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Diagnostic value of the six-minute walk test (6MWT) in grown-up congenital heart disease (GUCH): Comparison with clinical status and functional exercise capacity☆

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ABSTRACT

Background: Exercise testing for the assessment of functional capacity plays an important role in long-term follow-up of GUCH patients. CPX is the favored modality for decision-making recommended in the current guidelines. In contrast to this complex method, the 6MWT is a simple, easy-to-perform, safe, and commonly available exercise test. Although well-established in various cardiopulmonary diseases, the diagnostic impact of the 6MWT in GUCH patients is not known so far.

Methods: 102 GUCH patients were evaluated by 6MWT and CPX simultaneously. Clinical symptoms were assessed, according to the NYHA classification. Additionally, an echocardiography study, and selected cardiac blood tests (N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitive Troponin T) were performed.

Results: Ranges of six-minute walk distance (6MWD) and peak oxygen consumption ($peakVO_2$) were 116–765 m and 6.4–36.2 ml/kg/min, respectively. 6MWD and $peakVO_2$ showed a close correlation ($r = 0.72$, 95% CI, 0.63 to 0.79). Patients with a $peakVO_2$ of ≤15.5 ml/kg/min were excellently identified by 6MWT (c-value = 0.82). A cut-off value of 482 m was optimal to predict reduced $peakVO_2$. In multivariate regression analysis, 6MWD and NYHA class were identified as relevant predictors of $peakVO_2$. In subgroup analysis, Eisenmenger patients achieved the shortest 6MWD (280, SD 178 m).

Conclusion: In our study population of GUCH patients, the 6MWD shows a close correlation to $peakVO_2$, and an excellent prediction of reduced $peakVO_2$. Thus, it seems to be an easy-to-perform and reliable screening parameter to evaluate functional capacity of these patients (Controlled Clinical Trials number, NCT02193243).

1. Introduction

The number of GUCH patients continuously grows, as survival improves [1]. Long-term follow-up and decision-making of (re)interventions in this complex patient population likewise gain importance, and strategies for identifying deteriorate conditions are still a critical issue [2]. Cardiopulmonary exercise testing (CPX) gives a broad evaluation of function and fitness, furthermore, peak oxygen consumption ($peakVO_2$), retrieved from CPX, was found to be a predictor of hospitalization and death in GUCH [3]. GUCH patients with a $peakVO_2 \leq 15.5$ ml/kg/min were found to have a 2.9-fold risk of hospital admission or death compared to patients with a $peakVO_2 > 15.5$ ml/kg/min. Hence, CPX is recommended for serial testing of GUCH patients in the current European Society of Cardiology (ESC) guidelines [2].

In contrast to this complex method, the six-minute walk test (6MWT) is a simple, well-available, cost-efficient and safe exercise test [4,5]. In patients with heart failure, coronary artery disease, pulmonary hypertension (PHT) and other lung diseases, its diagnostic and prognostic value has been established [6–13]. In comparative studies, the six-minute walk distance (6MWD) was found to be a superior predictor of $peakVO_2$ in patients with dilative cardiomyopathy and chronic heart failure [14,15]. Despite widespread use, the role of the 6MWT in the evaluation of GUCH remains unknown so far, with a few promising studies pointing towards its usefulness in this patient population [16,17]. Thus, the aim of our study was to compare the 6MWT with CPX, as established gold standard, as well as the patient's clinical status.

2. Methods

2.1. Study population

Data of this prospective observational study was surveyed at the University Hospital Duesseldorf, Division of Cardiology, Pulmonology and Vascular Medicine, between June 2013 and July 2014. Patients were referred for exercise testing as part of routine outpatient follow-up or during inpatient stay. Patients were eligible for study inclusion, if they were

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>18 years old, and diagnosed with a congenital heart defect. Exclusion criteria were severe psychiatric diseases, mental incapability of exercise testing, non-cardiac limitations of physical capacity, as orthopedic diseases or ongoing febrile infections. Patients in an unstable clinical status as acute heart failure with symptoms at rest were also excluded from participation. The study was conducted in accordance to the provisions of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practices, and protocol approval was obtained from the local Ethics Committee. All patients gave written informed consent. Fig. 1 delineates screening, enrollment, and analysis of the study cohort.

2.2. Six-minute walk test (6MWT)

The 6MWT was performed standardized on a hospital corridor of 30 meter length. The test was conducted following the American Thoracic Society guidelines [18] and the recommendations of Guyatt and colleagues [19]. A trained nurse, blinded to the CPX-results, administered the patients during 6MWT. Patients walked as fast as possible for a period of 6 min. Rest was allowed when needed, and time was called out every minute by protocol. The 6MWD was measured by a meter-counting wheel, which the patient carried with him.

2.3. Cardiopulmonary exercise testing (CPX)

CPX was performed with bicycle exercise in half-recumbent workout position within 3 weeks and a minimum of 4 hour time lag to the 6MWT. Before walking and after 2 min of rest, capillary blood gas analysis was performed. The exercise protocol started with a 3 minute reference phase at 0 W, followed by an initial workload of 25 W. By protocol, workload was continuously increased with a 25-Watt augmentation every 2 min. During the whole test, a 12-lead electrocardiogram monitoring was derived, and recorded every minute. Blood pressure was measured every 2 min. Ventilation ($\dot{V}E$), carbon dioxide production (VCO_2), oxygen consumption (VO_2), and peak respiratory exchange ratio (RER) were calculated from standard formulas, as described before [3,20,21]. The patient was encouraged to exercise to exhaustion. Blood gas analysis was again performed at peak exercise, when the patient indicated that he or she needed to stop.

2.4. Other methods of clinical and functional evaluation

During presentation, the NYHA class was registered, based on the patient's self assessment [22]. Following the protocol for GUCH at our institution, every patient received a transthoracic echocardiography study by an experienced physician according to the recommendations of the European Society of Cardiovascular Imaging (ESCVI; [23]) and ESC guidelines for GUCH [2].

Standard blood tests for kidney and liver function, electrolytes, total protein, inflammation, iron, glucose and lipid metabolism, uric acid, thyroid levels, full blood count, and coagulation were performed. Additionally, cardiac biomarkers as creatine kinase with its isoenzyme MB, high-sensitive Troponin T and N-terminal pro-brain natriuretic peptide (NT-proBNP) were determined.

2.5. Statistical methods

Test variability of the 6MWT was assessed by the correlation between the first and the second measurement, i.e. the Cronbach's alpha coefficient in repeat measurements. The correlation between 6MWD and peakVO_2 was investigated by Pearson's correlation coefficient. C-statistics and linear regression were calculated to test the 6MWT's capability to predict peakVO_2. We estimated the 95% confidence intervals of the correlation coefficient and the regression parameters with the BCa bootstrap method (number of bootstrap samples 10,000). A cut-off for optimal peakVO_2 prediction was determined using receiver-operating characteristics. For the comparison of 6MWD among various heart defects, one-way ANOVA with post-hoc Tukey's test was applied. p-Values < 0.05 were considered statistically significant.

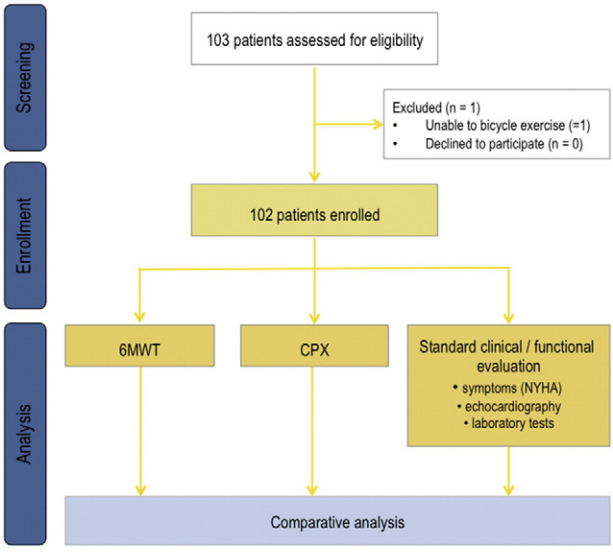

Fig. 1. Consort diagram: Overview of screening, enrollment, and analysis of the study cohort. To avoid bias by consecutive exercise testing, 6MWT and CPX were performed with a minimum time interval of 4 hours in a cross-over design.

3. Results

3.1. Study population

103 patients were screened for eligibility. Of those, 1 patient had to be excluded, because he was not able to conduct CPX due to early exhaustion after climbing the bicycle. This patient was exclusively evaluated by 6MWT, which showed the mostly impaired 6MWD of 116 m. A comparable reduction in 6MWD was only seen in 1 other patient. In the study collective of 102 patients, mean age was 35.4 years (SD 13.6). 50% of the study population was male. NYHA class was 1.1 (SD 1.1), with 11 (10.8%) patients reporting NYHA class ≥ III. The most frequent congenital heart defects were left-to-right intracardiac shunts (33%, n = 34), tetralogy of Fallot (TOF; 27%, n = 28), left ventricular outflow tract obstruction (LVOT; 13%, n = 13) and systemic right ventricle conditions (13%, n = 13). A detailed overview about baseline characteristics and types of heart defects is shown in Tables 1 and 2.

3.2. Test–retest reliability of 6MWT in GUCH

To analyze reliability of 6MWT in our study of GUCH patients, we performed repeat measurements in a subset of patients (n = 18). We used the correlation coefficient between two distances completed by the same patient in the same clinical condition. Fig. 2 displays the scatter plot between the two time points of measurements. The correlation between measures was r = 0.92, 95% CI, 0.77 to 0.98, which in the scale of the Cronbach's alpha coefficient indicates excellent test reliability.

Table 1
Baseline characteristics.

	n = 102
Age [years]	35.4 (SD 13.6)
Male patients	51 (50%)
NYHA-class	1.1 (SD 1.1)
NYHA I	58 (56.8%)
NYHA II	33 (32.4%)
NYHA III	10 (9.8%)
NYHA IV	1 (1.0%)
Left systemic ventricle	87 (85.3%)
Reduced function of systemic ventricle <45% LVEF or <18 mm TAPSE	LV: 5 (4.9%), RV: 2 (1.9%)
Pulmonary hypertension [26]	42 (41.2%)
Cyanosis	4 (3.9%)
Pre-existing heart medication	37 (36.3%)
ICD or ICD/CRT	8 (7.8%), 5 (4.9%) for 2nd prevention
Pacemaker	7 (6.9%)
pO_2 at rest [mm Hg]	82.4 (SD 13.2)
pCO_2 at rest [mm Hg]	36.9 (SD 4)
NT-pro BNP [pg/ml]	388.5 (SD 699.3)
High-sensitive Troponin T [ng/l]	7.1 (SD 7.5)

Values are given as mean (SD = standard deviation) or numbers (percentage). A more detailed overview of the underlying pathology is given in Table 2. CRT = cardiac resynchronization therapy; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; NT-pro BNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association [22]; pCO_2 = (arterial) carbon dioxide partial pressure; pO_2 = (arterial) oxygen partial pressure; TAPSE = tricuspid annular plane systolic excursion [36].