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Respiratory Mechanics, Respiratory Muscle Strength, Control of Ventilation and Gas Exchange in Patients with Autoimmune Liver Disease

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Abstract

Objectives: To assess respiratory elastance and resistive properties in patients with autoimmune liver disorders using the passive relaxation expiration technique and compare findings to a group of patients with non-autoimmune liver disease and control subjects. These findings were then related to control of ventilation and gas exchange. A secondary objective was to assess respiratory muscle strength and gas exchange and their relation to respiratory mechanics. **Methods**: Measurements included respiratory elastance and resistance using the passive relaxation method. Pulmonary function, gas exchange and control of ventilation were assessed using standard methods. **Results**: a) Compared to control subjects, Ers in patients with liver disease was on average 50% greater than in controls; b) mean respiratory resistance, expressed as the respiratory constants, K_1 and K_2 in the Rohrer relationship, $Pao/V' = K_1 + K_2V'$, was not different from control resistance; c) mean maximal inspiratory and maximal expiratory pressures averaged 36% and 55% of their respective control values; d) inspiratory occlusion pressure in 0.1 sec ($P_{0.1}$) was increased and negatively associated with FVC; and e) increases in $P_{0.1}$, mean inspiratory flow (Vt/Ti) and presence of respiratory alkalosis confirmed the increase in ventilatory drive. Despite inspiratory muscle weakness in patients, $P_{0.1}$/Pimax averaged 5-fold higher than in control subjects. **Conclusions**: Despite inspiratory muscle weakness and a V'_E similar to that in normal subjects, central drive is increased in patients with chronic liver disease. The increase in ventilatory drive is related to smaller lung volumes and weakly associated with increase in respiratory elastance. Findings confirm that $P_{0.1}$ is a reliable measure

of central drive and is an approach that can be used in the evaluation of control of ventilation in patients with chronic liver disease.

Keywords

Autoimmune Liver Disease, Control of Ventilation, Occlusion Pressure, Passive Relaxation Method, Primary Biliary Cirrhosis, Respiratory Elastance, Respiratory Resistance

1. Introduction

Autoimmune liver diseases include primary biliary sclerosis (PBC), primary sclerosing cholangitis and autoimmune hepatitis. This group of disorders is less often encountered in clinical practice than patients with alcoholic or steatorrheic liver disease. Subclinical alveolitis [1] [2] and pulmonary functional abnormalities [3] [4] have been reported in PBC patients without clinical evidence of lung involvement. There is extensive literature on aspects of gas transfer and exchange in patients with cirrhosis, much of which concerns the hepatopulmonary and portopulmonary hypertension syndromes [4] [5] [6] [7]. By contrast, information on respiratory elastance and resistance and their effect on control of ventilation in patients with autoimmune liver disease is relatively scarce [7].

In this study, we assessed respiratory mechanics using the passive relaxation expiratory technique in patients with autoimmune liver disorders and compared findings to a group of non-autoimmune related liver patients and control subjects. A second objective was to assess respiratory muscle strength and gas exchange and their relation to respiratory mechanics.

2. Methods

2.1. Patients

In this prospective observational study, stable, anicteric patients with autoimmune liver disease were screened in the clinic or hospital between June 1987 and February 2000. Individuals without cardiorespiratory or hepatic disorders were recruited as a control group. Autoimmune liver disease, including PBC, was confirmed according to the criteria of the American Association for the Study of Liver Diseases [8]. Patients with PBC had positive antimitochondrial antibody tests. Diagnosis of autoimmune liver disease was confirmed by percutaneous liver biopsy provided patients gave consent and in the absence of coagulation and platelet disorders. Patients with other causes of liver disease such as viral, Wilson's and drug-induced hepatitis and were excluded. Those with advanced liver disease in which the underlying etiology remained unknown after evaluation were diagnosed as cryptogenic cirrhosis [8]. Patients with lung infection, chest wall and neuromuscular disorders, left ventricular heart failure, encephalopathy and those unable to perform lung function testing were excluded. The

study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was reviewed and approved by the institutional review board of Rancho Los Amigos National Rehabilitation Medical Center (F.U.R.P. #93). All patients signed an informed consent prior to undergoing procedures.

2.2. Lung Function Testing

Patients underwent pulmonary function testing according to ATS/ERS guidelines and classified as having obstructive or restrictive respiratory disease [9]. Predicted values for spirometric indices, lung volumes and single-breath carbon monoxide diffusion capacity (DLCO) were from Schoenberg *et al.* [10], Crapo *et al.* [11] and Knudson *et al.* [12], respectively. Arterial blood gases were obtained in seated and supine positions through an indwelling radial arterial line.

2.3. Respiratory Muscle Strength

Respiratory mouth pressures were measured according to ATS/ERS guidelines [13]. Maximum static expiratory and inspiratory mouth pressures (Pemax and Pimax, respectively) were measured at total lung capacity (TLC) and residual volume (RV), respectively, with a rubber flanged mouthpiece fitted to an occlusion valve mounted on a breathing circuit with a 3-way tap, modified to a design of Black and Hyatt *et al.* [14]. A differential pressure transducer (range ± 250 cm H_2O, Validyne MP45-36-871, Validyne Co, Northridge, CA) was connected to the 3-way tap with a 70 cm long, 1.4 mm inner diameter polyethylene catheter. Subjects were seated comfortably in a high-backed chair at 90˚ in a quiet room with a noseclip on and breathed through a heated pneumotachograph (Fleisch Lausanne, Switzerland, type No. 1). Before each study the pressure transducer was calibrated with a U-tube water manometer. Pressures were displayed on a 4-channel strip chart recorder (Gould, Dataq Instruments Inc., Akron, Ohio). A flanged mouthpiece was held in the mouth behind the lips and gripped firmly by the teeth. Prior to a maximal expiratory or inspiratory effort (Pemax or Pimax, respectively), the operator closed the 3-way tap with the subject at total lung capacity or residual volume, respectively. All measurements followed the criteria of Ringqvist and Ringqvist [15] such that: 1) no extra leakage occurred; 2) the three highest pressures were within 5%; and 3) subjects felt that they had given a maximum effort.

2.4. Control of Ventilation

Control of ventilation was recorded using a separate breathing circuit. At least 5 min rest was allowed following the Pmax measurements between with a noseclip on through a heated pneumotachograph (Fleisch Lausanne, Switzerland, type No. 1) while seated comfortably in the high-backed chair. For measurement of $P_{0.1}$, the inspiratory line of the circuit was equipped with a silent, hydraulically operated occlusion valve (Foon XP-1, McGill University, Montreal) that could

be closed during expiration and automatically opened about 0.3 sec after onset of the occluded inspiratory effort [16]. Mouth pressure was measured at a side port on the occlusion valve connected to a pressure transducer (Validyne MP45, range ±2.5 cm H_2O) with a polyethylene catheter (width 1.4 mm; length 94 cm). Airflow was measured with the pneumotachograph and volume obtained by integrating flow. The pneumotachograph-mouthpiece assembly had a resistance of 2.3 cm H_2O/L/sec that was linear over flows up to 2 L/sec. Dead space of the breathing circuit amounted to 45 mL.

Variables were measured after the patient had become familiar with the procedure and once ventilation had remained constant for at least 10 min [17]. Inspiratory time (Ti) and respiratory cycle duration (Ttot) were obtained from the flow signal. A minimum of four occlusions was made in each subject at intervals of 10 - 15 breaths while ensuring that the subject had no warning of the occlusions. Ventilatory measurements were averaged over 10 breaths immediately preceding the occlusions. From these values, mean inspiratory flow (Vt/Ti), duty cycle (Ti/Ttot) and effective inspiratory impedance [$P_{0.1}$/(Vt/Ti)] were computed. Normal values for breathing pattern were obtained from Šorli *et al.* [18].

2.5. Respiratory Elastance and Resistance

The single-breath passive relaxation technique was used to assess pressure-flow characteristics of the respiratory system during relaxed quiet breathing [19]. Patients breathed quietly through the same circuit with an occlusion valve mounted distal to the pneumotachograph. The occlusion valve described above could also be inverted, and with a stopper placed in its expiratory port, could serve to occlude the valve in both directions. End-inspiratory occlusions while relaxed were performed at approximately every 10 breaths which provided the elastic recoil pressure of the respiratory system. Respiratory elastance (Ers) was derived from the ratio of the end-inspiratory occlusion pressure and tidal volume. The average of 3 end-inspiratory occlusions was computed. Respiratory resistive properties (Rrs) were measured using Rohrer's pressure-flow relationship during passive expiration, $Pao/V' = K_1 + K_2V'$, where Pao is the pressure measured at the mouth at an end-inspiratory occlusion, V' is expiratory flow and K_1 and K_2 are flow resistance constants. This relationship is a linear function of the form $y = a + bx$, with K_1 being the intercept and K_2 being the slope of the curve. The flow resistance of the pneumotachograph-mouthpiece assembly was also defined by the Rohrer relationship, and its K_1 and K_2 during expiration was 0.12 cm $H_2O \cdot L^{-1} \cdot s$ and 0.07 cm $H_2O \cdot L^{-2} \cdot s^2$, respectively, indicating that its flow-resistive properties were almost linear and negligible. K_1 and K_2 of the equipment were subtracted from the total K_1 and K_2 to obtain the intrinsic resistive properties of the respiratory system.

2.6. Imaging and Ventilation-Perfusion Scanning

All patients had upright postero-anterior chest roentgenograms. Quantitative whole-body technetium^{99} macroaggregated albumin perfusion scanning was also

performed in 14 patients to assess for ventilation-perfusion (V/Q) mismatching, indicative of parenchymal or small airway dysfunction. Scanning was also used for assessment for right-to-left shunting through intrapulmonary vascular dilatations.

3. Statistical Analysis

Descriptive data are shown as mean and standard deviation. Differences amongst cohorts were determined by analysis of variance (ANOVA) [20]. Associations between physiologic variables were determined by multivariate Pearson's correlation, expressed as r^2. A p-value of <0.05 was considered statistically significant for intergroup comparisons and for inter-variable associations.

4. Results

4.1. Patients, Pulmonary and Respiratory Muscle Functions

All patients were stable, asymptomatic and anicteric at the time of study. Table 1 lists the anthropomorphic and physiologic data for patients with liver disorders (n = 29) and healthy control subjects (n = 21). The liver patients consisted of 17 patients with PBC (all female) and 12 with non-PBC disorders (7 female). One of the latter group was diagnosed with primary sclerosing cholangitis. Healthy control subjects also consisted mostly of females (n = 13) and were younger by a mean of 9 years. Individuals of Latino origin comprised 19 (66%) of liver patients and 7 (33%) of control subjects, respectively. Three patients had associated CREST syndrome (2 with PBC) and one had limited scleroderma. Evidence for other autoimmune conditions such as Sjögren syndrome, systemic lupus erythematosus, polymyositis, dermatomyositis, autoimmune thyroiditis, rheumatoid arthritis and common variable immune deficiency was absent. None of the PBC patients had ever smoked while 3 patients with non-PBC autoimmune liver disorders were former smokers. Patients with PBC were treated with ursodeoxycholic acid. No patients were receiving potentially pulmotoxic drugs such as methotrexate for treatment of their liver disease.

All subjects underwent lung function testing. Overall, mean FVC and FEV_1 (in L) in patients was 32% and 36% less, respectively, than in the control group (both $p < 0.01$) (Table 1). Their mean FEV_1/FVC was not significantly different from the control subjects. Five patients (4 with PBC) exhibited a restrictive defect and one (non-PBC, a former smoker) an obstructive pattern by spirometry. Forced expiratory flow at 50% VC (FEF_{50}, as % pred) averaged 33% less than in the controls ($p< 0.01$); 5 patients with PBC and 4 with non-PBC diseases had FEF_{50} values that were <80% predicted. All 3 patients who were former smokers had reduced FEF_{50}. There were no significant differences in spirometric values between patients with PBC and those with other forms of autoimmune liver disease. Similarly, TLC, FRC and RV (in L) in the liver patients was 25%, 21% and 14% less, respectively, than in the controls ($p < 0.01$, <0.02 and = 0.02, respectively). RV/TLC was 15% higher in the liver group ($p < 0.05$). DLCO and DL/VA

Table 1. Anthropometric characteristics and lung function data for 29 patients with autoimmune liver disease and 21 control subjects.

	All liver patients (n = 29)	PBC (n = 17)	Non-PBC (n = 12)	Controls (n = 21)	p†
Age, years	56 ± 11.1	57.5 ± 10.2	52.7 ± 11.7	46.8 ± 7.6	0.05
Sex, M/F	5/24	0/17	5/7	8/13	---
BMI, kg/m^2	24.3 ± 4.63	23.9 ± 4.1	24.8 ± 5.3	28 ± 4.7	0.05
FVC, L	2.58 ± 0.83	2.28 ± 0.61	2.87 ± 0.96	3.81 ± 0.85	<0.02
FVC, % pred.	84.1± 20.6	83.1 ± 18.6	86 ± 15.6	106.2 ± 10.3	<0.01
FEV1, L	2.05 ± 0.72	1.81 ± 0.45	2.30 ± 0.67	3.22 ± 0.67	<0.02
FEV1, % pred.	86.4 ± 19.7	83.1 ± 18.6	88.8 ± 16.7	113.1 ± 13.4	<0.01
FEV1/FVC, %	80.8 ± 9.2	80.7 ± 11.1	81.1 ± 5.9	84.5 ± 3.5	NS
FEF50, % pred.	82 ± 28.5	78.2 ± 32.3	87.4 ± 23	121.7 ± 23.3	<0.01
TLC, L	4.11 ± 1	4.01 ± 0.82	4.18 ± 1.03	5.48 ± 0.97	<0.01
TLC, % pred.	90.5 ± 13.9	89 ± 16.9	92 ± 10	102.5 ± 8	<0.01
FRC, L	2.14 ± 0.47	2.15 ± 0.51	2.12 ± 0.46	2.7 ± 0.61	<0.02
FRC, % pred.	84 ± 17	82.2 ± 16.2	85.8 ± 17.1	90.2 ± 15.2	NS
RV, L	1.37 ± 0.43	1.43 ± 0.41	1.28 ± 0.42	1.59 ± 0.31	0.02
RV, % pred.	87.8 ± 25.3	89.2 ± 23	86 ± 27.5	90.5 ± 15.7	NS
RV/TLC, %	33.6 ± 9.6	35.3 ± 6.8	32.3 ± 11	29.3 ± 4.4	0.05
DLCO, ml/min/mm Hg	12.5 ± 7.2	12 ± 6.7	13.5 ± 7.9	24.5 ± 5.5	0.01
DLCO, %pred.	61.8 ± 28.3	58.1 ± 29.9	68.4 ± 23.9	86.9 ± 23.2	<0.01
DL/VA	3.87 ± 1.15	3.67 ± 1.05	4.12 ± 1.23	4.56 ± 0.64	0.02
DL/VA, % pred.	78.9 ± 17.1	75.7 ± 14.8	82.8 ± 18.8	88.9 ± 15.7	0.01

†Analysis of variance. Abbreviations: PBC, primary biliary cirrhosis; M/F, male/female; BMI, body mass index; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; FEF50, forced expiratory flow at 50% VC; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; DLCO, single breath carbon monoxide diffusion capacity; VA, alveolar volume.

in the liver patients were significantly reduced, amounting to 51% and 85%, respectively, of corresponding control values ($p = 0.01$ and $p = 0.02$, respectively).

Respiratory muscle strength was impaired in liver patients: mean Pimax and Pemax were respectively, 64% and 45% less than corresponding control values (both $P < 0.01$). Mean Pemax was 59% higher than Pimax ($p < 0.01$) in liver patients. In normal subjects both values were normal and did not differ from each other.

4.2. Imaging

Upright chest roentgenograms showed elevated diaphragms in 7 patients and 3 showed lower lobe atelectasis. Reticulonodular changes were identified in 4 patients; 3 had PBC, 1 had non-PBC autoimmune liver disease; one of these patients had clinically evident ascites. Pleural effusions were identified in 3 patients

with non-PBC autoimmune liver disease. No patient had clinical evidence of congestive heart failure or pleuropulmonary or intraabdominal infection.

Fourteen patients underwent ventilation-perfusion (V/Q) scanning, all of whom demonstrated patchy or diffuse V/Q matching, consistent with parenchymal abnormalities or small airway dysfunction. Tracer utilization revealed one patient who exhibited an intrapulmonary shunt (33%).

4.3. Gas Exchange

Twenty-two patients underwent arterial blood gas analysis (Table 2). PaO_2, obtained while upright and breathing room air, averaged 8 mm Hg less than in the control subjects ($p = 0.02$). The PaO_2 decreased by a mean of 7 mm Hg in supine position. Non-PBC autoimmune patients exhibited a greater degree of hypoxemia than PBC patients in both positions. No patients exhibited orthodeoxia, including the patient with the intrapulmonary shunt. Their mean $PaCO_2$ and pH were consistent with a chronic respiratory alkalosis and did not change in supine position.

4.4. Total Respiratory Elastance and Resistance

Nine liver patients and all 21 control subjects consented to undergo testing for total respiratory elastance (Ers) (Table 3). Mean Ers of the liver patients was 50% higher than that of the control subjects ($p < 0.05$). When corrected for lung volume (Ers/1% of VC) [19], the ratio was 48% higher in the liver group ($p < 0.01$). Of 7 patients whose Ers was >9.58 cm H_2O/L (mean Ers of the normal cohort), 4 showed elevated hemidiaphragms; all 7 had matching V/Q defects on radioisotope scanning. The patient with the highest Ers (39.28 cm H_2O/L) had PBC and exhibited reticulonodular changes on chest roentgenogram. Of the two patients whose Ers was <9.58 cm H_2O/L, one exhibited an elevated left hemidiaphragm on chest x-ray; the other had clear lung fields; both exhibited matching V/Q defects on chest scintigraphy, consistent with parenchymal lung disease.

Rohrer's constants for respiratory resistive properties, K_1 (range 0.163 - 3.26) and K_2 (range 3.26 - 23.8) varied widely and did not differ significantly from control values. They did not correlate with FEV_1 or FEF_{50}.

4.5. Control of Ventilation

Mean tidal volume (Vt) in liver patients was 22% less than in controls ($p < 0.02$), while Vt/Ti averaged 18% higher ($p < 0.05$) (Table 3). Minute ventilation (V_E) was marginally higher ($p < 0.05$) while duty cycle (Ti/Ttot) did not differ significantly. Mean occlusion pressure at 0.1 sec ($P_{0.1}$) and effective impedance [$P_{0.1}$/(Vt/Ti)] of the liver group was, respectively, 78% and 58% higher than in control subjects (both $p < 0.02$). When $P_{0.1}$ was controlled for Pimax ($P_{0.1}$/Pimax), the ratio was 5.4 times higher in liver patients. Amongst patients there was a negative association between FVC (% predicted) and $P_{0.1}$ ($r = -0.69$, $p = 0.03$). We found tendencies for associations between Ers and $P_{0.1}$ and between Ers and $P_{0.1}$/(Vt/Ti), although they did not reach statistical significance

Table 2. Gas exchange in 22 patients with autoimmune liver disease.

	Liver patients combined (n = 22)	PBC (n = 13)	Non-PBC liver (n = 9)	Control subjects (n = 21)	p†
PaO_2, mm Hg, upright*	84.3 ± 16	90.1 ± 12.4	77.6 ± 17.1	92.6 ± 6.7	0.02
PaO_2, mm Hg, supine	77.4 ± 10.1	83 ± 9.4	70.5 ± 10.5	---	0.05
$PaCO_2$, mm Hg, upright	33.2 ± 2.9	32.8 ± 3.1	33.9 ± 2.3	---	NS
pH, upright	7.43 ± 0.03	7.43 ± 0.03	7.43 ± 0.03	---	NS

*Arterial blood gases obtained on room air. Abbreviations: PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension; $AaDO_2$, alveolar-arterial oxygen difference.

Table 3. Total respiratory elastance, respiratory muscle strength and control of ventilation in 9 patients with autoimmune liver disease and 21 control subjects.

	Liver patients	Control subjects	p†
	n = 9	n = 21	
Ers, cm H_2O/L	14.4 ± 9.3	9.58 ± 0.58	<0.02
Ers/1% VC, cm H_2O/L	0.37 ± 11	0.25 ± 0.01	<0.01
Vt, L	0.59 ± 0.25	0.75 ± 0.05	<0.02
Vt/Ti, L/s	0.41 ± 0.12	0.35 ± 0.09	NS
Ti/Ttot	0.41 ± 0.04	0.41± 0.05	NS
V'E, L/min	9.97 ± 3.53	8.36 ± 1.86	NS
P0.1, cm H_2O	1.62 ± 0.67	0.91 ± 0.38	0.02
P0.1/(Vt/Ti), cm H_2O/L/s	4.19 ± 1.31	2.65 ± 1.06	0.02
Pimax, cm H_2O	39.5 ± 17	109.2 ± 33.5	0.001
P0.1/Pimax, %	5.01 ± 2.66	0.93 ± 0.54	0.001
Pemax, cm H_2O	62.7 ± 22.4	114.7 ± 37.3	<0.01

†Unpaired Student t-test. Abbreviations: Ers, total respiratory elastance; Vt, tidal volume; Ti, inspiratory time; Ttot, duration of breath; Vt/Ti, mean inspiratory flow; Ti/Ttot, duty cycle; V'_E, minute ventilation; P0.1, occlusion pressure in 0.1 second; P0.1/(Vt/Ti), effective impedance; Pimax, maximum inspiratory mouth pressure; Pemax, maximum expiratory mouth pressure.

(r = 0.64 and r = 0.62, respectively, both p = 0.06). There were no associations between $P_{0.1}$ or between $P_{0.1}$/(Vt/Ti) and Rohrer's constants of respiratory resistance (K_1 and K_2).

5. Discussion

To our knowledge, this is the first study that has assessed total respiratory elastance and resistance using the passive relaxation technique and their relation to control of ventilation in patients with autoimmune liver disease. The important findings were that: a) compared to control subjects, most patients with liver disease exhibited an increase in total respiratory elastance (Ers); b) respiratory muscle force generation was impaired; and c) $P_{0.1}$ was increased, negatively asso-

ciated with FVC and compensated for the inspiratory muscle weakness. These findings indicate that increase in ventilatory drive is related to smaller lung volume and increase in respiratory elastance.

5.1. Pulmonary Function, Gas Exchange and Acid-Base Status

We found lung volumes to be reduced in several patients, explained by elevated diaphragms, pleural effusion, atelectasis and/or interstitial lung disease. Patients with autoimmune liver disorders, particularly those with primary biliary cirrhosis, exhibit a number of pulmonary function abnormalities [21]. Other investigators have described spirometric values to be normal or mildly reduced [5] [6] [22] [23]. FEF_{50} was reduced in 9 of our patients, consistent with small airway dysfunction, confirmed by ventilation-perfusion mismatching seen on lung scans. Overall mean K_1 and K_2 were similar to those of normal subjects, indicating overall normal airway resistance, at least over the range of respiratory flows during resting breathing, although there was variability. Only 3 of our patients had ever smoked. We found gas transfer to be reduced, reflecting lung parenchymal changes [1] [22] [23].

Despite impaired gas transfer, oxygenation while breathing room air was normal or minimally impaired in our patients, as reported by others [3]. PaO_2 *decreased* by an overall mean of 7 mm Hg in supine position. Non-PBC autoimmune patients exhibited a greater degree of hypoxemia than PBC patients in both positions; three of these patients exhibited pleural effusions on chest x-ray, likely resulting in lung compression and increase in small airway closure. That no patients exhibited orthodeoxia or platypnea render less likely the presence of hepatopulmonary syndrome [24]. Respiratory alkalosis was present in all patients; it is reported as the most common acid-base disorder in patients with chronic liver disease [25] [26] [27]. The alkalosis was associated with increase in ventilatory drive, as evidenced by increases in Vt and Vt/Ti (see Section 4.4).

5.2. Respiratory Elastance

Mean total respiratory elastance, Ers, in liver patients was 50% higher than in normal subjects. In at least one patient the increased Ers may have been related to the presence of ascites. In a study of six supine patients with ascites Duranti *et al.* [7] found that swings in pleural and gastric pressures were increased during spontaneous breathing before large volume paracentesis (LVP) and decreased significantly following the procedure. By contrast, only one our patients had clinically detectable ascites. We suggest that the increase in Ers in most patients was due to a decrease in lung compliance related to early airway closure, interstitial fibrosis and edema, as suggested by findings in lung scintigraphy.

Using the passive relaxation single-breath technique in conscious patients with restrictive respiratory disorders and healthy controls, Baydur and Carlson [19] found curvilinear pressure-flow characteristics in both groups. The time course of volume during relaxed expirations has been studied previously in conscious normal subjects by Shee *et al.* [28], and validates the approach used to as-

sess respiratory resistance. Findings can be attributed to the viscoelastic and elastoplastic behavior of the respiratory system. Despite the greater elastic recoil pressure of the restrictive patients, their pressure-flow characteristics were similar to those of healthy control subjects [19], similar to the current findings, and can be explained by the effects of retractile forces along airways compensating for reduced lung volumes in patients with interstitial fibrosis or edema.

5.3. Respiratory Muscle Weakness

Pimax and Pemax in liver patients averaged 36% and 55% of their respective control values, lower than the overall 87% and 89%, respectively, reported by Kaltsakas *et al.* in 40 patients with and without ascites [27]. The reasons for this variable respiratory muscle weakness in liver patients are multifactorial, with some authors reporting a decreased Pimax in patients with ascites [27] and others showing no effect of LVP on Pimax [7]. We also found that mean Pemax was 59% higher than Pimax, a finding similar to that of others [4] [27] [29], indicating a greater weakness of the diaphragm compared to the abdominal musculature. Abdominal distension by ascites may compromise the length-tension relationship of the diaphragm even as its appositional zone increases with cephalad displacement. Other factors are known to contribute to respiratory muscle weakness: nutritional status, hyperparathyroidism, adrenal insufficiency, and inflammatory and drug-induced myopathies [30] [31]. In our patients, endocrine and myopathic conditions were ruled out by history, physical examination and relevant diagnostic studies.

5.4. Control of Ventilation

The finding of increases in $P_{0.1}$ and Vt/Ti and respiratory alkalosis in patients confirms an increase in ventilatory drive [16] [27] and can be attributed to a number of factors, including increase in serum progesterone concentration, a known respiratory stimulant [32] [33], sympathetic overactivity [34] and changes in respiratory mechanics. Kaltsakas *et al.* [27] found significant correlations between $PaCO_2$ and V'_E and Vt/Ti in patients with end-stage liver disease. They also found that Vt/Ti was higher in patients with ascites than in those without ascites. Increases in the elastic properties of the respiratory system are associated with increases in ventilatory drive, reflected by an increase in $P_{0.1}$, as exhibited by individuals with interstitial lung disease [35] [36] [37] and chest wall and neuromuscular disorders [38] [39].

Mean effective respiratory impedance [$P_{0.1}$/(Vt/Ti)] in liver patients was 58% higher than in control subjects. This finding reflects an increased load imposed on breathing due to pulmonary (atelectasis, small airway closure, interstitial lung disease) and extrapulmonary (e.g., ascites, muscle atrophy or weakness) factors or even central in origin. The increase in $P_{0.1}$/(Vt/Ti) is similar to that observed in patients with neuromuscular disease [38] [39] and in normal subjects undergoing progressive curarization [40]. Baydur [39] found $P_{0.1}$/(Vt/Ti) in 21 neuromuscular patients to be 85% higher than in normal control subjects. Despite

the overall weakness of respiratory muscles, an elevated, more domed diaphragm (due to ascites or atelectasis) results in increase in operational length compensation [41] and force generation, at least during first 100 msec of inspiratory drive during quiet breathing. Despite the level of muscle weakness observed in our patients, $P_{0.1}$/Pimax averaged 5-fold higher than in control subjects.

There were limitations to our study. It is a single-center study which recruited a relatively small number of patients. Nevertheless, changes in lung and respiratory muscle function were similar to findings in patients with chronic liver disease in previous studies. Regarding the main objective of this study (measurements of respiratory elastance and resistive properties), while not all patients agreed to undergo assessment of respiratory mechanics, 7 of 9 individuals who underwent testing exhibited Ers values higher than control subjects, a finding consistent with clinical and imaging findings. We did not have available computerized chest tomography (CT) at the time of the study so that subtle details of thoracic structures not seen by plain chest x-ray may have been missed. We did, however, evaluate gas exchange and had available ventilation-perfusion scanning that provided physiologic evidence for structural changes.

6. Conclusions and Potential Areas for Further Research

In summary, the results of this study show that in patients with chronic liver disease, despite respiratory muscle weakness and a V'_E similar to that in normal subjects, central drive is increased and associated with reduction in FVC and likely increase in Ers. $P_{0.1}$ is a reliable measure of central drive and is an approach that can be used to evaluate control of ventilation in patients with chronic liver disease. In many respects, ventilatory control in patients with chronic liver disease is similar to that of patients with other forms of restrictive respiratory impairment. A potential area of research would be to evaluate control of ventilation following liver transplantation once the acute effects of the surgery have resolved and patients have been weaned off mechanical ventilation. In conjunction with resolution of ascites, pulmonary congestion, pleural effusions and hypoxemia, one would expect reductions in Ers, Rrs, $P_{0.1}$ and Vt/Ti, correlating with reversal of respiratory alkalosis [42].

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Wallaert, B., Bonniere, P., Prin, L., *et al.* (1986) Primary Biliary Cirrhosis. Subclinical Inflammatory Alveolitis in Patients with Normal Chest Roentgenograms. *Chest*, **90**, 842-848. https://doi.org/10.1378/chest.90.6.842

[2] Spiteri, A., Johnson, M., Epstein, O., *et al.* (1990) Immunological Features of Lung Lavage Cells from Patients with Primary Biliary Cirrhosis May Reflect Those Seen in Pulmonary Sarcoidosis. *Gut*, **31**, 208-212. https://doi.org/10.1136/gut.31.2.208

[3] Uddenfeldt, P., Bjerle, P., Danielsson, Å., *et al.* (1988) Lung Function Abnormalities in Patients with Primary Biliary Cirrhosis. *Acta Medica Scandinavica*, **223**, 549-555. https://doi.org/10.1111/j.0954-6820.1988.tb17694.x

[4] Hourani, J., Bellamy, P., Tashkin, D., *et al.* (1991) Pulmonary Dysfunction in Advanced Liver Disease: Frequent Occurrence of an Abnormal Diffusion Capacity. *The American Journal of Medicine*, **90**, 693-700. https://doi.org/10.1016/0002-9343(91)90664-J

[5] Krowka, M.J., Grambsch, P.M., Edell, E.S., *et al.* (1991) Primary Biliary Cirrhosis: Relation between Hepatic Function and Pulmonary Function in Patients Who Never Smoked. *Hepatology*, **13**, 1095-1110. https://doi.org/10.1002/hep.1840130615

[6] Fallon, M.B. and Abrams, G.A. (2000) Pulmonary Dysfunction in Chronic Liver Disease. *Hepatology*, **32**, 859-865. https://doi.org/10.1053/jhep.2000.7519

[7] Duranti, R., Laffi, G., Misuri, G., *et al.* (1987) Respiratory Mechanics in Patients with Tense Ascites. *European Respiratory Journal*, **10**, 1622-1630. https://doi.org/10.1183/09031936.97.10071622

[8] Lindor, K.D., Bowlus, C.L., Boyer, J., *et al.* (2019) Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. *Hepatology*, **69**, 394-419. https://doi.org/10.1002/hep.30145

[9] Pellegrino, R., Viegi, G., Brusasco, V., *et al.* (2005) Interpretative Strategies for Lung Function Tests. *American Journal of Respiratory and Critical Care Medicine*, **26**, 948-968. https://doi.org/10.1183/09031936.05.00035205

[10] Schoenberg, J.B., Beck, G.J. and Bouhuys, A. (1978) Growth and Decay of Pulmonary Function in Healthy Blacks and Whites. *Respiration Physiology*, **33**, 367-393. https://doi.org/10.1016/0034-5687(78)90063-4

[11] Crapo, R.O., Morris, A.H., Clayton, P.D., *et al.* (1982) Lung Volumes in Healthy Nonsmoking Adults. *Bulletin Européen de Physiopathologie Respiratoire*, **18**, 419-425.

[12] Knudson, R.J., Kaltenborn, W.T., Knudson, D.E., *et al.* (1987) The Single-Breath Carbon Monoxide Diffusing Capacity. Reference Equations Derived from a Healthy Nonsmoking Population and Effects of Hematocrit. *American Review of Respiratory Disease*, **135**, 805-811. https://doi.org/10.1164/arrd.1987.135.4.805

[13] (2002) ATS/ERS Statement On Respiratory Muscle Testing. *American Journal of Respiratory and Critical Care Medicine*, **166**, 518-624. https://doi.org/10.1164/rccm.166.4.518

[14] Black, L.F. and Hyatt, R.E. (1969) Maximal Respiratory Pressures: Normal Values and Relationship to Age and Sex. *American Review of Respiratory Disease*, **99**,

696-702.

[15] Ringqvist, I. and Ringqvist, T. (1971) Respiratory Mechanics in Untreated Myasthenia Gravis with Special Reference to the Respiratory Forces. *Acta Medica Scandinavica*, **190**, 499-508. https://doi.org/10.1111/j.0954-6820.1971.tb07466.x

[16] Whitelaw, W.A., Derenne, J.P. and Milic-Emili, J. (1975) Occlusion Pressure as a Measure of Respiratory Center Output in Conscious Man. *Respiration Physiology*, **23**, 181-99. https://doi.org/10.1016/0034-5687(75)90059-6

[17] Milic-Emili, J. (1982) Recent Advances in Clinical Assessment of Control of Breathing. *Lung*, **160**, 1-17. https://doi.org/10.1007/BF02719267

[18] Šorli, J., Grassino, A., Lorange, G., *et al.* (1978) Control of Breathing in Patients with Chronic Obstructive Lung Disease. *Clinical Science and Molecular Medicine*, **54**, 295-304. https://doi.org/10.1042/cs0540295

[19] Baydur, A. and Carlson, M. (1994) Respiratory Mechanics by the Passive Relaxation Technique in Conscious Healthy Adults and Patients with Restrictive Respiratory Disorders. *Chest*, **105**, 1171-1178. https://doi.org/10.1378/chest.105.4.1171

[20] Dixon, W.J. and Massey, F.J. (1983) Introduction to Statistical Analysis. 4th Edition, McGraw Hill, New York, 385-414.

[21] Rodriguez-Roisin, R., Pares, A., Bruguera, M., *et al.* (1981) Pulmonary Involvement in Primary Biliary Cirrhosis. *Thorax*, **36**, 208-212. https://doi.org/10.1136/thx.36.3.208

[22] Costa, C., Sambataro, A., Baldi, S., *et al.* (1995) Primary Biliary Cirrhosis: Lung Involvement. *Liver*, **15**, 196-201. https://doi.org/10.1111/j.1600-0676.1995.tb00670.x

[23] Kalashnikov, M., Akulkina, L., Brocko, M., *et al.* (2023) Interstitial Lung Disease in Primary Biliary Cholangitis: A Cohort Prospective Study. *Life* (*Basel*), **13**, Article No. 416. https://doi.org/10.3390/life13020416

[24] Krowka, M.J., Wiesner, R.H. and Heimbach, J.K. (2013) Pulmonary Contraindications, Indications and MELD Exceptions for Liver Transplantation: A Contemporary View and Look Forward. *Journal of Hepatology*, **59**, 367-374. https://doi.org/10.1016/j.jhep.2013.03.026

[25] Heinemann, H.O., Emirgil, C. and Mijnssen, J.P. (1960) Hyperventilation and Arterial Hypoxemia in Cirrhosis of the Liver. *The American Journal of Medicine*, **28**, 239-246. https://doi.org/10.1016/0002-9343(60)90187-X

[26] Snell, R.E. and Luchsinger, P.C. (1963) The Relation of Arterial Hypoxemia to the Hyperventilation of Chronic Liver Disease. *The American Journal of the Medical Sciences*, **245**, 289-292. https://doi.org/10.1097/00000441-196303000-00007

[27] Kaltsakas, G., Antoniou, E., Palamidas, A.F., *et al.* (2013) Dyspnea and Respiratory Muscle Strength in End-Stage Liver Disease. *World Journal of Hepatology*, **5**, 56-63. https://doi.org/10.4254/wjh.v5.i2.56

[28] Shee, C.D., Ploy-Song-Sang, Y. and Milic-Emili, J. (1985) Decay of Inspiratory Muscle Pressure during Expiration in Conscious Humans. *Journal of Applied Physiology*, **58**, 1859-1865. https://doi.org/10.1152/jappl.1985.58.6.1859

[29] Augusto, V.S., Castro, E., Silva, O., Souza, M.E., *et al.* (2008) Evaluation of the Respiratory Muscle Strength of Cirrhotic Patients: Relationship with Child-Turcotte-Pugh Scoring System. *Transplantation Proceedings*, **40**, 774-776. https://doi.org/10.1016/j.transproceed.2008.03.002

[30] Milosevic, M. and Adams, P. (1990) Primary Biliary Cirrhosis and Polymyositis. *Journal of Clinical Gastroenterology*, **12**, 332-335. https://doi.org/10.1097/00004836-199006000-00022

[31] Bohan, A. and Peter, J.B. (1975) Polymyositis and Dermatomyositis. *The New England Journal of Medicine*, **292**, 344-347. https://doi.org/10.1056/NEJM197502132920706

[32] Lustik, S.J., Chhibber, A.K., Kolano, J.W., *et al.* (1997) The Hyperventilation of Cirrhosis: Progesterone and Estradiol Effects. *Hepatology*, **25**, 55-58. https://doi.org/10.1002/hep.510250110

[33] Contreras, G., Gutiérrez, M., Beroíza, T., *et al.* (1991) Ventilatory Drive and Respiratory Muscle Function in Pregnancy. *American Review of Respiratory Disease*, **144**, 837-841. https://doi.org/10.1164/ajrccm/144.4.837

[34] Passino, C., Giannoni, A., Mannucci, F., *et al.* (2012) Abnormal Hyperventilation in Patients with Hepatic Cirrhosis: Role of Enhanced Chemosensitivity to Carbon Dioxide. *International Journal of Cardiology*, **154**, 22-26. https://doi.org/10.1016/j.ijcard.2010.08.066

[35] Renzi, G., Milic-Emili, J. and Grassino, A.E. (1982) The Pattern of Breathing in Diffuse Lung Fibrosis. *Bulletin Européen de Physiopathologie Respiratoire*, **18**, 461-472.

[36] Londner, C., Al Dandachi, G., Plantier, L., *et al.* (2014) Cross-Sectional Assessment of the Relationships between Dyspnea Domains and Lung Function in Diffuse Parenchymal Lung Disease. *Respiration*, **87**, 105-112. https://doi.org/10.1159/000351110

[37] Gorini, M., Spinelli, A., Ginanni, R., *et al.* (1989) Neural Respiratory Drive and Neuromuscular Coupling during CO_2 Rebreathing in Patients with Chronic Interstitial Lung Disease. *Chest*, **96**, 824-830. https://doi.org/10.1378/chest.96.4.824

[38] Begin, R., Bureau, M.A., Lupien, L., *et al.* (1982) Pathogenesis of Respiratory Insufficiency in Myotonic Insufficiency: The Mechanical Factors. *American Review of Respiratory Disease*, **125**, 312-318.

[39] Baydur, A. (1991) Respiratory Muscle Strength and Control of Ventilation in Patients with Neuromuscular Disease. *Chest*, **99**, 330-338. https://doi.org/10.1378/chest.99.2.330

[40] Holle, R.H.O., Schoene, R.B. and Pavlin, E.J. (1984) Effect of Respiratory Muscle Weakness on $P_{0.1}$ Induced by Partial Curarization. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology*, **57**, 1150-1157. https://doi.org/10.1152/jappl.1984.57.4.1150

[41] Banzett, R. and Mead, J. (1985) Reflex Compensation for Changes in Operational Length of Inspiratory Muscles. *The Thorax Part A, Lung Biology in Health and Disease*, **29**, 595-604.

[42] Krowka, M.J., Dickson, E.R., Wiesner, R.H., *et al.* (1992) A Prospective Study of Pulmonary Function and Gas Exchange Following Liver Transplantation. *Chest*, **102**, 1161-1166. https://doi.org/10.1378/chest.102.4.1161