Hepatopulmonary syndrome in noncirrhotic patients with chronic viral hepatitis

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Background Hepatopulmonary syndrome (HPS) is hypoxemia and functional intrapulmonary right-to-left shunts in patients with liver disease. It is a well-known complication of liver cirrhosis, portal hypertension, and acute liver failure.

Aim The aim of this study was to determine the extent to which pulmonary functions were affected and the possible existence of HPS in noncirrhotic patients with chronic viral hepatitis.

Patients and methods Lung function tests were carried out on 60 patients with chronic viral hepatitis (43 with hepatitis C and 17 with hepatitis B). All hypoxemic patients or patients with reduced diffusion capacity were subjected to contrast echocardiography to demonstrate intrapulmonary shunting.

Results Twelve patients showed pulmonary dysfunction. Only seven of 60 patients (11.67%) showed hypoxemia. Intrapulmonary shunting was observed in three of those 12 patients. Two of these patients fulfilled the diagnostic criteria of HPS.

Conclusion HPS exists in some patients with chronic viral hepatitis and is thus not restricted to patients with end-stage liver disease. *Egypt J Broncho* 2014 8:175–180

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Introduction

Hepatopulmonary syndrome (HPS) is a frequent complication of end-stage liver disease. Clinically, it is defined as platypnea (dyspnea increasing in the upright position) and hypoxemia in patients with liver disease in the absence of a primary cardiopulmonary disease. Pathologically, it is a triad of chronic liver disease, hypoxemia, and intrapulmonary vasodilatation in the absence of primary cardiopulmonary disease [1,2].

The pathogenic mechanisms underlying HPS are not yet fully understood. Precapillary and capillary vasodilatation in the lung most probably results in an impaired oxygenation of the central capillary bloodstream resembling intrapulmonary right-to-left shunting [3]. In addition, hypoxic vasoconstriction in poorly ventilated lung areas (Euler–Liljestrand reflex) is frequently impaired in patients with HPS, thereby contributing toward the observed hypoxemia [4,5].

The diagnosis of HPS is established by the detection of combined functional and anatomical abnormalities. The functional one is hypoxemia, whereas the anatomical abnormality is the detection of intrapulmonary vasodilatation and functional pulmonary right-to-left shunting [6–11].

Blood gas analysis in the supine and upright positions frequently indicates deoxygenation in the upright position (orthodeoxia).

The simplest method to detect pulmonary vascular dilatation is contrast-enhanced transthoracic echocardiography. The test depends on the fact that microbubbles do not pass through normal capillaries (normal range of the capillary diameter, <8 to 15 μm). After the administration of agitated saline in a peripheral vein, microbubble opacification of the left atrium within three to six cardiac cycles after right-atrial opacification indicates microbubble passage through an abnormally dilated vascular bed [3,4].

The reported prevalence of HPS in end-stage liver disease ranges from 10 to 17% [12,13]. HPS occurs predominantly in patients with liver cirrhosis and/or portal hypertension of varying etiology. In addition, HPS may develop in some patients with acute liver failure [14]. To the best of our knowledge, the prevalence of lung function abnormalities and HPS in patients with chronic liver disease without cirrhosis and portal hypertension is unknown. Thus, the aim of this study was to evaluate the frequency and extent of pulmonary dysfunction in noncirrhotic patients with chronic viral hepatitis with respect to the biochemical and histological disease activity.

Patients and methods

All participants were patients with chronic viral hepatitis referred to the outpatient clinics of Internal Medicine and Tropical Medicine Departments,

Menoufiya University Hospital, Egypt, between January and December 2012.

All patients were subjected to liver biopsy, routine liver function tests, and abdominal ultrasound. Routine liver function tests included serum bilirubin, aspartate transaminase, alanine transaminase (ALT), g globulin, and synthetic functions parameters (albumin and prothrombin time). The inclusion criteria were the histological documentation of noncirrhotic hepatitis, normal bilirubin and liver synthesis parameters, a platelet count of at least 150×10^3/ml, a sonographic documented spleen size of less than 15 cm, and a portal vein flow above 12 cm/s. Disease activity and the extent of fibrosis were assessed histologically according to the 1994 revised classification of chronic hepatitis [15].

Any patient with liver cirrhosis, portal hypertension, or any abnormalities of synthetic liver function tests were excluded.

Informed consents were obtained from the patients before enrollment in the study. Patients with primary chest disease were excluded after a thorough clinical examination and posteroanterior view chest radiograph. Sixty patients (38 men and 22 women) fulfilled the inclusion criteria of the study. Thirty-five patients (58.3%) were cigarette smokers (15 ± 1.3 pack-years). Patients who had quit smoking less than 1 year earlier were also considered to be smokers. Dyspnea on exertion was graded according to the American Thoracic Society Shortness of Breath Scale [16].

Serological tests

Forty-three patients (71.6%) had chronic hepatitis C and 17 patients (28.3%) had chronic hepatitis B. The diagnosis was established by commercially available enzyme-linked immunoassays for anti-hepatitis C virus (anti-HCV), HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc combined with serum HBV-DNA and HCV-RNA determination by PCR [17]. Viral infection was serologically documented for at least 6 months.

Pulmonary function tests

Pulmonary function tests were performed in a whole-body plethysmograph (Jaeger, Wurzburg, Germany) meeting the guidelines of the American Thoracic Society [18,19]. Measurements included the following:

Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), airway resistance (Raw), and total lung capacity (TLC).

Diffusion capacity for carbon monoxide (DLCO) was quantified using the single breath method. Values were corrected for blood hemoglobin levels. The best of three consecutive recordings was used for analysis and expressed as percent predicted.

Arterial blood gas (ABG) analyses were carried out for all patients. The test was repeated in the supine and upright positions for patients with hypoxemia or reduced diffusion capacity.

Echocardiography

In patients with a diffusion capacity of less than 70% predicted and/or hypoxemia (PaO_2 < 70 mmHg), transthoracic contrast echocardiography was performed. Ten milliliters of a D-galactose suspension (Echovist; Schering, Berlin, Germany) were administered as a bolus through the left cubital vein. After intravenous administration, the galactose suspension resolves and free gas-filled microbubbles with a mean diameter of 3 μm are released into the bloodstream. Under physiological conditions, these microbubbles become completely dissolved during passage of the pulmonary capillary bed [20,21].

Therefore, after intravenous administration, Echovist appearing in the left atrium or ventricle is because of the presence of a cardiac or a pulmonary right-to-left shunt [22]. A parasternal view, showing the left atrium and the left ventricle, and an apical four-chamber view were obtained by ultrasound using a 2.5-MHz transducer (V 219; Siemens medical engineering company, California, USA).

Detection of microbubbles in the left ventricle after more than three heart cycles following the appearance of the contrast agent in the right ventricle was considered to be a positive result, indicating intrapulmonary shunting. Patients with primary congenital heart disease were excluded from the study.

Statistical analysis

Data are presented as mean ± SD (range). Clinical and functional parameters were compared using the Mann–Whitney *U*-test. A probability limit of *P*-value less than 0.05 was considered significant. The relationships between pulmonary function parameters and liver function tests were determined by Spearman's rank linear correlation. Statistical analyses were carried out using the SPSS program, version 4.5 (Abacus Concepts, Berkeley, California, USA).

Results

The current study included 43 patients with chronic hepatitis C as well as 17 patients with chronic hepatitis B. All patients with chronic hepatitis C were positive for anti-HCV. HBsAg and anti-HBc were detectable in all 17 patients with chronic hepatitis B. All cases were documented by RT-PCR as discussed before.

In all patients, bilirubin, liver synthesis parameters (albumin, prothrombin time), and platelet count were within the normal limits. The mean ALT, aspartate transaminase, and γ globulin values were elevated. However, ALT values were normal in three patients (17.6%) with chronic hepatitis B and in three patients (6.9%) with chronic hepatitis C. Other demographic criteria of all patients are presented in Table 1.

Stage of liver disease

Histological examination showed minimal to mild chronic hepatitis in 35 of the 60 patients (58.0%) and moderate to severe chronic hepatitis in 25 patients (42%). Fibrosis grade 3 was found in 19 of the 60 patients (31.6%) as shown in Table 1. Liver cirrhosis was excluded in all patients.

Pulmonary functions

The mean results of lung function tests, DLCO, and ABG analyses were within the normal range, irrespective of the type of viral infection and smoking status (Table 2). All values are shown as mean. Values are expressed as percent predicted. Normal reference ranges: 70–100 mmHg for PaO_2, 35–45 mmHg for $PaCO_2$, and 7.35–7.45 for pH.

There was no correlation between lung function parameters (FEV_1, FVC, FEV_1/FVC, TLC, or Raw), DLCO measurements, or arterial oxygen tension and aminotransaminases, bilirubin, albumin, or prothrombin time. The results of lung function tests, DLCO measurements, and ABG analyses indicated no significant differences between patients with chronic hepatitis B and C. Nor was there any relationship between pulmonary function parameters and the histological degree of inflammation and fibrosis.

FEV_1 and DLCO results of cigarette smokers were lower than those in nonsmokers (data not shown).

The American Thoracic Society defined pulmonary dysfunction by impaired DLCO, hypoxemia, or obstructive or restrictive ventilation defects [23,24]. Accordingly, in the present work, four of 60 patients (6.6%) were diagnosed with pulmonary dysfunction. Spirometry showed chronic obstructive pulmonary disease (FEV_1<70% predicted) in four of 60 patients (6.6%; range FEV_1: 64.9–69.8% predicted). Three patients had mild chronic obstructive bronchitis. In addition, two of the four patients had radiological evidence of emphysema, whereas chest radiographs were normal in the other two patients. Three of the four patients with obstructive pulmonary disease were smokers; one of them has dyspnea on exertion.

Mild restrictive ventilatory defects (TLC and/or FVC <70% predicted) were observed in three different patients (5%). Two of these patients had a TLC reduction below 70% predicted (63.4 and 66.8% predicted, respectively) and one patient had an FVC reduction to 69.6% predicted and a TLC of 71.3% predicted in the presence of a normal FEV_1/FVC ratio. One of these three patients was a smoker and another patient had dyspnea on exertion. None of the patients with restrictive ventilation defects had an impaired gas exchange or hypoxemia. Further evaluation, including chest radiographs, did not indicate any abnormalities explaining the consistently reduced vital capacity.

A reduction in the DLCO to less than 70% predicted was the most frequent lung function abnormality observed in patients with chronic viral hepatitis. There was no correlation between DLCO measurements and the degree of fibrosis. Seven of 60 patients (11.6%) had a DLCO of less than 70% predicted (mean DLCO, 67.7%; minimum, 62.5%; maximum, 69.2%). Six of the patients

Table 1 Demographic, biochemical, serological, and histological characteristics of all patients

Like head of table	Patients with chronic hepatitis C	Patients with chronic hepatitis B
Male/female	9/8	29/14
Age (mean ± SD) (years)	32.9 ± 11.3	40.2 ± 12.8
Smokers/nonsmokers	5/12	10/33
AST (U/l)	73.6 ± 23.7	68.4 ± 19.6
ALT (U/l)	48.6 ± 8.4	37.4 ± 9.1
Bilirubin (mg/l)	1.8 ± 0.4	1.4 ± 0.1
Albumin (g/l)	4.7 ± 1.6	4.9 ± 1.4
Prothrombin time (%)	85.7 ± 12.7	91.5 ± 16.8
γ Globulin (g/l)	1.9 ± 0.6	1.6 ± 0.4
Platelets count (10^3/ml)	182 ± 33.6	210 ± 41.2
HBsAg+	17	0
Anti-HCV+	0	43
Minimal to mild chronic hepatitis	11	24
Moderate to severe chronic hepatitis	6	19
Fibrosis score 0–2	10	31
Fibrosis score 3	7	12
Fibrosis score 4	0	0

ALT, alanine transaminase; AST, aspartate transaminase; HCV, hepatitis C virus.

Table 2 Pulmonary function tests in all patients

Data %	Patients with chronic hepatitis C	Patients with chronic hepatitis B
FEV_1	88	93
FVC	86	89
FEV_1/FVC	102	104
TLC	104	101
Raw	58	61
DLCO	96	98
$PaCO_2$ (mmHg)	40	42
PaO_2 (mmHg)	88	86
pH	7.36	7.49

DLCO, diffusion capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; Raw, airway resistance; TLC, total lung capacity.

were smokers. Spirometry and chest radiographs were normal in all patients with a reduced DLCO.

Hepatopulmonary syndrome

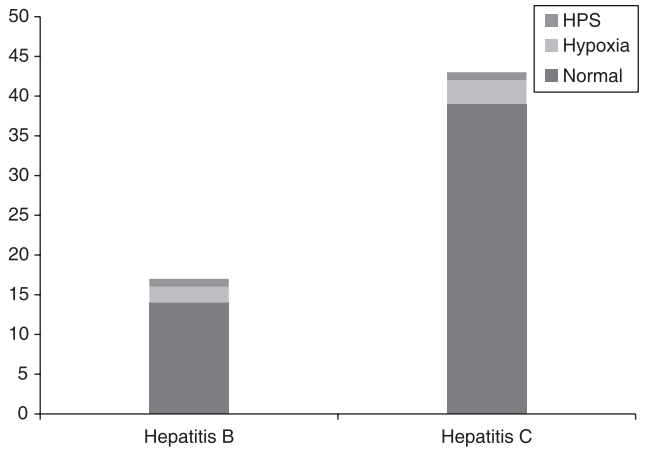
Hypoxemia (PO_2 < 70 mmHg) was observed in seven of the 60 patients (11.6%). PCO_2 values were not affected. No relationship was found between the extent of hypoxemia and fibrosis. Six of the seven patients were active smokers.

Two patients complained of dyspnea on exertion. Results of chest radiographs and lung function were normal in all seven patients. Contrast echocardiography indicated intrapulmonary right-to-left shunting in two patients, including one patient with a marked DLCO reduction. Only these two patients fulfilled the criteria of HPS, that is, hypoxemia and intrapulmonary vasodilatation (Fig. 1). In a third patient with isolated DLCO reduction, echocardiography showed functional intrapulmonary right-to-left shunting; however, this was not sufficient to cause hypoxemia. A small decrease in the arterial oxygen tension in the upright position compared with the supine position was observed in five patients, including the two patients with HPS.

Discussion

There is no doubt that the incidences of liver diseases have been increasing in the last few years. Most of the burden arises from direct morbidity and mortality from the disease and its complications. However, extra hepatic manifestations are a hidden burden that the physicians must be aware of, along with its diagnosis and management. Dyspnea in patients with liver disease is one of the extra hepatic manifestations that affect the quality of life. In addition, it may be an indicator of an underling grave complication such as pleural effusion, pericardial effusion, or HPS in patients with liver disease. In the present study, mild dyspnea was found in 20% of patients (12/60) with chronic viral hepatitis. This is in agreement with other reported prevalences of dyspnea in other epidemiological studies [23,24]. This may be explained by the fact that dyspnea may be caused by smoking habits and body weight. Most of the patients who had dyspnea were smokers.

Fig. 1



Prevalence of hypoxia and hepatopulmonary syndrome (HPS) in all patients.

Pulmonary dysfunction in chronic liver disease may be secondary to either liver or pulmonary disease, or both. In the present study, pulmonary dysfunction was found in 15% of patients (9/60) with chronic viral hepatitis without cirrhosis or portal hypertension. Two of them also fulfilled the criteria of HPS. However, in the majority of patients with chronic viral hepatitis, abnormalities in pulmonary function, in particular hypoxemia and reduced diffusion capacity were obviously related to smoking (Table 3).

As reported for patients with liver cirrhosis, DLCO was the most frequently affected parameter in patients with chronic viral hepatitis [20,21]. However, the frequency of DLCO reduction was significantly lower than the reported incidence of ~50% in patients with end-stage liver disease. Nevertheless, without evidence of ventilation–perfusion mismatch, veno-occlusive disease, or interstitial lung disease, the pathomechanisms underlying DLCO impairment in chronic liver disease remain unclear [25].

Functional intrapulmonary shunting could be observed in three of the 17 patients with DLCO reduction and/or hypoxemia by contrast echocardiography. On strict application of the diagnostic criteria, HPS was diagnosed in two of the 60 noncirrhotic patients with chronic viral hepatitis (Fig. 1). Thus, we could show in this study that the development of HPS is not restricted to the presence of liver cirrhosis, portal hypertension, or acute liver failure, and that it may also occur in noncirrhotic patients with chronic hepatitis. Of interest, transient HPS was also reported in patients with acute nonfulminant hepatitis A [26] and patients with acute hypoxic hepatitis [27].

We considered the possibility of subclinical portal hypertension or liver cirrhosis in these patients. In contrast to patients with liver cirrhosis, clinical symptoms of HPS, platypnea, or significant orthodeoxia were not observed in our patients. This finding may be explained by the mild degree of hypoxemia observed in patients with chronic viral hepatitis than in patients with end-stage liver disease.

The observed prevalence of HPS in patients with chronic hepatitis B and C (1.1%) is considerably lower than the

Table 3 Volumetric lung function and diffusion capacity for carbon monoxide in all patients with respect to smoking

Data %	Smokers	Nonsmokers	*P*-value
FEV_1	83	89	0.34
FVC	82	87	0.14
FEV_1/FVC	101	102	0.51
TLC	89	97	0.26
Raw	53	61	0.23
DLCO	91	98	0.57

DLCO, diffusion capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; Raw, airway resistance; TLC, total lung capacity.

reported prevalence of 34% in Egyptian [28] patients with advanced liver disease and 13.3% in noncirrhotic patients with liver fibrosis [29]. In the present study, intrapulmonary vasodilatation with consecutive right-to-left shunting explained the observed diffusion defect in only two of 11 patients.

Recently, an improved sensitivity for the detection of intrapulmonary shunts has been reported for transesophageal compared with transthoracic echocardiography [22]. Thus, the prevalence of intrapulmonary vasodilatation and HPS may have been underestimated in our noncirrhotic patients with hypoxemia or impaired diffusion capacity.

The pathophysiological mechanisms leading to intrapulmonary vasodilatation in patients with liver cirrhosis or portal hypertension are not yet fully understood. An imbalance between pulmonary vasodilators and vasoconstrictors, caused by a reduced production or an insufficient clearance of these factors by the injured liver, has been assumed to be involved in the pathogenesis of HPS. Recently, an increased endothelial nitric oxide synthase concentration within the lung has been shown to be related to pulmonary gas exchange abnormalities and intrapulmonary vascular dilatation. Furthermore, the reported increase in endothelial nitric oxide synthase in the pulmonary vasculature was associated with an increased production and activity of nitric oxide, resulting in an impaired responsiveness to vasoconstrictors. Correspondingly, increased nitric oxide levels in exhaled air have been shown in patients with HPS compared with cirrhotic patients without HPS [24,30,31]. This study was not designed to evaluate the potential causes of pulmonary dysfunction observed in patients with chronic viral hepatitis.

HCV is reported to induce the expression of hepatic nitric oxide synthase, leading to elevated nitric oxide serum levels in some patients with chronic hepatitis C [32]. Thus, it is tempting to speculate that nitric oxide may also contribute toward the observed intrapulmonary dilatation in some of our patients with chronic hepatitis C.

In the present study, pulmonary dysfunction without any evidence of primary cardiopulmonary disease was observed in 8.5% of noncirrhotic patients with chronic viral hepatitis. The development of pulmonary abnormalities seems to be a gradual process and may occur early in the natural course of chronic liver disease. However, we could not identify risk factors allowing the early identification of patients at risk for lung dysfunction. As a consequence, patients with chronic viral hepatitis, in particular those with respiratory symptoms, should be monitored with pulmonary function tests.

HPS, as a possible cause of an impaired gas exchange, was found only in a small percentage of our noncirrhotic patients. The prognosis of HPS in patients with chronic hepatitis in the absence of liver cirrhosis has to be determined by clinical long-term follow-up.

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Conflicts of interest

None declared.

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