Pulmonary Function Testing in Children with Chronic Liver Disease

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Abstract:

Hepatopulmonary syndrome (HPS) is a rare but severe complication in children with chronic liver disease (CLD) that may necessitate "urgent" liver transplantation. This study aimed at studying the feasibility and usefulness of pulmonary function testing (PFT) in the diagnosis of lung affections in a group of Egyptian children with chronic liver disease (CLD) in order to diagnose HPS in them. Twenty five Egyptian children (aged 10-16 years with a mean of 12.4 ±1.8 years) with different causes of CLD and 8 age-matched, healthy controls were subjected to arterial blood gas analysis, PFT and measurement of mean pulmonary artery pressure (MPAP). Arterial oxygen pressure (PaO_2) less than 80 mmHg was present in 10 patients, forced expiratory volume in 1 second (FEV_1) less than 80% predicted in 15, forced vital capacity (FVC) less than 80% predicted in 15 and the ratio FEV_1 : FVC less than 65% predicted in 20. Carbon monoxide diffusion capacity (DL_{CO}) was less than 80% predicted in 15 patients and 4 controls. Hypoxemia occurred in 60% of patients with decreased DL_{CO} but none of controls. MPAP was significantly lower in patients than controls, it increased with exercise but not significantly. Neither portal hypertension nor sclerotherapy showed a significant relation to hypoxemia, or low MPAP. Also the duration of CLD, its histological severity and grading of fibrosis were not related to any of the pulmonary function tests.

Conclusion: *Arterial hypoxemia is present in CLD. PFT was rather "tedious" but non-invasive investigation in children with CLD. It did demonstrate obstructive airway as well as diffusion defects in these children. Therefore we may recommend PFT in the work–up of children with CLD, particularly if liver transplantation is contemplated.*

Abbreviations:

HPS: hepatopulmonary syndrome, PFT: pulmonary function testing, CLD: chronic liver disease, MPAP: mean pulmonary artery pressure, PaO_2: arterial oxygen pressure, DL_{CO}: carbon monoxide diffusion capacity, ABS: arterial blood gas, CEE: contrast enhanced echocardiography, LTx: liver transplantation, US: ultrasonography, SVC: slow vital capacity, FVC: forced vital capacity, FEV_1: forced expiratory volume in 1 second, FEF_{25-75}: Forced mid expiratory flow rate.

Introduction:

The hepatopulmonary syndrome (HPS) is defined as arterial hypoxemia (arterial oxygen pressure or PaO_2 < 80 mmHg) which occurs in patients with liver cirrhosis in the absence of a primary cardiorespiratory disease.[1] Auand et al.,[2] in 2001, reported HPS in 17.5% of cirrhotic adults. In children it may occur at any age and with many types of liver diseases.[3] Mowat,[4] in 1994, estimated the incidence of hypoxemia to reach 36% of children with cirrhosis. Hypoxemia occurs due to intrapulmonary vasodilatations resulting in arterio-venous shunting. The cause(s) of these intrapulmonary vascular dilatations is not yet clearly known, but increased circulation of pulmonary vasodilator(s) is the favored mechanism,[5] along with blunted pulmonary vasoconstriction response to hypoxia.[6]

According to Lange and Stoller,[7] in 1995, diagnosis of the HPS depends upon arterial blood gas (ABG) analysis, pulmonary function testing (PFT) and carbon monoxide diffusion capacity (DL_{co}). Chest radiographs, contrast enhanced echocardiography (CEE), perfusion lung scanning and pulmonary arteriography may be also needed.[8]

HPS may worsen if left even with clinically stable liver disease, but may reverse after liver transplantation (LTx). Therefore LTx may be "urgently" indicated in this setting.[9]

We aimed at studying the feasibility and usefulness of PFT in the diagnosis of lung affections in a group of Egyptian children with chronic liver disease (CLD) in order to diagnose HPS in them.

Subjects and Methods:

We enrolled 25 children from the Hepatology Unit, Cairo University New Children Hospital, diagnosed as CLD and free of ascites and/or hydrothorax. Their age varied from 10-16 years with a mean of 12.4 ±1.8 years. Eleven were females and 14 were males. Eight healthy children of matched age (mean 13.3 ± 1.4 years) and sex were taken as controls.

All patients were subjected to:

- Careful history and thorough clinical examination.

- Laboratory investigations including liver functions, complete blood picture, hepatitis markers, immunoglobulins and auto antibodies.
- Abdominal ultrasonography (US), upper gastrointestinal endoscopy and percutaneous liver biopsy.
- Chest X-ray, electrocardiography and echocardiography were done as needed.

All patients and controls were subjected to:-

- ABG analysis at rest and after 15 minutes of 100% O_2 inhalation.
- Ventilatory PFT using a dry seal Spirometer (*Nodel^T Auto link ,TT Morgan, England*) and measuring:-
  1. Slow vital capacity (SVC): by allowing the child to inspire maximally and then exhale completely without time limit.
  2. Forced vital capacity (FVC): the child inspires and expires maximally and as rapid as possible.
  3. Forced expiratory volume in one second (FEV_1): which is the volume exhaled in the first second.
  4. Forced expiratory volume in one second/forced vital capacity (FEV_1/ FVC) ratio:-

$$FEV_1\ \% = \frac{FEV_1 \times 100}{FVC}$$

  5. Forced mid expiratory flow rate (FEF_{25-75}): which is the time required to expire the middle 50% of the FVC.
  6. Peak expiratory flow rate which is the maximum flow rate attained during FVC maneuver
- DL_{CO} using the single breath method from a Spirometer containing a gas mixture of 0.3% CO, 10% helium, 21% oxygen and the rest nitrogen then holds the breath for 10 seconds.

$$DL_{CO} = \frac{VCO}{PaCO - PcCO}$$

  Where VCO= milliliters of CO transferred per minute, PaCO = mean alveolar partial pressure of CO, PcCO = mean capillary partial pressure of CO, usually assumed to be zero.
- MPAP was measured at rest and after maximum exercise by non invasive method using Morgan Benchmark^T exercise test, which included a bicycle ergometer (Med fit 1000_S).

Statistical Methods:

Statistical analysis was presented as mean ± SD and frequency distributions (numbers and percentages). Analytical tests used included unpaired Student t test, analysis of variance (F test), post hoc test and chi square test. Correlation and regression analysis were performed when appropriate. Significance level of probability (p) with a value < 0.05 was used.

Results and Discussion:

The results of this study are illustrated in tables I-X and figures 1-3.

Table I. Etiological classification of the studied cases

Diagnosis	Number (n=25)	%
Chronic hepatitis C	4	16
Autoimmune hepatitis	6	24
Chronic hepatitis B	2	8
Glycogen storage disease	1	4
Wilson disease	1	4
Chronic hepatitis B and C	1	4
Chronic hepatitis of unknown etiology	9	36
Congenital hepatic fibrosis	1	4

Arterial hypoxemia is the hallmark of the HPS with a reported incidence in adults with CLD ranging from 13 – 47 %.[10]

In our study, 10 patients (40%) had arterial hypoxemia (PaO_2 <80 mmHg) at rest, while 15 (60%) had normal arterial oxygen tension (table II).

Table II. Incidence of arterial hypoxemia among patients

PaO_2	Number	%
Normal (≥ 80 mm Hg)	15	60
Decreased (< 80 mm Hg)	10	40

This incidence is comparable to the higher incidence reported in adults.[10] The mean values of PaO_2, SaO_2 and pH in our patients at rest were statistically significantly lower than that of controls which increased after 15 minutes of 100% O_2 inhalation but still statistically significantly lower than those of controls (table III) .

Table III. Mean values of arterial blood gases among cases and controls (at rest and after 15 minutes of O_2 inhalation)

Arterial blood gases	Patients (n=25) Mean ± S.D	Controls (n=8) Mean ± S.D	p value
Measured at rest:			
Pa O_2 (mmHg)	78.8 ± 0.7	94.7± 8.1	0.04*
Sa O_2 (%)	86.4 ± 12.03	96.4 ± 0.7%	0.02*
pH	7.2± 0.8	7.39 ± 0.03	0.50
After 15 min of 100% O_2 inhalation			
Pa O_2 (mmHg)	86.8±22.3	103.6±5.4	0.04*
Sa O_2 (%	90.02±9.30%	97.05 ± 0.26	0.04*
pH	7.39±0.02	7.4± 0.01	0.20

** Statistically Significant*

This is explained by the intrapulmonary vascular dilatations causing diffusion/perfusion impairment. Oxygen provides enough driving force to overcome this abnormality.[7] The incidence of hypoxemia was not significantly related to the duration of illness, histological severity and necroinflammatory activity, or histological grading according to the stage of fibrosis (figures 1-3).

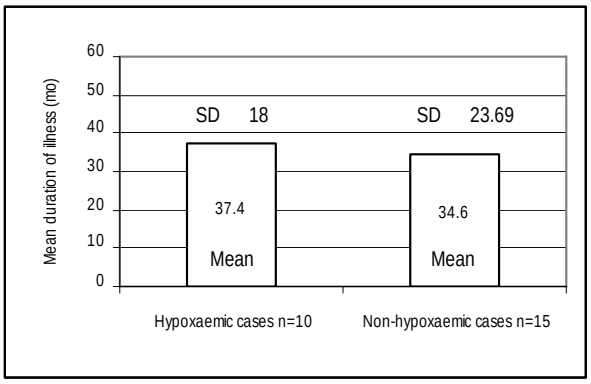


Fig.1: Comparison of the duration of illness between hypoxemic and non-hypoxemic cases

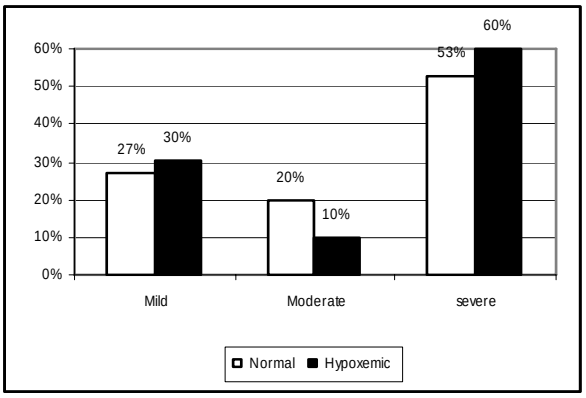


Fig.2: Grading of histological severity (necroinflammatory activity) in normal and hypoxemic cases (by application of histological activity index of Knodel, 1981)

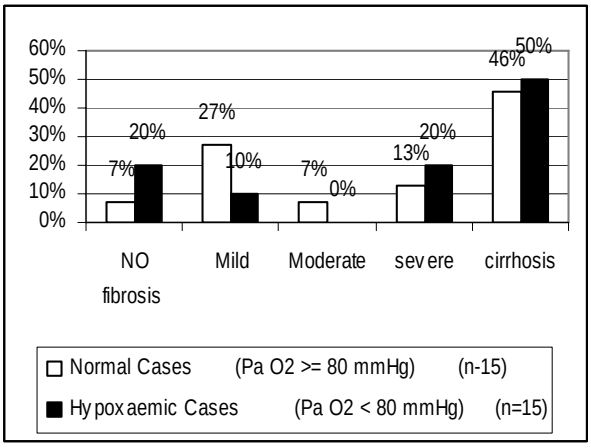


Fig.3: Histological staging (based on the extent of fibrosis and development of cirrhosis) in normal and hypoxemic cases.

This was also reported by Rodriguez–Roisin et al.,[1] in 1993 and by Krowka et al.,[11] in 2000, who showed no consistent relation between the severity of liver disease and the degree of hypoxemia. Therefore, severe liver dysfunction is not a mandatory criterion for diagnosis of the HPS.

Regarding pulmonary function testing (table IV), the mean values of SVC, FVC, FEV_1 and PEFR in patients were statistically significantly lower than the corresponding values in controls. This was not achieved when lung volumes were compared as percentage of the predicted value for age, sex, weight and height which could be explained by the statistically significant difference in mean weight and height between patients and control group.

Table IV. Mean values of lung volumes and their percentage of the predicated value among patients and controls

	Patients (n=25) **Mean ± S.D**	**Controls** (n=8) **Mean ± S.D**	**P value**
SVC (L)	1.82 ± 0.33	2.66 ± 0.44	0.001*
SVC %*	74.56 ± 12.36	76.50 ± 9.69	0.600
FVC (L)	1.8 ± 0.36	2.6 ± 0.33	0.001*
FVC%*	80.86 ± 19.67	83.0 ± 11.84	0.700
FEV1 (L)	1.6 ± 0.32	2.37 ± 0.38	0.001*
FEV1 %*	80.8 ±19.09	83.87 ± 9.44	0.600
FEV1/FVC ratio	90.83 ± 2.57	90.87 ± 5.69	0.900
FEV1/FVC%*	106.3 ± 7.42	106.5 ± 6.9	0.900
F25-75 (L/sec)	2.27 ± 1.1	2.86 ± 0.9	0.100
F25-75%*	83.04 32.12	89.12 ± 19.89	0.600
PEER (L/sec)	3.67 ± 1.11	5.88 ± 1.68	0.001*
PEER%*	74.87 ± 24.56	95.50 ± 16.07	0.060
PIFR (L/sec)	2.44 ± 0.82	3.95 ± 1.57	0.001*
PIFR%*	42.59 ± 12.68	54.5 ± 18.72	0.050

** statistically significant*

The forced mid expiratory flow rate (FEF_{25-75}) was significantly low in eight patients and none of the controls (table V). This may suggest early small airway abnormalities as suggested by Ruppel,[12] in 1991. In cirrhosis, reduced plasma osmotic pressure may cause a cuff of fluid surrounding the terminal airways.[13]

Table V. Incidence of abnormal lung volumes among patients and controls

Abnormal lung volume	**Patients** (n = 25)	**Controls** (n = 8)	**p value**
SVC < 80%	14	6	0.6
FVC < 80%	15	3	0.2
FEV1 < 80%	15	4	0.5
FEV/FVC (<65% or >85%)	20	6	0.6
F25-75 (<65%)	8	0	0.01*
PEFR (<80%)	13	2	0.18

** Statistically Significant*

In this study, there was no statistically significant abnormalities in lung volumes characteristic of restrictive lung defect. This does not agree with Lange and Stoller,[7] who reported 25% incidence of restrictive pattern versus only 3 % air flow obstruction in cirrhosis.

Table VI. Carbon monoxide diffusion capacity in patients and controls

DL_{CO}	**Patients** (n= 25)	**Controls** (no = 8)
Normal value: 80% of the predicted	10 (40%)	4(50 %)
Abnormal: < 80% of the predicted	15 (60%)	4(50%)
P value	0.6	

DL_{CO} was low in 60% of our patients compared to 50% of controls (table VI). This is in contrast to Minidis et al,[14] in 1998, who reported that DL_{CO} is the most common lung function abnormality seen in the HPS. This might be explained by the air pollution in Cairo, the over populous capital of Egypt, with increased carboxyhemoglobin levels in controls causing significant carbon monoxide back pressure.[15] Sixty percent of the studied cases with reduced DL_{CO} were also hypoxemic (table VII).

Table VII. Relationship between the incidence of low DL_{CO} and arterial hypoxemia among patients

Cases with Abnormal DL_{CO}	Cases with Hypoxemia ($Pa O_2$ < 80 mmHg)	Normal cases ($Pa O_2$ ≥ 80 mm Hg)
(n=15)	9 case	6 cases
Percentage	60 %	40%
p value	0.01*	

** statistically significant*

In other studies, the incidence of hypoxemia ranged from 55%,[13] to 100% of patients with low DL_{CO}.[14] This might be explained by dilatations of the small pulmonary vessels or thickening of the walls of the small veins and capillaries by collagen.[16]

Table VIII. Comparison of MPAP± SD at rest and with maximum exercise among patients and controls

MPAP (mm Hg)	Patients (n=25) Mean ± S.D	Controls (n=8) Mean ± S.D	p value
At rest	11.24 ± 3.48	16.92 ± 3.31	0.001*
After max. exercise	18.8 ± 5.71	26.66 ± 4.15	0.001*

** statistically significant*

The MPAP (table VIII) at rest was significantly lower in patients than in controls. After maximum exercise, the mean value of MPAP increased but remained significantly lower in patients than in the control group, i.e. there is normal vasoconstriction reaction of the pulmonary vascular bed to exercise. This is opposite to the findings of Edell et al.,[17] in 1989, and Thorens and Junod,[18] in 1992, who reported that low pulmonary vascular resistance in cirrhotics failed to respond to hypoxia and exercise.

Portal hypertension, as evidenced by the presence of varices was found in 60% of the studied cases. There was no statistically significant relation between portal hypertension and low mean pulmonary artery pressure or hypoxemia (table IX).

Table IX. Relation between the incidence of portal hypertension, low MPAP and low PaO_2 in patients

	Patients with portal hypertension (n=15)		**Patients with no portal hypertension** (n=10)		
	Normal	**Low**	**Normal**	**Low**	**P**
MPAP	9 (60%)	6 (40%)	8 (75%)	2 (25%)	0.1
$Pa O_2$	9 (60%)	6 (40%)	6 (60%)	4 (40%)	0.1

This is in agreement with Scott et al,[10] in 1999, who reported that HPS may be seen in the absence or presence of portal hypertension.

In this study, no statistically significant relation could be found between sclerotherapy (only 5 cases) and the incidence of hypoxemia or low lung volumes (table X).

Table X. Relation between the incidences of hypoxemia (PaO_2 < 80 mmHg) and sclerotherapy in patients

Patients with history of sclerotherapy (n=5)		**Patients with no history of sclerotherapy** (n=20)	
Normoxemic patients	**Hypoxemic patients**	**Normoxemic patients**	**Hypoxemic patients**
3 (60 %)	2 (40 %)	12 (60 %)	8 (40 %)
p value = 0.1			

This agrees with Korula and Colleague[19] in 1986, who reported that sclerotherapy has no long term effects on pulmonary function tests. However, Samuels and Colleagues, in 1994,[20] found that sclerotherapy may cause significant restrictive pulmonary defects and decreased PaO_2 and vital capacity 24 hours after the procedure.

Conclusion:

Arterial hypoxemia does occur in children with CLD, therefore periodic checking of blood gases might be recommended in each child with chronic liver disease to diagnose this abnormality. We do not recommend PFT as a routine because they are tedious , costly and also abnormalities in lung volumes, flow rates , DL_{CO} and pulmonary vascular pressure are not always encountered in HPS and actually are not essential for its diagnosis. However, if LTx is contemplated , PFT are best evaluated preoperatively.

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