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Respiratory muscle strength and exercise capacity of children and adolescents with chronic liver diseases

Força muscular respiratória e capacidade de exercício de crianças e adolescentes com hepatopatias crônicas

Michelli Christina Magalhães Novais[1]*, Mansueto Gomes Neto[2], Yuri da Silva Oliveira[3], Tatiane de Souza Pereira[4], Suzana Souza Moreira de Almeida[5], Luciana Rodrigues Silva[6]

[1]Post-graduation Program in Interactive Processes of the Organs and Systems, Federal University of Bahia, Salvador, BA, Brazil; [2]Physiotherapy Department of Federal University of Bahia, Salvador, BA, Brazil. Post-graduation Program in Interactive Processes of the Organs and Systems, Federal University of Bahia, Salvador, BA, Brazil; [3]Physiotherapist Specialist in Family Health, State Family Health Foundation (FESFSUS/Fiocruz), Salvador, BA; [4]Physiotherapist for the Federal University of Bahia- UFBA, Salvador, BA; [5]Physiotherapist Specialist in Collective Health, State University of Southwest Bahia, Jequié, BA, [6]Titular Professor of Edgard Santos University Hospital (HUPES), Salvador, BA, Brazil. Post-graduation Program in Interactive Processes of the Organs and Systems, Federal University of Bahia, Salvador, BA, Brazil.

Abstract

***Introdution**: Chronic liver diseases are characterized by inflammatory and fibrotic lesions of the liver that cause systemic complications. These complications can negatively interfere with the respiratory muscle strength and exercise capacity of developing children and adolescents. **Objectives**: to compare respiratory muscle strength and exercise capacity in children and adolescents with chronic hepatopathy, using predicted values from healthy individuals of the same age. **Methodology**: a cross-sectional study was performed. Children and adolescents from 6 to 16 years old with chronic hepatopathies were included. For the evaluation of respiratory muscle strength, the maximal respiratory pressures were measured through manovacuometry. A six-minute walk test was used to assess exercise capacity. The Wilcoxon test was used to verify the difference between the evaluated and predicted values of the distance traveled. **Results**: In total, 40 subjects were analyzed; 57.5% of the subjects were female, and the subjects had a mean age of 11.68±2.82 years. In the comparison between the measured and predicted maximal respiratory pressures, a median (IQR) difference of -21,47 (33-95) cmH_2O (p< 0.001) was found for the maximal inspiratory pressure, and a mean difference of 30.68±17,16 cmH_2O (p< 0.001) was found for the maximal expiratory pressure. Regarding exercise capacity, the measured average distance traveled was 346.46±49.21 m, which was 185.54±63,90 m (p< 0.001) less than the predicted value. **Conclusion**: Children and adolescents with chronic liver disease have reduced respiratory muscle function and exercise capacity.*

***Keywords:** Liver Diseases. Chronic Disease. Maximal Respiratory Pressures. Walk Test.*

Resumo

Introdução: as doenças hepáticas crônicas são caracterizadas por lesões inflamatórias e fibróticas do fígado que causam complicações sistêmicas. Essas complicações podem interferir negativamente na força muscular respiratória e na capacidade de exercício de crianças e adolescentes em desenvolvimento. Objetivo: comparar a força muscular respiratória e a capacidade de exercício em crianças e adolescentes com hepatopatia crônica, utilizando valores preditos de indivíduos saudáveis da mesma idade. Metodologia: trata-se de um estudo transversal. Foram incluídas crianças e adolescentes de 6 a 16 anos com hepatopatias crônicas. Para a avaliação da força muscular respiratória, as pressões respiratórias máximas foram medidas por meio da manovacuometria. Teste de caminhada de seis minutos foi usado para avaliar a capacidade de exercício. O teste de Wilcoxon foi utilizado para verificar a diferença entre os valores avaliados e previstos da distância percorrida. Resultados: no total, 40 sujeitos foram analisados; 57,5% dos sujeitos eram do sexo feminino, idade média de 11,68±2,82 anos. Na comparação entre as pressões respiratórias máximas medidas e previstas, foi encontrada diferença mediana (IQ) de -21,47 (33-95) cmH2O (p<0,001) para a pressão inspiratória máxima e diferença média de 30,68±17,16 cmH2O (p<0,001) para a pressão expiratória máxima. Em relação à capacidade de exercício, a distância média percorrida foi 346,46±49,21 m, média 185,54±63,90 m (p<0,001) inferior ao valor previsto. Conclusão: crianças e adolescentes com doença hepática crônica apresentam redução da função muscular respiratória e da capacidade de exercício.

Palavras-chave: Hepatopatias. Doença Crônica. Pressões Respiratórias Máximas. Teste de Caminhada.

Corresponding/Correspondente: *Michelli Christina Magalhães Novais – Universidade Federal da Bahia- UFBA. Instituto de Ciências da Saúde. – End:Av. Reitor Miguel Calmon s/n – Vale do Canela Salvador, BA, Brazil CEP 40.110-100 – Tel: (71) 98727-4948 – E-mail: novaismichelli@outlook.com

INTRODUÇÃO

Liver diseases may progress to the chronic form, in which histological (MANTANO-LOZA et al., 2012; MENDES et al., 2011), hematological and clinical changes occur (FAINTUCH et al., 2000; MATTAR et al., 2005). Malnutri-

tion frequently plays a role in these changes (FAINTUCH et al., 2000; MATTAR et al., 2005) and can determine the reduction of muscle mass and, consequently, of strength and exercise capacity (SHIRAI et al., 2018).

The preservation of respiratory muscle strength is essential for proper respiratory performance and defense and mucus clearance mechanisms. However, patients with chronic liver disease may have a reduction in this strength (PEREIRA et al., 2016). Changes in respiratory muscle strength measured by maximum respiratory pressures may be associated with reduced exercise capacity (CARVALHO et al., 2008) and worse clinical prognosis (PEREIRA et al., 2011; PEREIRA et al., 2016).

Physical ability can be measured by the six-minute walk test (6MWT) (ATS, 2002). Reduced exercise capacity (DHARANCY et al., 2008; EPSTEIN et al., 2004; MANCUZO et al., 2015; OW et al., 2014) and respiratory muscle strength in patients with chronic liver disease may decrease the distance covered in this test (SANTOS et al., 2014), indicating difficulty in performing activities of daily life.

Studies evaluating respiratory muscle strength and/or exercise capacity in adults with liver diseases have identified that lower values of maximal inspiratory pressure (MIP) and shorter distances walked on the 6MWT were associated with higher mortality rates (ALAMERI et al., 2017; CAREY et al., 2010; CARVALHO et al., 2008; PEREIRA et al., 2016;). However, to the best of our knowledge, there has been only one study on the exercise capacity of children and adolescents with liver diseases; however, this study analyzed patients after liver transplantation (DA SILVA et al., 2015). Thus, studies analyzing respiratory muscle strength and exercise capacity in children and adolescents with chronic liver disease are necessary to identify possible changes and to develop strategies to prevent and treat those changes. Therefore, the purpose of this study was to compare respiratory muscle strength and exercise capacity in children and adolescents with chronic liver disease, using predicted values for healthy individuals of the same age group. In addition, the correlation between exercise capacity and respiratory muscle strength was analyzed.

METHODOLOGY

An analytical, observational and transversal study was carried out. We included male and female children and adolescents aged between 6 and 16 years with clinical, laboratory (low albumin level, prolonged prothrombin time and hypergammaglobulinemia) and histological findings compatible with chronic liver disease. Children and adolescents with a previous diagnosis of heart disease, pneumopathies (as well as clinical respiratory disease), psychiatric disorders, musculoskeletal and neuromuscular diseases, or cognitive impairment and those who had difficulty understanding the techniques were excluded. Those with hemodynamic instability, decreased peripheral oxygen saturation, cutaneous pallor, cyanosis, vertigo, lipothymia, sudden diaphoresis, or dyspnea, before or during the evaluation, were also excluded.

The study was carried out in an ambulatory clinic at the Professor Hosannah Oliveira Pediatric Center (Department of Pediatric Gastroenterology and Hepatology), at the Professor Edgard Santos University Hospital Complex of the Federal University of Bahia, in Salvador, Bahia, with a convenience sample selected from June to December 2017. The project was approved by the Research Ethics Committee of the Professor Edgard Santos University Hospital, Salvador, BA, Brazil, under the number 2,254,208, in compliance with resolution 466/12 of the National Council for Ethics in Research (CEP) of Brazil and the Declaration of Helsinki.

Initially, sociodemographic and clinical data were recorded. The evaluation of respiratory muscle strength was performed using an analog manovacuometer (Wika®, GA, USA) with an operating range of -150 cmH_2O to + 150 cmH_2O. Following the evaluative method used in the study from which the reference values were drawn, during the procedure, the volunteers were positioned in orthostasis and a nasal clip was attached (LANZA et al., 2015). A 2-mm hole was inserted between the occlusion site and the mouth. Prior to the procedure, the evaluator explained the maneuver to be performed. To measure the MIP, the child was asked to perform a maximal expiration (up to the residual volume) followed by a maximal inspiration (up to the total lung capacity). To measure the maximal expiratory pressure (MEP), the child was asked to perform a maximal inspiration (up to the total lung capacity), followed by a maximal expiration (up to the residual volume). A minimum plateau of two seconds was necessary to measure the value of the MIP or MEP. The volunteer's hands supported the cheeks during the measurement of MEP (LANZA et al., 2015). All maneuvers were repeated three times, with a one-minute interval between measurements. The measurements were accepted when the tests were performed in a technically correct and reproducible manner (without variation greater than 10% between the two major maneuvers) (ATS, 2002; HEINZMANN-FILHO et al., 2012). The highest measured value was selected for the results (HEINZMANN-FILHO et al., 2012). The MIP and MEP were expressed as absolute values (cmH_2O), and the predicted percentage was calculated according to the method in Lanza et al. (2015), which takes into account factors such as gender, age and BMI. Weight and height data were obtained from medical records made by the multidisciplinary team.

Exercise capacity was evaluated via the 6MWT based on criteria established by the American Thoracic Society (ATS, 2002). The 6MWT was performed in an enclosed corridor with a flat, hard surface. The starting line was marked on the floor with colored tape, and marks were placed every three meters. The rotation points were also flagged. The patient rested in a chair located near the starting position for at least 10 minutes prior to the evaluation. During the rest period, the patient's blood pressure, heart rate, peripheral oxygen saturation and level of fa-

tigue were measured. The level of fatigue was evaluated with the Borg modified subjective effort scale. If before or during the evaluation the child presented any of the exclusion criteria specified in the methods of this project, the evaluation was discontinued. Before walking, the volunteer received the following instructions: "The purpose of this evaluation is for you to walk for 6 minutes. However, in this time frame you are allowed to slow down or stop to rest, if you feel the need, and to walk again when you feel able." The evaluator gave a practical demonstration to the child of how the test should be performed.

To start the test, the patient was positioned at the starting line, where the evaluator remained during the evaluation. As soon as the patient started walking, the timer was started. The evaluator did not walk with the patient during the procedure because such behavior could interfere with their walking speed. During the patient's test, the number of laps covered each time he crossed the starting line was recorded. In the following standardized way, the volunteer was informed that when 15 seconds were left to complete the test: "In a moment I'm going to ask you to stop walking. When I ask, stop exactly where you are, and I will come to you." At the end of the six minutes, the evaluator said, "Stop!" The place where the patient stopped was marked with tape. At the end of the walk (after the completion of the sixth minute), the Borg modified subjective effort scale was used to reevaluate the patient's level of fatigue, and the patient's blood pressure, peripheral oxygen saturation and heart rate were measured. The distance walked during the 6MWT was expressed as the absolute value (m) and the predicted percentage was calculated according to the method in Cacau et al. (2018), which takes into account gender, age, weight and change in heart rate (pre- and posttest).

DATA ANALYSIS

Categorical variables were expressed in absolute and relative frequencies. For the numerical variables, a measure of central tendency (mean and median) and its variability (standard deviation and interquartile range) were used, according to the data distribution. Initially, the Shapiro-Wilk test was used to analyze the normality of the data. The data were nonparametrically distributed, so the Wilcoxon test was used to verify the difference between the measured and predicted MIP, MEP and distance walked during the 6MWT. Spearman's correlation was applied to determine the relationship between the distance traveled and the MIP and the MEP. The statistical analysis was performed using Statistical Package for the Social Sciences software. The level of significance was set at p <0.05. The statistical treatment was performed using the Statistical Package for the Social Sciences, version 21.0.

RESULTS

In total, 52 children and adolescents were screened. Of these, 12 were excluded, 7 because they had neuromuscular diseases, 1 heart diseases, 2 respiratory diseases, 1 psychiatric disorders and 1 cognitive impairment.

The final sample consisted of 40 children and adolescents of both sexes with chronic hepatopathies; the patients ranged from 6 to 16 years of age. The mean age was 11.68 ± 2.82 years, the mean height was 1.43 ± 0.13 m and the mean weight was 38.17 ± 11.92 kg. A total of 36 (90%) of children and adolescents had the following clinical problems: hepatomegaly, splenomegaly, cirrhosis and ascites. Information on clinical characteristics and diagnosis is described in Table 1.

Table 1 – *Sample Characteristics (n=40).*

Characteristics	*Frequency (%)*
Female sex	*23 (57.5)*
Clinical Characteristics	
Hepatomegaly	*12 (30)*
Splenomegaly	*12 (30)*
Cirrhosis	*9 (22.5)*
Ascites	*3 (7.5)*
Diagnosis	
Portal hypertension syndrome	*10 (25)*
Congenital hepatic fibrosis	*4 (10)*
Budd-Chiari syndrome	*3 (7.5)*
Cholestatic hepatitis	*3 (7.5)*
Cryptogenic cirrhosis	*3 (7.5)*
Glycogenosis type IX	*3 (7.5)*
Wilson's disease	*3 (7.5)*
Deficiency of alpha-1 antitrypsin	*2 (5)*
Toxic hepatic disease	*1 (2.5)*
Niemann-Pick type B	*1 (2.5)*
Fibrocystic disease of the liver	*1 (2.5)*
Hepatoportal sclerosis	*1 (2.5)*
Hipobetalipoproteinemia	*1 (2.5)*
Gligenose type 1A	*1 (2.5)*
Homozygous familial hypercholesterolemia	*1 (2.5)*
Gaucher disease type 1	*1 (2.5)*
Parenchymal liver disease	*1 (2.5)*

Source: Survey Data

There was a median difference (IQR) of 21,47 (33-95) cmH_2O ($p < 0.001$) between the predicted MIP and the measured MIP and a mean difference of 30.68 ± 17,16 cmH_2O ($p < 0.001$) between the predicted MEP and the measured MEP. The mean distance traveled by the participants during the 6MWT was 346.46 ± 49.21 m (Table 2), and the mean distance predicted for individuals of the same age group was 532.43 ± 48.01 m, with a significant mean difference of 185.97 ± 63,90 m ($p < 0.001$).

Table 2 – *Difference between evaluated and predicted MIP, MEP and 6MWT values.*

Variable	Evaluated Mean (SD)	Predicted Mean (SD)	p
MIP (cmH_2O)	- 77.13 (23.31)	- 94.84 (11.59)	<0.001*
MEP (cmH_2O)	65.87 (18.18)	96.55 (10.21)	<0.001*
6MWT (m)	346.46 (49.21)	532.43 (48.01)	<0.001*

** Significant difference according to the Wilcoxon test; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; SD: standard deviation.*

Source: Survey Data

There was no intercurrence during or up to 5 minutes after the 6MWT, and no volunteer interrupted the test. The variables evaluated before and after the 6MWT are presented in Table 3. There was no correlation found between the MIP and the distance traveled (0.24, p=0.12) and weak correlation between the MEP and walked distance (0.35, p=0.02).

Table 3 – *Pre- and post-6MWT measurements.*

Variable	Pre-6MWT	Post-6MWT	p
HR (bpm)	86.25±12.17	98.42±13.78	<0.001*
SBP (mmHg)	101.17±13.34	107.17±20.51	0.05*
DBP (mmHg)	63.15±16.16	69±11.44	0.00*
RR (ipm)	19.85±3.4	24.67±12.71	0.01*
SpO_2 (%)	96.97±9.63	94.82±15.04	0.23
Borg, median (IQR)	0 (3-4)	4 (5-10)	<0.001*

** Significant difference according to the Wilcoxon test; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; RR: respiratory rate; SpO_2: peripheral oxygen saturation.*

Source: Survey Data

DISCUSSION

Children and adolescents with chronic liver disease presented values of maximal respiratory pressures and exercise capacity below the predicted values. The results revealed important considerations for developing individuals. To the best of our knowledge, our study is the first to identify that children and adolescents with chronic liver disease have reduced respiratory muscle strength and exercise capacity. Patients with chronic liver disease may have insufficient nutrient intake due to energy-protein malnutrition caused by the disease (MATTAR et al., 2005). First, it should be noted that this is a cohort of patients with chronic liver diseases caused by several etiologies.

Some factors may be associated with these results. The maintenance of normal blood glucose between meals is dependent on hepatic glycogen. The glycogen stored in muscle provides glucose for energy production, which is essential for muscle contraction (BURDA; HOCHULI et al., 2015). Type IX glycogen storage disease is an inborn error of metabolism that interferes with glycogen storage (BURDA; HOCHULI et al., 2015). This change was present in 7.5% of children and adolescents. Complications arising from glycogenosis type IX include hepatomegaly, liver cirrhosis, dyslipidemia hypoglycemia, muscle weakness and exercise intolerance (BURDA; HOCHULI et al., 2015). These complications may be correlated with the results presented in this study. However, our sample also included volunteers with other etiologies.

Portal hypertension syndrome, characterized by increased resistance to blood flow in the portal vein (VECCHI et al., 2014), was the most common liver disorder in this study. This condition can be caused by damage, such as cirrhosis of the liver intrahepatic; post-hepatic conditions, as Budd-Chiari syndrome; and prehepatic conditions (VECCHI et al., 2014). Portal hypertension syndrome can cause complications such as varicose veins, peripheral edema, ascites, gastroesophageal conditions and hypersplenism, as a consequence, anemia, thrombocytopenia, leukopenia and increased abdominal circumference may occur (VECCHI et al., 2014). Anemia is a common complication that interferes with oxygen transport by red blood cells (MENDES et al., 2011), which can lead to a reduction in the oxygenation level of the muscles associated with breathing and locomotion. Conditions that impair diaphragmatic movement (ROCHA et al., 2017), such as the presence of hepatosplenomegaly or ascites (present in portal hypertension syndrome), may interfere with chest compliance, resulting in a mechanical disadvantage that may influence the reduction in the MIP and MEP. Tachypnea and dyspnea may also result from portal hypertension syndrome. However, no such changes were observed in this study, which may be explained by the lack of children showing hepatopulmonary syndrome (MARTINELLI, 2014; VECCHI et al., 2014).

Many patients with chronic liver disease develop liver cirrhosis (PEREIRA et al., 2011), including cirrhosis-consequent disorders such as liver atresia, active chronic hepatitis, alfa 1 antitrypisin deficiency, Wilson's disease (DE BRITO et al., 2005; ROBERTS; SCHILSKY, 2008) and type IX glycogen storage disease (BURDA; HOCHULI, 2015). In the present study, 22.5% of the individuals had liver cirrhosis and reduced values of the MIP, MEP, and distance traveled on the 6MWT. Pereira et al. (2011) found that the respiratory muscle strength and exercise capacity of adults with hepatic cirrhosis were proportional to the severity of the disease and were lower in patients with more advanced cirrhosis than in those with less advanced disease. Patients with cirrhosis have hepatic insufficiency, which is commonly accompanied by several findings, such as decreased muscle mass (MANTANO-LOZA et al., 2012), changes in growth and development, and malnutrition (FAINTUCH, 2000), besides lower synthesis of albumin and others proteins. Such characteristics may compromise the motor (SANTOS et al., 2016) and cognitive activities of children with liver disease.

Individuals with hepatic cirrhosis may need liver transplantation (CARVALHO et al. 2008). Children and adolescents with reduced respiratory muscle strength may experience weaning difficulties and ineffective coughing, impairing the postoperative clinical course. In addition,

the study by Carvalho et al. 2008 showed that adults in the transplant queue with lower MIP values had a higher mortality rate. Reduced values of peak oxygen consumption were associated with higher short-term mortality after liver transplantation (DHARANCY et al., 2008). The reduction of the distance covered in the 6MWT identified in the present study may be associated with a higher mortality rate (ALAMERI et al., 2007; CAREY et al., 2010).

In the present study, there was no correlation found between the MIP and walked distance in 6MWT. Santos et al., (2017) were found different results with adults candidates for liver transplantation, the walked distance was correlated with MIP. The authors explained the correlation between MIP and 6MWT by muscle weakness, deconditioning and fatigue (SANTOS et al., 2017). It is important to emphasize that candidates for transplantation are more severe than the outpatient sample investigated in this study. About MEP, the mechanical diaphragmatic disadvantage (ROCHA et al., 2017) present in diverse chronic hepatopathies may influence in the MEP, whit possible impair on the action of the abdominal muscles. However, was weak correlation between the MEP and walked distance in the present study.

In addition to the possible respiratory complications mentioned above, many of the liver diseases presented by children and adolescents may promote lung damage. However, despite the potential to cause respiratory alterations of the abovementioned diseases, the children and adolescents studied had no clinical diagnosis of pulmonary disease and were asymptomatic at the time of evaluation.

The alterations found in this sample may indicate a worsening of the clinical prognosis of children and adolescents with chronic liver diseases. The reduction in respiratory muscle strength and exercise capacity may be associated with a worsening of the chronic liver disease, serving as a marker of the progression of the disease and thus emphasizing the need for intervention. Investigating the exercise capacity and respiratory muscle strength of children and adolescents with chronic liver disease is relevant because the reduction of these measurements may interfere with the ability of the children to perform activities necessary in their daily lives, their ability to participate in school activities and their quality of life, which are essential factors for developing individuals.

The results of this study need to be analyzed with caution due to some limitations. The small sample size should be considered. The 6MWT formula available for Brazilian children used in this study was developed for children aged 7 to 12 years (DE ASSIS PEREIRA CACAU et al., 2018). Another limitation is the lack of a detailed nutritional evaluation and the measurement of the level of physical activity, and the absence of the time of diagnosis of chronic liver disease makes it difficult to interpret the results obtained. Many children with chronic liver diseases have no symptoms until overt hepatic insufficiency appears. Such data could help in the determining the level of interference of the energy reserve and energetic demand in the exercise capacity of the individuals studied. This information, if added to future studies, may contribute to the discussion and understanding of the findings. Thus, new studies with larger sample sizes and the analysis of the factors that may be associated with the alterations found may contribute to a better understanding of this condition and contribute to adequate therapeutic targeting.

CONCLUSION

Children and adolescents with chronic hepatopathies had reduced respiratory muscle strength and exercise capacity. There no correlation between the inspiratory muscle strength and the exercise capacity and weak correlation between the expiratory muscle strength and exercise capacity these children and adolescents. Professionals should be aware of these changes during the functional evaluation and clinical course of children and adolescents with chronic liver disease.

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