to assess, using S-MRCP, the short-term effects of PDDP on pancreatic exocrine function in patients with CP. Therapeutic endoscopy and stone fragmentation by ESWL are performed, in CP patients experiencing pain, to obtain duct drainage and clearance in the elective treatment of pain. The rationale of this treatment is that pain is related to pancreatic juice outflow obstruction due to the presence of stones and/or strictures, with subsequent increased duct pressure. Besides the beneficial effect in the management of pain, it seems that drainage procedures could avoid further worsening of pancreatic function [6, 26, 27]. The success of these procedures is evidenced immediately by a decrease of duct diameter and by duct clearance and at long-term by clinical improvement based on partial or complete relief of pain, increase in body weight and improvement of the exocrine function, evaluated in most cases by indirect tests that lack sensitivity. The present study is a pilot that proposes S-MRCP as a non-invasive, reproducible quantification method to quantify short-term effects of PDDP on pancreatic exocrine function. Our results showed an improvement of PFO after PDDP in those patients who had impaired pancreatic exocrine function at S-MRCP before treatment while in patients with a preserved pancreatic exocrine function, PFO did not increase significantly. These results lead to two main conclusions. First, PDDP may also improve impaired pancreatic exocrine function in patients with CP. A long-term follow-up might be helpful to see whether this immediate improvement would be confirmed and if it delays pancreatic exocrine insufficiency. Second, the morphology of the pancreatic ducts does not always correlate with the functional status. In 50% of our patients with CP, pancreatic exocrine function was still preserved at S-MRCP. Furthermore, in these patients, we obtained values for PFO and TEV higher than reference values, with a plateau phase in more than 50% of the examinations. These observations were not related to specific clinical or morphologic findings.

Three patients presented post-procedural acute pancreatitis 24 h after endoscopy. In these patients, we found a transient decrease in PFO and TEV. These observations corroborate the results of both invasive and non-invasive studies, which showed, as we did, transient impairment of exocrine pancreatic function during acute pancreatitis attacks [28, 29]. After treatment, we also observed a significant decrease in main pancreatic duct diameter ($P < 0.05$), confirming that PDDP were successful. However, the variation of the diameter of the main pancreatic duct during secretin stimulation did not statistically significantly differ before and after treatment, possibly because of the loss of elasticity due to the fibrosis of the parenchyma encountered in CP.

In conclusion, this study demonstrated that dynamic multi-slice S-MRCP is a non-invasive test to quantify pancreatic exocrine function. In patients with CP, it allows monitoring of morphologic and functional post-therapeutic changes. The present results need to be confirmed by further follow-up studies designed to assess the long-term functional outcome in these patients. Quantification of pancreatic exocrine output by S-MRCP may also have a role in the functional assessment of acute pancreatitis.

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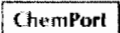


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