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Limited cardiopulmonary capacity in patients with liver cirrhosis when compared to healthy subjects

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SUMMARY

OBJECTIVES: The present study compared cardiorespiratory capacity between cirrhotic patients and healthy subjects.

METHODS: Nineteen cirrhotic patients and 19 healthy subjects, paired by age and gender, participated in the study. Volunteers performed an incremental cardiopulmonary test with a ramp protocol, a ventilatory and metabolic variables were obtained and analyzed. The recovery was analyzed by calculating the time needed for 50% of oxygen consumption (VO_2) recovery to occur as the median between the peak of the exercise and the end of recovery on the VO_2 curve ($T_{1/2}$). The VE/VCO_2 slope were performed by the linear regression of ventilation (VE) and carbon dioxide production (VCO_2) data.

RESULTS: During resting condition, cirrhotic patients presented significantly higher levels of VO_2 compared to healthy subjects. The VE/VO_2 and VE/ VCO_2 values were significantly higher in the control group at the anaerobic threshold and at the peak of the test compared to cirrhotic patients. Time under effort was significantly higher for healthy subjects.

CONCLUSIONS: Based on these findings, it is possible to conclude that liver cirrhosis can compromise the patients' quality of life, mainly by inducing metabolic alterations which can impair functional capacity and lead to a sedentary lifestyle.

KEYWORDS: Liver cirrhosis. Oxygen consumption. Exercise test. Physical fitness.

INTRODUCTION

Cirrhosis is the end-stage of several chronic liver diseases, including hepatitis, and alcoholic and non-alcoholic steatosis[1]. This condition is characterized by fibrous scar tissue resulting from aggression and distortion of the liver parenchymal architecture[2]. In this stage, patients can be affected not only by hepatic dysfunction, but also by portal hypertension and ascites[3]. Moreover, cirrhosis can result in hepatorenal and hepatopulmonary syndromes, cardiomyopathy, encephalopathy, and other metabolic alterations[4-8].

Skeletal muscle dysfunction has been described as a comorbid status, reflecting the systemic impact of cirrhosis. Decreased mitochondrial amount and volume, and limited oxidative enzyme activity are contributing factors to peripheral muscle weakness[9]. Depending on the disease stage, patients may experience sarcopenia as consequence of muscle disuse and impaired protein

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synthesis by the liver[10]. This condition could help explain the reduction in strength observed in these patients, which results in impaired functional capacity and reduced quality of life[11]. Additionally, a strong association was found between reduced mobility and mortality, suggesting that people with reduced functional capacity, mainly evidenced in elderly individuals, tend to die at a younger age[12].

Oxygen uptake (VO_2) is a metabolic parameter used to evaluate the cardiorespiratory system capacity to carry oxygen (O_2) to the target muscles[13]. The cardiorespiratory test by ergospirometry is the gold standard technique for determining this capacity, as it quantifies the respiratory gas exchange during exercise, consisting in VO_2 and carbon dioxide production (VCO_2)[14]. In incremental exercise, lactate concentration and other metabolites tend to accumulate in the muscle and in the bloodstream and the hydrogen ions (H^+) increase, resulting in an acid-base imbalance and in a pH reduction[15]. In an incremental ergospirometry test, this situation corresponds to the anaerobic threshold (AT), in which the muscle tissue and blood require the activation of the metabolites removal mechanism[16]. As the exercise continues, the participant reaches the peak VO_2 ($VO_{2\ peak}$), which is related to the stroke volume, the cardiac output, the O_2 distribution, and the muscle O_2 uptake mediated by the oxidative mechanism[17].

Most cirrhotic patients lead an inactive and sedentary lifestyle, which can compromise their functional capacity and aggravate their health status. The practice of physical activity is recommended in this population, as it can improve cardiorespiratory capacity, increasing $VO_{2\ peak}$ and muscle mass, thus reducing fatigue sensation and improving functional ability and mobility capacity[18]. However, little is known regarding cardiorespiratory capacity in cirrhosis patients and how the disease can influence their quality of life. Thus, the aim of the present study was to compare cardiorespiratory capacity between liver cirrhosis patients and healthy subjects by applying ergospirometry during an incremental test. For this purpose, relative and absolute VO_2 and VCO_2 and the power output at the AT and at the peak of the test were considered. $T_{1/2}$ was measured at the end of the test. We hypothesized that the investigated parameters would be altered in patients with liver cirrhosis, reflecting lower cardiorespiratory fitness.

METHODS

Subjects

Patients were randomly selected to participate in the study among those that underwent clinical visits at the hepatology center of the *Hospital Universitário Clementino Fraga*, Rio de Janeiro, Brasil. The investigation was conducted inside the hospital by a multidisciplinary group. The study is in accordance with the Declaration of Helsinki and with the Good Clinical Practice Guidelines of 1975 and was approved by the research ethics committee of the University under the number 36888314.7.0000.5257.

Inclusion criteria were: diagnosis of liver cirrhosis with a Child-Pugh (CP) score= A or B, age between 50 and 70 years, and an inactive lifestyle, consisting of daily routine activities and never having been engaged in exercises programs for a long time. Patients were excluded from the study if they had had any decompensation episodes with upper gastrointestinal bleeding within two weeks before the intervention, had presented hepatocellular carcinoma, coronary artery disease or any infectious condition or had reported lower limb joint pain. Patients were also excluded from the study if they were smokers, pregnant or made use of corticoids. Thirty-eight individuals participated in the study, divided into two groups. Nineteen patients (ten females, nine males) with clinical diagnosis by imaging (magnetic resonance and elastography) or biopsy composed the liver cirrhosis group (LCG). The characteristics of the LCG are presented in Table 1. Nineteen healthy subjects (10 females, 9 males), matched according to age and gender, with inactive lifestyle, composed the control group (COG – age: 59.7±5.1 years; weight: 80.4±16.4 kg; height: 1.64±7.7 cm; body mass index (BMI): 29.99±6.3 kg/m^2).

Study design

All tests were performed in an air-conditioned laboratory with temperature between 22 and 24°C and relative humidity between 50 and 60%, always at the same period of the day (between 08:00 a.m. and 12:00 a.m.). Patients were advised to avoid the intake of stimulating drinks, not to perform physical activity, and to have light meals the day before the test and to have at least eight hours of sleep the night before the test. First, the volunteers were familiarized with the experimental set-up and the involved researchers. Then, systolic and diastolic arterial blood pressure were measured. Each volunteer performed an incremental cardiopulmonary test (ICT) with a ramp protocol; the ICT was performed on an electromagnetic braking cycle ergometer (Corival, Lode BV, Groningen, The Netherlands) with the subjects sitting in an upright position. After one minute of rest sitting on the cycle ergometer, subjects pedaled without load (about 15 W) during a three-minute warm-up period. Afterward, the exercise protocol was initiated, with power increments determined according to the functional capacity reported by subjects during their clinical assessment (10 W/min) and a constant speed of 60 rpm, until a respiratory exchange ratio

(R) higher than 1.0 was reached. The load distribution was controlled through the ventilatory expired gas analysis system (VO2000 System, Medical Graphics Corporation, St. Paul, MO, USA). The post-test recovery monitoring period consisted of three minutes of active recovery followed by two minutes of rest. The electrocardiogram (ECG) (CardiO2 System, Medical Graphics Corporation, St. Paul, MO, USA) (modified derivations MC5, DII, DIII, aVR, aVL and aVF and V1 to V6) was continually monitored during all experimental procedures and arterial pressure was intermittently assessed throughout the protocol. The tests were carried out by a team of researchers, composed of physical therapists and physicians, who monitored physiological responses and signs/symptoms exhibited by subjects.

Ventilatory and metabolic variables were obtained through a computerized ergospirometric measurement system

Table 1. Liver cirrhosis group (LCG) and control group (COG) characterization.

	LCG (n=19)	COG (n=19)	p-value, t-test
Age (y)	56.8±12.1	59.7±5.1	0.890
Height (cm)	1.60±0.2	1.64±7.7	0.985
Weight (kg)	76.8±24.7	80.4±16.4	0.535
BMI (kg/m^2)	30.4±5.7	29.99±6.3	0.648
Child-Pugh score (A/B)	18/1	–	–
MELD score	10.6±4.3	–	–
Sodium (mg/L)	138.3±4.4	–	–
Potassium (g/dL)	4.5±0.4	–	–
Creatinine (mg/dL)	1.0±0.2	–	–
Platelets	141.5±60.2	–	–
Leukocytes	6194±2666	–	–
Urea (µmol/L)	33.7±7.3	–	–
Glucose (mg/dL)	121.6±33.4	–	–
Albumin (g/L)	4.3±0.4	–	–
PT (%)	77.3±26.4	–	–
INR	1.2±0.3	–	–
Total bilirubin (mg/dL)	1.1±1.2	–	–
AST (U/L)	40.4±20.7	–	–
ALT (U/L)	47.2±27.5	–	–
Etiology			
Alcohol	1 (5%)	–	–
Virus	20 (53%)	–	–
Steatosis	8 (42%)	–	–
Ascites (n)	0	–	–
Edema (n)	1	–	–
Previous variceal bleeding (n)	2	–	–
Portal vein thrombosis (n)	2	–	–
Esophageal varices (n)	5	–	–
Encephalopathy (n)	0	–	–
Beta-blockers (n)	4	–	–

BMI: body mass index; MELD: model for end-stage liver disease; PT: prothrombin activity time; INR: international normalized ratio; AST: aspartate transaminase; ALT: alanine transaminase.

(VO2000 System, Medical Graphics Corporation, St. Paul, MO, USA) using the Aerograph software. The tidal volume was obtained through a Pitot pneumotachometer connected to the VO2000 System and attached to a face mask selected considering the volunteer's face size, providing an adequate fit in order to avoid air leakage. The device provides real-time values for applied power (W), pedaling speed (rpm), VO_2, VCO_2, and minute ventilation (VE). Ventilatory equivalent values (VE/VO_2 and VE/VCO_2) and R were also calculated and registered. The power applied during the exercise protocol was controlled by the system through an interface with the cycle ergometer.

Breath-to-breath VO_2 and VCO_2 correlation curves, VE/VO_2 and the expiratory fraction (FEO_2) were graphically represented. Subsequently, two independent observers determined the AT according to the following criteria: 1) VE/VO_2: nadir point of this ratio, after which a systematic increase occurs; and 2) FEO_2: nadir point of this variable, after which a systematic increase occurs. The section selected for subsequent AT determination was set from the beginning of the responses of ventilatory and metabolic variables to the end of exercise. Each observer performed the analysis independently, on a 15-inch monitor (SyncMaster 550V, Samsung) connected to MedGraphics software. Additionally, the time needed for 50% of VO_2 recovery to occur ($T_{1/2}$) was calculated on the VO_2 curve as the median between the peak of the exercise and the end of recovery. To determine the VE/VCO_2 slope, the linear regression (y=mx+b, m=slope) were performed to VE and VCO_2 data, from the beginning until the peak of exercise.

Statistical analysis

The power of the sample size was determined using G*power version 3.1.9.2., based on the R response at the peak of the exercise. Considering the study sample size and an alpha error of 0.05, the power (1 – ß) was calculated to be 0.85. Statistical analysis was performed using SigmaPlot version 11.0.0.007 (for Windows®) with the level of significance set at 0.05. Data were submitted to a normality test (Shapiro-Wilk). For parametric variables and sample characterization (age, height, weight, and body mass index), the unpaired *t*-test was performed. For non-parametric variables, the Mann-Whitney test was performed. A significance level of $p \leq 0.05$ was used for all inferential variables. The Cohen's *d* effect size was calculated by the following formula: difference between mean of LCG and COG divided by standard deviation of COG. The magnitude of the effect size was rated as small (<0.41), moderate (0.41–0.70), and large (>0.70). Demographic, anthropometric, and clinical data are presented as mean ± standard deviation.

RESULTS

Cardiopulmonary variables at baseline, at the AT and at the peak of the exercise for the LCG and for the COG are presented in Table 2. In the resting condition, significantly higher values were observed in the LCG when compared to the COG for absolute VO_2 (p=0.05). At the AT, significantly higher values were found for the COG when compared to the LCG for VE/VO_2 and VE/VCO_2 (p<0.001). At the peak of the exercise, the time under effort was significantly higher for the COG when compared to the LCG (p=0.02), and VE (p=0.05), VE/VO_2 (p<0.001) and VE/VCO_2 (p=0.01) were significantly higher for the COG when compared to the LCG. There was no significant difference for $VO_{2\ peak}$ between groups. For the VE/VCO_2 slope, significant differences were observed between groups (p=0.01) with lower values for LCG. There were no significant differences for the recovery kinetics parameters between groups (Figure 1).

DISCUSSION

The main findings of the present study were that, in resting condition, the LCG presented significantly higher metabolic demand, as indicated by higher levels of VO_2 and VCO_2. VE/VO_2 and VE/VCO_2 values were significantly higher in the COG at the AT and at the peak of the ICT, indicating higher cardiopulmonary capacity when compared to the LCG. The COG presented greater exercise tolerance during the ICT, as indicated by the time under effort, which was significantly higher than in the LCG. However, $VO_{2\ peak}$ did not significantly differ between groups.

In the resting condition, VO_2 and VCO_2 were significantly higher in the LCG than in the COG. None of the patients presented a diagnosis of hepatopulmonary syndrome, which is notably known to induce several complications in the cardiorespiratory dynamics, including ventilation-perfusion imbalance, impaired oxygen diffusion, and pulmonary vascular dilatation[19]. However, it is well established that even liver cirrhotic patients without HPS can present gas exchange abnormalities, such as widened alveolar-arterial oxygen gradient ($P(A\text{-}a)O_2$) and altered single-breath diffusing capacity for carbon monoxide (TLCO), that can compromise exercise capacity[20]. Several metabolic alterations triggered by portal hypertension are considered to be the main causes of circulatory dysfunction and pulmonary complications in cirrhotic patients[3,19]. One of these metabolic alterations consists of the accumulation of carbon monoxide, which contributes to the patients' hyperdynamic circulatory state[3].

An important finding of the present study was that the exercise tolerance was significantly higher in the COG when compared to the LCG. This justifies the higher values of VE/ VO_2 and VE/ VCO_2, since hyperventilation was necessary to maintain the workload and the energy demand. Mechanisms of peripheral fatigue, including inorganic phosphates (Pi), H^+, and regulatory proteins, as well as the buffer system to remove metabolites, are important to increase physical activity capacity[21,22]. As expected, cirrhotic patients presented lower effort tolerance, which may be associated with these patients' impaired daily physical activity that negatively affects their quality of life[5]. Despite this, $VO_{2\ peak}$, which is considered an important marker of cardiopulmonary capacity, was not significantly different between groups. Additionally, the VE/VCO_2 slope whose values >34 reflects pulmonary congest was not observed in cirrhotic patients. It is important to note that the cirrhotic patients that participated in the present investigation were in absence of ascites and only one Child-Pugh B were included. Previous studies found a relationship between lower $VO_{2\ peak}$ values and the severity of the disease[5,23,24].

Another important finding is that, despite the greater intensity reached during the test by the COG, the VO_2 off-kinetic measured by $T_{1/2}$ did not differ from that observed in the LCG. This result indicates that healthy subjects have the capacity to perform higher-intensity exercise with elevated energy demand, but then recover similarly to the cirrhotic patients, who present lower tolerance to exercise. The COG presented longer ICT duration, which requires higher energy expenditure and is

Table 2. Cardiopulmonary variables at baseline, at the anaerobic threshold and at the peak of the exercise for the liver cirrhosis patients group and for the control group.

	LCG (n=19)	COG (n=19)	p-value	Cohen's d
Baseline				
VO_2 (l.min)	0.50±0.30*	0.31±0.20	0.05	0.93 (large)
VO_2 (mL.kg.min)	6.41±3.78	4.26±3.01	0.06	0.71 (large)
VCO_2 (l.min)	0.43±0.31	0.26±0.15	0.10	1.13 (large)
Anaerobic threshold (AT)				
Time under effort (s)	476±143	511±121	0.44	0.29 (small)
VE	25.29±10.03	26.29±9.97	0.70	0.10 (small)
VO_2 (l.min)	1.20±0.44	1.03±0.51	0.32	0.32 (small)
VO_2 (ml.kg.min)	15.68±5.08	13.19±6.00	0.08	0.41 (moderate)
VCO_2 (l.min)	1.13±0.45	0.95±0.56	0.30	0.32 (small)
R (VCO_2/ VO_2)	0.94±0.09	0.95±0.10	0.64	0.15 (small)
VE/ VO_2	21.19±2.86*	27.22±6.07	0.00	0.99 (large)
VE/ VCO_2	22.62±2.56*	29.09±7.87	0.00	0.82 (large)
Work (W)	63±18	66±35	0.73	0.09 (small)
Peak of the exercise				
Time under effort (s)	590±133*	697±148	0.02	0.72 (large)
VE	35.05±14.85*	47.76±21.91	0.05	0.58 (moderate)
VO_2 (l.min)	1.46±0.63	1.45±0.51	0.94	0.02 (small)
VO_2 (ml.kg.min)	18.85±9.15	18.55±5.29	0.66	0.06 (small)
VCO_2 (l.min)	1.50±0.67	1.61±0.57	0.60	0.19 (small)
R (VCO_2/ VO_2)	1.03±0.12	1.11±0.15	0.70	0.55 (moderate)
VE/ VO_2	24.25±3.77*	33.13±11.83	0.00	0.75 (large)
VE/ VCO_2	23.60±2.94*	29.50±8.13	0.01	0.73 (large)
Work (W)	86±19	105±47	0.20	0.51 (large)

VO_2: oxygen consumption; VCO_2: carbon dioxide production; VE: minute ventilation; R: respiratory exchange ratio. *: indicates significant difference between groups (p≤0.05).

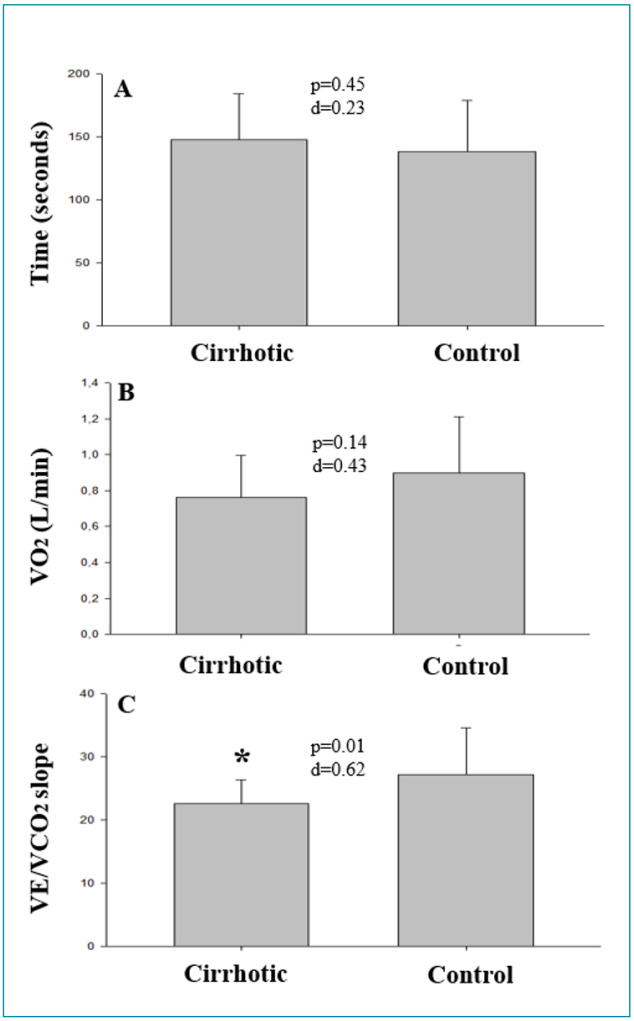

Figure 1. Recovery kinetics parameters for the control group and for the liver cirrhosis patients group. A: recovery time after effort; B: VO_2; C: VE/CO_2 slope. *: indicate significant differences between groups ($p \leq 0.05$). d: indicates the Cohen's effect size Cohen's

associated with greater release of catecholamines, higher glycogen depletion, and metabolites accumulation (such as lactate)[25]. Regular physical exercise can improve the skeletal muscle aerobic capacity to efficiently provide cellular energy as well as remove residues originating from the reactions necessary for its resynthesis[18]. Aerobic and anaerobic metabolic improvement due to regular exercise is associated with greater functional capacity, which can lead to a better quality of life[18,23,24].

The major limitation of the present study was the small number of cirrhotic patients investigated. However, it is worth noting that inclusion criteria were strict and only patients with better health conditions were selected. In addition, disease prevalence is low, making it difficult to find recruitable subjects.

CONCLUSION

In conclusion, the present study showed that metabolic demand in resting conditions is higher in cirrhotic patients when compared to healthy individuals, as a consequence of the disease complications. Cirrhotic patients have lower aerobic capacity and exercise tolerance when compared to healthy subjects, which can compromise the performance of daily activities and possibly reduce quality of life. Future studies should investigate the effects and potential health benefits of specific exercise programs in order to promote better quality of life for this population.

AUTHORS' CONTRIBUTIONS

IN: Conceptualization, Administration, Visualization, Data Curation, Formal Analysis, Methodology, Writing – Original Draft, Writing – Review & Editing. **HM:** Conceptualization, Administration, Visualization, Writing – Original Draft, Writing – Review & Editing. **RMP:** Conceptualization, Funding Acquisition, Supervision and Visualization. **RC:** Visualization, Writing – Original Draft, Writing – Review & Editing. **LM:** Methodology, Project Administration, Writing – Original Draft, Writing – Review & Editing. **ID:** Conceptualization, Funding Acquisition, Supervision. **AB:** Funding Acquisition, Methodology, Validation, Visualization. **MSR:** Conceptualization, Administration, Visualization, Data Curation, Formal Analysis, Methodology, Writing – Original Draft, Writing – Review & Editing.

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