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Acute Recurrent Pancreatitis and Dysfunction of the Sphincter of Oddi: Comparison between Invasive and Non-Invasive Techniques

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The sphincter of Oddi (SO) is a structure consisting of smooth muscle fibers which surround the distal common bile duct, the main pancreatic duct and the ampulla of Vater. Its role is to regulate the flow of bile and pancreatic juices into the duodenum as well as to prevent the reflux of the duodenal contents into the pancreato-biliary system [1].
The abnormalities of SO contractility (sphincter of Oddi dysfunction: SOD) may be related to either the biliary or the pancreatic segments of the sphincter, or both [2]. On the basis of anatomic or functional abnormalities, two types of SOD have been postulated. SO stenosis is a chronic inflammatory process secondary probably to biliary lithiasis or microlithiasis which becomes a fibrosis with consequent narrowing of a part or the entire sphincter [2, 3]. SO dyskinesia is a functional alteration of the physiological motility of the sphincter which causes some delay in the passage of biliary or pancreatic juices into the duodenum [2, 3, 4].
Distinct clinical syndromes relating to specific sphincter segments may be recognized. Recurrent episodes of acute pancreatitis are a possible clinical expression of the alteration of the pancreatic portion of the SO [5].
The diagnosis of SOD may be difficult because the clinical symptoms may not correlate temporally with the demonstrated abnormalities of SO motility; in particular, the assessment of SO motor activity is limited to a brief period and may not document the presence of a motor disorder which may be intermittent [6]. A mixed classification, based on clinical data, laboratory tests and instrumental findings, has been proposed and has been introduced: "*definitive"* SOD diagnosis (SOD Type I, all parameters pathologic), "*probable"* (SOD Type II, presence of typical clinical symptoms associated with abnormal laboratory tests or instrumental investigation) or "*possible"* (SOD Type III, only typical clinical symptoms) (Milwaukee Biliary Group classification for biliary SOD and later classification of pancreatic SOD by Sherman *et al*.) [4, 7].
In the last decade, some interesting non-invasive procedures have been proposed to study SOD. Those commonly available to diagnose SOD are: 1) direct investigation of sphincter motility - SO manometry -, 2) indirect assessment of the normal function of the sphincter - endoscopic retrograde cholangio-pancreatography (ERCP), ultrasound-secretin test (US-S test), magnetic resonance (MR) under stimulation of secretin, endoscopic ultrasound-secretin test (EUS-S test), and hepato-biliary scintigraphy (HBS) - and 3) detection of anatomic alterations of the sphincter - ERCP, ultrasound (US), MR, and computed tomography (CT) scan -. These procedures are, for the most part, safe, but, unfortunately, the most sensitive are invasive and associated with complications (e.g. SO manometry and ERCP).
The clinical challenge is the identification of the correct instrumental procedures to be performed on patients with suspected SOD on the basis of clinical data and laboratory tests findings in order to avoid post-procedure

complications and unnecessary instrumental procedures.

Sphincter of Oddi Manometry

SO manometry is performed endoscopically through cannulation of the papilla of Vater with a standard triple lumen side-hole catheter perfused with distilled water at a constant flow. The water pressure is transmitted continuously to external transducers connected to a computerized recording system [8].
Normal activity of the sphincter is characterized by a basal pressure (up to 30-40 mmHg) with the presence of phasic contractions of high amplitude (up to 200-300 mmHg) and low frequency (up to 7/min). The propagation of these contractions is anterograde (toward SO), but, physiologically, we may observe a certain amount of retrograde propagation (up to 30%) [8].
Manometric abnormalities related to SOD include an increase of basal pressures (>40 mmHg), an increase of the amplitude (>240 mmHg) or frequency (>10/min) of the phasic contractions, a high incidence of retrograde propagation (>50%) and a paradoxical (excitatory) response to cholecystokinin or cerulein [2, 5, 8].
Several problems occur with this procedure. First of all, SO manometry is quite expensive and can be performed only in specialized hospital centers.
Secondly, there are many technical problems involved. A satisfactory examination may be achieved in only a part of the patients (50 to 87%) [9, 10, 11, 12]. Very little data are available on normal manometric values, because few authors have studied normal volunteers and the number of control subjects in these studies is very low. Some drugs, such as sedatives or gabexate (used in Italy for the prevention of post-procedure pancreatitis), used in the preparation of the patients may interfere with the manometric behavior of the sphincter [13]. The cannulation of the papilla with a relatively large tube and the low-pressure water perfusion modify the SO motility, so that the procedure probably does not reproduce a physiological condition.
Thirdly, interpretation of the data is not completely standardized. Criteria for the interpretation of the SO tracing are codified, but probably still remain an unsatisfactory inter-observer variability [8].
Finally, the incidence of complications, namely post-procedure acute pancreatitis, is higher than that observed after other endoscopic procedures on the papilla of Vater, ranging from 9 to 33% [14, 15, 16, 17, 18]. In patients with stenosis, the incidence is even higher.
However, SO manometry is still the gold standard for the diagnosis of SOD and manometric findings may predict the response to therapy. It can be postulated that SO manometry may indicate a positive clinical outcome for patients suffering from SOD, because it has been shown that basal pressure may be a good parameter in order to identify patients who will be asymptomatic after endoscopic sphincterotomy.

Ultrasonography-Secretin Test (US-S Test)

The pancreas and the biliary tract have secretory functions that permit dynamic imaging. The US-S test is a functional instrumental procedure which was introduced in the 80s [19] and indirectly explores the function of SO.
This test, using trans-abdominal ultrasonography, measures the diameter of the main pancreatic duct at the level of the body under i.v. stimulation with secretin, a hormone that physiologically elicits water-bicarbonate secretion from the pancreatic duct cells [19, 20]. In healthy subjects rapid administration of pharmacological doses of secretin leads to a secretory peak approximately 4 minutes after the stimulus [19, 20] and, at roughly the same time (3 minutes), manometric studies have shown an increase in the amplitude and frequency of SO waves (early excitatory effect of secretin) [21]. Later, after 6 minutes, using manometry, we observe a reduction of SO activity. Within 10 minutes, the diameter of the main

pancreatic duct, measured using ultrasonography, returned to its baseline value [19, 20].
The increase in the diameter of the main pancreatic duct, after the infusion of secretin, is probably due to the pancreatic juice secretion in the ductal system during the early excitatory state of the SO. After relaxation of the sphincter, the pancreatic juice flows into the duodenum, and the diameter returns to its baseline value within a few minutes.
This test explores the presence of the alteration of the SO function. If the sphincter does not function correctly, the test results indicate a pathologic condition, with a persistent dilatation of the main pancreatic duct for more than 20 minutes [20]. This has been demonstrated, for example, in patients suffering from acute recurrent pancreatitis [20]. Di Francesco *et al*. recently demonstrated that US-S test is reliable compared to SO manometry [10] and, therefore, the US-S test may offer a valid alternative to the more expensive and invasive manometric procedure in the assessment of SOD in patients with recurrent acute pancreatitis.
The US-S test is inexpensive, non-invasive, reproducible and also reliable when performed in non-specialized centers. However, it is necessary for the operator to spend time (at least 60 minutes) to follow the dynamics of the emptying of the duct of Wirsung after secretin infusion. Furthermore, the pancreas may be visualized by trans-abdominal ultrasonography in only 70-90% of the control subjects and the main pancreatic duct is measurable in only 55-90% of cases [22, 23, 24] because of interference from bowel gas, the pancreas being localized in the retroperitoneum.

Endoscopic Ultrasonography-Secretin Test (EUS-S Test)

The endoscopic ultrasonography secretin test is performed by measuring the main pancreatic duct using endoscopic ultrasound before secretin infusion and then every minute for 15 minutes after secretin infusion at dose of 1 IU/kg [24]. The main parameters evaluated are: a) the basal diameter of the main pancreatic duct, b) its maximum dilatation after secretin infusion and c) the diameter at 15 minutes. In control patients, the dynamics are similar to those observed during the US-S test, namely, there is a dilatation of the duct in the first 2-3 minutes after secretin infusion which returns to its baseline value within 15 minutes.
Catalano *et al*. [25] proposed the EUS-S test as a useful procedure in the diagnosis of SOD. Twenty patients with suspected SOD underwent a EUS-S test before SO manometry. Thirteen patients had normal SO manometry and 7 abnormal. Twelve of the 13 patients with normal SO manometry had a normal EUS-S test (92%) and only one (8%) abnormal. In 3 patients with SO manometry which demonstrated pancreatic SOD, EUS identified all patients whereas in the 4 patients with biliary SOD, the EUS-S test indicated a pathology in 1 patient (25%) and was normal in 3 (75%).
The authors found the following advantages with respect to the US-S test: 1) no technical impediment from bowel gas, 2) accurate morphological information so as to exclude the presence of pancreatic inflammatory or neoplastic disease, 3) a more accurate assessment of the main pancreatic duct and its variation under secretin stimulation and 4) the possibility of predicting which patients will respond clinically to pancreatic sphincterotomy.
Therefore, the EUS-S test seems to be specific and sensitive to pancreatic SOD whereas in patients with involvement of the biliary side of the SO, the sensitivity is quite low.
The EUS-S test is certainly more accurate than the US-S test and may be performed on all patients. However, it is invasive, probably reliable only in specialized centers, time consuming and expensive. Further studies is needed in order to define the sensitivity and the specificity of the test but we believe that it should be performed only on selected patients.

MR-Pancreatography after Secretin Stimulation

Magnetic resonance cholangio-pancreatography is a non-invasive technique for the visualization of the morphologic features of the biliary and pancreatic ducts [26]. Its high correlation with ERCP images has been demonstrated and MR has been proposed as an alternative to diagnostic ERCP [27, 28, 29, 30]. Recently, the utilization of secretin stimulation has been proposed in order to better visualize the pancreatic and biliary ductal system, and to quantitatively estimate the exocrine pancreatic secretion on the basis of duodenal filling. In control subjects, we may observe dynamics of pancreatic emptying very similar to those observed in other procedures involving secretin stimulation. The baseline diameter of the main pancreatic duct is 2 mm (less than 3 mm in all subjects) and after secretin i.v. infusion, it increases to maximum value in 2 minutes (3 mm) and returns to baseline value within 15 minutes. The duodenal filling was normal in all these control subjects. In patients with papillary stenosis, the main pancreatic duct did not return to baseline value after 15 minutes.

MR pancreatography with secretin stimulation allows a better visualization of the pancreatic duct system and may provide information regarding the morphology of the pancreatic gland in order to carry out a diagnosis of the "organic" cause of pancreatitis, visualization of the duct of Santorini which may permit a diagnosis of a "dominant dorsal pancreatic duct syndrome", the dynamics of the emptying of the main pancreatic duct and the functional status of the exocrine pancreas by duodenal filling.

This procedure has an acceptable sensitivity and a good specificity, gives both functional and morphologic data, is non-invasive. However, presently only few centers are capable of performing it and it is quite expensive.

Hepato-Biliary Scintigraphy (HBS)

Dynamic hepato-biliary scintigraphy may be used to indirectly evaluate the SO function [2, 5]. SO tone regulates the bile delivery into the duodenum. SOD may alter this function and determine a partial obstruction of the SO with a delay of biliary emptying.

HBS is performed with i.v. ^{99m}Tc-DISIDA and gives quantitative and qualitative information by measuring the time of the radio-nucleotide emptying from the liver and the biliary tract [31, 32]. The main parameters used in the diagnosis of SOD are: a) the time in minutes between basal value and maximum radioactivity count in the region of interest (liver, hilar, extrahepatic biliary tract), b) percentage of biliary emptying at 45 minutes, that is the ratio between the maximum count of the region of interest and the count in the same area after 45 minutes and c) the percentage of biliary emptying at 60 minutes [31, 32]. The first two parameters, measured at the hilar region, are the most useful criteria for differentiating the normal population from patients suffering from SOD [33].

HBS may be more sensitive in patients with an organic (stenosis) alteration of the SO [2, 5], whereas it may be less sensitive in functional disorders of the sphincter [34]. Some authors proposed functional stimuli, such as cholecystokinin [28] and morphine [35], to increase the sensitivity of the test by accentuating the differences in bile flow between the normal controls and the patients. A scintigraphic score system which involves many parameters (e.g. time of peak liver activity, time of first visualization of the intra-hepatic biliary tree and common bile duct emptying) has been proposed with a high sensitivity and specificity [28].

HBS has a good sensitivity for biliary SOD Type I, whereas in biliary SOD Types II and III, it is less sensitive. However, HBS mainly explores the biliary side of the functionality of SO and perhaps, indirectly, the pancreatic side. Therefore, this test may sometimes be

employed in selected patients suffering from pancreatic SOD when we suspect an involvement of the common sphincter. This procedure is time consuming, reliable even in non-specialized centers, non-invasive and reproducible.

Endoscopic Retrograde Cholangio-Pancreatography (ERCP)

The radiological features observed during ERCP give important information which can be used to exclude organic causes for recurrent upper abdominal pain. Some biliary parameters which can be measured in this exam, such as the diameter of the common bile duct which should not exceed 12 mm and the delayed emptying time of the contrast medium from the bile (>45 min), may suggest a diagnosis of biliary SOD [2, 5]. The diameter of the main pancreatic duct (normally not greater than 5 mm) and the delayed emptying of the contrast medium from the main pancreatic duct (>10 min) may indicate a pancreatic SOD [2, 5].
ERCP is an excellent investigative tool which gives accurate images of both the biliary and the pancreatic ducts, and identifies the "structural" causes of recurrent pancreatitis. However, this procedure is poorly standardized because the amount of contrast medium injected is variable, and, as in manometry, both the sedative utilized and gabexate, may modify the result [13]. Moreover, trauma of the papilla of Vater may cause edema of the SO with a secondary delay of biliary/pancreatic emptying. ERCP is the most invasive procedure in the diagnosis of pancreatic diseases having an incidence of post-ERCP pancreatitis ranging from 5 to 10% [36, 37].

Provocative Test (Nardi Test)

Some provocative tests have been proposed for the diagnosis of SOD. The most well-known is the morphine-prostigmine provocation test (Nardi test) [38]. This test is performed using an intramuscular injection of morphine (10 mg) and neostigmine (1 mg) which may induce a spasm of the SO with stimulation of exocrine pancreatic secretion, and, consequently, reproduce the typical pain (biliary or pancreatic) found in patients suffering from SOD. The test is considered positive in the presence of pain and/or an increase of pancreatic or hepatic enzymes.
The test is cheap and easy to perform but has a low sensitivity and specificity. It has been suggested that it may predict which patients will respond to sphincterotomy or septectomy [31].
Recently, a combination of scintigraphy and stimulation with morphine (0.04 mg/kg) has been proposed to identify patients with a high SO pressure [35]. When this parameter is high, it correlates with a good clinical response to sphincterotomy, and the authors have proposed this test to avoid SO manometry and its complications in these patients.
The low specificity of the Nardi test limits its use in clinical practice and it is not frequently used as an initial level test in patients suffering from recurrent pancreatic type pain with a suspected SOD.

What Should Be Done with Patients Having Pancreatic SOD?

There are principally two goals in the diagnosis of pancreatic SOD. The first is to suggest the instrumental tools and the algorithm, if any, needed to achieve the diagnosis and the second is to carry out the instrumental, clinical or bio-humoral criteria that identify which patients should be treated pharmacologically (hormones, calcium channel blockers, nitrates, toxin botulinum), endoscopically (sphincterotomy and/or stenting) or surgically (sphincteroplasty).
The only method that may directly detect pancreatic SOD is SO manometry. However, it is invasive, difficult to perform and interpret, and is available in only a few specialized centers.
We therefore think that the first step in studying patients suffering from recurrent abdominal pain should be a careful clinical evaluation of the pain (pancreatic type) and

the serum dosage of pancreatic enzymes. Using these parameters, we should exclude the presence of a) chronic pancreatitis, b) the more common causes of acute recurrent pancreatitis such as biliary lithiasis or microlithiasis and genetic mutations (CFTR, SPINK, cationic trypsinogen) and c) pancreatic or biliary tumors. In particular, abnormal liver function tests may indicate a possible cause of the recurrent attack of pancreatitis or a concomitant biliary pathology. In the absence of these pathologies, the diagnosis may tend towards SOD Type I (definitive) or Types II and III (probable or possible).

A second step is to consider the role of the gallbladder and to evaluate the abdominal symptoms before and after cholecystectomy. SOD may be present in patients with an intact biliary tree, but its incidence is much higher in patients who underwent cholecystectomy. In these patients, the finding of a dilated biliary or pancreatic duct favors a diagnosis of SOD Type I. These patients are the most responsive to endoscopic treatment.

If these steps are negative, we must investigate the SO function more carefully, with even more invasive techniques. Our recommendation is to send these patients to a specialized center, considering the difficulty of arriving at a diagnosis of SOD and the complications associated with the more invasive procedures needed. In particular, ERCP and SO manometry should be performed by experienced endoscopists.

It is difficult to devise an algorithm for these patients. Every case should be carefully evaluated, as well as the cost, safety, sensitivity and specificity of each procedure.

One or more tests with secretin stimulation should be used in these patients as a first-choice examination. MR pancreatography gives more morphological and functional information and should probably be the first test. The US-S test is a valid alternative, and if the morphological pancreatic aspect has been studied by other instrumental tools (e.g. CT or ERCP), it should be used first because it represents a safer and cheaper approach to the functional problems of the SO. The EUS-S test, like MR pancreatography, gives morphological and functional information, but it is not standardized, poorly documented, quite expensive and available in only specialized centers. Like HBS, it may be used only in selected patients who have a low sensitivity for pancreatic SOD.

ERCP is indicated in the presence of documented episodes of pancreatitis whereas it may not be as necessary in patients where the disease is only suspected.

SO manometry is the most sensitive test for patients suffering from SOD, but it is available in only very few centers; it is the most invasive and is associated with a high incidence of pancreatitis. However, it is justified on the basis of the clinical history and provides useful information in identifying those patients who may benefit from treatment, especially in identifying those patients with SOD Types II and III (elevated basal pressure of the SO) who will benefit from endoscopic sphincterotomy. Its role is less important in SOD Type I, where it is not indicated.

Finally, provocative tests may be used, but their clinical utility is very limited.

In conclusion, the diagnosis of pancreatic SOD is quite difficult and requires a lot of instrumental investigation which may be invasive and associated with pancreatic complications. Patients, particularly those with suspected SOD type II or III, should be sent to a specialized center. Few comparative studies are present in the literature and we need additional studies in order to better understand which procedures we should use to safely make a correct diagnosis of SOD.

Keywords Diagnosis; Manometry; Oddi's Sphincter; Pancreatitis, Acute Necrotizing; Secretin (diagnostic use)

Abbreviations CT: computed tomography; ERCP: endoscopic retrograde cholangio-pancreatography; EUS: endoscopic ultrasound; EUS-S test: endoscopic ultrasound secretin test; HBS: hepato-biliary scintigraphy; MR: magnetic resonance; SO:

sphincter of Oddi; SOD: sphincter of Oddi dysfunction; US: ultrasound; US-S test: ultrasound-secretin test

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