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Analysis of biomarkers and functional capacity in children and adolescents with congenital heart disease and pulmonary hypertension

Análise dos biomarcadores e capacidade funcional em crianças e adolescentes com cardiopatia congênita e hipertensão pulmonar

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Abstract

Background: With advances in diagnosis and intervention, there has been a growing improvement in the management of congenital heart disease (CHD) and its complications. The natural course of patients with CHD is associated with late sequelae, such as pulmonary arterial hypertension (PAH). The treatment of pediatric PAH is based on risk stratification, with predictors of poor prognosis similar to those in adults. In the CHD population with PAH, few studies have correlated clinical and laboratory predictors with disease severity. **Aim:** To correlate functional capacity with pre-established markers in the literature among children and adolescents with CHD and PAH. **Methods:** A retrospective study using a database of children and adolescents with CHD and PAH from an outpatient clinic in São Paulo. Clinical data, six-minute walk test distance (6MWD), World Health Organization functional class (WHO-FC), and laboratory tests were collected. Epidemiological variables were analyzed according to normality, and Spearman's or Pearson's correlation was applied when appropriate. **Results:** The sample consisted of 25 patients, 52% of whom were female, with a mean age of 15.1 years (±1.25). The predicted 6MWD was 46.1% in the female group and 46.7% in the male group (p= 0.180). The correlation between WHO-FC and 6MWD was very weak (r = 0.093), and between WHO-FC and B-type natriuretic peptide was weak (r = 0.346). No significant difference was found between WHO-FC groups in relation to 6MWD (p = 0.449). **Conclusion:** No strong correlation was found between the patients' functional capacity and the biomarkers used for PAH follow-up.

Keywords: Congenital Heart Disease, Functional Status, Pulmonary Hypertension.

Resumo

Introdução: Com o avanço no diagnóstico e intervenção houve um crescente aperfeiçoamento no manejo das cardiopatias congênitas (CC) e suas complicações. O curso natural do paciente com CC está associado a sequelas tardias, como a hipertensão arterial pulmonar (HAP). O tratamento de HAP infantil é baseado na estratificação do risco, com preditores de piores prognósticos semelhantes a adultos. Na população de CC com HAP poucos estudos correlacionam os preditores clínicos e laboratoriais à gravidade. **Objetivo:** Correlacionar a capacidade funcional com marcadores pré-estabelecidos na literatura de crianças e adolescentes com CC e HAP. **Métodos:** Estudo retrospectivo, com banco de dados de crianças e adolescentes com CC e HAP de um Ambulatório em São Paulo. Foram coletados dados clínicos, distância do teste de caminhada de 6 minutos (DTC6), classificação funcional da Organização Mundial de Saúde (WHO-FC) e exames laboratoriais. As variáveis epidemiológicas foram analisadas de acordo com a normalidade, além da utilização da correlação de *Spearman* e *Pearson*, quando aplicável. **Resultados:** A amostra foi composta por 25 pacientes, sendo 52% pacientes do sexo feminino, com média de idade de 15,1 anos (±1,25). A DTC6 predita foi 46,1% no grupo feminino e 46,7% no masculino (p= 0,180). A correlação entre a WHO-FC e TC6 foi muito fraca (r= 0,093) e entre WHO-FC e peptídeo natriurético tipo-B foi fraca (r= 0,346). Não houve diferença entre os grupos da WHO-FC em relação a DTC6 (p= 0,449). **Conclusão:** Não foi encontrada uma correlação forte entre a capacidade funcional dos pacientes e os biomarcadores utilizados para o acompanhamento da HAP.

Palavras-chaves: Cardiopatias Congênitas; Estado Funcional; Hipertensão Pulmonar.

INTRODUCTION

According to the World Health Organization[1], congenital disorders are responsible for approximately 240,000 deaths annually. Among these conditions, congenital heart disease (CHD) accounts for the most common structural defect and the leading cause of childhood mortality[2,3]. In recent decades, advances in diagnosis, interventional techniques, and surgical treatment have significantly increased the survival of these patients , decreasing mortality by 50% to 70% in about 20 years[3]. However, the natural course of CHD can evolve with late sequelae, including pulmonary hypertension (PH), which impacts the morbidity and mortality of this population[3].

PH is a multifactorial hemodynamic syndrome found in different clinical conditions[4] and can manifest at any age, with high morbidity and mortality[5]. In pediatrics, pulmonary arterial hypertension (PAH) stands out as the most prevalent form in this age group[6]. Its occurrence associated with CHD is estimated at 2.2 cases per million children[6]. PAH is characterized by an increase in mean pulmonary artery pressure ≥25 mmHg, with normal pulmonary capillary pressure, indicating primary impairment of the pulmonary vasculature[7]. In CHD with pulmonary hyperflow, vascular remodeling can progress to PAH, culminating at advanced stages in Eisenmenger syndrome (ES)[8].

The symptoms of PAH are nonspecific. In older children, exertional dyspnea and progressive fatigue are common[4-6,9]. Risk stratification guides treatment and uses parameters similar to those applied in adults[4]. Among these, the progression of symptoms, the World Health Organization functional classification (WHO-FC), serum levels of natriuretic peptides (BNP/NT-proBNP), and functional assessment instruments stand out[4-6].

Clinical, laboratory, hemodynamic, and echocardiographic assessments are used in risk stratification, prognosis, and therapeutic monitoring in adults with PAH[4,10-13]. Among serum markers, BNP and NT-proBNP are widely recognized as indicators of the progression of cardiac dysfunction, including in pediatrics[4]. WHO-FC, in turn, correlates with exercise capacity and prognosis in PAH[4,12,13].

Exercise intolerance is one of the main characteristics of PAH, making functional capacity (FC) assessment crucial[14]. In adults, the distance covered during the six-minute walk test (6MWT) is a simple and reproducible measure of functional assessment that is linked to survival[13,14]. In the pediatric population, there are still few established cutoff values; however, distances less than 350 m suggest a worse prognosis[4]. The American Heart Association (AHA) and the American Thoracic Society (ATS) acknowledge the 6MWT as a valuable tool for assessing the severity of PH in children, relating lower performance to greater disease severity[15].

In a study involving 41 children with PAH — idiopathic, associated with CHD and ES — the 6MWT corresponded to 47.7% of the predicted value and correlated with maximum oxygen consumption up to 300 m. Beyond this limit, a cardiopulmonary exercise test is recommended[16].

Despite growing recognition of the importance of clinical and laboratory markers in pediatric PAH, there is still little literature on the integrated correlation between FC, biomarkers, and WHO-FC in children and adolescents with CC and PAH. Thus, this study hypothesizes that 6MWT correlates with disease severity according to WHO-FC, and that high BNP levels are associated with worse functional performance and greater clinical impairment**.**

This study aims to correlate functional capacity with previously established clinical and laboratory markers in children and adolescents with CHD and PAH.

METHODS

This is a retrospective study that analyzed a database of children and adolescents with CC and PAH from the Pulmonary Hypertension Outpatient Clinic of the *Irmandade da Santa Casa de Misericórdia de São Paulo*. Approved by the Ethics and Research Committee of the *Irmandade da Santa Casa de Misericórdia de São Paulo*, approval number: CAAE: 791107'24.3.0000.5479.

A convenience sampling method was used for this retrospective database analysis, and no sample calculation was performed. Participants aged 4 to 17 years and 11 months were included, with the youngest and oldest ages assessed at the service where the evaluations were performed, both sexes, with CHD and PAH, whose data were available in the medical records for analysis from January 2018 to April 2023. The study waived the Free and Informed Consent Form (FICF) and the Free and Informed Assent Form (FIAF). Participants with physical and/or cognitive limitations that prevented completing the WT6 and those with no data available for analysis were excluded.

The following data were collected: name, age (years), weight (kg), height (meters), underlying disease, BNP value up to one year before the last consultation, medications in use (divided into three groups: none or up to one medication; up to two medications; more than two medications), undergoing some type of cardiac surgery for treatment (corrective or palliative) (yes or no), use of home oxygen (yes or no), undergoing cardiopulmonary rehabilitation (yes or no), 6MWT (meters), and WHO-FC.

The WHO-FC for PH is based on symptom severity and physical limitation to classify patients into four classes: “Class I: no limitations, normal physical activity”; “Class II: mild limitations, symptoms with excessive exertion”;

"Class III: significant limitations, symptoms with normal activities"; and "Class IV: inability to perform physical activity, symptoms at rest."[17]

The underlying disease was classified according to pulmonary flow and divided into three categories: pulmonary hyperflow, pulmonary normoflow, and pulmonary hypoflow, since the development of PAH in CC is greatly influenced by changes in pulmonary flow[17,18]. Regarding the 6MWT, the distance covered in the outpatient consultation test was collected, according to the local routine based on the American Thoracic Society Guidelines, 2002[19]. The test was performed only once by the outpatient department physiotherapist while the patient was waiting for the consultation or after it, and the predicted distance was calculated using the equation by Oliveira et al.[20] based on sex, height, weight, and age.

The collected data were entered into an Excel spreadsheet and analyzed using SPSS Statistical Package for the Social Sciences for Windows®, version 26.0 (SPSS Inc., Chicago, IL, USA). The statistical significance level was set at 5% ($p < 0.05$). Data normality was calculated using the Shapiro-Wilk test.

Epidemiological data were presented in tables with mean and standard deviation calculated for parametric variables by the t-test. Pearson's correlation test (r) was used to assess the correlation between parametric variables, while Spearman's correlation test (r) was used for nonparametric variables. The Kruskal-Wallis test was performed to analyze nonparametric variables and independent groups, with a significance level of $p<0.05$ and H0 accepted.

RESULTS

Twenty-five patients were included from the analyzed database (Figure 1). The sample was divided by gender calculating the predicted 6MWD based on the prediction equation[20]. The sample consisted of 13 female and 12 male patients. BNP was higher in the female group ($p = 0.014$). WHO-FC II was more prevalent in both groups. Most of the female participants underwent surgical intervention, while only half of the male group did. No female participants underwent cardiopulmonary rehabilitation, and only one male participant did ($p = 0.031$). The most prevalent heart disease in both groups was pulmonary hyperflow. Regarding the number of medications, most of the female group used up to two medications, while the male group used none or only one ($p = 0.009$). Table 1 shows the epidemiological data of the sample.

The average 6MWT was 344 meters (46% of the predicted value), in the female group and 402 meters (47% of the predicted value) in the male group. Table 2 shows the mean 6MWT, the predicted value in meters, and the percentage of the distance covered by the groups compared to the predicted distance according to the equation by Oliveira et al.[20] based on weight, height, and age in healthy children and adolescents.

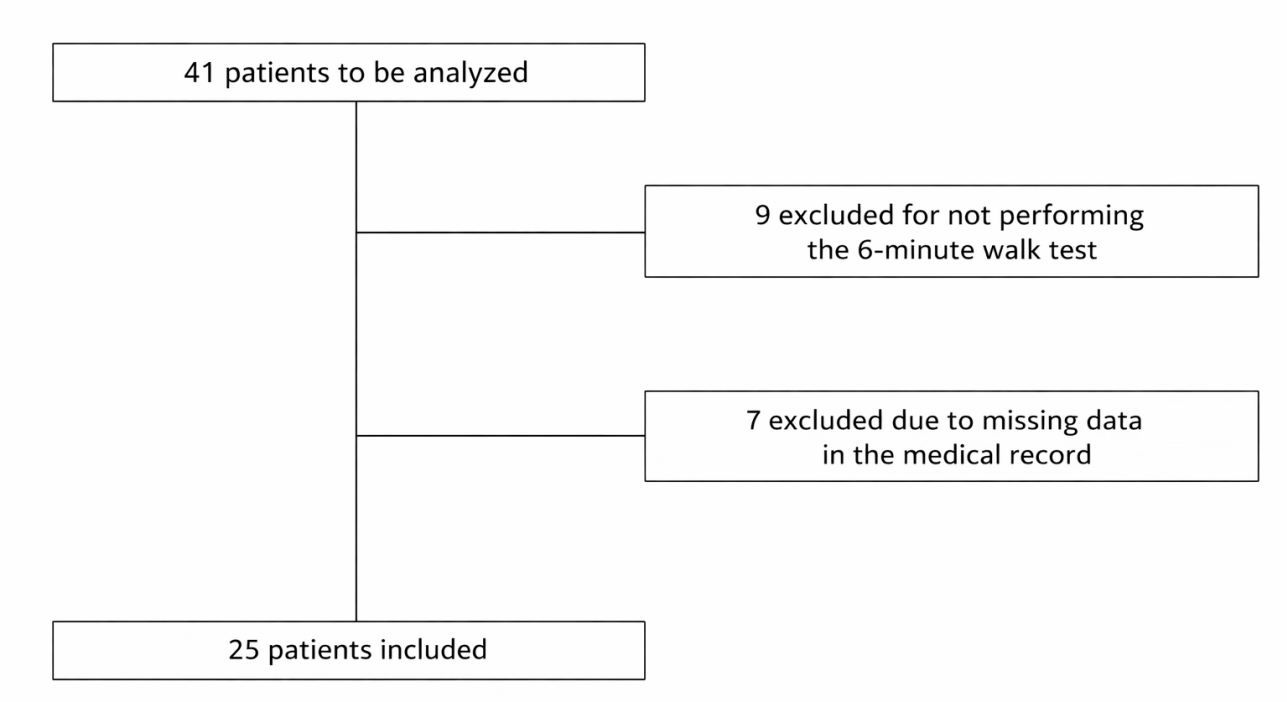

Figure 1. Flowchart of included and excluded patients.
Source: Figure by the authorfigure by the author.

Table 1. Clinical, anthropometric, and functional characterization of the sample.

	Female (n=13)	Male (n=12)	*p*
Age (years) (mean/SD)	15.1 ±1.25	16.5 ±1.75	0.576
Age classification (n/%)			0.063
Preschool	0	1 (8.3)	
School	1 (7.7)	1 (8.3)	
Adolescent	12 (93.7)	10 (83.6)	
Height (mean/SD)	1.47 ±0.2	1.47 ±0.3	0.570
Weight (mean/SD)	40.78 ±11.9	44.7 ±19.4	0.229
Heart disease (n/ %)			0.770
Normal flow	0	1 (8.3)	
Hyperflow	11 (84.6)	11 (91.7)	
Hypoflow	2 (15.4)	0	
BNP (pg/ml) (mean/SD)	366.3 ±144.4	195.8 ±45.8	*0.014*
WHO-FC (n/ %)			0.260
I	2 (15.4)	1 (8.3)	
II	7 (53.8)	8 (66.7)	
III	4 (30.8)	3 (25)	
Surgery (n/ %)			0.180
Yes	9 (69.2)	6 (50)	
No	4 (38.2)	6 (50)	
Rehabilitation (n/ %)			*0.031*
Yes	0	1 (8.3)	
No	13 (100)	11 (91.7)	
Use of oxygen (n/ %)			0.831
Yes	3 (23.1)	3 (25)	
No	10 (76.9)	9 (75)	
Medications (n/ %)			*0.009*
None or 1	4 (30.8)	7 (58.3)	
Up to 2	6 (46.2)	4 (33.3)	
More than 2	3 (23.1)	1 (8.3)	

n: sample; SD: standard deviation; BNP: B-type natriuretic peptide; WHO-FC: functional classification of the World Health Organization; pg/ml: picograms per milliliter.

The correlation between WHO-FC and 6WT was r = 0.093, with p = 0.66, whereas the correlation between WHO-FC and BNP was r = 0.346, with p = 0.09, indicating a weak correlation between the variables analyzed (Table 3).

There was no difference between the functional classification groups in 6MWD, with p=0.449, accepting the null hypothesis, as shown in Figure 2.

DISCUSSION

The patients with CC and PAH assessed were, on average, 15.1 years old (girls) and 16.5 years old (boys). Regarding the WHO functional classification, most cases fell into categories I–III, with no cases in category IV. Hyperflow was the most frequent alteration in the pulmonary bed. Most had not undergone cardiopulmonary

Table 2. Performance in the six-minute walk test.

	Female	Male	p
6MWD (meters) (mean/SD)	344 ±133.2	402 ±81.2	0.209
Predicted (meters) (mean/SD)	745 ±61.3	860 ±100.9	0.379
Predicted percentage (mean/SD)	46 ±18.4	47 ±15.4	0.180

6MWD: Distance covered in the 6-minute walk test; SD: standard deviation.

Table 3. Correlation between functionality and laboratory marker.

	WHO-FC
6MWT	r= 0.093 (p= 0.66)
BNP	r= 0.346 (p=0.09)

WHO-FC: functional classification of the World Health Organization; 6MWT: Distance covered in the 6-minute walk test; BNP: B-type natriuretic peptide.

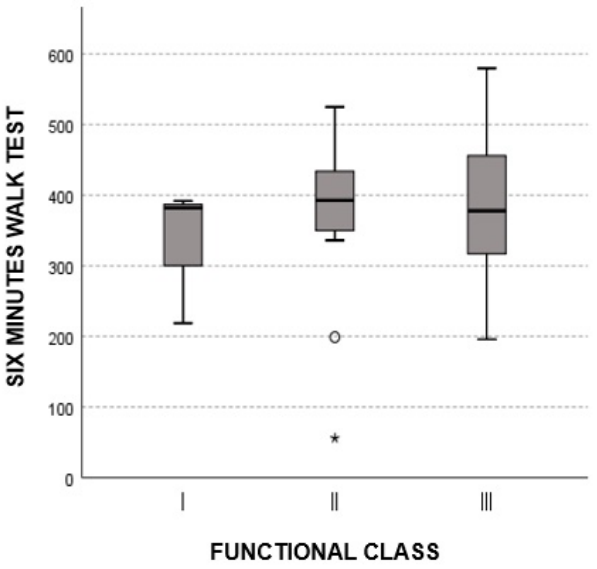

Figure 2. Distance covered in the 6-minute walk test according to the WHO-FC.
Source: Figure by the authorfigure by the author.

rehabilitation or home oxygen therapy and used up to two specific medications for PAH. No significant correlation was observed between functional capacity and the biomarkers used to monitor the disease.

This study shows that lab tests often do not reflect the clinical severity or reduced functional capacity in children with CC accurately. The reduction in 6WT distance may suggest a worse prognosis and lower survival rate.

Some previous studies have observed that children with PAH in worse WHO-FC walked longer distances in the 6MWD (22%–109% of predicted), suggesting a relationship between these variables, unlike our study, which found no statistical differences between 6MWD and WHO-FC[21]. Another study comparing WT6 and TCPE in children with PAH observed that, in cases of lesser cardiopulmonary impairment, WT6 does not accurately represent maximum capacity. Thus, TCPE can complement the assessment in those who walk more than 300 m in the WT6[22].

The 6WT distance alone does not predict survival, but when associated with biochemical markers such as BNP and WHO-FC, it can assist in estimating transplant-free survival, severity, and therapeutic definition[14,21]. In children with PAH, 6MWT has been shown to predict death and the need for transplantation, as well as a lower than expected percentage (47.7%)[22,23], which is similar to the findings of our study (46.1% girls; 46.7% boys).

WT6 represents general physical capacity and may reflect quality of life[14]. Patients with PAH have lower exercise capacity compared to healthy individuals and those undergoing rehabilitation[24,25]. This is believed to occur due to a decrease in cardiac output secondary to RV impairment, inadequate ventilation/perfusion ratio, and impaired gas exchange[26].

BNP and NT-proBNP are widely used in PAH because they are simple and non-invasive. BNP has faster elimination and may better reflect hemodynamic changes in real time, while NT-proBNP has a longer half-life due to renal elimination and shows a stronger correlation with echocardiographic and exercise findings. Both are associated with severity and prognosis[27].

WHO-FC is widely used to assess severity and progression and is a predictor of survival and the need for transplantation[6,12,28]. Despite its subjectivity, it is a therapeutic goal and a frequent outcome in studies[6,12]. There is a described association between exercise capacity, RV function, hemodynamic data, BNP, and WHO-FC in PH, but with little pediatric data[6,12,29]. In other studies, class IV patients showed higher BNP levels[30], whereas our study found a weak correlation between WHO-FC and BNP (r=0.346; p=0.09). Our study also found no correlation between 6MTW and WHO-FC.

A study involving 28 patients with PAH showed a difference in BNP levels between WHO-FC II and III, as well as a strong inverse correlation between WHO-FC and 6MWT[31]. Patients in WHO-FC IV showed a higher risk of mortality within one year, lower 6MWT, and higher BNP levels[32].

Although the WHO-FC is commonly used in pediatrics, it does not address symptoms specific to this age group,

prompting the creation of the Panama-FC, which is adapted for age[29]. It stratifies patients into five age groups and five severity levels, considering symptoms, motor and physical development, social aspects, and appetite[33]. Panama-FC covers non-invasive markers, such as WT6 and BNP, with changes over time linked to morbidity, mortality, and development, adding to the assessment[34].

The WHO-FC is more practical for rapid assessment, while the Panama-FC may be more suitable for prolonged follow-up. European guidelines recommend the use of the WHO-FC in risk assessment[4]. Panama-FC adoption has been growing in clinical practice and research, offering the potential to better stratify functional changes according to age group.

This study has limitations such as 1. its retrospective nature, limiting the collection of additional data; 2. the small number of patients, which may have prevented the detection of significant differences; and 3. the absence of stratification by age group, which may have influenced the results referring to biomarkers and functional capacity.

CONCLUSION

Our study found no significant correlation between 6MWT, BNP levels, and WHO-FC in patients with CHD and PAH. Although the literature suggests a relationship between these parameters in pediatric and adult populations with PAH, the data from this sample indicate that, in isolation, these markers may not reflect the functional capacity of patients with CHD and PAH reliably.

These findings highlight the need for complementary and customized approaches to evaluating this population, considering other factors such as age, clinical, and functional heterogeneity. Studies involving a larger number of participants, with a prospective design and age stratification, may provide more robust evidence for understanding the relationship between biomarkers and functionality in pediatric patients with PAH associated with CHD.

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CONFLICT OF INTEREST

Nothing to declare.

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RESEARCH DATA AVAILABILITY

Research data is available upon request only.

ARTIFICIAL INTELLIGENCE USE

No AI was used at any stage of the manuscript's production.

AUTHOR CONTRIBUTIONS

Design: Mariana Oliveira, Maria Eduarda Malosá Jorge; Data curation: Mariana Oliveira, Maria Eduarda Malosá Jorge, Vitor Ricardo; Formal analysis: Mariana Oliveira; Financing acquisition: Mariana Oliveira, Flávia Navarro; Investigation: Mariana Oliveira, Flávia Navarro; Methodology: Mariana Oliveira, Luciana Sampaio Project management: Mariana Oliveira, Luciana Sampaio; Computer software/programs: Mariana Oliveira; Supervision: Luciana Sampaio; Validation: Mariana Oliveira, Luciana Sampaio; Visualization: Mariana Oliveira, Luciana Sampaio; Writing – original draft: Mariana Oliveira; Writing – review and editing: Mariana Oliveira, Luciana Sampaio; Translators: Mariana Oliveira.

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