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ИНТЕГРАЛЬНАЯ ОЦЕНКА ВНУТРИПЕЧЕНОЧНОГО КРОВОТОКА — НОВОЕ НАПРАВЛЕНИЕ В НЕИНВАЗИВНОЙ ДИАГНОСТИКЕ ХРОНИЧЕСКИХ ЗАБОЛЕВАНИЙ ПЕЧЕНИ

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Integral Assessment of Intrheateral Blood Flow — a New Direction in Non-Invasive Diagnostics of Chronic Liver Diseases

Резюме

Цель исследования. Оценить чувствительность, специфичность и диагностическую точность способа неинвазивной дифференциальной диагностики заболеваний печени методом полигепатографии. **Материалы и методы.** Методом случайной выборки было обследовано 45 пациентов (28 женщин, 17 мужчин). Всем пациентам для определения нарушений внутрипеченочной микроциркуляции при первичном обращении была проведена полигепатография. На основании выявленных изменений внутрипеченочной гемодинамики на основе морфофункциональной гемодинамической модели было сделано заключение о нарушении внутрипеченочного кровотока и высказано предположение об этиологии и стадии заболевания печени. В последующем верификация диагноза заболеваний печени осуществлялась после детального изучения общепринятых в гепатологии клинико-лабораторных, инструментальных и морфологических данных. У 5 (11,1%) исследуемых была проведена пункционная биопсия печени по методу Menghini. **Результаты.** На основании полученных данных о нарушении внутрипеченочной микроциркуляции при проведении полигепатографии все исследуемые были разделены на три группы. I группу составили пациенты с нарушенным венозным притоком, во II группу вошли пациенты с нарушенным артериовенозным притоком, в III группу — с нарушенным венозным оттоком. *Полученные данные полигепатографии (ПГГ) были сопоставлены с результатами клинико-лабораторных, инструментальных и морфологических данных. Определена высокая чувствительность, достаточная специфичность и точность метода полигепатографии в диагностике хронических заболеваний печени.* **Заключение.** Проведенные исследования свидетельствуют, что ПГГ — простой, доступный и необременительный для пациента метод обследования, который позволяет неинвазивно оценить локализацию нарушений внутрипеченочного кровотока, и с определенной долей вероятности предположить этиологический фактор заболевания и стадию заболевания. Учитывая специфичность изменений гемодинамики печени в зависимости от этиологического фактора и стадии заболевания, исследование внутрипеченочной гемодинамики методом полигепатографии может быть рекомендовано в качестве скринингового метода при обследовании пациентов с заболеваниями печени, что позволит сократить время диагностического поиска.

Ключевые слова: *внутрипеченочная гемодинамика, внутрипеченочная микроциркуляция, полигепатография, хронические заболевания печени, аутоиммунные заболевания печени, стеатогепатит, вирусный гепатит, диагностика хронических заболеваний печени*

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Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Purpose of the study. To assess the sensitivity, specificity and diagnostic accuracy of the method for non-invasive differential diagnosis of liver diseases by polyhepatography. **Materials and methods.** A random sampling method examined 45 primary patients. Polygepatography was performed on all patients to detect disorders of intrahepatic microcirculation during primary contacting. Based on the detected changes in intrahepatic hemodynamics and based on the morphofunctional hemodynamic model, a conclusion was made about the violation of intrahepatic blood flow and an assumption was made about the etiology and stage of liver disease. Subsequently, the diagnosis of liver diseases was verified after a detailed study of clinical-laboratory, instrumental and morphological data generally accepted in hepatology. Puncture liver biopsy by the Mancini method was performed in 11.1% of the subjects. **Results.** All subjects were divided into three groups based on the data obtained on impaired intrahepatic hemodynamics during polyhepatography (PHG). The group I consisted of patients with impaired venous inflow, the group II included patients with impaired arteriovenous inflow, and group III — with impaired venous outflow. The obtained polyhepatographic data were compared with the results of clinical-laboratory, instrumental and morphological data. The high sensitivity, sufficient specificity and accuracy of the polyhepatography method in the diagnosis of chronic liver diseases have been determined. **Conclusion.** The studies carried out indicate that PHG is a simple, accessible and not burdensome examination method for the patient, which makes it possible to assess the localization of intrahepatic blood flow disorders, and, with a certain degree of probability, to assume the etiological factor of the disease and the stage of the disease. Given the specificity of changes in liver hemodynamics, depending on the etiological factor and stage of the disease, assessment of intrahepatic hemodynamics by polyhepatography can be recommended as a screening method for examining patients with liver diseases, which will shorten the diagnostic search time.

Key words: *intrahepatic hemodynamics, intrahepatic microcirculation, polyhepatography, chronic liver disease, autoimmune liver diseases, steatohepatitis, viral hepatitis, diagnosis of chronic liver diseases*

Conflict of interests

The authors declare no conflict of interests

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AILDs — autoimmune liver diseases, ALP — alkaline phosphatase, CIC — circulating immune complexes, CLDs — chronic liver diseases, EGDS — esophagogastroduodenoscopy, ESR — erythrocyte sedimentation rate, HSCs — hepatic stellate cells, PHG — polyhepatography

Introduction

Chronic liver diseases (CLDs) are a serious problem of the present-day health care. This is due not only to their prevalence, but also to mortality associated with the development of liver cirrhosis and hepatocellular carcinoma [1].

Inapparent and polymorphous clinical presentation of CLDs cause certain difficulties in their timely diagnosis, lead to the progression of the pathological process and to the development of life-threatening complications [2].

Experimental and clinical data demonstrate that vascular failure precedes the parenchymal one and is observed along with a slightly altered functional state of liver. According to literature sources, hemodynamic disorders are observed in 94% of patients with CLDs. In the structure of the overall mortality in such patients, hemodynamic disorders account for up to 60% [3].

It is essential that the morphofunctional heterogeneity of hepatocytes determines the different nature of intrahepatic blood flow disorders depending on the etiology and stage of liver disease. It is known that a hemodynamic block in the periportal zone (the first zone) of hepatic acinus most often develops in autoimmune or viral diseases, while in the patients with non-alcoholic fatty liver disease or alcoholic hepatitis it takes place in the area of central hepatic veins (the third zone of hepatic acinus). Moreover, recent studies confirm the significant

role of hepatic stellate cells (HSCs) in the pathogenesis of liver diseases. HSCs regulate blood flow at the level of hepatic sinuses and are the main source of collagen production in liver when they interact with fibroblasts. Activated HSCs and fibroblasts exhibit profibrogenic properties due to their ability to synthesize substances that inhibit the breakdown of fibrin and substances that promote the synthesis of fibrous matrix proteins (type I collagen, fibronectin, hyaluronic acid). The development of fibrogenesis processes in liver is one of the important steps in the pathogenesis of chronic hepatitis. In turn, it is known that liver structure is not the result of a rigid anatomical organization, however, it is developed under the effect of functional hemodynamic factors, and the heterogeneity of intrahepatic blood flow disorders determines the mosaic development of liver fibrosis. Intrahepatic blood flow disorders trigger a cascade of metabolic and neurohumoral processes leading to changes in central hemodynamics; such changes further exacerbate liver microcirculation disorders and contribute to the progression of the pathological process with the development of portal hypertension, fibrosis and reorganizing of liver architecture. Besides, the intrahepatic blood flow pattern depends on the effectiveness of the biliary system function and lymph flow. In view of the above, it can be assumed that the diagnosis of CLDs can be based on the identification of intrahepatic blood flow and central hemodynamic disorders; timely identification and management of the identified disorders can increase the effectiveness of pathogenetic therapy and significantly reduce the risk of liver fibrosis [4].

The process of liver regeneration is considered extremely promising. It is known that in the experiment with resection of 50–70 % of liver, its initial weight and dimensions restored in 10–14 days [5]. However, in a pathological process, impaired intrahepatic blood flow does not provide close interaction between blood and hepatocytes, thus impairing their metabolism and resulting in the development of less blood-requiring connective tissue together with changes in the liver architecture. Therefore, regardless of the disease etiology, impaired intrahepatic hemodynamics is an important part in the CLD pathogenesis. Thus, it seems extremely important to have an available non-invasive technique for the control of changes in liver hemodynamics. However, this field of hepatology has significant limitations due to the lack of an affordable technique for assessing the state of intrahepatic blood flow [6].

This problem can be solved with the help of a simple, affordable and non-invasive method — polyhepatography. Polyhepatography (PHG) is a technique for assessing liver hemodynamics based on the simultaneous analysis of several rheograms (blood filling curves) of the intrahepatic area and central pulse curves [4].

Study Objective

To assess the sensitivity, specificity and diagnostic accuracy of the polyhepatography technique for non-invasive diagnosis of chronic liver diseases.

Materials and Methods

This study was carried out in the Research Laboratory of Innovative Methods of Functional Diagnostics of the I. I. Mechnikov North-Western State Medical University of the Ministry of Health of Russia; for this study 45 patients (28 females, 17 males) were randomly examined; the average age of the patients was (49.0 ± 8.4) years. During their initial presentation, the patients complained of various signs of asthenic vegetative syndrome: general weakness (97.7 %, n = 44), rapid fatigability (95.5 %, n = 43). Pain syndrome (heaviness and/or discomfort in right hypochondrium) was reported by 42 (93.3 %) subjects. Patients also complained of different signs of dyspeptic syndrome: heartburn (64.4 %, n = 29), burping (46.7 %, n = 21), bloating (37.7 %, n = 17), loose stools (8.9 %, n = 4), tendency to constipation (2.2 %, n = 1). Cholestasis syndrome in the form of pruritus was mentioned by 7 (15.5 %) subjects.

All patients underwent polyhepatography with functional hemodynamic tests (at the height of inhalation and with nitroglycerin) to identify changes in the state of intrahepatic blood flow during the initial visit; the results of these tests allowed to make a conclusion about persistent or functional hemodynamic disorders of arteriovenous inflow and venous outflow in liver and spleen. Based on the results of this examination, a conclusion was made on the state of intrahepatic hemodynamics, severity and localization of hemodynamic disorders, the presence of liver fibrosis according to METAVIR score, and an assumption was made about the etiology of the disease. PHG was carried out using the Valenta+ hardware and software complex with the modified set of devices and programs (NEO Research and Production Company, St. Petersburg). A morphofunctional hemodynamic model of liver was taken as the basis of the algorithm for interpreting PHG results [4]. Based on the developed model and PHG results, an assumption was made about the etiology of liver disease [7].

Subsequent verification of the diagnosis of CLD was carried out after a thorough analysis of the results of clinical and instrumental examinations and laboratory tests. To verify the etiology of the disease, serological and molecular genetic markers of viral liver damage were determined: hepatitis A IgM antibodies (Anti-HAV IgM), hepatitis A IgG antibodies (Anti-HAV IgG), hepatitis B surface antigen (HBsAg), hepatitis B surface antigen protective antibodies (HBsAb), hepatitis B

e-antigen (HBeAg), hepatitis B e-antigen antibodies (HBeAb), nuclear core antigen antibodies (HBcAb), hepatitis B virus DNA (HBV DNA); antibodies to hepatitis C virus (anti-HCV), hepatitis C virus DNA (HCV RNA). To exclude autoimmune damage, patients were screened for autoimmune liver diseases: smooth muscle antibodies (SMA), liver-kidney microsomal antibody type 1 (LKM1), antimitochondrial antibodies (AMA), antinuclear antibodies (ANA). If antimitochondrial antibodies to M2 subtype antigen (AMA M2) and LKM1 were detected, the antibodies to the autoantigens of liver diseases were assessed (antibodies to the pyruvate-decarboxylase complex of mitochondria AMA M2 (PDC), antibodies to liver cytosolic antigen type 1 (LC-1), antibodies to soluble liver/pancreas antigen (SLA/LP), antibodies to Sp100 nuclear granule proteins and PML protein, antibodies to integral nuclear membrane protein gp210). In addition, the presence of circulating immune complexes (CIC), as well as class A, M, G immunoglobulins was determined. All patients underwent general clinical tests: complete blood count, urinalysis with a qualitative reaction to urobilin and bile pigments, coprogram, and fecal occult blood test by immunochemical method. Biochemical tests included assessment of total protein and protein fractions, prothrombin index, concentration of bilirubin and its fractions, levels of serum enzymes (alanine aminotransferase and aspartate aminotransferase), alkaline phosphatase (AP), amylase, glucose, blood lipid profile, urea, electrolytes (potassium, calcium, sodium). Ultrasound examination of abdominal organs was performed to assess the size and structure of the parenchyma of liver, pancreas, gallbladder, spleen, and portal vein. Esophagogastroduodenoscopy was performed to detect signs of portal hypertension — esophageal varices and gastric cardia. Five (11 %) patients underwent a percutaneous liver biopsy according to the Menghini technique. During the histological analysis of biopsy samples, the activity of inflammatory process and the stage of liver fibrosis were assessed using semiquantitative scales developed by R. J. Knodell et al. (1981), as well as fibrosis severity according to METAVIR score. Clinical diagnosis was defined on the basis of ICD-10 classification.

Statistical processing of values obtained was carried out using Statistica 10.0 software package. In cases of the normal distribution of sample data, results were presented as the mean and standard deviation (M ± SD); in case of non-compliance with the normal distribution, as a median (Me), and lower and upper quartiles (Q25 %, Q75 %). When comparing independent groups, the Mann — Whitney U test or Kolmogorov — Smirnov test was used for non-parametric values, and Student's t-test for parametric values [8, 9]. Differences in the results of the comparison of samples were considered significant at $p < 0.05$. Specificity, sensitivity, likelihood ratios, and predictive ability of the detected diagnostic aspect were determined using two-row by two-column tables (contingency tables). Evaluation of the information value of PHG results for each of the detected signs of patient's condition was calculated using the corresponding formulas [10, 11].

Results

Based on the obtained PHG data on impaired intrahepatic hemodynamics, all studied patients were divided into 3 groups. Group I included patients with impaired venous inflow (Figure 1); group II included patients with impaired arteriovenous inflow (Figure 2); and group III included patients with impaired venous outflow (Figure 3). If a patient had both inflow and outflow impairments, the prevailing one was considered.

According to the results of clinical examinations and laboratory tests in group I (n = 15), complete blood count revealed elevated ESR (erythrocyte sedimentation rate); blood biochemistry test demonstrated the presence of cytolysis and cholestasis syndromes (Table 1).

According to liver ultrasound: hepatomegaly (54 %, n = 8), diffuse changes in liver parenchyma (67 %, n = 10), gallbladder deformity (47 %, n = 7), diffuse changes in pancreas (74 %, n = 11). Esophagogastroduodenoscopy (EGDS) revealed the signs of chronic gastroduodenitis in 47 % (n = 7) cases, erosive gastritis in 14 % (n = 2), cardia insufficiency in 27 % (n = 4). Viral hepatitis was confirmed in 67 % of cases (n = 10): four patients had viral hepatitis B, and six patients had viral hepatitis C. One patient had increased IgG anti-HAV level with negative IgM anti-HAV; these results were regarded as past viral hepatitis A. In three patients with negative markers of hepatitis viruses, there was increased titer of antinuclear factor and the presence of antimitochondrial antibodies that indicated the presence of an autoimmune liver disease. Morphological changes in liver biopsy samples of patients with viral hepatitis were characterized by the presence of "ground glass" hepatocytes, "sanded" nuclei, lymphoid infiltration of portal tracts, less often — fatty degeneration of hepatocytes. The degree of necroinflammatory response according to Knodell score was 4–5 points, liver fibrosis according to METAVIR was F 1–2.

Laboratory tests in group II (n = 13) revealed cytolytic and cholestatic syndromes, however, the increase in transaminases and cholestasis enzymes was more significant in group II (Table 1). According to the liver ultrasound, the following changes were revealed: hepatomegaly (47 %, n = 6), splenomegaly (39 %, n = 5), diffuse changes in liver parenchyma (85 %, n = 11), gallbladder

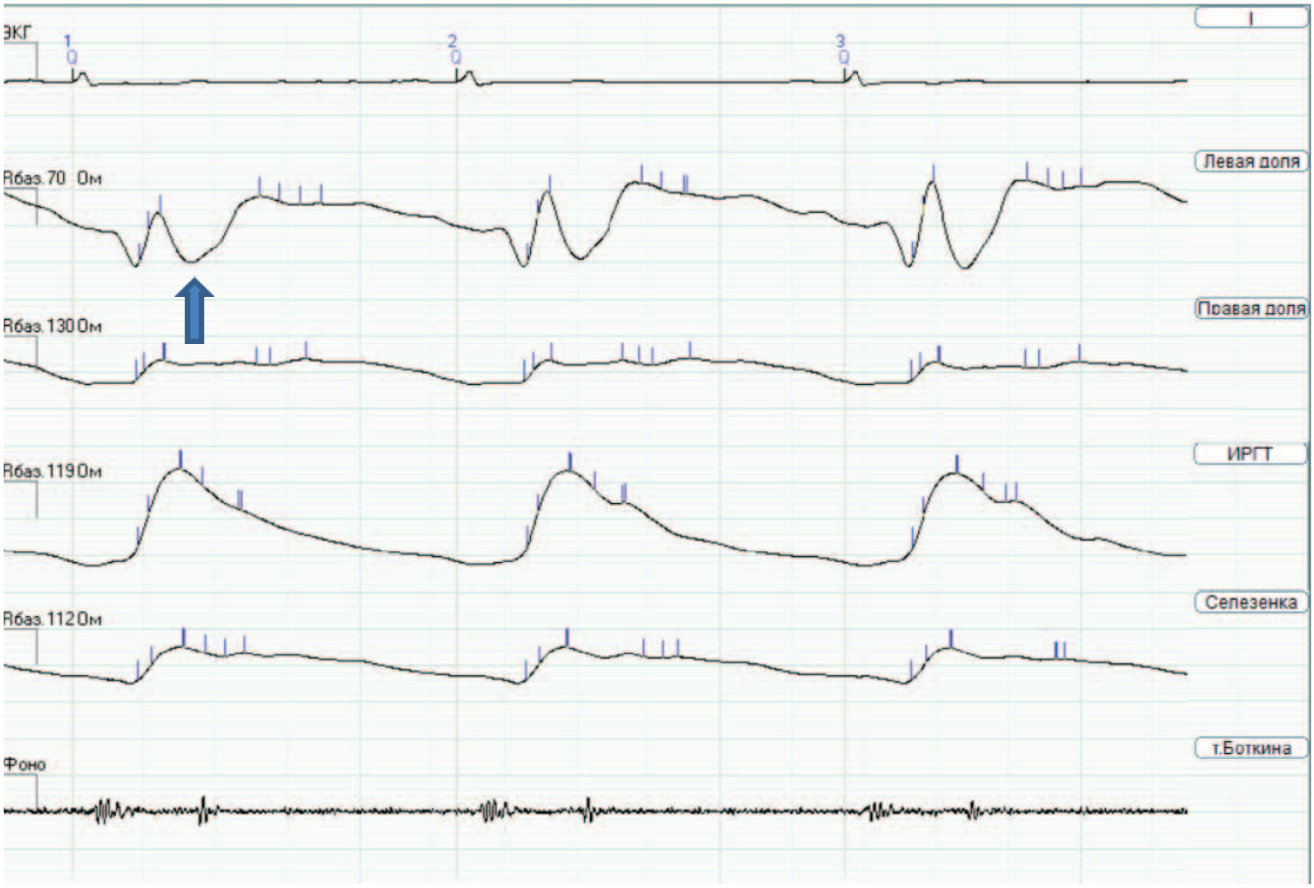

Figure 1. *Polyhepatogram. Lying background. Severe venous inflow disorders in the left lobe of the liver. The arrow indicates the zone of violation*

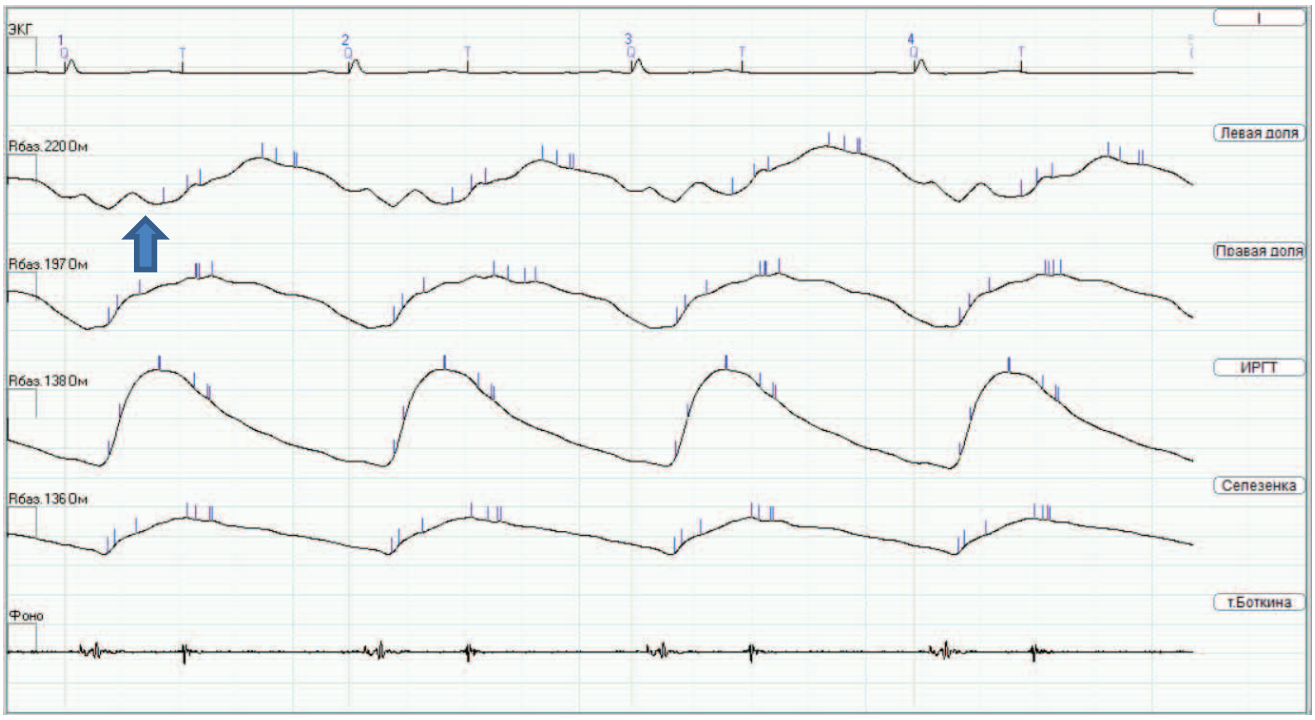

Figure 2. *Polyhepatogram. Lying background. Arteriovenous inflow disorders mainly in the left lobe of the liver. The arrow indicates the zone of violation*

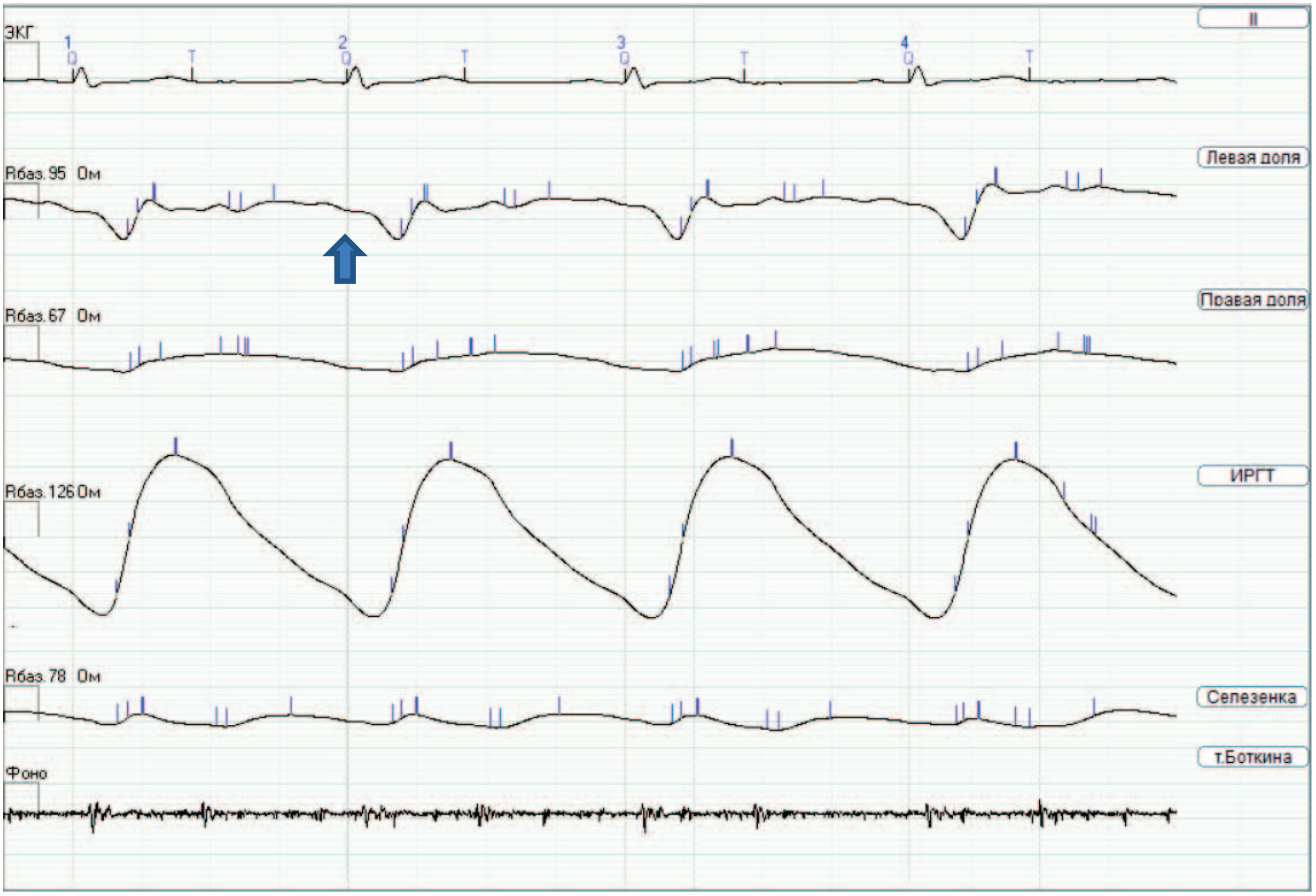

Figure 3. *Polyhepatogram. Lying background. Signs of impaired venous outflow from the liver. The arrow indicates the zone of violation*

Table 1. *The main laboratory parameters in the study groups, Me [Q25 %; Q75 %]*

Indicator	Group I (n=15)	Group II (n=13)	Group III (n=17)
1	2	3	4
Hemoglobin, g/l	127[121; 140]	128,9[110; 149]	132 [117; 138]
Erythrocytes, x10^{12}/l	4,34[3,2; 4,9]	4,25[3,03; 5,2]	4,52[3,9; 5,4]
Platelets, x10^{9}/л	231[134; 403]	174,5[98; 480]	210 [158; 390]
Leukocytes, x10^{9}/л	5,4[3,2; 8,7]	5,9[3,1; 10,6]	6,1 [3,9; 9,4]
Erythrocyte sedimentation rate, mm/h	27,2[7; 39]	30[5; 52]	26[14; 48]
General protein, g/l	67 [64; 78]	70 [63; 83]	72,4 [63; 82]
Albumin, g/l	40,6[36; 42]	39 [32; 43]	43,2 [34; 46]
AST, unit/l	69,2[34; 102]	82 [52; 206]	84,4[27; 74]
ALT, unit/l	113,2[49; 180]	83 [56; 265]	98[37; 159]
General bilirubin, μmol/l	14[9;28]	19 [5; 77]	16[12; 23]
Alkaline phosphatase, unit/l	158[114; 229]	381 [222; 1480]*	137[92; 280]
Gamma glutamyl transferase, unit/l	87,1[48; 145]	306 [183; 1157]*	71,2[54; 102]
Cholesterol, mmol/l	5,4[3,9; 6,8]	6,8 [4,7; 12,2]	6,9[4,3; 9,7]
Glucose, mmol/l	4,7[3,4; 5,7]	4,8 [3,3; 6,7]	5,9 [3,8; 7,4]
Circulating immune complexes, unit	72,1[55; 180]	177,4[75; 350]*	68 [44; 167]

Note: * p <0.05 when compared with group I and III.

deformity (54 %, n = 7), diffuse changes in pancreas (74 %, n = 11), indirect signs of portal hypertension (31 %, n = 4). EGDS revealed the signs of chronic gastritis or gastroduodenitis (70 %, n = 9), erosive gastritis (31 %, n = 4), cardia insufficiency (54 %, n = 7), esophageal varices (1.6 %, n = 2). One patient was diagnosed with chronic viral hepatitis C. When interpreting the results of an autoimmune liver panel, autoimmune origin of the disease was confirmed in 69.2 % (n = 9) of cases: increased titers of ANA (min. 1:640, max. 1:20,480) were detected; more often with a cytoplasmic type of luminescence, SMA (1:40), AMA (min. 1:320; max. 1:5,120). Morphological changes in liver biopsy samples were characterized by the presence of piecemeal (rarely — bridging) necrosis, portal tract infiltration with plasma cells, periductal lymphocytic infiltration, and periductal fibrosis. The degree of necroinflammatory response according to Knodell score was 6–9 points, liver fibrosis according to METAVIR was F 2–3.

During the analysis of clinical and laboratory data in group III (n = 17), attention was drawn to lipid metabolism disorders determined in 70.5 % (n = 12) of cases (Table 1). It should be mentioned that in 35.7 % (n = 5) of cases, impaired carbohydrate metabolism (increased fasting glucose level) was found, in contrast to groups I and II where blood glucose levels were within the reference values. Hepatitis virus markers were negative in all patients of this group. Liver autoimmune panel values were changed in two patients (11.7 %); they were characterized by increased ANA (1:320; 1:1,256) and AMA (1:160; 1:1,280).

According to ultrasound results, gallbladder pathology and signs of steatosis of the liver and pancreas were detected much more often in group III. Hepatomegaly was found in 52.9 % (n = 9) of cases, splenomegaly — in 35.2 % (n = 6), diffuse changes in liver parenchyma — in 35.2 % (n = 6), signs of liver steatosis — in 52.9 % (n = 9), thickening of gallbladder walls — in 70.6 % (n = 12), gallbladder deformation — in 41.2 % (n = 7), echo suspension in gallbladder — in 64.7 % (n = 11), diffuse changes in pancreas — in 47 % (n = 8), signs of pancreatic steatosis — in 35.2 % (n = 6), indirect signs of portal hypertension — in 17.6 % (n = 3).

According to EGDS results, there were signs of chronic gastritis or gastroduodenitis (70.6 %, n = 12), erosive gastritis (35.2 %, n = 6), cardia insufficiency (47 %, n = 8), esophageal varices (11.7 %, n = 2). The morphological presentation was characterized by fatty degeneration and inflammatory infiltration of sinusoids. In most cases, the degree of necroinflammatory reaction according to Knodell score was 4–5 points; liver fibrosis according to METAVIR was F 1–2.

To assess the reliability of signs, PHG data were compared to the results of the confirmation of patient condition (results of expert opinion obtained on the basis of total available data, excluding the PHG data). The correlation of sign values (positive or negative) with the results of the confirmation of patient condition is presented in Tables 2, 3 and 4. Specific aspects of intrahepatic blood flow disorders considering the level of localization of obstruction in the examined groups, are clearly described in Table 5.

Table 2. *Contingency table of the sign of viral hepatitis according to polyhepatography*

Polyhepatography result	Verification results*		Total
	VG not detected	VG not detected	
Impaired venous inflow	N= 11 (ИП)/ N= 11(TP)	N= 4 (ЛП)/ N= 4 (FP)	n=15
Other violations or absences	N= 1 (ЛО)/ N= 1 (FN)	N= 29 (ИО)/ N= 29 (TN)	n=30
Total	n=12	n=33	n=45

* Для верификации оценивались наличие или отсутствие маркеров вирусных гепатитов
Note: VG — viral hepatitis, TP — true positive, FP — false positive, TN — true negative, FN — false negative
* For verification, the presence or absence of markers of viral hepatitis was assessed

Table 3. *Contingency table of the sign of autoimmune liver disease according to polyhepatography*

Polyhepatography result	Verification results		Total
	AILD detected	AILD not detected	
Impaired arteriovenous inflow	N= 9 (ИП)/ N= 9 (TP)	N= 2 (ЛП)/ N= 2 (FP)	n=11
Other violations or absences	N= 5 (ЛО)/ N= 5 (FN)	N= 29 (ИО)/ N= 29 (TN)	n=34
Total	n=14	n=31	n=45

Note: AILD — autoimmune liver diseases

Table 4. Contingency table of the sign of steatohepatitis according to polyhepatography

Polyhepatography result	Verification results*		Total
	SG detected	SG not detected	
Impaired venous outflow	N= 14 (ИП)/ N= 14 (TP)	N= 6 (ЛП)/ N= 6 (FP)	n=20
Other violations or absences	N= 0 (ЛО)/ N= 0 (FN)	N= 25 (ИО)/ N= 25 (TN)	n=25
Total	n=14	n=31	n=45

Note: SG — steatohepatitis
* For verification of steatohepatitis, a set of indicators was taken, which included a set of data from clinical and biochemical blood tests, ultrasound of the abdominal organs, shear wave elastography of the liver with elastometry

Table 5. Characteristics of intrahepatic blood flow disorders among the examined patients, n (%)

PGG data (estimate Si)	Identified pathology (condition Ci)				ΣNSi
	C1	C2	C3	C4	
S1=VI	11 (24,4 %)	3 (6,7 %)	0	0	n=14
S2=AVI	1 (2,2 %)	9 (20 %)	0	1 (2,2 %)	n=11
S3=VO	0	2 (4,4 %)	14 (31,1 %)	4 (6,7 %)	n=20
ΣNCi	n=12	n=14	n=14	n=5	n=45

Note: VI — impaired venous inflow, AVI — impaired arteriovenous inflow, VO — disorders in the area of venous outflow, C1=viral hepatitis, C2=autoimmune liver diseases, C3=steatohepatitis, C4=liver pathology excluded

Based on the data obtained, sensitivity, specificity and accuracy of the proposed method of polyhepatography in the diagnosis of non-alcoholic steatohepatitis, viral and autoimmune liver diseases (AILDs) were determined. In cases of viral hepatic lesions, method sensitivity was 91.6 %, accuracy was 88.9 %, specificity was 87.8 %. When diagnosing AILDs, sensitivity was 64.2 %, method accuracy was 84.4 %, and specificity was 87.8 %. In non-alcoholic steatohepatitis, sensitivity was 100 %, accuracy was 86.7 %, specificity was 80.6 %.

Discussion

The main mechanism of intrahepatic blood flow disorders at the early stages of CLDs is a dynamic component determined by capillary vasoconstriction, activation of hepatic stellate cells (HSCs), decreased activity of nitric oxide (NO) and nitric oxide synthase (NOS). In patients with liver cirrhosis, this dynamic component amounts to 20–30 %. With the progression of a pathological process in liver, a significant place is taken by a mechanical component due to the development of fibrosis and inflammation [12]. Therefore, impaired portohepatic hemodynamics and CLDs progression has a close relationship that is recommended to use for the diagnosis of liver diseases. Our studies demonstrate that PHG as a technique for assessing intrahepatic blood flow is reasonable to be used as an instrument for the early diagnosis of liver diseases. The PHG technique has several advantages including non-invasiveness, easy conducting of examination, as well as the availability of the equipment required (a 4-channel rheograph with the ability to take a single-channel cardiogram and phonocardiogram is sufficient for examination according to PHG technique; rheographs of this type are the standard equipment of functional diagnostics room). PHG results are interpreted on the basis of the developed morphofunctional hemodynamic model that allows presenting complex intrahepatic hemodynamics in a simplified form. The developed algorithm for PGG data interpretation allows answering the clinically significant questions one by one: the presence of the signs of intrahepatic blood flow disorders, the level of localization of blood flow obstructions, the nature of disorders (persistent or functional), disease stage, changes in the state of liver during repeated examinations, personalized therapy selection and evaluation of its effectiveness. Considering the specificity of liver hemodynamic changes depending on the etiological factor, the data obtained can be additional diagnostic criteria in determining the etiology of liver diseases. If a patient has arteriovenous inflow disorders, it is highly likely that autoimmune hepatitis can be assumed; if a patient has venous inflow disorders, then it can be viral hepatitis; and if a patient has venous outflow disorders, it can be steatohepatitis. The analysis of the results obtained is in good agreement with known and generally accepted ideas about intrahepatic hemodynamics and morphofunctional hemodynamic model. Curves of the integral rheography of the body and of the rheography of

pulmonary artery demonstrate the initial conditions of systemic blood circulation — the pump function of left ventricle and the diastolic function of right ventricle. Correspondence of these curves to the conditional normal range is an important condition for the correct interpretation of rheograms in the area of the liver and spleen. If a patient has central hemodynamics disorders, the assessment of rheograms should be carried out considering the identified changes in central hemodynamics [13].

At the same time, despite the fact that PHG has critical advantages (non-invasiveness, a simple examination protocol, and the availability of the equipment required), the main difficulty for the widespread implementation of the PHG technique into clinical practice is the reliable interpretation of the obtained PHG data. However, at present this is not an insurmountable obstacle, since modern mathematical methods and software tools that implement them are widely used both for the primary analysis of instrumental data (for example, for automatic labeling of cardiograms and their primary analysis), and as a means of assisting in the interpretation of the results of instrumental examinations in particular, machine learning algorithms are used to define the possible presence and location of malignant neoplasms according to x-ray examinations). Using the capabilities of advanced computational methods significantly increases the availability of various diagnostic techniques and reduces the risk of errors. The use of this approach for the analysis of PHG data obtained will provide free access for patients to a simple instrument for early non-invasive diagnosis of liver diseases and subsequent follow-up of patients regardless of their proximity to the center of competence [4].

A current option for implementing this idea is the development of a telemedicine service that is a center of competence according to the PHG technique, accumulates the algorithm for training and retraining the predictive model, the training set, the trained model itself and provides services for the remote interpretation of study data. This scheme for the provision of services for the remote interpretation of instrumental examinations is currently already implemented in Russia. It should be mentioned that, according to the Accounts Chamber, the number of requests for remote description and interpretation of instrumental examination data is more than 96 % of the total number of requests for telemedicine consultations in 2017–2018 (among them — interpretation of electrocardiographic examinations (A05.10.004.001) — 81.4 %, description and interpretation of X-ray results (A06.30.002.004) — 15.4 %) [4]. Thus, the development of PHG in this direction is considered to be extremely promising.

Conclusion

1. Polyhepatography is a non-invasive technique for the integral assessment of intrahepatic microcirculation that is characterized by high sensitivity, sufficient specificity, and diagnostic accuracy.

2. Considering the specificity of liver hemodynamic changes depending on the etiological factor and the stage of the disease, polyhepatography can be used as a screening method for examining patients.

3. Changes in intrahepatic blood flow found during PHG can be additional diagnostic criteria in determining the etiology of liver diseases and control of changes over time during etiopathogenetic therapy.

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