

ON THE PROBLEM OF PANCREATIC FUNCTIONAL PATHOLOGY

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Frequency of functional pathology of the gastrointestinal tract has increased in recent years in Ukraine and in the world [3, 8]. This group of diseases is of particular interest for scientists as patients have non-specific picture of the disease, and diagnostics is largely quite subjective. Functional disorders of the gastrointestinal tract often occur on the background of other organic diseases, which significantly complicates diagnostics and treatment of such patients. Despite the advances of modern medicine, diagnostics and treatment of pancreatic diseases is a serious medical and social problem [2, 6, 11]. This is due to the nonspecific symptoms of pancreatic lesion, there are no simple, reliable diagnostic methods to identify such lesions, the complexity of combined therapy of these patients. There has recently been a tendency of increasing inflammatory pancreatic diseases and neoplasms, increased morbidity and mortality, so the problem of diagnosing and treating the functional pancreatic lesions as the basis of formation of inflammatory changes may allow in some cases to prevent the occurrence of pancreatitis. At the same time, functional lesions of the pancreas is one of the least studied problems of modern clinical pancreatology [5, 8].

Functional pancreatic disorder (FPD) is the state, accompanied by changes in pancreatic secretion in the absence of morphological changes in the pancreas. They can be characterized by an increase in the exocrine pancreatic function with increased secretion of bicarbonate and enzymes synthesis RV — "hyperpancreatism", reduced secretory activity of the pancreas — "hypopancreatism". But the pancreas produces a variety of enzymes, and in most cases there is a violation of production of certain enzymes with normal or elevated levels of others, that has been called

"dyspancreatism". This term is suggested in 1932 by M. M. Gubergrits [2], and so far it describes changes of the pancreas in FPD in the best way.

Exocrine pancreatic secretory activity is associated with many factors. Its secretion depends on the composition and amount of food, it is regulated by the autonomic nervous system, cyclical intestinal motility and biliary tract. Activity on exocrine pancreatic function is affected by the hormones (insulin, calcitonin, thyroid hormones), regulatory peptides (secretin, pancreozymin, cholecystokinin, bombesin, P substance, vasoactive interstitial peptide), catecholamines (histamine, serotonin), prostaglandin, bile acids, et al. [2, 9]. When you receive food in the duodenum, postprandial (food) phase of secretion of the pancreas begins in 20-30 minutes and lasts for 3-4 hours. The level of enzymes and bicarbonate of pancreatic juice normally correlates with the amount, energy intake and composition of food bolus. It is noted that energy intake of food largely determines the secretory activity of the pancreas. J. Keller et al. (2005) [10] investigated pancreatic secretion in healthy volunteers, when assigning different caloric diets, and found that upon a diet of 20, 30, or 40 kcal/kg of body weight maximum enzymatic synthesis was observed during calorie diet 20 kcal/kg (1500 kcal per day or 500 kcal per meal in healthy male weighing 75 kg). Thus, the excess energy intake does not lead to additional stimulation of the secretory activity of the pancreas [10]. Given that the energy consumption of the adult healthy person with average physical activity accounts for 2950-3300 kcal for men and 2550-2600 kcal for women, the pancreas at high-calorie diet can increase its exocrine activity only to a certain extent. Diet also plays an important role in the regulation of exocrine pancreatic activity. In addition to the frequency of food intake, speed of food, at which it enters the digestive tract, is important enough. M. Katschinski et al. (1992) [9] indicate that the maximal rate of arrival of food in the duodenum sufficient for its fermentation must not exceed 1,5-2,67 kcal/min, otherwise the level of secretion of the pancreas is not able to respond adequately to the food intake. This hypopancretism will manifest itself with a liquid stool, bloating, flatulence and other clinical signs of pancreatic insufficiency. For many people, both excessive food energy intake, and the increased speed of its

receipt by the duodenum contribute to the imbalance of exocrine pancreatic function. Widespread American-style food, "fast food", dry-food are one of the factors leading to the growth of the pancreatic pathology among the population. This makes the problem of FPD diagnostics disorders particularly acute.

For the diagnostics of FPD load food tests can be used, which are conducted by the doctor, but more often they are unconsciously used by the patients themselves. A detailed medical history, specifying the nature of the food load, leading to manifestations of dyspancreatism can help in the diagnostics of lesions of the pancreas. To investigate the adequacy of the synthesis of certain enzymes of the pancreas, doctor uses stress tests diet rich in protein, fats, carbohydrates. These tests must be carried out under the supervision of a physician, preferably accompanied by the study of enzyme activity in pancreatic secret.

FPD often occur in patients with diseases of other parts of the digestive tract, as hyper- and hypopancreatism with increased or decreased enzyme synthesis, levels and activity are most commonly associated with the modification of a stimulating effect on the pancreas, resulting in organic diseases of the digestive system. In patients with peptic duodenal ulcer, increased gastric secretion we marked increase in the synthesis of bicarbonates due to significant secretin stimulation. Upon liver cirrhosis and the early stages of primary sclerosing cholangitis due to the stimulatory activity of bile acids, hyperpancreatic manifestations are also possible, whereas in the advanced stage of cholestatic liver disease secondary (hepatogenic) exocrine pancreatic insufficiency is being developed due to lower activation of lipase bile acids [11]. At the same time, in patients with gastritis A the functional activity of pancreas secretion with its amount reduction is observed, with the low enzyme and bicarbonates levels therein. Prolonged low secretin stimulation of the pancreas leads to further organic pancreatic changes — "gastrogenous" pancreatitis [3]. In addition, modification of the activity of the pancreas can be induced not only by diseases of the gastrointestinal tract. Upon thyrotoxicosis, Cushing's disease can be observed hyperpancreatic manifestations can be detected, whereas diabetes, food allergies cause hypopancreatism [1, 2, 6, 12].

An increase or decrease in the activity of the pancreas may be drug-induced, especially if the drug is used for a long time. Drugs that inhibit gastric secretion have an indirect inhibitory effect on pancreatic exocrine activity, as they not only block the synthesis of hydrochloric acid, but also reduce the level of secretin, cholecystokinin-pancreozymin, which leads to a decrease in the stimulation of the pancreas. This mechanism of action of proton pump blockers is used successfully in treating certain forms of pancreatitis. Anticholinergics and blockers of H₂-histamine receptors reduce the external secretion of the pancreas directly and indirectly [11]. Appointment of drugs of bile acids, cholergics has a stimulating effect on the pancreas and can lead to hyperpancreatism. At the same time, preparations of 5-aminosalicylic acid, sulfasalazine, some antibiotics (tetracyclines), corticosteroids, metronidazole can induce hyperactivity of the pancreas and sometimes lead to the development of acute pancreatitis [11]. Macrolides, particularly erythromycin, having prokinetic effect, contribute to the increasing tone of Oddi's sphincter. With more or less prolonged use of erythromycin dysfunction of Oddi's sphincter develops, including its pancreatic variant [9, 11].

Clinically hyperpancreatism practically does not manifest itself and is diagnosed with increasing duration of postprandial pancreatic secretion, especially its intestinal phase, an increase in the amount of bicarbonates and enzymes in pancreatic secretion. Given the increased level of enzymes in the lumen of the duodenum, there may be their slight increase by endosecretion mechanism [4], while the content of elastase, chymotrypsin in feces is within normal limits.

The levels and activity of certain enzymes of the pancreas can be investigated using breath tests. Triglyceride breath test allows to determine the lipase activity in the lumen of the duodenum, protein — trypsin, corn-starch (amylase) test measures the activity of amylase. In patients with FPD these tests may reflect the insufficiency of some enzymes, although there are also false positive results [6].

Direct manometry of Oddi's sphincter is also used abroad, which is a rather complicated invasive test, but it gives more information on the functional capacity of the output sphincter of biliary tract (see below). Retrograde

cholangiopancreatography application is not always justified because of the complexity of the method and the risk of developing side effects, although this study is informative enough for the differential diagnostics of biliary dyskinesia with dyspancreatism and obstructive lesions of the biliary tract.

FPD with dyspancreatism may be clinically manifested by diarrhea alternating with episodes of a normal stool, while not only the frequency, but a stool consistency plays an important role in FPD diagnostics. With a slight decrease in the level of enzymes, on the background of the food load and normal bowel, stool frequency may not be changed, only its consistency changes. The stool may be pasty, semisolid, containing a small amount of undigested muscle fibers, neutral fat. Fat excretion in feces increases somewhat, but it is not necessary to expect true steatorrhea, as it appears only after the loss of 90% of exocrine pancreatic function. There are symptoms associated with increased flatulence: bloating, rumbling, feeling of transfusion, symptom of "air column". At the same time, these symptoms pass by and their relationship with violations of the regime and diet can be noted. Pain syndrome upon isolated dyspancreatism is variable enough. The pain may be localized in the epigastrium and right upper quadrant, around the abdomen, along the large intestine. Most often the pain is not sharp, aching, sometimes arching. Not always it is possible to determine pain's relationship with food intake over time, but the relationship with the character of eating, excessive abuse of fat or protein diet usually gives you the opportunity to suspect FPD. Food errors may cause nausea, accompanied by a decrease in appetite.

Not only study of the enzyme levels in the blood and pancreatic secret on the background of load tests, but also ultrasound of the pancreas confirms isolated FPD with dyspancreatism. One of the ultrasonic diagnostic criteria may be areas of echogenicity changes in the pancreas without changed structure. But the interpretation of these changes as FPD symptom is controversial, i.e. functional disorders of the digestive system, strictly speaking, are not accompanied by any organic changes [8]. In many patients of gastrointestinal profile abdominal ultrasound reveals diffuse induration of the pancreas without clinical symptoms of its lesion.

This may be one reason for overdiagnostics of chronic pancreatitis. At the same time, a local change in echogenicity of the pancreas may be indicative of FPD.

Very often functional lesions of the pancreas are combined with biliary dyskinesia and sphincter dysfunction. These patients usually have marked manifestations of dyspancreatism with alternating episodes of hyper- and hypopancreatism and inadequate or untimely receipt of enzymes and bicarbonates of pancreatic secretion in the duodenum. Clinically, these patients are characterized by pain that lasts for 30 minutes or more with painless "light" intervals. The pain is localized in the epigastrium or the right, left hypochondrium, very rarely has a belting character. In addition, clinical symptoms such as bloating, rumbling bowel, diarrhea may occur in patients with functional bowel disorders, especially irritable bowel syndrome. The use of standards for diagnostics of irritable bowel syndrome — Rome criteria III — not always excludes hypopancreatism, the more that these functional disorders of the digestive system are often combined.

Given the close relationship of FPD with pathogenic variant of Oddi's sphincter dysfunction, the physician should use Rome III criteria in the diagnostics of this dysfunction. Hypertonic disorders of Oddi's sphincter in pancreatic segment are divided into three types [8]:

- 1st type — **definitive** — patients with idiopathic recurrent pancreatitis and/or typical pancreatic pain upon increased activity of amylase/lipase in 2 times above the norm and more, enlarged pancreatic duct (more than 5 mm), and increased time of secret flow to pancreatic duct in duodenum more than 10 minutes;
- 2nd type — **presumptive** — patients have typical pancreatic pain and one or two criteria of the first type;
- 3rd type — **possible** — patients with pancreatic pain, but without objective signs common for first type (Wirsung's dyskinesia).

Patients with a first type of Oddi's sphincter dysfunction have structural disorders of the sphincter itself or duodenal papilla (e.g., stenosing papillitis), patients with the second and third types have functional disorders of Oddi's sphincter. In the

case of the first type of Oddi's sphincter dysfunction decision on the tactics of treatment must follow the algorithm (Fig. 1) [8].

"Gold standard" of diagnostic of Oddi's sphincter dysfunction is its endoscopic manometry (Fig. 2a, b).

The criteria for diagnostics are [8]:

- increase in basal pressure of sphincters, comprising Oddi's sphincter, above 40 mm. Hg.;
- peak pressure of phase waves above 240 mm. Hg.;
- increasing frequency of phasic contraction more than 10 per minute (tachyoddia);
- the absence of Oddi's sphincter relaxation after introduction of cholecystokinin (paradoxical response);
- increase in the incidence of retrograde contractions more than 50% of all contractions.

Provocative tests of Debrey (morphine and choleretic introduction) and Nardi (morphine and neostigmine introduction), biliary scintigraphy (Fig. 3) are used for the diagnostics Oddi's sphincter dysfunction [7].

Like other functional diseases of gastrointestinal tract, FPD is diagnosed by exclusion of more formidable inflammatory lesions. The presence of such "warning signs" as leukocytosis, neutrophilia, elevated erythrocyte sedimentation rate indicates the presence of an inflammatory process, rather than a functional failure. To confirm biliary dyskinesia we use dynamic, repeated ultrasound on the background of the test meal with the study of kinetic activity and contractility of the gallbladder and biliary tract. We also use provocative tests with fatty food (cholecystokinin test), secretin test, which allow to examine dilatation and diameter of biliary tract and sphincters. When conducting secretin test after intravenous administration of 1 mg/kg body weight secretin, duodenal contents are aspirated and bicarbonates level therein is studied. In patients with FPD bicarbonate level after the secretin test is 50-75 meq/l. Lower rates are detected in CP — upon the loss of 60% of the secretory function of the pancreas.

Functional lesions of the pancreas can be divided into several groups:

1. FPD without comorbidities.
2. FPD with comorbidities:
 - a) FPD combined with other gastrointestinal diseases;
 - b) FPD combined with non-gastroenterological pathology.
3. FPD on the background of taking drugs.
4. By the nature of changes in the enzymatic status of the pancreas:
 - a) with hyperpancreatism;
 - b) with hypopancreatism;
 - c) with dyspancreatism.

This division is rather conditional, and FPD can change the nature of the flow, but it helps to clarify the pathogenesis of FPD and choose individual therapy.

Thus, clarifying the nature of the functional lesions of the pancreas and other parts of digestive tract is a fairly complex diagnostic problem.

Diagnostic algorithm of patients with FPD should include a thorough collection of complaints and anamnesis, general analysis of blood and urine, level of blood sugar, blood biochemical analysis with definition of enzymatic spectrum, re-scotscopy, abdominal ultrasound with a dynamic study of the pancreas, biliary tract. It is advisable to conduct load tests of food, secretin test with the study of levels of enzymes and bicarbonates pancreatic secretion, study of elastase-1 in feces, if possible — conducting breath tests. Clinical, laboratory and instrumental diagnostic criteria of FPD are ambiguous and cause a large number of questions among the gastroenterologists around the world.

FPD treatment is usually limited to the appointment of a diet, selective antispasmodics for relief of Oddi's sphincter spasm (Duspatalin is particularly effective). Upon hypopancreatism it is appropriate to prescribe enzyme preparations (Creon).

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Despite advances in the modern medicine, diagnostics and treatment of pancreatic diseases is a serious medical and social problem. Functional diseases of the pancreas (FDP) are states with abnormalities of pancreatic secretion without morphological changes of the organ. Increase or decrease of pancreatic enzymes secretion may be caused by concomitant organic pathology of gastro-intestinal tract, long-term using of medicines, Oddi's sphincter dysfunctions.

Diagnostic algorithm in patients with FDP should include thorough complaints and anamnesis collection, hematological and urinary tests, blood glucose analysis, blood biochemical tests with enzymes investigations, repeated analysis of feces, ultrasound examination of abdomen with dynamic analysis of the pancreas and bile ducts. It is desirable to conduct loads or stress food tests, secretine test with enzymes and bicarbonate investigations in pancreatic secrets, elastase-1 test and breath tests. Clinical, laboratory and instrumental diagnostic criteria in FDP patients are ambiguous and cause a large number of questions from gastroenterologists around the world.

Diet, selective spasmolithics and enzymes are used for treatment of patients with FDP.

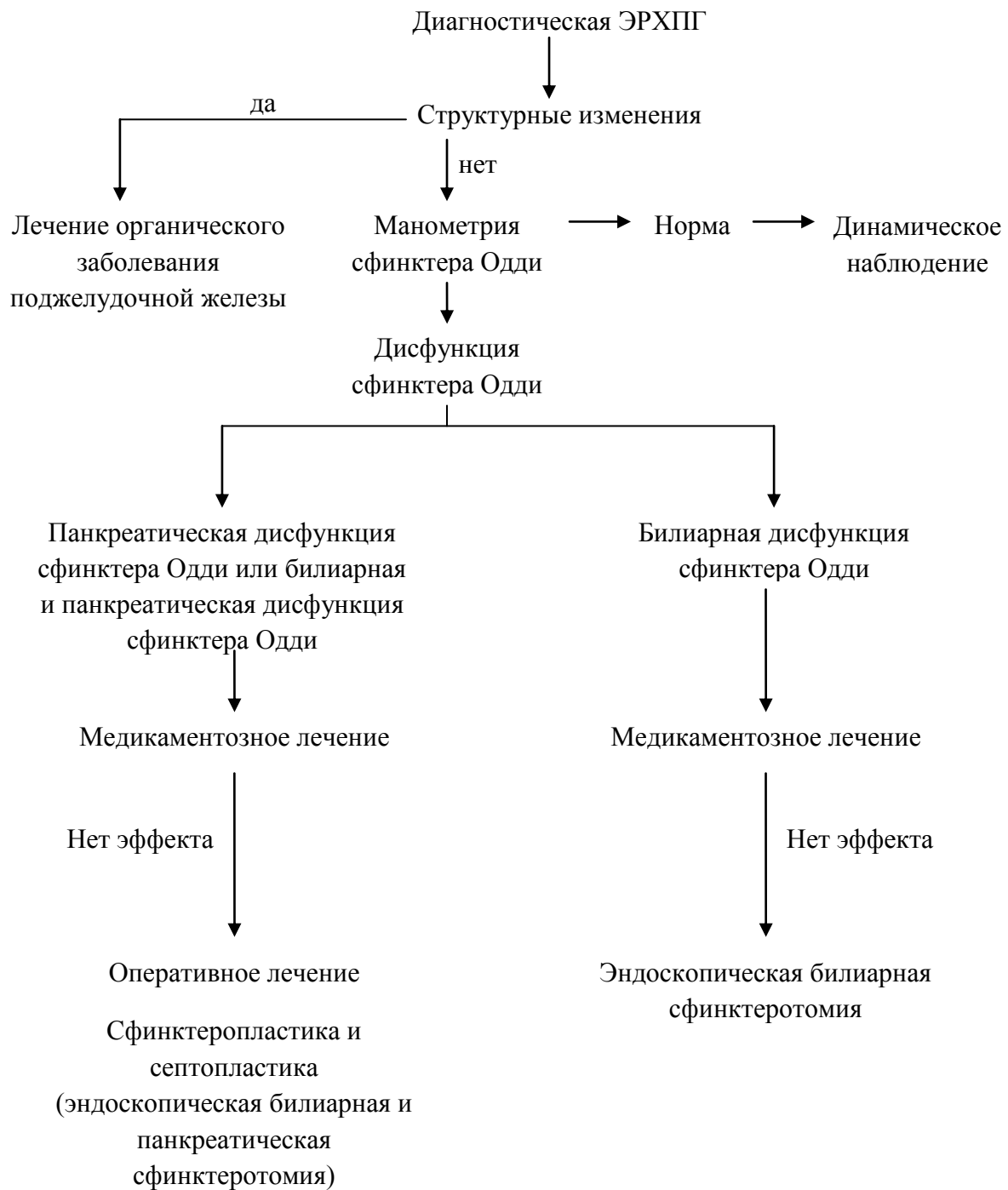


Fig. 1. Management of patients with clinical signs of Oddi's sphincter pancreatic dysfunction (by D. A. Drossman et al., 2000 [8]).

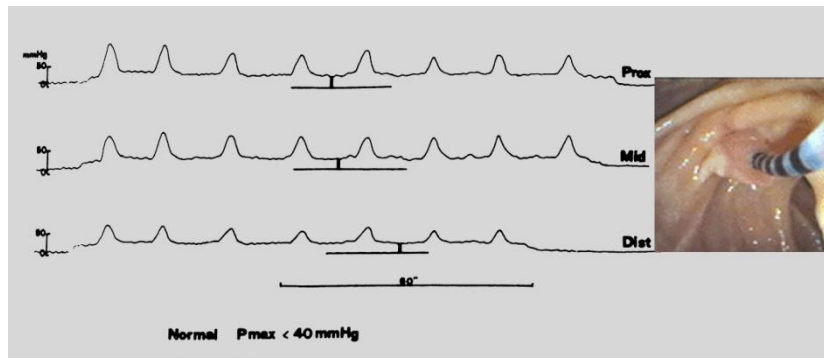


Fig. 2a. Endoscopic manometry of Oddi's sphincter. On the right — endoscopic cannulation of papilla by manometric catheter. On the left — recording of manometric curves with three sensors: proximal (Prox), middle (Mid), distal (Dist). Sensors are located within the limits of Oddi's sphincter and show sphincter activity phase superimposed on its basal pressure. Intraduodenal pressure is shown by horizontal lines. Current manometry results are normal (by D. A. Drossman et al., 2000 [8]).

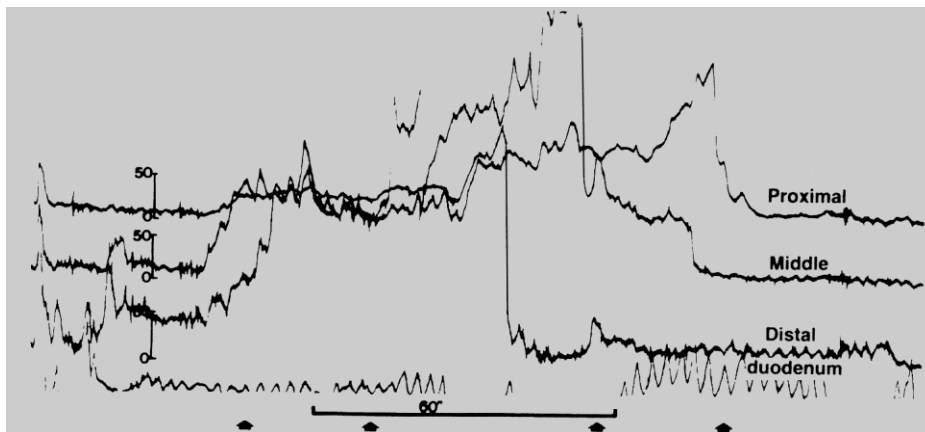


Fig. 2b. Endoscopic manometry of Oddi's sphincter. Recording of manometric curves with three sensors: proximal (Prox), middle (Mid), distal (Dist), introduced in the main pancreatic duct sphincter. The lower curve represents the pressure in the duodenum. We see a sharp increase in pressure of Oddi's sphincter, fixed by the top three sensors (for D. A. Drossman et al., 2000 [8]).

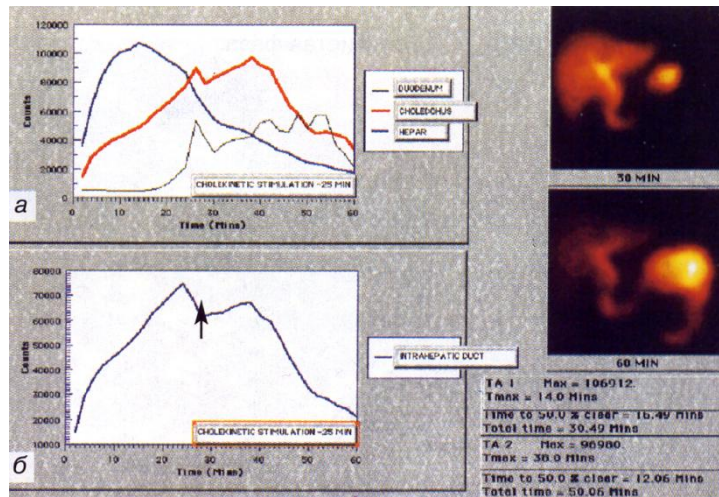


Fig. 3. Biliary scintigraphy upon Oddi's and Mirizzi sphincter dysfunction before (a) and after (b) stimulation. We see the repeated rise of the curve after administration of cholecystikinin, marked with arrow, which indicates spasm of the sphincter (by V. A. Petukhov, 2003 [7]).