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ГЕПАТОПУЛЬМОНАЛЬНЫЙ СИНДРОМ ПРИ ЦИРРОЗЕ ПЕЧЕНИ: РАСПРОСТРАНЕННОСТЬ, КЛИНИЧЕСКОЕ ЗНАЧЕНИЕ, ОСОБЕННОСТИ ДИАГНОСТИКИ, ПОДХОДЫ К ТЕРАПИИ

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Hepatopulmonary Syndrome in Patients with Liver Cirrhosis: Prevalence, Clinical Significance, Clinical Features, Therapeutic Approaches

Резюме

Гепатопульмональный синдром является тяжёлым осложнением хронических заболеваний печени, значительно снижающим качество и продолжительность жизни пациентов, патогенетическим проявлением которого является гипоксемия и внутрилёгочные вазодилатации. По данным некоторых авторов он выявляется у 35 % пациентов с терминальной стадией поражения печени. Основное клиническое проявление гепато-пульмонального синдрома — прогрессирующая одышка с возможным возникновением платипноэ и ортодексии. Однако, его диагностика вызывает трудности, так как «золотой стандарт» — трансторакальная эхокардиография с внутривенным введением контрастного препарата — инвазивная процедура, требующая специфического оснащения и не получившая широкого распространения в лечебных учреждениях Российской Федерации. В качестве дополнительного метода используется физикальный осмотр, при котором могут выявляться телеангиоэктазии, цианоз, изменение пальцев рук по типу «барабанных палочек», а ногтей по типу «часовых стекол», однако эти проявления не обладают высокой специфичностью. В связи с этим необходимо продолжать дальнейший поиск малоинвазивных, применимых в рутинной практике диагностических методов и лабораторных маркёров. В этом обзоре представлены данные о распространённости, патогенезе, клинической картине, диагностике и лечении этого синдрома. Его целью является структурирование

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современных данных и накопленного опыта для более ранней верификации диагноза и, соответственно, применения оптимальной тактики ведения пациентов с данной патологией. Основным эффективным методом лечения гепатопульмонального синдрома в настоящий момент является пересадка печени, поэтому его раннее выявление позволяет своевременно направить пациента в центр трансплантологии для включения в лист ожидания, назначив при необходимости длительную кислородотерапию, что значимо продлевает жизнь пациентов и улучшает ее качество.

Ключевые слова: *гепатопульмональный синдром, цирроз печени, гипоксемия, вазодилатации, одышка, ортодексия, платипноэ*

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

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Abstract

Hepatopulmonary syndrome is a severe complication of chronic liver diseases, significantly reducing the quality and duration of patient's lives, the pathogenetic manifestation of which is hypoxemia and intrapulmonary vasodilation. The disease is widespread enough: according to some authors, up to 35 % of patients with the terminal stage of liver damage suffer from this syndrome. The main clinical manifestation is progressive dyspnea with possible occurrence of platypnea and orthodexia. Diagnosis is difficult, since the "gold standard" — transthoracic echocardiography with intravenous injection of contrast agent — is an invasive procedure requiring specific equipment, that's why it is poorly used in medical institutions of the Russian Federation. Physical examination is used as an additional method, in which we see dyspnea, cyanosis, spider nevi, digital clubbing, but these manifestations are not highly specific. Therefore, there is an urgent need for minimally invasive, widespread diagnostic methods and clinical markers that can provide early verification of the diagnosis. This review presents data on the prevalence, pathogenesis, clinical presentation, diagnosis and treatment of this syndrome. The aim of this review is to structure the current data and the accumulated experience for an earlier verification of the diagnosis and accordingly, to apply the optimal management tactics for patients with this pathology. Liver transplantation is currently the main effective method of treatment. Patients with hepatopulmonary syndrome who underwent liver transplantation have been proven to have better survival rate.

Key words: *hepatopulmonary syndrome, cirrhosis, hypoxemia, vasodilatations, dyspnea, orthodeoxia, platypnea*

Conflict of interests

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A-a gradient — alveolar–arterial gradient, CO — carbon monoxide, DL_{CO} — diffusing capacity of the lungs for carbon monoxide, eNOS — endothelial nitric oxide synthase, ET-1 — endothelin 1, ETB — endothelin receptor type B, NO — nitrogen oxide, PaO_2 — partial pressure of arterial oxygen, Sat O_2 — oxygen saturation, TIPS — transjugular intrahepatic portosystemic shunt, VEGF — vascular endothelial growth factor, HPS — hepatopulmonary syndrome, chest CT — chest computed tomography, LT — liver transplantation, TNF-α — tumor necrosis factor alpha, EchoCG — echocardiography

Introduction

Hepatopulmonary syndrome (HPS) is a serious complication of liver disease, which is characterized by a triad of signs: cirrhosis and/or portal hypertension, arterial deoxygenation and intrapulmonary vascular dilatation. According to the published studies, this syndrome can worsen prognosis in patients with chronic liver disease in the presence of hepatic impairment. In a multivariate analysis with a statistical correction for the influence of such factors as severity of liver cirrhosis, age, gender, it was found that HPS is an independent factor of increased mortality [1–3].

In 1884, Fluckiger first published a clinical case report, describing a woman with liver cirrhosis, cyanosis, and drumstick fingers. Later, in 1977, the term "hepatopulmonary syndrome" was introduced by Kennedy and Knudson to describe these clinical symptoms of this condition. The postmortem morphological studies in these patients revealed dilation of pulmonary vessels and significant peripheral dilatation of pulmonary arteries at precapillary and capillary levels, without any other changes in the pulmonary parenchyma [4]. Prior to 1988, HPS was treated only with non-surgical methods, the efficacy of which was quite low [5]. For a long time, hepatopulmonary syndrome had been considered a contraindication for liver transplantation (LT); however, after numerous studies the situation changed radically: it was noted that transplantation could reverse hypoxemia and

contribute to a significant increase in survival. In combination with the absence of effective medical treatment, this discovery made LT the main method of HPS treatment [5].

This article describes a systematic analysis of studies on the relationship of clinical, laboratory, and instrumental markers with the clinical presentation, severity, and prognosis of HPS, and discussed possible directions for further work in this area.

The study was aimed at developing a list of the most significant clinical markers for early diagnosis verification and treatment initiation in real-life clinical practice based on the published data on prevalence, pathogenesis, clinical, laboratory and instrumental data on HPS in patients with liver cirrhosis.

Materials and methods

During the study, the search and analysis of articles published over the period: January 2017 to August 2022 was performed in the database PubMed (https://pubmed.ncbi.nlm.nih.gov/). The search query included the words "hepatopulmonary" and derivatives, "syndrome" and derivatives, "cirrhosis" and derivatives, "hypoxemia" and derivatives, "vasodilatation" and derivatives, "orthodeoxia" and derivatives, "platypnea" and derivatives, "treatment" and derivatives, "liver transplantation" and derivatives, "diffusing capacity" and derivatives, "cardiac involvement" and derivatives. To narrow the search, articles containing the word "children" and its variations were excluded. Therefore, the search algorithm was as follows: "liver cirrhosis" OR "prevalence" OR "diagnosis" OR "vasodilation" OR "clinical features" OR "orthodeoxia" OR "platypnea" OR "treatment" OR "liver transplantation" OR "pulmonary dysfunction" OR "diffusing capacity" OR "cardiac involvement" OR "myocardial function" AND "hepatopulmonary syndrome."

When using the described search algorithm, 255 articles were initially selected. Further, 47 articles including studies in patients under 18 years of age were excluded. Then, another 130 publications were excluded as they did not fully meet the purpose of this study (articles dwelt on the surgical treatment of HPS rather than its diagnosis; moreover, they mainly studied portal hypertension, not HPS). The reduced list included 78 articles.

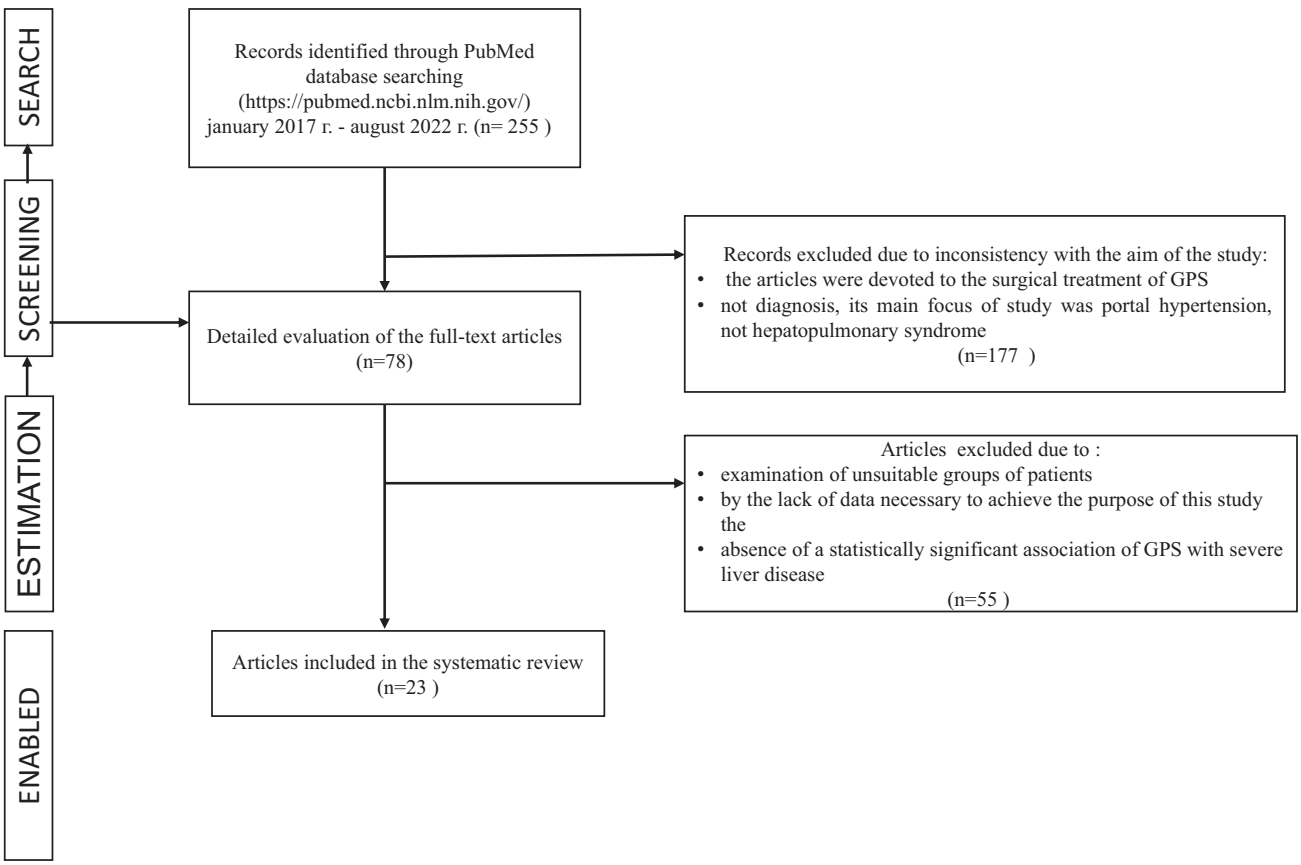

Figure 1. *Schematic representation of the selection process for publications on hepatopulmonary syndrome in patients with liver cirrhosis*

After a careful analysis of publications, the articles that either referred to the examination of patients with liver disease without cirrhosis or did not contain patient examination data essential for the purpose of this study were additionally excluded. Single clinical case reports were also excluded, since the patient data contained therein were sparse. The studies where the relationship between HPS and severe liver disease was statistically insignificant (p>0.05) were also excluded. Therefore, at the last stage of the literature analysis, another 55 publications were excluded from the 78 articles. After the search, a list of 23 publications was formed, which demonstrated a clear association between HPS with worsened quality of life and increased mortality, the importance of early screening and search for new study methods to improve survival and prognosis of patients with HPS (Figure 1).

Diagnosis and criteria

Hepatopulmonary syndrome is defined as hypoxemia caused by dilation of pulmonary vessels and formation of vascular shunts in patients with liver disease with or without portal hypertension [6]. Table 1 shows the criteria for HPS diagnosis.

The conducted studies revealed a correlation between HPS severity and severity of liver disease, assessed by the MELD (Model for End-Stage Liver Disease) scale [4], which is used to calculate the survival prognosis for patients with end-stage liver failure.

Table 2 shows the HPS classification, based on the evaluation of the severity of pulmonary gas exchange disorder, characterized by a decrease in arterial blood oxygen levels [6].

The given table shows that the HPS severity depends on the level of partial oxygen pressure in arterial blood, with alveolar-arterial gradient exceeding 15 mm Hg, which is one of the most sensitive markers for early arterial hypoxia detection.

Prevalence

According to the study data, HPS is found in 5 %–35 % of patients with end-stage liver disease. This data variation is likely due to the use of different diagnostic criteria for diagnosis [8,9]. For example, according to American scientists, HPS was revealed on contrast Echo-CG in 38 % of patients with chronic liver disease, but only 17.5 % of these patients were diagnosed with hypoxemia [30]. The frequency of HPS detection was the highest when using the alveolar–arterial gradient (A-a gradient) as a more sensitive marker of hypoxemia, as well as screening of asymptomatic patients with liver cirrhosis [10].

Pathogenesis

The HPS pathogenesis is not fully understood, since the literature contains contradictory data. This syndrome is most often associated with severe liver cirrhosis which is accompanied by portal hypertension syndrome; However, it can also occur in patients with other disease areas: non-cirrhotic portal fibrosis (idiopathic portal hypertension) and extrahepatic portal vein obstruction [11, 12].

Table 1. *Diagnostic criteria for hepatopulmonary syndrome (with changes) [6, 7]*

Parameter	Definition
Oxygenation	PaO_2 <80 mmHg or PA–a,O_2 > 15 mmHg; > 20 mmHg for patients aged > 64 years old
Pulmonary vasodilation	Positive CEE or 99mTcMAA, showing the presence of a shunt >6 %
Liver disease	Cirrhosis and/or liver failure

Note: CEE — contrast-enhanced echocardiography, PaO_2 — arterial oxygen tension, PA-a,O_2 — alveolar-arterial oxygen tension difference, 99mTcMAA — perfusion lung scanningusing technetium-99m-labelled macroaggregated albumin

Table 2. *Grading of severity of hepatopulmonary syndrome [6]*

Stage	PA–a,O_2, mmHg	PaO_2, mmHg
Mild	≥15	≥ 80
Moderate	≥15	≥ 60 <80
Severe	≥15	≥ 50 <60
Very severe	≥15	<300 on 100 % O_2

Note: PaO_2 — arterial oxygen tension, PA-a,O_2 — alveolar-arterial oxygen tension difference

The general information on HPS pathogenesis can be obtained in animal experiments. The most frequently used method was ligation of the common bile duct in rats, which caused secondary biliary cirrhosis in these rats and resulted in decreased blood oxygenation and intrapulmonary vasodilation [13]. The studies on experimental models demonstrated that the key cause of HPS formation is capillary dilation and formation of intrapulmonary shunts, leading to decreased blood oxygenation due to violation of ventilation/perfusion relationship and increased alveolar-arterial gradient. The study authors stated predominant dilation of pulmonary pre-capillary and capillary vessels up to 15–100 μm (normal diameter of these vessels varies from 8 to 15 μm), increase in their number and dilation of pleural capillaries [14].

The studies revealed a decrease in the lung diffusion capacity (DL_{CO}) in patients with HPS and normal ventilatory lung capacity. This decrease can be explained by the development of a pulmonary shunt and thickening of alveolar-capillary membrane against endotheliitis [7, 15-16]. Occurrence of the latter is related to activation of endothelin synthesis produced by cholangiocytes in the liver. These findings are confirmed on experimental rat models. Zhang J et al. have found that proliferating cholangiocytes produce endothelin-1 (ET-1), activating the pulmonary endothelin receptor-B (ETB), which, in its turn, mediates activation of endothelial NO synthase (eNOS), a NO precursor that leads to vascular endothelial inflammation [17–20]. In clinical studies in patients with HPS conducted in 1997–1998, Rolla G et al. noted an increased content of NO in the exhaled air, attributing it to the increased NO production by the pulmonary vascular endothelium. After liver transplantation, the level of exhaled NO level normalized [21, 22], which also confirms the role of endotheliitis in the HPS formation.

In HPS, the loss of pulmonary capillary tone and inhibition of pulmonary vasoconstrictors such as endothelin-1, serotonin, angiotensin II, histamine, prostaglandin and increased nitric oxide (NO) production are considered to be the main cause of pre-capillary and capillary vasodilation [16]. Moreover, according to the studies, carbon monoxide (CO) and tumor necrosis factor alpha (TNF-α) are among the mediators that cause pulmonary vasodilation [17, 18]. Rabiller A. (2002), Sztrymf B. (2005), Zhang H.Y. (2007) et al. considered the theory of bacterial translocation of intestinal flora from patients with portal hypertension, which leads to macrophage infiltration of lung parenchyma as another mechanism of pulmonary vasodilation. This hypothesis is supported by the positive effect of norfloxacin treatment in the experimental rat model of cirrhosis [23–25].

There is another hypothesis that hypoxemia in patients with HPS may be related to thickening of the alveolar-capillary membrane due to collagen accumulation during chronic inflammatory process caused by endotheliitis and against the background of bacterial translocation of intestinal flora [26–28].

Clinical presentation

The main clinical sign of HPS is progressing dyspnea. This was supported by the data from a multicenter study conducted by Michael B. Fallon and Michael J. Krowka in the USA in 2008. The researchers found that the incidence of dyspnea in patients with HPS is 1.65 greater than in patients without this syndrome [2]. A specific feature of dyspnea in HPS is the occurrence of platypnea and orthodexia, which are highly specific, but not pathognomonic signs. Platypnea is dyspnea that increases when moving the patient to an upright position, while orthodexia is a decrease in partial oxygen pressure by more than 4 mm Hg and/or a decrease in oxygen saturation by more than 5 % when the patient is upright [29]. It is considered that the cause of their development is intensification of ventilation-perfusion mismatch following a change in the body position due to an increase in the pulmonary shunt effect [30].

It should be noted that HPS can have an asymptomatic course, especially in patients with mild hypoxia. Observations show that dyspnea is more frequent in patients with a decrease in PaO_2 of less than 70 mm Hg, which can explain late detection of this syndrome [31].

Physical examination of a patient with HPS may reveal telangiectasia, cyanosis, drumstick fingers and watch-glass nails [32]. In patients with chronic liver disease and telangiectasia, the prevalence of HPS is greater than in the patients without this symptom [33].

Therefore, all patients with chronic liver disease complaining of dyspnea should be screened for HPS.

Methods of intrapulmonary vasodilation diagnosis

Contrast-enhanced transthoracic echocardiography with foamed saline is considered as the gold standard of intrapulmonary vasodilation diagnosis. The advantage of this method is low invasiveness and sufficient sensitivity. Common normal saline is shaken to form microbubbles >10 μm; after that it is injected into a peripheral vein of the arm during a four-chamber transthoracic Echo-CG to assess whether the foamy liquid enters the left heart. The size of pulmonary capillaries normally varies in the range 8 to 15 μm, therefore microbubbles cannot pass. However, in the presence of a dilated vascular bed and/or arteriovenous shunting, microbubbles are not captured by the lungs and reach the left heart within 3–6 cardiac cycles after their first appearance in the right atrium [34].

Although contrast-enhanced transesophageal Echo-CG is a more sensitive method of intrapulmonary vasodilation determination, it is not recommended for patients with cirrhosis because of a potential risk of damage to varicose esophageal veins [35, 36].

Another instrumental method for hepatopulmonary syndrome diagnosis is radioisotope scanning with macroaggregated albumin. In the presence of intrapulmonary vasodilation, technetium-labeled albumin particles can reach extrapulmonary sites and are found in the brain, kidneys, and other organs. Cerebral tissue absorption is considered abnormal if it is ≥6 % [3]. The advantage of this method is the quantitative assessment of intrapulmonary vasodilation, as well as its high specificity. Its main disadvantage is the impossibility of differential diagnosis of intracardiac and intrapulmonary shunting, as well as its lower sensitivity [37].

Additional study methods

The most common methods that are used to rule out concomitant pulmonary diseases are chest X-ray and chest computed tomography (chest CT). There are no convincing data on the use of these methods directly for diagnosis of HPS [6,38]. According to the retrospective study conducted by Yingming Amy Chen et al. in Canada in 2016, chest CT cannot be used for HPS diagnosis, since it can only find systemic vasodilation. The authors believe that bilateral nodular or reticular changes in the basal areas of the lungs caused by dilation of the peripheral pulmonary arteries in the lower lobes can still be detected on chest X-ray in patients with chronic liver disease. These data can be confirmed by chest CT: patients with chronic liver disease show an increase in the ratio of segmental arterial diameter to segmental bronchial diameter >2 with normal size of the central pulmonary arteries. However, this sign may be seen in patients with and without HPS, for example in case of pulmonary artery thromboembolia development. The conducted study shows that signs of systemic vasodilation in liver disease can be revealed by chest CT; however, these radiological signs do not have a significant role in the HPS diagnosis [39]. Only two small-scale studies have been found, according to which dilation of the basilar pulmonary arteries is more frequently detected in patients with HPS compared to the patients with cirrhosis but without this syndrome [40–41].

Angiopulmonography is also rarely used for HPS diagnosis. This is due to the invasiveness of this method and its low sensitivity for intrapulmonary dilation detection. It is indicated in patients with severe hypoxemia and a low response to 100 % oxygen inhalation, as well as to make a decision on embolization of arteriovenous shunt [42].

In patients with HPS, impairment of external respiratory function can be manifested as a decrease in vital capacity and forced expiratory volume in 1 second (FEV_1) [2, 43].

The test for diffusing capacity of the lungs for carbon monoxide (DL_{CO}), which is often decreased in patients with HPS, is a more sensitive functional method of pulmonary function testing in such patients [2,43]. Based on the data from the study conducted by Moon-Seung Park and Min-Ho Lee in South Korea in 2012, diffusion defects are more common in patients with progressive liver disease and correlate with liver severity. The authors clearly demonstrated that minimal changes in spirometry parameters in the form of a mild decrease in total lung capacity in patients with HPS was associated with is a decrease in pulmonary diffusion capacity. Therefore, changes in DL_{CO} may be an important diagnostic marker to predict hepatopulmonary syndrome development in patients with chronic liver disease [44].

The data from the study conducted by Z. Alipour et al. in 2020 to compare lung scintigraphy with technetium-99m human serum albumin and contrast-enhanced Echo-CG can be interesting. The obtained data showed that following lung scintigraphy findings, HPS was detected in 13 patients (48.1 %), compared to 5 (18.51 %) patients who were diagnosed using contrast-enhanced Echo-CG [45].

In 2022, A. Singhai et al. proposed the use of the 6-minute walk test as the screening method to reveal the risk of HPS development in patients with chronic liver diseases. The patients were asked to walk at their own tempo; the pulse oximetry was conducted at the beginning and at the end of the test. The test was positive at SpO2 <94 % or a decrease in SpO2 by ≥3 % of baseline. The study included 100 patients: 21 (21 %) patients were diagnosed with HPS based on the detected intrapulmonary shunts by contrast-enhanced transthoracic Echo-CG and arterial hypoxemia by arterial blood gas test. The 6-minute walk test was positive in 20 (95.23 %) patients with hepatopulmonary syndrome. The authors have demonstrated that the 6-minute walk test is an important instrument of this syndrome screening, having sensitivity of 95.24 % and specificity of 92.41 % [46].

Treatment

According to the published data, liver transplantation is the only effective method of HPS treatment that is available nowadays. In patients with HPS after liver transplantation, the five-year survival rate is 76 %–88 %, the ten-year survival rate is 64 % [47,48]. In patients without liver transplantation, the five-year survival rate is 5 %–12 %. There is evidence of improved blood gas

parameters (an increase in PaO2, a decrease in A-a gradient) 6–12 months after liver transplantation in patients with HPS [49,50]. Moreover, in patients who were on continuous oxygen therapy, the need for it often significantly decreases or disappears completely after liver transplantation [51].

Another method of surgical treatment for HPS can be transjugular intrahepatic portosystemic shunt (TIPS), which reduces hypoxemia due to reduced severity of portal hypertension. However, currently there are not enough studies, meeting the requirements of evidence-based medicine to form a final opinion on the effectiveness of this method in patients with HPS [52, 53]. The same could be said about embolization of arteriovenous shunts [42], which is associated with better oxygenation after embolization of arteriovenous malformation by placing the spiral into the feeding artery proximal to the malformation [54].

In patients with HPS, long-term oxygen therapy is recommended for severe hypoxemia; however, but no sufficient data on the effect of oxygen therapy on survival rate and disease prognosis could be found. There are two clinical case reports published in 2007 by Japanese researches describing liver function improvement following long-term oxygen therapy [45].

Currently available non-surgical methods of treatment for HPS are also low effective or poorly studied. The majority of these studies were conducted on animals [55–60].

During the literature search, 13 articles on non-surgical methods of HPS treatment in humans have been found. In these studies, the main purposes of treatment were NO-mediated pulmonary vasodilation and angiogenesis induction by proinflammatory cytokines. The most well-studied substance is pentoxifylline, a TNF-α inhibitor that reduces NO production by inhibiting eNOS. However, the results of its use in patients with HPS are contradictory [61]. Gupta LB et al. (2008) have found that pentoxifylline 400 mg three times daily improved oxygenation and reduced the level of TNF-α in 9 patients with HPS [62]. However, the results of another group of researchers demonstrated the absence of a significant therapeutic effect in patients with the studied syndrome and significant gastrointestinal side effects [63].

Garlic in the treatment of HPS has been shown to have unexpected efficacy (although it has not been tested on animals, and its true mechanism of action is not understood). A comparative study to assess garlic oil capsules versus placebo with a total sample size of 41 patients with HPS, and another non-controlled study involving 15 patients demonstrated favorable results with improved oxygenation and other symptoms [64, 65].

When injected intravenously, methylene blue, which is an oxidant limiting NO-mediated vasodilation by blocking stimulation of soluble guanylate cyclase by NO, reduced intrapulmonary shunting and improved oxygenation in experimental models and in a few patients with HPS [55, 56].

Indometacin (a cyclooxygenase inhibitor) was found to have a positive effect, which was considered to be due to a decrease in the synthesis of vasodilator eicosanoids that can impair gas exchange [66]. According to H. Silva et al., mycophenolate mofetil (an immunosuppressant) was also demonstrated to be effective in HPS treatment. However, neither indometacin nor mycophenolate have been studied in large randomized clinical trials [67].

There have been no data obtained on the efficacy of octreotide (somatostatin analog) in patients with liver cirrhosis [68], norfloxacin (antibiotic) [57], N-nitro-L-arginine methyl ester (NO synthesis inhibitor) [69], almitrine bismesylate (analeptic) [70], paroxetine (antidepressant) [71] in patients with HPS.

It should be noted that experimental studies have demonstrated the efficacy of norfloxacin in the treatment of HPS in rats [25]. This may be explained by the fact that the HPS rate model is significantly different from HPS with liver cirrhosis in humans. In the experimental model, the liver damage was caused by ligation of the bile ducts, whereas in the patient with HPS, the causes of liver cirrhosis are multiple [57].

Sorafenib (an antitumor agent) can become a promising option: in experimental models it improved oxygenation by reducing VEGH-mediated angiogenesis (VEGH, vascular endothelial growth factor) and suppressing eNOS activation by inhibiting tyrosine kinase receptor [58,59].

Another medicinal product that requires further study may be rosuvastatin. In 2015, Ching-Chih Chang et al. came to the view that it reduces A-a gradient, hypoxemia, intrapulmonary shunts, and VEGF and TNF-α plasma levels in experimental rat models, which may allow its use in the treatment of HPS [60]. However, it should be noted that there are currently insufficient data on the complete safety of this medicinal product in patients with liver cirrhosis.

Conclusion

Based on the analysis of the data published from January 2017 to August 2022, the following conclusions may be made.

Hepatopulmonary syndrome is a common and severe complication of chronic liver disease, which can worsen patients' quality of life and increase mortality rates.

Currently, there are clear criteria for HPS diagnosis; however, their use in routine practice is still difficult due to its invasiveness, inaccessibility, and high cost.

According to the published data, if hepatopulmonary syndrome is suspected in a patient with liver cirrhosis, hypoxemia assessment may be recommended, starting with oxygen saturation evaluation by pulseoximetry in a sitting or lying position [10, 72]. However, the evidence base of these recommendations was insufficient, and the patient should undergo further examination in the specialized center.

The available data on the role of respiratory function, diffusing capacity of the lungs, lung scintigraphy, Echo-CG with targeted examination of right heart function, 6-minute walk test in the diagnosis of HPS are scattered and insufficiently systematize.

It is necessary to continue the search for new methods of HPS diagnosis and to develop doctor-support programs (algorithms) for its early detection. This approach will improve the prognosis in patients with chronic liver disease and allow general practitioners to carry out their screening in order to identify and timely refer such patients to a liver transplantation center.

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