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Abbreviations

CHD, congenital Heart Disease

NYHA, New York heart association

GUCH, grown-up congenital heart

LF, lung function

FEC, functional exercise capacity

PeakVO_2, maximal oxygen uptake

CPET, cardiopulmonary exercise test

HR, heart rate

AT, anaerobic threshold

PA, physical activity

6MWT, 6-minute walk test

6MWD, 6-minute walking distance

COPD, chronic obstructive pulmonary disease

STST, 1-minute Sit-to-stand test

QoL, quality of life

HR-QoL, health-related quality of life

FITT factors, frequency, intensity, time and type of activity

METs, metabolic equivalents

VO_2, oxygen uptake

VCO_2, carbon dioxide production

RER, respiratory exchange ratio

VE/VO_2, ventilatory equivalent for oxygen

VE, minute ventilation

VD/VT, dead space-to-tidal volume ratio

VE/VCO_2, ventilatory equivalent for carbon dioxide

Watts, maximum workload

VO_2/HR, oxygen pulse

VE/VCO_2, ventilation efficiency

OUES, oxygen uptake efficiency slope

O_2, oxygen

CO_2, dioxide

PFTs, pulmonary function tests

FVC, forced vital capacity

FEV1, forced expiratory volume in the first second

$FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of the FVC

FEV_1/FVC, Tiffeneau-Pinelli index

PEF, peak expiratory flow

GLI, global lung function initiative

CHF, chronic heart failure

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1. Introduction

1.1 Definition, prevalence and classification of Congenital Heart Diseases

Congenital heart diseases (CHD) are a spectrum of structural or functional cardiac or vascular defects. It represents the most common form of congenital birth defects[1] and is usually diagnosed prenatally or early in infancy[2,3]. The structural defects are usually explained by an abnormal embryonic heart development during the first trimester of pregnancy.
The prevalence of CHD varies between 4 and 10 per 1.000 live births[4]. Currently, between 85% and 90% children with CHD will survive to adulthood, due to the advances in paediatric cardiac care[5,6].

The aetiology of the heart malformations may be genetic predispositions, environmental stimuli and other multifactorial parameters. For instance, chromosomal syndromes that comprise 8% to 10% of CHD like Down syndrome, trisomy 13, trisomy 18, Turner syndrome, and DiGeorge syndrome. However, approximately 15% of CHD can be traced to a single known cause. Currently, it is well known that one of the major risk factors are maternal diabetes mellitus, phenylketonuria (metabolic disease, inability to process protein phenylalanine), obesity, alcohol use, rubella infection, febrile illnesses, use of certain drugs (thalidomide and retinoic acid) and exposure to organic solvents[3].

As many type of heart defects we described, a precise CHD classification is extremly important. Currently, various classifications are used to describe CHD patients. First of all, it is important to make a difference between paediatric and adult population. In the adult population, the well-established New York Heart Association (NYHA) functional classification is the most common to determine the disease severity, including heart failure. Nevertheless, for obvious reasons, this classification does not apply to the paediatric population[7,8], and there is a clear need for other types of classifications. In the paediatric population, the modified Ross Classification, incorporates feeding difficulties, growth issues, and symptoms of exercise intolerance into a numeric score comparable with the NYHA classification for adults[8]. Other classification approaches are based on the CHD severity, as defined by Hoffman and Kaplan[9], on the anatomical defects as proposed by Houyel[10], or on to the patient‘s clinical condition, as proposed by Uzark[11]. Table 1 and 2 clarify and compare the aforementioned classifications.

Table 1: Classifications comparison for congenital heart disease in pediatric population

NYHA (adults with heart failure)		Modified Ross heart failure	Uzark
Class I Patient Symptoms No limitation of physical activity. Ordinary physical activity does not cause fatigue, palpitation, dyspnea (shortness of breath)	**Class A Objective Assessment** No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity	**Class I** Asymptomatic	**Mild** No therapy or effectively treated nonoperatively (catheter therapy)
Class II Patient Symptoms Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath)	**Class B Objective Assessment** Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest	**Class II** Mild tachypnea or diaphoresis with feeding in infants. Dyspnea on exertion in older children.	**Moderate (I)** No therapy or surgical corrected (curative)
Class III Patient Symptoms Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea	**Class C Objective Assessment** Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest	**Class III** Marked tachypnea or diaphoresis with feeding in infants. Marked dyspnea on exertion. Prolonged feeding times with growth failure.	**Moderate (II)** Surgical treated (≥ procedure) with no significant residual or need for additional surgery
Class VI Patient Symptoms Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases	**Class D Objective Assessment** Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest	**Class IV** Symptoms such as tachypnea, retractions, grunting, or diaphoresis at rest.	**Complex or Severe** Uncorrectable or palliated (includes single ventricle)

Table 2: Classification of Congenital Heart diseases in children based on the disease severity (Hoffman and Kaplan, 2002).

Hoffman and Kaplan Classification	
Severe	A. All those with cyanotic heart disease: d-transposition of the great arteries; Tetralogy of Fallot, including pulmonary atresia and absent pulmonary valve; Hypoplasic right heart (Tricuspid atresia, Pulmonary atresia with an intact ventricular septum and Ebstein anomaly); Hypoplasic left heart (Aortic atresia and Mitral atresia); Single Ventricule; Double outlet right ventricule; Troncus arteriosus; Total anomalous pulmonary venous connection; Critical pulmonary stenosis; Miscellaneous uncommon lesions like double outlet left ventricule, certain unusual malposition and some forms of 1-transposition of great arteries. B. Acyanotic lesions: Atrioventricular septal defect; Large ventricular septal defect; Large patent ductus arteriosus; Critical or severe aortic stenosis; Severe pulmonary stenosis; Critical coartation
Moderate	A. Mild or moderate aortic stenosis or aortic incompetence B. Moderate pulmonary stenosis or incompetence C. Noncritical Coarctation D. Large atrial septal defect E. Complex forms of ventricular septal defect
Mild	A. Small ventricular septal defect B. Small patent ductus arteriosus C. Mild pulmonary stenosis D. Bicuspid aortic valve without aortic stenosis incompetence; these may move to moderate or severe categories if they deteriorate with age E. Small or spontaneously closed atrial septal defect

1.2 Definitions of physical activity, exercise and functional exercise capacity

First of all, it is important to clarify some concepts and definitions in the field of physical activity and exercise. The term *physical activity* is sometimes

misused, as equivalent to *physical fitness* or *exercise*, but it actually refers to three different concepts. *Physical activity* describes any body movement produced by muscle actions that result in energy expenditure and can be characterized by type, intensity, duration, patterns and symptoms[12]. *Exercise* is a subset of physical activity and refers to planned, structured, repetitive and purposive activities with the objective of maintaining or improving one or more components of physical fitness. *Physical fitness* is the capacity to perform physical activity with energy and is composed of a set of attributes that people have or achieve. Consequently, physical fitness has more direct link with the overall health. Some health-related components of physical fitness are: cardiorespiratory endurance, muscular endurance, muscular strength, body composition and flexibility[13]. As we will introduce ourselves to the subject, the concept of functional exercise capacity and aerobic capacity will be mentioned. *Functional exercise capacity* (FEC) reflects the ability to perform activities of daily living requiring the aerobic metabolism[14]. The FEC is the relationship between the exercise performance and physical activity assessment, usually assessed by field tests as 6-minute walk test (6MWT), incremental shuttle walk test (ISWT) and endurance shuttle walk test (ESWT)[15] that we will discuss below.

1.3 Cardiopulmonary exercise test

It is well known, that peakVO_2 is an indicator of physical performance. It is assessed by a Cardiopulmonary Exercise test (CPET)[16] and is expressed in

ml/kg/min. The peakVO_2 is commonly used to describe the cardiorespiratory endurance in healthy population in whom of a plateau of VO_2[14] is observed. In CHD children, it is well documented, that some patients have physical limitations associated with reduced exercise capacity, or an impairment in their functional exercise capacity[17–20]. Functional exercise capacity obviously varies according to the type of CHD, surgical procedure, age and gender. Compared with healthy pairs, CHD patients with residual lesions even after surgical repair or palliation, present significant reductions in peak work rate and maximum ventilation shown in CPET[21]. Looking at the CPET parameters, the peakVO_2 is considered the gold standard for functional exercise capacity assessment. However the FEC is also assessed by field tests, such as the 6MWT. In some CHD patients with an insufficient chronotropic response, the maximal heart rate (HR) tends to decrease, thereby reducing their peakVO_2[21]. Another CPET parameter is the anaerobic threshold (AT), defined as the maximum intensity of exercise performed by an individual using her/his aerobic metabolism, is inversely related to the age[22]. In CHD children with complex CHD, the AT is lower compared with healthy pairs matched for age. These children usually have a lower ventilatory threshold, i.e. a limitation to perform aerobic exercise[21].

In addition, all these limitations add up to another risk factor not exclusive to CHD paediatric population. This risk factor is the *sedentary lifestyle*, usually higher in CHD children than in their healthy pairs[23]. *Sedentary behavioural* is used to refer specifically to walking behaviours characterized by energy expenditure ≤1.5 metabolic equivalents (METs) while in a sitting or reclining posture. However, *sedentary behavioural* or *lifestyle* should not

be confused with the term *inactive* which refer to an individual who is not sufficiently physically active[24]. A significant proportion of CHD children are less active and do not participate in exercise programs as observed by their reduced daily activity levels[20]. This might be explained at least in part by some residual structural lesions leading to haemodynamic or chronotropic impairments, as well as psychosocial factors such as parental overprotection[20,21]. For these reasons, and taking into account that they are a population already at risk due to their underlying cardiac pathophysiology, the evaluation of their physical condition as well as their lung function (LF) will provide us a valuable information on the evolution and status of their disease. This will also help us to propose early interventions to reduce their risks associated with low levels of PA.

1.4 Current guidelines on physical activity in healthy children and CHD children

In general, children need to move, play and perform activities. The PA is necessary for the optimal physical, emotional and psychosocial development of health[25]. They should accumulate at least 60 minutes of moderate-to vigorous-intensity daily; PA of amounts greater than 60 minutes daily will provide additional health benefits; most of daily PA should be aerobic, vigorous-intensity activities should be incorporated, including those that strengthen muscle and bone, at least 3 times per week[25–27]. The moderate-to-vigorous intensity refers to an energy cost of ≥ 3 metabolic equivalents (METs), which includes activities such as walking, stair climbing,

household chores and dancing[28]. A MET (metabolic equivalent) is the energy required for basal homeostasis and corresponds to approximately 3.5mL of O_2 per Kg of body weight. There is a relationship between METs and PeakVO_2 and PeakVO_2 can be expressed in mL/Kg/min or METs.

It is well documented that CHD children have low levels of PA compared with their healthy pairs. For this reason, it is highly recommended to assess the PA routinely, for example in the cardiology clinic[29]. In terms of recommendations, exercise and sport need to be based on patient's ability, the impact on their specific haemodynamics, and the risk of acute decompensation and arrhythmias[30]. However, regular exercise participation has well documented benefits for fitness, psychological well being, and social interactions, as well as for decreasing the future risk of acquired heart diseases[30]. There is a large choice of available training programs but virtually all of them lead to a documented improvement[20]. It is more and more recognized that a structured exercise program should be part of the routine management of CHD patients[20]. More specifically, endurance exercises are highly recommended in this population.

An easy way to describe the exercise is by using the FITT factors as defined by Takken[25], i.e. frequency, intensity, time and type of activity. Another factor to consider in children and adolescents is the importance of defining the aims of the exercise program and taking into account the age of the group. Indeed, children are more prone to be distracted and quickly tired of repetitive exercises when performing the "adult type" endurance training (e.g. treadmill or stationary cycling). The physical therapist thereby has to define strategies to improve the training efficiency[25].

We hope that our scientific contribution with this systematic and early evaluation of PA and LF in the CHD paediatric population will help to impact on the patient's QoL in adulthood. The overall aim of this analysis is that the paediatric population with CHD reaches adulthood in optimal physical conditions, thereby reducing the pressure on our healthcare system.

1.5 Evaluation of Functional exercise capacity and Physical activity level

In children with chronic diseases, like CHD children, the functional exercise capacity assessment is an important tool for the diagnosis, quantification of symptoms, prognosis and evaluation of potential therapeutic approaches[21]. Indeed, aerobic capacity evaluation is an important marker for morbidity and mortality in adults with cardiovascular and pulmonary diseases but also in children and adolescents. In children and young adults with congenital heart or lung diseases, a lower aerobic capacity predicts morbidity and mortality in later years [16]. This underlines our arguments in favour of regular and systematic clinical evaluations in this population.

Building on the functional exercise capacity assessment, field tests are a quick and easy way to systematically evaluate our CHD paediatric patients. As we already mentioned, one of the most commonly used tests is the 6-minute walk test (6MWT), already validated in healthy children[31] and well known and used in other chronic diseases as chronic obstructive pulmonary disease (COPD) patients[15,32]. Some field tests that are commonly used in other chronic diseases have not been yet validated in CHD children. This is

the case of the 1-minute Sit-to-stand test (STST). This test has been validated in healthy children[33], but has never been tested in children with CHD. We adressed this question in more in details in Part II of the manuscript.

Various evaluation methods are available to assess the physical activity levels. The first and one of the most used and known are the devices to assess the physical activity (PA) levels. Accelerometers that assess the intensity and duration of PA, but are expensive and sometimes not suitable in children because they require advanced technical expertise. One alternative is the pedometer, a simple-to-use and cost-effective alternative[29]. Another way to assess the PA levels is by using questionnaires. Questionnaires are often considered as the most cost- effective and time-effective methods but recall errors and bias in younger children that must be taken into consideration[29]. In addition, the lack of validated questionnaires in French is still a very limiting factor for conducting valid scientific research. This section will be further developed in Part II of the manuscript.

1. 6 Medical and Surgical Management

Currently, there is a growing population of adults with CHD, known as the Grown-up congenital heart (GUCH) disease population, benefiting from refined corrective surgeries and well-established paediatric cardiology programs. It is now considered that better diagnostic modalities, improved surgical techniques, and advances in the medico-surgical management allowed the current GUCH population to outgrow the CHD paediatric

population a few years ago[30,34]. This means that the life expectancy of CHD patients has been steadily increasing over the last few decades, to become an significant public health issue[35]. We believe that the longitudinal follow-up of these CHD children by the paediatric and adult cardiologist, together with a multidisciplinary approach including evaluation of physical activity and lung function is now extremely relevant.

1.7 Quality of life

Besides the evaluation of physical capacity of children born with CHD, it is important to address the impact of their potential physical limitations in their daily lives. It obvious that physical limitations entail an alteration in the quality of life (QoL). In children, it is even much clear because their limitations easily lead to an impairment of their social relationships, for example at school. In addition, these issues are often difficult to express for the child and this can easily lead to early social exclusion[21].

For these reasons we believe it is really important to study health-related quality of life (HR-QoL) in the population of CHD patients. This must include an evaluation of the physical, social, psychological, mental aspects of the patient[36]. In the CHD paediatric population, a good correlation was already observed between HR-QoL and CHD severity, with the most severe patients presenting lower HR-QoL levels[37]. When analysing the CPET parameters, low levels in peakVO_2 and AT were observed in the most severe patients, with a correlation between the lower levels in HR-QoL and peakVO_2 and AT in CPET[37].

One of the most used questionnaires is the PedsQL or KIDSCREEN-52. As we have mentioned, in young children, questionnaires can be difficult to rely on and these two questionnaires therefore include a section for parents[37]. As published by Amedro et al. (2015)[38], the HR-QoL was very effectively assessed by the KIDSCREEN-52 questionnaire in children and their parents. They observed similar scores between CHD children and to the healthy pairs of the same age, as opposed to the levels of physical well being, financial recourses, social and peers support and autonomy, all significantly impaired in CHD patients. This is another argument to think that when these children will grow-up, a systematic evaluation of their HR-QoL but also of their PA levels and LF is important, in part because of a close relationship in their QoL and life expectancy. This corroborates our argument for the early and systematic evaluation of CHD children.

To summarize, the main aims of this thesis were to describe which were the specific tools available to assess the functional exercise capacity and to describe the lung function pattern in this pediatric population. As secondary objectives, the validation of new tools to assess the functional exercise capacity taking as reference the healthy children and the CHD adult population was planned, i.e. grow-up congenital heart disease (GUCH), and study the relationship between the functional exercise capacity, the lung function and the peakVO_2 in CHD pediatric population.

PART I

Chapter I: Tools available for the evaluation of exercise capacity and physical activity levels in healthy children

When we evaluate functional capacity and physical activity level we have to consider the cardiopulmonary exercise test (CPET) as the gold standard. The CPET is a valuable, non-invasive procedure, routinely performed in the clinical follow-up of CHD patients to confirm surgical indications, evaluate their morbidity and mortality risk factors, and assess their functional status[16,39]. It provides an assessment of the cardiovascular, ventilatory and metabolic responses at rest and during exercise[40] and is also used to quantify the patient's aerobic capacity overtime[30,37]. With CPET, the clinician can measure the functional capacity and physiological responses of the patient, which provides a valuable information about the functional status of the heart, lungs and peripheral muscles[41]. Currently, there is no single standard testing protocol for children. The most commonly used is the modified Bruce treadmill protocol due to its suitability for most young and physically active patients, even if the incremental increases can sometimes be excessive[16,41]. Cycle ergometer is also used because it facilitates the fine physiological measurements during the exercise, although a 12-lead electrocardiogram and blood pressure measurements are also available on a treadmill[16]. The standardized modified Bruce protocol[41] routinely used in paediatrics consists of: 1-min rest, 3-min warm-up (1 km/h, slope 0%), and then 2-min increments in speed (from 2.5 to 10.5 km/h) and slope (from 3 to 18%), and finally a 3-min active recovery (2.5 km/h, 0% slope) preceding a final 2-min

rest. Exercise is pursued until the limit of the child's tolerance is reached, with active verbal encouragements. Motivating and encouraging the participant before and during the CPET is very important, especially in children[16].

The main variables measured during the CPET are listed below:

- Oxygen uptake (PeakVO_2; ml/kg/min) reflects the body's maximal capacity to generate energy through aerobic metabolism;
- Carbon dioxide production (VCO_2; ml/kg/min) increase linearly until the oxidative metabolism can no longer sustain the required workload,
- Respiratory exchange ratio (RER = VCO_2/VO_2) is an equal of respiratory quotient, which give us an information about the metabolic expenditure;
- Minute ventilation (VE; breaths/min) volume of gas exhaled per minute then the ventilatory threshold and respiratory frequency;
- Ventilatory equivalent for oxygen (VE/VO_2) litres of oxygen consumption;
- Ventilatory equivalent for carbon dioxide (VE/VCO_2) is the ventilatory efficiency and quantifies the ventilatory required to eliminate 1 litre of CO_2;
- Dead space-to-tidal volume ratio (VD/VT) in case of an inappropriately ventilation response the PaCO2 will drop and VE/VCO2 slope will steepen;
- Heart rate (HR; beats per minute - bpm);
- Maximum workload (Watts and METS) is the amount of work an individual can perform;
- Oxygen pulse (VO_2/HR; ml) is the ration consumption to HR and expresses the volume of O_2 ejected from the ventricles with each cardiac contraction;
- The peak oxygen uptake (peakVO_2), also known as maximal VO_2 (VO_2max);

- The ventilatory anaerobic threshold (AT) using Beaver's method[42] (the point when the body must switch from aerobic to anaerobic metabolism and is a useful measure to determine the exercise intensity);
- The ventilation efficiency (VE/VCO_2 slope with $VE = slope \times VCO_2 + b$);
- Oxygen uptake efficiency slope (OUES with $VO_2 = OUES \times \log10\ VE + b$)[43–45] are also determined by the clinician and provide information on the severity of heart failure.

The CPET has to be a truly maximal effort and this is the clinician's responsibility throughout the test. This information will help to interpret the symptoms-limitations. Criteria considered to define a true maximal effort are listed below[40]:

Maximal effort criteria during CPET:

- Failure of heart rate to increase with further increases in exercise intensity (achieving >85% of age-predicted maximal heart rate is a well-recognized indicator of patient effort
- A plateau in VO_2 (or failure to increase by 150ml/min) with an increased workload
- A respiratory exchange ratio (VCO_2/VO_2) at peak exercise >1.10
- A rating of perceived exertion >17 on the 6-20 Borg scale or >9 on the 0-10 scale
- Post exercise venous lactate concentrations >8-10mmol/litre

The reference values for the normal range of peakVO_2 and AT, are derived from the work by Wasserman and Cooper[46–48]. However, some peakVO_2 data derived from (limited) pediatric studies are also available and sometimes used as a reference show in Figure 1[16].

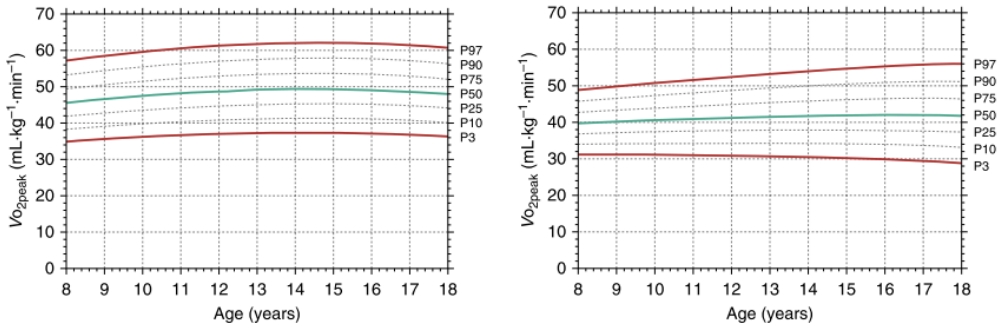

Figure 1: Age-related centile charts for aerobic fitness (VO_2peak/kg) for boys (left graph) and girls (right graph). Green curves show medians and red curves show the upper and lower limits of normal. P = percentile; VO_2peak = highest measured VO_2 per kilogram body mass.

The inhaled oxygen (O_2) and exhaled carbon dioxide (CO_2) are measured continuously through the CPET gas analyser, providing an accurate assessment of the patient's functional capacity and allowing to specify the main aetiology of their limitation[40]. The peakVO_2 during the CPET is considered the gold standard to assess the functional capacity[21]. This information is key in providing (differential) diagnosis, prognosis, and in refining indication for surgical or percutaneous interventions in Medicine[16]. During the test, a 12-lead electrocardiogram as well as repeated systolic and diastolic blood pressures are also recorded. The usual setup for a treadmill CPET is shown below.

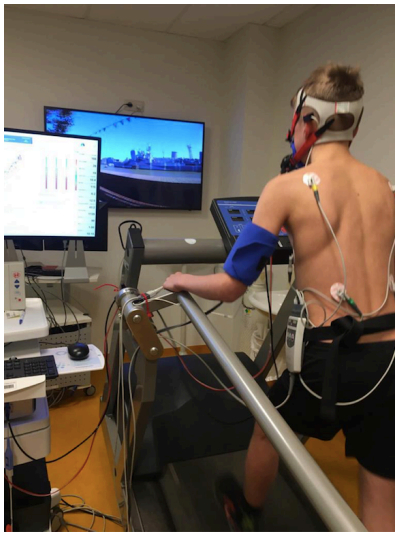

Figure 2 Selection of important parameters measured during CPET in pediatric populations. BF= breathing frequency (breaths·min^{-1}); $\Delta VO_2/\Delta WR$= oxygen cost of work (ml·min^{-1}·W^{-1}); EqCO2= ventilatory equivalent for carbon dioxide; EqO2 = ventilatory equivalent for oxygen; HR= heart rate (beats·min^{-1}); OUE = VO_2 efficiency; OUEP = VO_2 efficiency plateau; OUES = VO_2 efficiency slope; PET_{CO2} = partial end-tidal carbon dioxide tension (mm Hg); PET_{O2} = partial end-tidal oxygen tension (mm Hg); RER= respiratory exchange ratio; SpO_2 oxygen saturation as measured by pulse oximetry (%); TV= tidal volume; VAS= visual analog scale; VE/VCO_2 = slope of the relationship between the VE and VCO_2; VE/VO_2= slope of the relationship between the VE and VO_2; WR= work rate (W). Note: reference[16].

The ideal duration for a maximal CPET is between 6 and 10 minutes for children and between 8 and 12 minutes for adolescents and adults. This is critically important to assess the patient's maximal (anaerobic) capacity and not her/his aerobic performance (or endurance)[16].

As we mentioned in the introduction of the manuscript, other tools to assess the functional capacity are available, such as the field tests. One of the most commonly used is the 6MWT. As opposed to the CPET maximal effort, the 6MWT is a submaximal effort. Since most daily activities are performed at this submaximal level, the 6MWT is a better reflection of physical capability and daily life limitations and is also better to assess the functional exercise

capacity[49]. It accurately predicts morbidity and mortality, the effects of treatment (e.g. before and after a rehabilitation program) and the patient's functional status. This field test is reliable, and validated to measure the functional capacity in the paediatric population[31]. To take the anthropometric changes and age variations during the childhood and adolescence into account, the equation proposed by Geiger et al.[50] helps to express the 6-minute walking distance (6MWD) as a percentage of the predicted value: Males 6MWD= 196.72 + (39.81·Age) - (1.36·Age^2) + (132.28·Height); Females 6MWD= 188.61 + (51.50·Age) - (1.86·Age^2) + (86.10·Height). In the adult population, a learning effect was described for most field tests, including the 6MWT[51]. However, in the paediatric population, such learning effect was not reported, at least after an initial training test[15]. The repeatability of a 6MWT in children was assessed by Martins et al.[52] when the test was repeated twice, there was no significant difference in the walked distance between both tests, repeated 30 minutes apart. Li et al.[31] similarly demonstrated good 6MWT reproducibility in children who repeated the test after 18 days.

In the introductory section of this manuscript, we underlined the importance of PA evaluation and reviewed the various tools available to assess the functional capacity in children. The gold standard currently remains the CPET and a field test such as the 6MWT is a good substitute when needed. Currently, other field tests commonly used in adults and tested in healthy children, such as the 1-minute sit-to-stand test (STST), have not been validated yet in CHD children. We will address this issue in Part II of the manuscript.

Another important aspect of the global assessment of CHD children is the lung function (LF), which can be significantly affected in the mid- to long-term follow-up of those patients. Pulmonary function tests (PFTs) like spirometry are used to diagnose airway obstruction, assess its severity and prognosis, delineate risk factors (e.g. pre-operative assessment), detect early lung disease and monitor for normal lung growth and lung function decline[53]. Spirometry is a physiological test that measures the maximal volume of air that an individual can inspire and expire with maximal effort. This test, similarly to the CPET, requires cooperation between the patient and the examiner[54]. The most relevant measurements are the forced vital capacity (FVC), which is the volume delivered during an expiration made as forcefully and completely as possible starting from full inspiration, and the forced expiratory volume in the first second (FEV_1), assessed during an FVC manoeuvre and very useful to categorize the severity of the lung obstruction or for the reversibility test with bronchodilatator[55,56]. Other data derived from spirometry: FEV_1/FVC helps to detect the airways obstruction; forced expiratory flow between 25% and 75% of the FVC ($FEF_{25-75\%}$) also known as the maximum mid-expiratory flow is useful to detect impairments in the middle and/or small airways; peak expiratory flow (PEF) usually obtained from flow-volume curve, is the maximum expiratory flow achieved from a maximum forced expiration, starting without hesitation and useful to know the cough efficacy and for asthmatic patients with an exacerbation[56]. In the routine clinical follow-up of CHD children, the spirometry is recommended before the CPET as an effective tool to detect a ventilatory limitation as a primary cause or as a contributor to exercise intolerance[40]. The modern

normal values for spirometry recommended by European Respiratory Society were published in 2012 (GLI: Global lung function initiative)[53].

Chapter II: Relationship between functional exercise capacity and lung function in Congenital Heart disease children

Correlation between Cardiopulmonary Exercise test, Spirometry, and Congenital Heart Disease severity in pediatric population

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Abstract

Background: Congenital Heart Disease (CHD) is a common chronic disease. This study aimed to verify the relationship between spirometry and exercise capacity in children, considering the CHD severity.

Methods: All cardio-pulmonary Exercise testing (CPET) and Spirometry from CHD children (5 to 18 years) were retrospectively reviewed during three years. CPET and Spirometry were analyzed and correlated based on the CHD severity (modified Ross classification (mR)).

Results: Patients (n=321) were analysed and subdivided for CHD severity (n=49, n=149, n=80, n=43, from mR1 to mR4 respectively). The maximal workload (Wmax) in mR1 and mR2 was higher than in patients from mR3 and mR4. Peak oxygen uptake (peakVO_2) was reduced in mR3 and mR4 compared to mR1 and mR2. Carbon dioxide output was only significantly lower in mR4. Although spirometric parameters were globally in the normal

range, forced expiratory volume and forced vital capacity were different between subgroups ($p<0.001$ and $p=0.002$, respectively). Wmax and peakVO_2 were weakly or moderately but significantly correlated with spirometry. Respiratory exchange ratio and final blood oxygen saturation were only significantly and weakly correlated to obstruction in small airways.

Conclusions: The most severe CHD patients had lower exercise capacity and lung function parameters. A weak to moderate correlation between CPET and spirometry was found. However, the lung function reported in our study was normal, but with a negative correlation with the age. It reinforce the benefits of precocious and regularly spirometry and CPET assessment in CHD children.

Key words: Congenital heart disease, spirometry, cardiopulmonary exercise test, pediatrics.

1. Introduction

Congenital Heart Disease (CHD) is a frequent chronic disease among children and adolescents, with an incidence of 4 to 8 per 1000 live births[17].

In CHD pediatric and adult populations, Cardio-pulmonary Exercise Test (CPET) is a routine testing in the clinical follow-up to evaluate their morbidity and mortality[39]. It is also used to detect changes in cardiovascular and respiratory adaptation during exercise and to investigate the disease severity and long-term evolution[30,37].

In adults, cardiac (Chronic Heart Failure, CHF) and pulmonary (Chronic Obstructive Pulmonary Disease, COPD) diseases are frequently coexisting[57]. The CPET is useful to discriminate the respective impact of lung and heart defects[58] and spirometry is performed as part of the standard care[40] to assess (obstructive, restrictive, or mixed) pulmonary diseases[59].

The CHD pediatric population suffers from physical limitations associated to reduced exercise capacity[17–20]. As previously demonstrated, CHD children who underwent sternotomy or thoracotomy, are also more likely to have a pattern of restrictive lung function[60–62]. Consecutive chest mechanical alterations were well described and impact on lung function[63]. On the contrary, physical fitness and exercise capacity were recently correlated with enhanced lung function in adolescents and young adults[64]. Despite these evidences, potential correlation between lung function, exercise capacity and CHD severity have never been studied.

Our study aimed to verify this potential relationship between lung function and exercise capacity in a cohort of children and adolescent with CHD, taking into account the severity of their cardiac disease.

2. Methods

2.1. Subjects and Study design

All Children with CHD aged from 5 to 18 years were retrospectively selected from our database at the Cliniques universitaires Saint-Luc (UCL, Belgium) between January 2013 and December 2015. All patients performed simultaneous CPET and spirometry as part of their annual follow-up. Patients evaluated for other reasons than CHD (cardiac exploration for syncope/faint, thoracic pain, palpitations, dyspnea, etc.), and children with concomitant severe chronic disease (neurodevelopmental disorder, chronic renal or respiratory failures) were excluded from this study. Only the most recent CPET was selected for each child when they had performed more than one CPET during the period of recruitment.

The study was approved by the regional Ethics Committee at the Cliniques universitaires Saint-Luc and Université Catholique de Louvain (2016/026).

2.2. Outcomes

2.2.1. CPET

All children performed a maximal CPET, with a pediatric face mask (Hans Rudolph), a calibrated gas analyser (Oxycon Pro, Jaeger), a breath-to-breath measurements software (Windows 98, Jaeger), a 12-lead ECG monitoring

(Cardiosoft, GE Healthcare), a pulse oxymeter (Nellcor), and an automated sphygmomanometer with adapted pediatric cuffs.

All CPET were performed on the same treadmill following a standardized modified Bruce protocol[41]: 1 min rest, 3-min warm-up (1 km/h, slope 0%), an then 2 minutes increments in speed (from 2.5 to 10.5 km/h) and slope (from 3 to 18%), and finally a 3-min active recovery (2.5 km/h, 0% slope) and then 2-min rest. Exercise was pursued until the limit of the child's tolerance was reached, with active verbal encouragements. The following CPET variables were measured: oxygen uptake (VO_2; ml/kg/min), carbon dioxide production (VCO_2; ml/kg/min), respiratory exchange ratio ($RER=VCO_2/VO_2$), minute ventilation (VE; breaths/min), ventilatory equivalent for oxygen (VE/VO_2), ventilatory equivalent for carbon dioxide (VE/VCO2), dead space to tidal volume ratio (VD/VT), heart rate (HR; beats per minute - bpm), maximum workload (Watts and METS), and oxygen pulse (VO_2/HR; ml). For all CPET performed, the same senior qualified investigator manually established the peak oxygen uptake ($peakVO_2$), the ventilatory anaerobic threshold (AT) using Beaver's method[42], the ventilation efficiency (VE/VCO_2 slope with $VE=slope \times VCO_2+b$) and the oxygen uptake efficiency slope (OUES with $VO_2=OUES \times \log10\ VE+b$)[43–45]. $PeakVO_2$ and AT were normalized in percentage of predicted $peakVO_2$ using normal values published by Wasserman and Cooper[46–48].

2.2.2. Spirometry

Lung function tests were performed systematically and simultaneously with a spirometric gas analyser (Oxycon Pro, Jaeger) before and after each exercise test, assessing forced expiratory volume in 1 sec (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio[65]. Values were expressed in percentage of predicted values, as determined by European Respiratory Society (GLI 2012)[66].

2.2.3. Modified Ross classification

In CHD adult population the NYHA functional classification is the most common classification used to determine the disease severity, including heart failure. Nevertheless, this classification does not apply in pediatric patients. For this reason, we classified our pediatric CHD population into 4 severity groups using the modified Ross classification (Table 1) which was developed to assess the heart failure severity in all pediatric ages[7,67].

Table 1: Modified Ross classification

Score	Symptoms
1	No limitations or symptoms
2	Mild tachypnea or diaphoresis with feeding in infants; dyspnea at exertion in older children; no growth failure
3	Marked tachypnea or diaphoresis with feeding or exertion and prolonged feeding times with growth failure from congestive heart failure
4	Symptomatic at rest with tachypnea, retractions, grunting, or diaphoresis

2.3. Analysis

Clinical data were analyzed by SPSS Statistics 24.0 (IBM Corp., Armonk, NY, USA). Descriptive results were expressed as mean ± standard deviation (SD) and confidence interval of 95%. To verify intergroup differences based on

severity (modified Ross classification), an analysis of variance (ANOVA) was used, followed by post hoc analyses (Tukey). Correlations between CPET and spirometry were evaluated using Pearson's correlation coefficient (r). The criteria for statistical significance were set at $p < 0.05$ (significant), $p < 0.01$ (very significant) and $p < 0.001$ (highly significant).

3. Results

This retrospective study was carried out on 321 patients diagnosed with CHD. In total, we analysed 597 CPET protocols and excluded 276 patients (they did not have a CHD). Their anthropometric and pathophysiological characteristics are shown in Table 2, divided in subgroups based on the modified Ross classification (n=49, 149, 80, and 43, respectively). Age and body mass index (BMI) varied significantly between subgroups ($p = 0.002$ and $p = 0.011$, respectively), and as expected, all cardiovascular performance parameters were or tended to be reduced with CHD severity. Two hundred and twenty-three children previously underwent a cardiac surgery, while the 98 others were free of any surgical intervention.

It is worth observing that Wmax was higher than the predicted value in all subgroups. However, mR1 and mR2 (139.9 ± 25.3 and 128.9 ± 30.0) subgroups showed higher values than mR3 and mR4 subgroups (113.3 ± 32.6 and 95.9 ± 29.9). Moreover, these two last subgroups differed significantly from each other.

Table 2: Characteristics of the sample

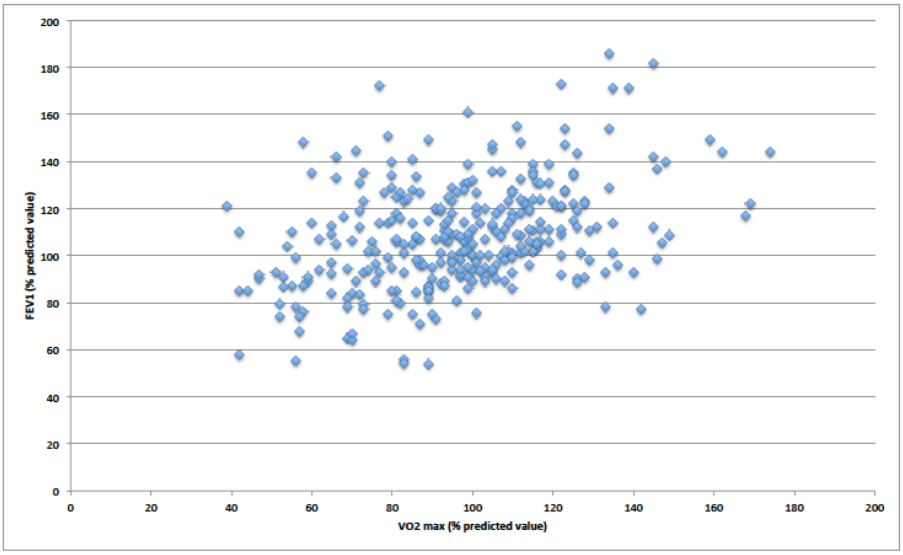
	All	Modified Ross 1	Modified Ross 2	Modified Ross 3	Modified Ross 4	p
n	321	49	149	80	43	
Age (y)	13.4 ± 4.6 [4.4 ; 22.3]	12.6 ± 3.5 mR3 [5.8 ; 19.4]	12.6 ± 4.2 mR3 [4.5 ; 20.8]	14.8 ± 5.0 mR 1,2 [4.9 ; 24.6]	14.2 ± 5.4 [3.6 ; 24.8]	0.002*
Gender (male/female)	197/124	33/16	98/51	42/38	24/19	
Weight (kg)	44.6 ± 17.7 [9.8 ; 79.3]	43.5 ± 15.0 [14.1 ; 72.8]	42.7 ± 16.2 mR 3 [10.9 ; 74.4]	49.3 ± 20.4 mR 2 [9.3 ; 89.3]	43.7 ± 19.5 [5.5 ; 81.9]	0.052
Height (cm)	151.3 ± 18.8 [114.5 ; 188.1]	152.1 ± 17.2 [118.3 ; 185.8]	149.6 ± 19.5 [111.3 ; 187.9]	153.9 ± 18.1 [118.4 ; 189.4]	151.7 ± 19.0 [114.5 ; 189.0]	0.416
BMI (kg/m^2)	18.7 ± 4.0 [10.9 ; 26.5]	18.2 ± 3.1 [12.2 ; 24.2]	18.3 ± 3.3 mR 3 [11.8 ; 24.9]	19.9 ± 4.7 mR 2 [10.6 ; 29.2]	18.0 ± 5.0 [8.3 ; 27.8]	0.011*
Wmax (% pred)	122.3 ± 32.7 [58,1 ; 186.5]	139.9 ± 25.3 mR 3,4 [90.3 ; 189.4]	128.9 ± 30.0 mR 3,4 [70.1 ; 187.6]	113.3 ± 32.6 mR 1,2,4 [49.3 ; 177.2]	95.9 ± 29.9 mR 1,2,3 [37.4 ; 154.5]	<0.001 *
VE (L/min)	61.6 ± 23.7 [15.2 ; 108.1]	66.9 ± 23.3 mR 4 [21.3 ; 112.6]	64.3 ± 24.0 mR 4 [17.2 ; 111.5]	59.8 ± 23.1 [14.6 ; 105.0]	48.5 ± 20.2 mR 1,2 [9.0 ; 88.1]	0.007*
Peak VO2 (% pred)	97.1 ± 24.7 [48.6 ; 145.5]	111.0 ± 20.3 mR 3,4 [71.2 ; 150.8]	104.8 ± 22.4 mR 3,4 [60.9 ; 148.8]	85.0 ± 20.8 mR 1,2 [44.2 ; 125.8]	76.8 ± 21.5 mR 1,2 [34.6 ; 119.0]	<0.001 *
VCO2 (mL/min)	1963.4 ± 876.0 [246.4 ; 3680.3]	2282.4 ± 956.9 mR 4 [406.8 ; 4158.0]	2057.3 ± 852.2 mR 4 [387.0 ; 3727.6]	1906.0 ± 830.2 mR 4 [278.8 ; 3533.1]	1313.4 ± 603.1 mR 1,2,3 [131.4 ; 2495.5]	<0.001 *
RER	1.32 ± 0.17 [1.02 ; 1.67]	1.4 ± 0.2 mR 3,4 [1.1 ; 1.7]	1.4 ± 0.2 mR 4 [1.1 ; 1.7]	1.3 ± 0.2 mR 1,4 [1.0 ; 1.6]	1.2 ± 0.1 mR 1,2,3 [0.9 ; 1.5]	<0.001 *
AT (mL/min/kg)	28.1 ± 7.5 [13.4 ; 42.8]	29.9 ± 6.5 mR 3,4 [17.1 ; 42.7]	30.1 ± 7.1 mR 3,4 [16.2 ; 44.0]	25.6 ± 7.0 mR 1,2 [11.9 ; 39.4]	23.4 ± 8.0 mR 1,2 [7.7 ; 39.0]	<0.001 *
FEV1/FVC (%)	102.5 ± 13.9 [75.3 ; 129.7]	101.9 ± 10.6 [81.2 ; 122.7]	102.3 ± 15.5 [72.0 ; 132.6]	103.7 ± 13.5 [77.2 ; 130.1]	101.9 ± 12.4 [77.6 ; 126.3]	0.866
FEV1 (% pred)	108.5 ± 22.1 [65.2 ; 151.9]	111.8 ± 18.5 mR 4 [75.5 ; 148.1]	113.1 ± 21.5 mR 3,4 [71.0 ; 155.1]	102.9 ± 21.9 mR 2 [59.9 ; 145.9]	99.4 ± 24.1 mR 1,2 [52.2 ; 146.6]	<0.001 *
FVC (% pred)	105.1 ± 23.4 [59.2 ; 150.9]	107.4 ± 27.0 [54.4 ; 160.4]	109.5 ± 21.8 mR 3,4 [66.8 ; 152.2]	99.5 ± 22.0 mR 2 [56.3 ; 142.7]	97.5 ± 23.7 mR 2 [51.2 ; 143.9]	0.002*
FEF 25-75 (% pred)	97.2 ± 29.4 [39.6 ; 154.7]	97.8 ± 24.9 [49.0 ; 146.7]	101.9 ± 30.0 mR 4 [43.2 ; 160.6]	93.1 ± 30.7 [32.9 ; 153.3]	87.4 ± 26.9 mR 2 [34.8 ; 140.1]	0.017*

*p: p value corresponding to the comparison between Modified Ross classification; * = significance p < 0.05; BMI: body index mass; CPET: cardio-pulmonary exercise test; Wmax: Maximal Workload; VE: minute ventilation; VO2max: peak oxygen uptake; VCO2: carbon dioxide output; RER: respiratory exchange ratio; AT: aerobic threshold; FEV1/FVC: Tiffeneau index; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; FEF 25-75%: forced expiratory flow at 25 - 75% of forced vital capacity; mRx: differences between Modified Ross classifications*

Mean peakVO_2 (expressed in % of predicted value) was in the normal range for all groups except for mR4 (76.8 ± 21.5). In the mR3 and mR4 subgroups peakVO_2 (85.0 ± 20.8 and 76.8 ± 21.5) were reduced compared to the mR1 and mR2 subgroups (111.0 ± 20.3 and 104 ± 22.4). However, given the large coefficients of variation that we observed in each of the subgroups, not only the most severe patients had lower values in terms of exercise capacity parameters (% of patients with peakVO_2 < 80% of predicted value in mR1 = 8%, mR2 = 11%, mR3 = 40% and mR4 = 49%; with p = < 0.001).

Regardless the CHD severity, even if the spirometric values were in the normal range (expressed in % of predicted value) for all subgroups, FEV_1 and FVC differ significantly (p < 0.001 and p = 0.002, respectively), and 13% and 9% of children (exclusively in the surgical group) had abnormal FVC and FEV_1/FVC, respectively. Negative correlations were found between age and peakVO_2 (r = -0.492; p < 0.001), FEV_1 (r = - 0.397; p < 0.001) and FVC (r = - 0.289; p < 0.001). Some patients showed a reduced peakVO_2 with normal FEV_1 (Figure 1).

Figure 1: Distribution of patients with respect to peakVO_2 and FEV_1



The Wmax and VO_2 were correlated to all spirometric parameters, even though the intensity of all correlations was moderate to weak (Table 3). RER and final SpO_2 were significantly and weakly correlated to obstruction in small airways ($FEF_{25-75\%}$).

Table 3: Spirometry correlation with CPET

	FEV_1 (% pred)	**FVC (% pred)**	**FEF $_{25–75\%}$ (% pred)**
Wmax (% pred)	0.182**	0.112*	0.160*
VO_2 max (%pred)	0.386***	0.310***	0.211***
VCO_2 (mL/min)	− 0.051	− 0.104	0.142*
AT (mL/min/kg)	− 0.269***	0.230**	0.159*
RER	0.057	0.006**	0.143*
SpO_2f	0.141*	0.109	0.116*

%pred = % of predicted value, *Wmax* maximal Workload, *VO_2max* peak oxygen uptake, *VCO2* carbon dioxide output, *AT* anaerobic threshold, *RER* respiratory exchange ratio, *SpO_2 f* final pulse oximetry saturation, *FEV_1* forced expiratory volume in the first second, *FVC* forced vital capacity, *FEF25-75* forced expiratory flow. *Significance $p < 0.05$; **Significance $p < 0.01$; ***Significance $p < 0.001$

4. Discussion

The aim of this study was to investigate the relationship between lung function and exercise capacity considering the CHD severity in pediatric population. We highlighted weak to moderate correlations between CPET and spirometry. The most severe CHD were related to lower exercise capacity performances even though all spirometric values were in the normal range. Pulmonary and cardiac disease are commonly coexisting in CHD adults[68]. However, it is not well described why and when these lung function impairments might appear in pediatric population with CHD.

There are several classifications for CHD. In clinical practice, the classification proposed by Uzark[11] (2008) or Houyel[10] (2011) is considered to be the most useful. However, the NYHA functional classification is the most commonly used in literature, especially in adults. In CHD pediatric population, the modified Ross classification[67] is preferred because it incorporates feeding difficulties, growth problems and symptoms of exercise intolerance into a numeric score equivalent to the NYHA classification[69] used in CHD adults, and its sensitivity allows to assess and capture the progression of a heart failure[7].

In our study in pediatric CHD patients, CPET and spirometric parameters were in the normal range (Table 2) with Wmax, peakVO_2, FEF 25-75%, FEV_1, FVC and FEV_1/FVC within the predicted values (122.3% of predicted value, 97.1%, 102.5%, 108.5%, 105.1% and 97.2% of predicted value, respectively). This is consistent with the study previously described by Müller[70], where the CPET parameters measured on cycloergometer were also in the normal

range. Indeed, the patients from Müller had a value of mean peakVO_2 of 87.1% of predicted value like in our entire cohort of CHD patients (97.1% of predicted value). However, in our cohort, the peakVO_2 was significantly lower in the groups with more severe heart disease (mR1 = 111%, mR2 = 104%, mR3 = 85% and mR4 = 76%; p = < 0.001). Müller also showed an association between the severity of the heart defect and the peakVO_2 (r = -0.410; p < 0.001) in CHD children. Note that the mean Wmax studied on treadmill in our study was also higher than the predicted value (122% of predicted value), as well as in Müller study which was performed on cycloergometer (133% of predicted value)[70].

It is well known that CHD children are less active than their healthy peers[23] and overprotection is common in children with CHD[71]. This could explain their lower CPET performance. However, physical activity and active life style are highly recommended for all CHD patients without demonstrated cardiovascular risk in CPET (ventricular dysfunction, arrhythmias...), as stated in the guidelines from the Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology[25,30]. Furthermore, sedentary behaviours are increasingly recognized as risk factors for cardiovascular diseases, and they increase the risk of comorbidities[23]. On this basis, we promote regular physical activity during childhood in our CHD patients, as part of a healthy general behaviour[72].

Rhodes[73] showed a significant improvement in peakVO_2 (p = 0.005), Wmax (p < 0.001) and FEV_1 (p = 0.001) (expressed as a % of predicted value) after cardiac rehabilitation (12 week, 2 times/week during 1 hour) in CHD children

(6 to 17 years old) with initial peakVO_2 and Wmax lower than 80% of predicted values and mR4 severity as inclusion criteria. This confirms that normal CPET and spirometry parameters reported in our cohort can be, at least in part, explained by the children's active behaviour and lifestyle.

Although we and others[73,74] showed that the spirometry values were higher than 80% of predicted value for FVC (82.2 ± 16.0 before, 81.1 ± 14.6 after) and FEV_1 (81.7 ± 16.3 before, 82.2 ± 15.8 after), they usually become abnormal with the age[68], compromising the exercise tolerance and contributing to respiratory comorbidities[63,75]. In fact, in our cohort study, we observed a negative moderate correlation between the age of the children and the peakVO_2 ($r = -0.492$), FEV_1 ($r = -0.397$) and FVC ($r = -0.289$) suggesting a negative evolution related to age.

Hawkins[60] found a restrictive lung function in CHD children (n = 220) after cardiothoracic surgery by sternotomy, thoracotomy or both (25.6%, 23.5% and 54.2% respectively; $p < 0.0001$). In our cohort, although 70% of children (n = 223) had a previous operation at the time of their CPET evaluation, only 13% (FVC) and 9% (FEV_1/FVC) presented abnormal lung function.

Adults surviving with CHD can develop more complications compared to children. The pulmonary disease is one of the most common comorbidity in these patients[68]. In our study, we observed that CPET and spirometry presented a weak to moderate correlation, and the parameters decreases (< 80% of predicted value) with the CHD severity. However, looking at CPET and spirometry parameters and their high level of variability, it is

straightforward to understand that there is a significant proportion of children with less severe CHD showing poor CPET and spirometric.

As suggested by others[40,59], our results highlight the need for performing early lung function test in the regular follow-up of these patients, starting in childhood as a part of the prevention of future comorbidities. Indeed, we observed negative correlations between age and the different cardio-respiratory parameters.

We acknowledge some limitations in our study. A lower proportion of mR4 patients were included compared to mR1, mR2 and mR3. However, this subgroup still included 43 children (13%). The heterogeneity of lung function test reference values available in the literature (Zapletal, Cooper, Miller, GLI...) can somehow compromise inter-study and intra-study comparisons, particularly between genders.

In conclusion, while CPET parameters were normal, as expected, they were lower in the most severe CHD children. Even if the lung function reported in our large CHD paediatric population was also normal, it does not imply that these patients will not have lung impairments in adulthood as illustrated by the negative correlation with age. Moreover, we demonstrated significant correlations between Wmax and FEV_1, peakVO_2 and FEV_1, and peakVO_2 and FVC. These results suggest the potential benefits of precocious and regularly spirometry and CPET assessment in CHD children. These patients will likely benefit from an earlier and more careful evaluation to guide their postoperative rehabilitation and prevent further lung impairments in adulthood.

Chapter III: Lung function in Congenital Heart disease children

Lung function in pediatric patients with Congenital Heart Disease children: A systematic review

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Abstract

Introduction: Congenital Heart Disease (CHD) is a common chronic disease in paediatric population. In CHD adults, cardiac and pulmonary diseases are frequently coexisting. The aim of this systematic review was to analyse the lung function (LF) in CHD children, to clarify the differences in LF taking into account the type of CHD (cyanotic and non-cyanotic), and to study the LF variations before and after cardiac surgery.

Methods: Using the PubMed, PEDro and Scopus database, we searched for randomised controlled trials and observational studies in CHD children (< 18 years old). Downs and Black quality index was established and PRISMA recommendations were followed

Results: A total of 16 articles met inclusion criteria with 14.5 of median quality index. Restrictive LF has been observed as the most common pattern. However, obstructive LF has been also observed in non-cyanotic CHD. The patients who underwent cardiac surgery improved their restrictive LF but not the airways obstruction.

Conclusion: In conclusion, the most frequent pattern observed in CHD patients was restrictive. Obstructive pattern was more frequent in non-cyanotic patients and did not disappear with surgery.

1. Introduction

Congenital heart diseases (CHD) are defined as structural anomalies of the heart. These occur during fetal development[76]. These malformations affect 0.8% of live births, regardless of gender and 30% of the case are associated with other malformations as well as genetic anomalies[77]. Various classifications were described to categorize the patient's clinical condition and the underlying structural malformation, such as the Anatomic and Clinical Classification of Congenital Heart Defects (ACC-CHD) based on the International Pediatric and Congenital Cardiac Code (IPCC)[10] as well as Ross Heart Failure[69] and the Uzark classification[11] used to determine the severity of the disease. Patients suffering from non-cyanotic diseases are described as those with normal arterial oxygen saturation (SaO2>93%). This category includes common malformations such as atrial and ventricular septal defects. Patients born with cyanotic malformations present with an abnormal arterial oxygen saturation (SaO2 < 93%), as seen in patients with tetralogy of Fallot, transposition of the great arteries or functionally univentricular hearts.

Prematurity is a risk factor for chronic diseases, such as CHD and 25% of premature children born with severe CHD will require surgical or percutaneous interventions during the first twelve months of life[77]. However, the age of the corrective (complete correction), palliative or

staged surgery (primarily designed to modify pulmonary blood flow, enhance intracardiac mixing, or rehabilitate a ventricle prior to definitive surgery) will depend on the underlying defect and can be performed up to adulthood.

Over the past 40 years, advances in diagnostics, surgical techniques and health care have dramatically improved the life expectancy of CHD children[11]. Nowadays, more than 90% of children with these diseases reach adulthood[78]. The reduction in mortality means that this population became older[4] with specific health problems such as physical and functional limitations that affect their quality of life[79,80]. These complications can be attributed to poor cardiac development, chronic respiratory infections or pulmonary hypertension[76].

Many review articles have focused on cardiac and hemodynamic abnormalities related to CHD[81–84]. On the contrary, the respiratory and pulmonary systems have not been extensively explored, although some studies reported changes and abnormalities in pulmonary function in CHD children and adults[60,75]. Based on lung function assessment in CHD children, the aims of this systematic review were (1) to define the LF profiles (restrictive and/or obstructive), (2) to clarify the differences in LF patterns taking into account the specific heart disease and (3) to study the pulmonary function variability in the pre-operative and post-operative (or palliative) stage.

2. Methods

2.1. Protocol

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were consulted during the stages of design, analysis and reporting of this Systematic Review[85]. According to these guidelines, the structured search, study selection, risk-of-bias assessment of individual studies and best evidence syntheses for relating risk-of bias to consistency of effect sizes were performed. The protocol has been registered in the international prospective register of systematic reviews PROSPERO (Registration No. 160362).

2.2. Eligibility criteria, sources and search strategy

Eligible studies were identified using the following databases: PubMed, PEDro and Scorpus database. The studies were screened to search the publications between 1960 and February 2019. A combination of MeSH terms (MEDLINE) and free text words (all databases) were used. The research question was "Lung function test/assessment in CHD children and adolescents". The main terms searched were "respiratory function test" and all the volumes that we can assess (i.e. Forced expiratory volume, vital capacity), "Heart Defects, Congenital" and all types of CHD (i.e. ventricular septal defect, heart malformation) and "adolescent" and "child*". A hand searching reference lists from the identified articles and use of PubMed related articles option completed the database searches to avoid missing relevant studies. Three key terms were combined: "congenital heart disease", "children" and "respiratory function tests".

2.3. Study selection and exclusion criteria

After removal of duplicates, abstracts were checked critically and independently for relevance by two independent investigators (G.R. and N.M.). Articles were included if they assess the lung function in CHD patient's ≤ 18 years old, written in French, Spanish or English and not classified as case report, review or meta-analysis. Respiratory, neurologic and hematologic diseases were excluded, as were children with Marfan and Down syndrome. The investigators reviewed full-text articles when inclusion or exclusion was unclear based on the title and abstract. Any disagreement about eligibility criteria was resolved by consensus.

2.4. Data extraction, study quality appraisal and risk of bias assessment

Two investigators (G.R. and N.M.) extracted study details and data. Collected data for each study included design, sample characteristics (including number of participants, age group, inclusion/exclusion criteria) lung function pattern, lung function tool assessment, surgical approach and age at surgery.

The same two investigators applied the quality Index developed by Downs and Black to assess the quality (10 items), the external validity (3 items), the bias and confounding elements (13 items) and statistical power (1 item) of all studies selected[86]. This quality index comprises 27 questions. Downs and Black (D&B) quality index[87] were applied for all items. According to O'Connor[88] each study was graded from "Excellent" (24-28 points), "Good" (19-23 points), "Satisfactory" (14-18 points) to "Poor" (<14 points).

2.5. Data synthesis

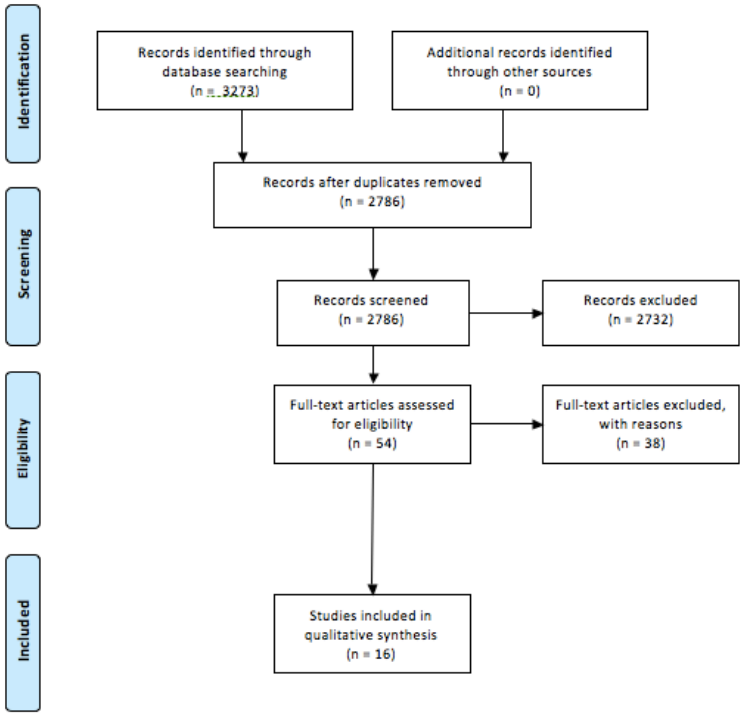
The investigators considered the results of the studies. Descriptive results, mean comparison, cyanotic and non-cyanotic CHD, lung function tool and reference values, lung function pattern and type of surgery and years old of surgery were reported when available.

3. Results

3.1. Study selection

A total of 3273 references were originally retrieved from the different databases (Figure 2). After duplicate removal, 2786 articles were identified and screened. At the end of the process, sixteen studies were included.

Figure 2: PRISMA Flow Diagram



3.2. Characteristics of the studies

The characteristics of studies in non-cyanotic patients are presented in Table 4, whereas cyanotic and mixed populations are reported in Table 5 and 6, respectively.

3.3. Population

The mean age ranged from 6 to 16.2 years. Among the 16 studies, 6 focused on non-cyanotic CHD (2 were pre- and post-surgical studies), 7 on cyanotic CHD (all postoperatively) and 3 did not differentiate the type of CHD. The

age at surgical procedures differed and varied according to the CHD severity, type of lesions and type of interventions (corrective or palliative).

3.4. Interventions

All studies assessed pulmonary function by spirometry (10) and/or body plethysmography (9) in various contexts, i.e. before and after surgery, evaluating different types of surgeries (palliative or corrective), comparing CHD to healthy-control subjects and taking into account the different type of CHD.

3.5. Outcomes

Different outcomes were analysed in the reviewed studies. The selected lung function parameters considered as relevant were: TLC, FEV_1, FVC, FEV_1/FVC, $FEF_{25-75\%}$, RV, FRC/TLC.

3.6. Quality and design of the studies

The median D&B scores for the selected articles were 14.5 points with extreme values between 7 and 18 points. Eleven studies were rated as "Satisfactory" (14-18 points) and four were rated "Poor" (< 14 points).

3.7. Result of the studies

3.7.1. Non-cyanotic CHD

Atrial Septal Defect

Four studies analysed atrial septal defect. LF parameters were expressed by Zapletal predicted value in 3 studies[61,89,90] and one by Chang predicted

value[91]. Three studies evaluated LF by body plethysmography and one used spirometry.

Before surgery, FVC, TLC, FEV_1 and FEV_1/FVC were within the normal range[90,91]. However, $FEF_{25-75\%}$ ($p< 0.05$) and FRC/TLC ($p< 0.01$) were reduced compared to the expected values[90,91]. After surgery, FVC, TLC, FEV_1 and FEV_1/FVC parameters were still in the normal ranges. Despite that, $FEF_{25-75\%}$ did not recover ($p< 0.05$) and stayed abnormal.

Another factor to take into account is the surgical approach. Central sternotomy was evaluated in three studies (Sulc 1992[89] and 1998[90], Zaqout 2010[61]). Only one study (Zaqout 2010) observed a reduced FVC ($p= 0.0302$) in the sternotomy surgery group compared to the percutaneous transcatheter closure group, suggesting a possible restrictive pattern in this group[61]. All studies indicated that abnormal pulmonary haemodynamic, like pulmonary hypertension (PH), contribute to develop an abnormal LF and increases the pulmonary blood flow in ASD children. Once normal physiology and haemodynamic are obtained, LF improves, suggesting that this changes was reversible[61,89–91].

Ventricular Septal Defect (VSD)

Two studies assessed LF in VSD children. Both studies used Zapletal as predicted values for LF parameters. Sulc[79] assessed LF by body plethysmography and Binkhorst[92] by spirometry.

In this population, TLC, FRC, RV, FRC/TLC and RV/TLC were within the normal range[79]. However, some parameters such as FEV_1 ($p< 0.05$) and FVC ($p< 0.05$) were significantly reduced[92].

Sulc[79] divided the VSD children in two groups based on the surgical procedure, i.e. primary repair and two-stage repair (pulmonary artery banding and secondary closure of VSD). In both groups airways obstruction was observed but hyperinflation was only present in the two-stage repair group. The authors concluded that in some cases there is no correlation between LF and pulmonary haemodynamic.

3.7.2. Cyanotic CHD

Tetralogy of Fallot (ToF)

Two studies[93,94] evaluated the LF in ToF children. One study used body plethysmography and Zapletal reference values[93] whereas the spirometry and Global Lung function Initiative (GLI) values were used for the other study[94].

Comparing with healthy controls a reduced FVC (p= 0.005), FEV_1 (p= 0.005), $FEF_{25-75\%}$ (p= 0.004) and inspiratory capacity (p= 0.005) were observed[94]. These two authors[93,94] found 40% of patients with a mild restrictive pattern, 12% with an obstructive pattern, 4% with a mild mixed restrictive and obstructive pattern, 16% with a mixed impairment and 28% with normal LF[94].

Children with ToF, who underwent to a surgery before the age of 2 years had less pulmonary impairments compared to children operated at a later age. Based on these results, the study recommended a complete correction of ToF before the age of 2 years, when possible, to minimize the LF alterations[93].

Transposition of great arteries (TGA)

In this population of patients, Samanek[95] and Gilljam[84] assessed LF by spirometry and body plethysmography. However, they did not cite the predicted values that they used.

TGA children who had palliative surgery had an impaired VC ($p< 0.01$), TLC ($p< 0.001$) and FRC/TLC ($p< 0.001$)[95]. Depending on the type of palliative surgery (Mustard or Senning), it was observed an abnormal LF (88%) based on VC ($p< 0.01$), TLC ($p< 0.01$) and FEV_1 ($p< 0.0001$)[84].

Both studies concluded that abnormal LF parameters were observed in CHD children with TGA after the palliative surgery.

Functionally univentricular hearts

Three studies assessed the LF in Functionally Univentricular Hearts CHD children. In the first study they used the spirometry (n= 33) and helium dilution (n= 27) and Zapletal as reference values[96]. In the second study, they analysed the LF by spirometry and the reference values were not reported in the manuscript[62]. In the last study, they assessed their population by spirometry and compared their results to the NHANES III reference values[97]. Restrictive pattern were predominant in all the three aforementioned studies. However, that pattern did not turn to be exclusive because mild obstruction were also observed[62,97].

3.7.3. Mixed studies

Three studies were categorized in the mixed CHD group, and did not study the specificities of the two types of CHD.

In the first study, patients with ASD, VDS, ToF, aortic stenosis (AS) and coarctation of the aorta (CoAo) were included. They performed LF tests using spirometry and body plethysmography and they used Zapletal as predicted normal values[98]. In the second study, they used the spirometry for LF evaluation and the ERS (2005) predicted values[60]. And the third, they used the spirometry with Zapletal as reference values and they performed a cardiopulmonary exercise test[99].

A restrictive pattern was observed in both studies with abnormal VC or TLC (ASD= 43%; VSD= 47%; ToF= 55%; AS=45%; CoA= 38%), a pulmonary hyperinflation with RV or RV/TLC alteration (ASD= 30%; VSD= 50%; ToF= 45%; AS=38%; CoA= 50%) and an airways obstruction represented by MEF25-50% (ASD + VSD= 20%; ToF= 22%; AS=6%; CoA= 21%)[98]. The prevalence of restrictive pattern was higher in children who had undergone surgery (25.5% vs 74.5%) and it was more pronounced in children who underwent the surgery within the first year of life (32.6 vs 67.4%)[60]. Moreover, children who had undergone both sternotomy and thoracotomy (54.2%) had greater prevalence of restrictive pattern than those who had sternotomy or thoracotomy alone (25.6% vs 23.5%). Restrictive LF increased significantly with each additional surgical intervention.

Table 1: Chronological results for non-cyanotic Congenital Heart Disease

Author	Subjects	Outcomes	Tool	LFT % Predicted value	Results
		Atrial Septal Defect (ASD)			
Sulc et al. (1992)	n= 74 (22M/ 52F) Age: 15.00 ± 2.5 years Time between Surg and S: 5.1 ± 2.5 years	PSurg vs %PV	P	Zapletal	PSurg vs %PV FVC = 101 ± 15; p = NS TLC = 100 ± 14; p = NS TLC ≤ 2 SD = 12.2% FVC ≤ 2 SD= 9.5%
Sulc et al. (1998)	PrSurg: n= 26 (12M / 14F) Age: 11.8 ± 3.8 years Time between S and Surg: 3 days PSurg: n= 24 (2lost) Time between Surg and S: 1.79 ± 0.21 years	PrSurg vs %PV PSurg vs %PV PrSurg vs PSurg	P	Zapletal	PrSurg vs %PV : FVC, TLC; p = NS FRC/TLC= 105.9 ± 9.1; p ≤ 0.01 PSurg vs %PV: FVC, TLC; p = NS FRC/TLC= 94.2 ± 10.5 ; p < 0.005 PrSurg vs PSurg: FVC, TLC; p = NS FRC/TLC= -11%; p ≤ 0.0001 Restrictive: TLC≤ 2 SD: 7.7 vs 8.3 (p = NS) Hyperinflation: FRC/TLC≥ 2 SD: 19.2 vs 4.2 (p = NS) Peripheral Obstruction FEF_{25-75}≤ 2SD: 15.4 vs 16.7 (p = NS)
Lee et al. (2009)	n = 55 (24M / 31F) Age: 9.5 ± 3.1 years Time between S and C: 1 day	PrSurg vs %PV PSurg vs %PV PrSurg vs PSurg	LFT	Chang	PrSurg vs %PV: FVC, FEV_1, FEV_1/FVC; p = NS FEF_{25-75} = 76% ± 22; p < 0.05

	Time between Surg and S: 6 months				<u>PSurg vs %PV:</u> FVC, FEV_1, FEV_1/FVC; p = NS FEF_{25-75} = 81% ± 24; p < 0.05 <u>PrSurg vs PSurg:</u> FEF_{25-75}; p = NS FVC: 94 ± 9% vs 98 ± 15%, p = 0,034 FEV_1: 90 ± 20% vs 96 ± 19%, p = 0.008 Normal (FVC andFEV_1 ≥ 80% andFEV_1/FVC normal): 61.8% vs 78.2% Obstructive (FEV_1/FVC < 80%): 16.4% vs 10.9% Restrictive (FVC < 80% andFEV_1/FVC normal): 21.8% vs 10.9%
Zaqout et al. (2010)	n= 46 (21M / 25F) <u>Gr 1: percutaneous closure</u> n= 26 Age: 11.3 ± 2.73 years Time between Surg and P: 5.81 ± 1.62 years <u>Gr 2: chirurgical closure</u> n = 20 Age: 10.2 ± 2.64 years Time between Surg and P: 5.87 ± 2.07 years	Gr 1 vs Gr 2	P	Zapletal	<u>Gr 1 vs Gr 2:</u> TLC: p = NS FVC: 100,2% ± 10.66 vs 94.55% ± 10.81; p = 0.032 FEV_1: p = NS Restrictive (FVC, TLC/FVC and FEV_1 ≤ 2SD): 7.5% vs 5% Obstructive (FEF_{25-75} ≤ 2SD): 4% vs 5% Normal (≥80% PV): Gr 1 + Gr 2= 86%
		<u>Ventricular Septal Defect (VSD)</u>			
Sulc et al. (1996)	n = 47 <u>Gr 1: primary reparation</u> n= 34 Age: 13.0 ± 2.8 years	Gr 1 vs %PV Gr 2 vs %PV Gr 1 vs Gr 2	P	Zapletal	<u>Gr 1 vs %PV:</u> FVC, TLC, FRC/TLC; p = NS FVC < 2 SD = 24%; TLC < 2 SD = 27% <u>Gr 2 vs %PV</u>: FVC, TLC; p = NS

	Time between Surg and P: 9.6 ± 2.0 years <u>Gr 2: procedure in 2 times</u> n= 13 Age: 16.2 ± 2.9 years Time between Surg and P: 9.1 ± 2.6 years				FRC/TLC: 111% ± 10; p < 0.001 FVC and TLC < 2 SD = 39% <u>Gr 1 vs Gr 2</u> LFT abnormal Gr 1 vs Gr 2; p = NS
Binkhorst et al. (2008)	<u>Gr 1: VSD Surg</u> n= 13 (7M / 6F) Age: 13.0 ± 2.5 years Time between Surg and S: 12 years 5 months <u>Gr 2 : VSD not Surg</u> n = 14 (6M/8F) Age: 12.5 ± 3.0 years Follow-up: 7 years 2 months <u>Gr 3: control</u> n= 15 (7M/8F) Age: 12.5 ± 3.0 years	Gr 1 vs Gr 3 Gr 2 vs Gr 3	LFT	Zapletal	<u>Gr 1 vs Gr 3</u> FVC: 74% ± 13; p= NS FEV_1: 87% ± 13 vs 98 ± 14%; p < 0.05 <u>Gr 2 vs Gr 3</u> FVC: 70% ± 14 vs 84 ± 12%; p < 0.05 FEV_1: 81% ± 15 vs 98 ± 14%; p < 0.05

M = male; F = famele; SD = standard deviationl; %PV = % of predicted value; NS = non significant; Surg= surgery; PSurg = post-surgery; PrSurg = Pre-surgery; n= total of subjects – exclusion; P = Body Plethysmography; LFT = Lung Function Test; FVC = forced vital capacity; TLC = total lung capacity; FRC/TLC = lung hyperinflation/central obstruction measure; FEF_{25-75} = forced expiratory flow in peripheral airways; FEV_1= forced expiratory volume in the first second; FEV_1/FVCF= Tiffeneau index; FRC = functional residual capacity; Gr = group.

Table 5: Chronological results in cyanotic Congenital Heart Disease

Author	Subjects	Outcomes	Tool	% Predicted value	Results
			Tetralogy Of Fallot (TOF)		
Sadeghi et al. (2013)	n= 322 (206M/116F) Age: 13.4 ± 3.85 years Age in the Surgery: Gr 1: ≤ 2 years n= 10 (3.1%) Gr 2: 2-8 years n= 159 (49.4%) Gr 3: > 8 years n= 153 (47.5%)	Gr total Gr 1 vs Gr 2 vs Gr 3	LFT	ERS (2012)	All : VC: 87.54% ± 12.70; FVC: 87.39% ± 12.9; FEV_1: 88.06% ± 13.04; FEV_1/FVC: 96.94% ± 3.66 Gr1 vs Gr2 vs Gr3 : VC: 107% ±10.96 vs 91.10% ± 12.25 vs 82.35% ± 10.62 ; p < 0.001 FVC: 95.90% ± 18.77 vs 90.83% ± 12.52 vs 83.26% ± 11.71 ; p < 0.001 FEV_1: 104.84% ± 13.64 vs 90.61% ± 12.59 vs 84.31% ± 12 ; p < 0.001 FEV_1/FVC: 98.67% ± 1.14 vs 97.37% ± 3.34 vs 96.40% ± 3.99 ; p = 0.024
Demirpence et al. (2015)	Gr 1 : ToF PSurg n = 25 14H / 11F Age : 11.6 ± 2.7 years Gr 2 : Ctrl n= 25	Gr 1 vs Gr 2	P	ERS (2012)	VC, FVC, FEV_1, FEV_1/FVC: Gr 1 > Gr 2 et Gr 3 Gr 1 vs Gr 2 FVC: 76% ± 13 vs 91% ± 13 ; p < 0.005 FEV_1: 79% ± 15 vs 92% ± 15 ; p < 0.05 FEF_{25-75}: 2.3% ± 0.6 vs 3.1%± 0.6 ; p < 0.004 FEV_1/FVC: 105 ± 9% vs 102 ± 9% ; p = NS

	14H / 11F Age: 12.3 ± 2.3 years				<u>Gr 1 (by ERS) :</u> Mild restrictive= 40% Obstructive= 12% Mixed pattern= 20% Normal= 28% <u>Gr 2 (by ERS):</u> Mild restrictive= 15% Normal= 85% <u>Corrélation :</u> Right venrtricular MPI and FEV_1 (r= 0.490; p= 0.013)
		<u>*Transposition of the Great Arteries (TGA)*</u>			
Samanek et al. (1989)	n= 35 Age: 11.6 ± 2.92 years Time between Surg: 7.2 ± 1.45 years	PSurg vs VP%	LFT, P	-	VC: 87.5% ± 12.9; p < 0.01 TLC: 92.6% ± 12.5; p < 0.001 FRC/TLC: 106.4% ± 19.4; p < 0.001 Abnormal LFT in: VC: 60%; FRC/TLC: 40%; TLC: 34%
Gilljam et al. (1995)	n = 30 (21M/9F) Age: 13.0years (7.2 - 22.0) <u>Gr 1: PSurg (Mustard)</u> n =15 (12M/3F) Age: 13.6years (12.2 -22.0) Time between Surg and P: 14.3 years <u>Gr 2: PSurg (Senning)</u> n = 15 (9M/6F) Age: 9.4 years (7.2 – 12.1)	Gr 1 Gr 2 Gr 1 + Gr 2 vs VP%	LFT, P	-	<u>Gr 1:</u> Abnormal LFT in: VC: 27%; TLC: 0%; FEV_1: 27%; FRC/TLC: 50%; FEV_1/CV: 27% <u>Gr 2:</u> Abnormal LFT in: VC: 27%; TLC: 20%; FEV_1: 20%; FRC/TLC: 33%; FEV_1/CV: 7% <u>Gr 1 + Gr 2 vs VP%</u> VC: -1.0 ± 1.5; p < 0.01 TLC: -0.7 ± 1.3; p < 0.01 FEV_1: -1.2 ± 1.4; p < 0.0001 FRC/TLC: 1.5 ± 1.1; p < 0.0001

	Time between Surg and P: 8.7year				FEV_1/CV: -0.1 ± 1.9; p = NS
			Single Ventricle		
Matthews et al. (2006)	n = 33 (20M/13F) Age: 12.6 ± 2.4 years (M) 12.9 ± 2.4 years (F)	PSurg vs VP%	LFT (n =33), P (n= 29) and helium dilution (n= 27)	Zapletal	FVC: 85.7% ± 17.1 (12%) FEV_1: 94.3% ±18.7 TLC by P: 99.1% ± 12.8 (2 patients) TLC by helium dilution: 87.7% ± 12.7 (2 patients) FVC et FEV_1 vs thoracotomies: r = - 0.38 ; p = 0.03 TLC by helium dilution vs thoracotomies: r = - 0.44 ; p= 0.016 FVC: M < F; p = 0.027
Giannico et al. (2006)	n= 165 Age of Surg: 72.2 months (13.1 to 131.3 months)	Assess after Surg	Pneumotachograph	-	Restrictive pattern (FVC and FEV_1 <80%; FEV_1/FVC >80%) - Mild n= 27 - Moderate n= 18 Obstructive pattern (FVC >80%; FEV_1 and FEV_1/FVC <80%) n= 4
Opotowsky et al. (2014)	n= 260 (155M/105F) Age: 13.1 ± 3.0 years <u>Gr 1: FVC< LLN</u> n = 119 (71M/48F) Age: 13.6 ± 2.7 years <u>Gr 2: FVC≥ LLN</u> n = 141 (84M/57F) Age: 12.8 ± 3.3 years	Gr all vs VP% Gr 1 vs Gr2	LFT	NHANES III	<u>Gr sll vs VP% :</u> FVC: 83.1% ± 17.3; p = NS Restrictive pattern: FVC< 80% = 43.9% (Knudson) Obstructive pattern (VEMS/CVF < LLN) = 7.8% <u>Gr 1 vs Gr 2</u> Obstructif (FEV_1/FVC < LLN) = 6.8% vs 8.5% ; p = NS

M = male; F = female; %PV= % of predicted value; NS = non significant; LFT= lung function test; Surg= surgery; PSurg = post-surgery; PrSurg = Pre-surgery; n= total of subjects – exclusion; P = Body Plethysmography; FVC = forced vital capacity; TLC = total lung capacity; FRC/TLC = lung hyperinflation/central obstruction measure; FEF_{25-75} = forced expiratory flow in peripheral airways; FEV_1= forced expiratory volume in the first second; FEV_1/FVCF= Tiffeneau index; FRC = functional residual capacity; Gr = group; ERS = European Respiratory Society

Table 6: Chronological results for mixed studies in Congenital Heart Disease

Author	Subjects	Outcomes	Tool	LFT % Predicted value	Results
Lubica et al. (1996)	n= 213 Age: 11.3years (6-21) Gr1: Shunt L-R (ASD + VSD) n, sex, age = NR Gr 2: Sunt R-L (ToF) n, sex, age = NR Gr 3 (AS + CoAo) n, sex, age = NR	PrSurg	LFT P	Zapletal	Restrictive pattern (abnormal VC or TLC) ASD= 43%; VSD= 47%; ToF= 55%; AS=45%; CoA= 38% Pulmonary hyperinflation (abnormal RV or RV%/TLC) ASD= 30%; VSD= 50%; ToF= 45%; AS=38%; CoA= 50% Airways obstruction (Abnormal $MEF_{25-50\%}$) ASD + VSD= 20%; ToF= 22%; AS=6%; CoA= 21%
Hawkins et al. (2014)	n= 876 (590M/286F) Age: 15.5 ± 7.7 years Gr1: CHD nonSurg n= 233 (NR) Age= NR Gr2: CHD Surg n= 444 (NR) Age: NR Gr: Control (nonCHD) n= 220 (135M/85F) Age: 13.9 ± 3.3 years	Gr1 vs GrControl Gr2 vs GrControl Gr1+Gr2 vs GrControl Gr2 vs years of Surg G2 vs Surg approach	LFT	ERS 2005	Restrictive pattern All vs GrControl: 19.7% vs 13.2% (p= 0.03) Restrictive pattern Gr1 vs Gr2 vs GrControl: 8.6%, 25.5%, 13.2% (p< 0.0001) Restrictive pattern G1 vs type of lesion: Not significantly associated (p= 0.96) Restrictive pattern G2 vs year of 1rs Surg: 32.6% Surg < 1month; 30.2% Surg < 1year; 18.1% Surg > 1year (p= 0.016) Restrictive pattern All vs Surg approach: 23.5% in thoracotomy; 25.6% in sternotomy; 54.2% in thoracotomy + sternotomy (p< 0.0001)

Abassi et al. (2019)	n= 834 n= 555 CHD (326M/229F) n= 279 Control 158M/121F) Age CHD: 12.2 ± 3.3 Age Control: 11.1 ± 2.6	Spirometry CPET Kidscreen-27 (quality of life questionnaire)	LFT	Zapletal	Comparison between CHD and Control Group - Z-score FVC: p< 0.001 - Z-score FEV1: p< 0.001 - Z-score FEV1/FVC: non significant (in M p= 0.88 and F p= 0.46)

M = male; F = female; %PV= % of predicted value; NS = non significant; LFT= lung function test; Surg= surgery; PSurg = post-surgery; PrSurg = Pre-surgery; n= total of subjects – exclusion; P = Body Plethysmography; FVC = forced vital capacity; TLC = total lung capacity; FRC/TLC = lung hyperinflation/central obstruction measure; FEF_{25-75} = forced expiratory flow in peripheral airways; FEV_1= forced expiratory volume in the first second; FEV_1/FVCF= Tiffeneau index; FRC = functional residual capacity; Gr = group; ERS = European Respiratory Society; CPET= cardiopulmonary exercise test

4. Discussion

To the best of our knowledge, this is the first systematic review examining the LF in CHD patients.

Because the predicted values used in the fifteen studies included in this review are not homogeneous, conducting definitive comparison is difficult. Currently, the recommended predicted values are from the Global Lung function Initiative (GLI), as described by the European Respiratory Society[53]. The inconsistency of the used predicted values can be explained in part by the extended publication period of the analysed papers, some published before 2000 (40%). This great amount of relatively old studies can also explain the moderate scores observed in the Downs and Black Quality Index. In most of the studies, the tools to evaluate LF were the spirometry and body plethysmography, known as the gold standards to assess the pulmonary function[55].

The main objective of this systematic review was to observe the most common LF pattern in CHD patients, which turned out to be the restrictive pattern. However, an obstructive pattern was also observed in some patients, although with a lower incidence. The second objective was to establish a possible difference between the pulmonary profiles of paediatric patients with cyanotic CHD and non-cyanotic CHD. Obstructive patterns, predominantly present in non-cyanotic CHD, have emerged as the major difference between the two categories of heart diseases. Finally, the last objective was to verify the differences in pulmonary function before and after surgery. The evidence presented in this systematic review reveal that CHD children have worst levels of restrictive pulmonary function after the

surgery. However, obstruction related issues also persist after surgery, even if they are relatively limited when the surgery occurs during the first years of life. To understand the impact of these interventions, an overview of pulmonary profiles in adults will be discussed below.

All studies suggest that CHD children are predisposed to develop an abnormal pulmonary function. These alterations are not specific to a particular CHD[98]. However, this statement should be used with caution because each type of heart disease has its own set of peculiarities, which depend on the origin of this restriction.

A restrictive LF has been observed in ToF patients who underwent surgical correction. The main causes of this restrictive pattern could be the thoracic deformations, the pulmonary hypoplasia and the excess of pulmonary blood flow, impacting the airways. However other factors could explain the restrictive pattern such as altered pulmonary haemodynamics, postoperative lung complications or the consequences of mechanical ventilation[100,101]. A late age at correction and the succession of multiple surgeries could also have a detrimental influence on the alveolar qualitative and quantitative development, leading to pulmonary hypoperfusion and contributing to the restrictive pattern[93]. Similarly, in ToF children and patients who have undergone to Fontan surgery for the palliation of functional univentricular hearts, a reduction in TLC was observed, at least when measured by gas dilution. However, TLC is normal when measured by bodyplethysmography, as explained by the phenomenon of air trapping[96,97]. Pulmonary function alterations in CHD are therefore often caused by pulmonary blood flow as well as pulmonary pressure. Samanek[95] found that

pulmonary abnormalities in non-operated CHD are usually caused by pulmonary vascularization and/or parenchymal impairment. By contrast, the main aetiology of pulmonary abnormalities in children who have had surgery are diaphragmatic paralysis, stiffness of the rib cage or weakness of the respiratory muscles[60].

As already mentioned, airway obstruction is also observed in children with CHD, mainly in non-cyanotic CHD and ToF. Small airway obstruction (peripheral obstruction) affects 22% of children with ToF, 20% of children with ASD and VSD combined[98]. This is shown by a decreased $FEF_{25-75\%}$[94]. Similarly, the obstruction of large airways was present in 11% of children with ToF and in 5% of ASDs[98]. Some studies showed the presence of an obstructive pattern that could be caused by abnormal vascular growth[102]. However, all studies did not agree on the pulmonary status of ToF patients. The study by Sadeghi[93] identified only 2.4% of children with this CHD as obstructive, as observed in healthy children.

It is worth noting that peripheral airway obstruction is not limited to ToF patients. Non-operated ASD patients for example also showed a reduction in $FEF_{25-75\%}$[91]. Sulc[90] explained this decrease in $FEF_{25-75\%}$ by an increase in pulmonary blood flow and volume, particularly in small airways. This type of obstruction is more pronounced when the patient undergoes to open-heart surgery[94]. As we already mentioned this could be explained by an increase in blood volume in the capillaries or hypertrophy of the heart[103]. Children with VSD are also subject to peripheral airway obstruction, and are more affected when they undergo a two-stage surgery rather than a single surgery (39% versus 12%)[79]. The obstruction was even more significant when these

multiple surgeries are associated with prolonged intubation and mechanical ventilation[79].

Now that we clarified the type of pulmonary profile in children with CHD, we can focus on these two other important factors: (i) the impact of surgery on CHD children pulmonary patterns and (ii) the ideal age at which the surgery would give the best LF outcome.

Lubica[98] showed that CHD children who underwent to open-heart surgery after the age of three years showed some LF impairments. This dysfunction is caused, on one hand by haemodynamic variations and, on the other hand by histological changes in the pulmonary tissue. The latter is related to abnormal pulmonary flow during the pre- and postnatal periods, which will result in a decreased growth of elastic tissue and collagen. Therefore, it is recommended that children who have undergone to an open-heart surgery after the age of two years are screened by LF tests to determine the evolution of pulmonary profiles and to treat them accordingly[98].

Like the pulmonary patterns, each heart disease presents its own specificity in terms of ideal age of intervention and postoperative profile. The most appropriate time to perform surgery in ASD children has been evolving with the overcoming of technical limitations. Indeed, in the early 90's, children were operated around the age of 10-15 years. At that time, 50% of the postoperative LF tests were classified as "abnormal"[89,90]. Sulc[90] also showed a negative correlation between the age of surgery and postoperative pulmonary recoil pressure and a positive correlation between the age of the surgery and lung volume. That means that the earlier the surgery is performed, the better the elasticity and the growth of the lung result in the

post-surgical period. However, the subjects included in this study had a rather late surgery (11.8 years), as opposed to the classic timing of surgical management of simple lesions (usually between 1 and 4 years). These subjects may therefore have a milder form of ASD involving only mild cardiac and pulmonary dysfunction[90]. By contrast, other studies reporting an earlier surgical management demonstrated decreased and abnormal LF after surgery[90,91]. This reduction in LF could be explained by the fact that children were less exposed to an increased pulmonary blood flow[91]. Zaqout[61] found the same results in terms of LF reduction even though, it could be explained by a longer interval between surgery and LF tests. After surgical correction, no improvement in $FEF_{25-75\%}$ was observed in ASD children, likely because they presented a remodelling of the parenchyma with some degree of fibrosis[104]. Other studies showed that remodelling process can persist long after surgery[89,90,98] or percutaneous closure of an ASD[91]. This may explain the persistence of airflow limitation of peripheral airways[61]. Further long-term studies are needed to confirm this hypothesis[91].

Restrictive LF, suggested by a FVC decreased, seems to be more common in children who had open-heart surgery than in those who had percutaneous interventions[61]. Cardiopulmonary bypass procedures (CPB) and sternotomy can induce lung function abnormalities in contrast to transcatheter interventions[61,105,106]. Transcatheter closures alleviate the need for thoracotomy or prolonged mechanical ventilation. Unlike surgery, the transcatheter interventions do not result in detrimental functional or anatomical alveolar changes[91] and lead to a faster recovery and normalization of pulmonary hemodynamics[83]. Also, Zaqout[61] argued that

early correction and follow-up would allow early detection of abnormal LF in ASD children.

On the other hand, 77% of children with corrected VSD had abnormal LF, with a restrictive pattern and a decreased TLC and FVC[79]. Even when the children were operated at a young age (in average, 3.4 to 7 years), the abnormalities persisted until at least 10 years after the intervention[79]. According to some studies, persistent structural changes in the pulmonary vessels[82,107], possible pulmonary fibrosis and parenchymal modification[104,108] may contribute to the durability of these abnormal LF values. This could be explained by the need for repeated surgeries (via thoracotomy and/or sternotomy) in some patients with more complex heart diseases. These multiple interventions could cause abnormal growth of the parenchyma (alveolar development) and induce a reduction of the pulmonary volume[108]. According to Sulc[79], it would be possible to have less LF impairments if the surgery was performed at younger age.

Children with ToF are affected by pulmonary restriction but also airway obstruction. It is worth remembering that the majority of pulmonary development occurs in two phases: a phase called "glandular" which ends at the end of the second year of life, and an "alveolar" phase which ends at the age of 8 years[93]. Pulmonary perfusion plays an important role in the development of lung structures and therefore lung volumes in adulthood[98,109]. In this context, Sadeghi[93] study showed that children who underwent surgery before the age of two years had improved FVC, FEV_1, FEV_1/FVC and $FEF_{25-75\%}$ values. These results are also valid for children who underwent surgery before the age of 8 years[93]. When the surgery was

performed during the first period of development (first 2 years of life), they might prevent the abnormal growth of the lung, even when a normal pulmonary blood flow is restored[102]. The surgical approach of ToF can vary from patient to patient, and includes various techniques. Gaultier[102] showed that early open-heart surgery preserved the LF. However, the morphometric data indicated less impairment in alveolar growth in patients treated first by shunt palliation. This suggests that the systemic shunt to the lung might improve the alveolar development. However, when a two-stage approach was chosen, the LF abnormalities were still observed[102,110,111].

Nowadays it exists two groups of TGA patients, those with a palliative surgery (Mustard and/or Senning) and those with corrective surgery (Arterial Switch). Currently, the majority of TGA children are operated thought Arterial Switch technique. However, in our review, only two types of surgeries were considered taking to account our inclusion and exclusion criteria. Several articles indicated that 10 years after a Mustard or Senning procedure, children had impaired LF[84,95]. As in other CHDs, the abnormal pulmonary hemodynamic could have play a deleterious role on the pulmonary vasculature. Longer exposure to these conditions may cause further vascular wall remodelling that may persist over the time[95]. A later study, comparing Mustard and Senning surgery, revealed that in a group of Mustard surgery the children were older and they had a longer postoperative period with higher prevalence of pulmonary abnormalities[84]. However, we must remain cautious in the interpretation of these results because the medical and surgical management of these patients has dramatically improved over the last decades, including through the

incorporation of the Arterial Switch operation in most surgical programs around the world[112]. This could explain the more important post-surgical sequels in older series. In TGA, lung stiffness could also be an important determinant of LF. Samanek[95] demonstrated that this parenchymal stiffness was present preoperatively and reported a 66% reduction in recoil pressure even in early surgery.

Children with a functionally univentricular heart greatly benefit from a staged approach to the so-called Fontan circulation (total cavopulmonary anastomosis), both in terms of morbidity and mortality. In 27% of children, a restrictive pattern is still observed after the interventions, despite early interventions and the fenestrated extracardiac technique[62]. A drop in FVC was also observed after 13 years of follow-up[97], but there was no correlation between the age at surgery and LF parameters[96]. This long-term postoperative restriction can be explained by other factors, such as chronic modifications in pulmonary vascularization and parenchyma[81,113,114]. The surgery itself could also explain this restriction. Indeed, there was a negative correlation between the number of thoracotomies and the FVC, FEV_1 and TLC parameters[96]. Paralysis of the diaphragm is another well-known complication of the Fontan procedure and could also play a role[115,116]. In addition, the completion of the total cavopulmonary anastomosis requires CBP, which is know to result in more pronounced inflammatory and structural pulmonary changes, than in palliative surgeries[115]. Finally, surgical complications, such as respiratory and skeletal muscles deconditioning, could probably play an additional role in the pulmonary restriction in these children [117].

This systematic review focused exclusively on studies in the paediatric population. However, technical and surgical advances have dramatically increased the life expectancy of these children, allowing them to reach adulthood. A similar systematic review, which analysed the different LF parameters depending on the type of CHD and before and after surgery, would be an interesting and complementary add-on to our scientific contribution.

The main limitation of this systematic review is that it did not include all types of CHD (e.g. valvular diseases, patent ductus arteriosus, genetic cardiomyopathies…). Only the most frequently reported CHD were included. A second limitation lies in the inclusion criteria of the population, and more particularly in the age of the subjects. Selected articles include samples of patients with an average age of less than 18 years. This implies that some subjects were probably young adults.

However, this is the first systematic review that aimed to explore the impact of various CHD on LF *per se*, in paediatric populations, while, so far, previous studies focused rather on exercise tolerance and cardiac function. This study has helped to describe the pulmonary function of CHD children and the impact of the surgical management on their outcome.

5. Conclusion

To conclude, this broad analysis of pulmonary profiles of CHD children, regardless of the type, showed that the main pulmonary pattern is restrictive. This restriction is sometimes associated with an airway obstruction, more present in non-cyanogenic CHD children. Corrective surgeries are able to reduce this restriction, but unfortunately seem to have

no impact on the obstructive pattern. The surgical timing, and the type and number of surgeries determine the pulmonary state of the patients after their interventions. Further studies are required to clarify the ideal age of surgery for each disease group, leading to an optimal LF and the aetiology of the restriction pattern in each type of CHD.

PART II

Chapter IV: Tests validation in the pediatric population: 6MWT and STST

INTRODUCTION

Currently, there are many tools to assess the functional exercise capacity in pediatric patients. As already mentioned, the gold standard is the cardiopulmonary exercise test (CPET). However, it is not always possible to perform this test because it requires a lot of time to be performed, it is an expensive test and specific infrastructures are needed. Several field tests are used as surrogated to replace the CPET, and allow to collect useful data on the patient's functional exercise capacity. Nevertheless, these field tests are not always applicable to pediatric patients and even less in patients with underlying cardiac diseases, because they have not been validated yet. The same issues apply to field test and questionnaires, in which language and questions about activities of the daily life must be adapted to each specific country.

In this chapter we will define some aspects of field tests, highlighting the differences between their applications in adult and children. Furthermore, we will validate a field test in pediatric population and a questionnaire for the French speaking patients, since it was required in our specific scenario.

Learning and Encouragement Effects on Six-Minute Walking Test in Children

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Abstract

Objectives: To evaluate learning and encouragement effects on the 6-minute walk test in children between 6 and 12 years of age.

Study design: Two 6-minute walk tests separated by a 10-minute resting period were performed by healthy children between 6 and 12 years of age to evaluate the learning (part 1) and encouragement effects (part 2; randomization with and without encouragement). Distance and cardiorespiratory variables were used as outcomes.

Results: 148 children were recruited. The intraclass correlation coefficient estimates were 0.927 (95% CI, 0.893- 0.951; part 1) and 0.844 (95% CI, 0.744-0.907; part 2). The test-retest agreement was verified for distance (*P* = .679) with a bias of 1.1 m (95% CI, −4 to 6), but the increase in distance with encouragement was significantly and clinically relevant (P < .001; +41 m; 95% CI, 33-50).

Conclusion: No training is required for the 6-minute walk test in children, in contrast with adults, but there was an encouragement effect on the walked distance in these children. Guidelines should take these results into account.

Trial Registration ClinicalTrials.gov: NCT03276299.

1. Introduction

The evaluation of functional exercise capacity is important in children with various diseases[18,118–120]. The 6-minute walk test is the criterion standard for this purpose and it has been regularly used in children[50,121,122]. The validity and reliability of this test have been verified in children[31,49,123–125].

Performance on the 6-minute walk test in adults is influenced by many technical factors, such as instructions, location, path length, track layout, or walking aid[126–130]. Ethnicity is also considered as an influencing element[51]. A recent technical standard for adults was co-published by the European Respiratory Society and the American Thoracic Society[15]. Two of the influences on the 6-minute walk test were the learning and encouragement effects. Neither learning nor encouragement effect have been specifically evaluated in children, and children were not included in the international technical standard on standardization of this test[15].

We hypothesized that these effects could be different in children under 12 years of age. Indeed, the intrinsic motivation that is related to these effects is different between adults and in children under 12 years of age[131]. The 6-minute walk test is a submaximal test[132] and probably easier for children than for adults. Moreover, time perception is underdeveloped in children[133]. Encouraging children during the test can be attractive to stimulate performance and could influence the results of the 6-minute walk test. An encouragement effect has been demonstrated in the intrinsic motivation of children[134]. The aim of this study was to verify

the learning and encouragement effects on functional exercise performance in the 6-minute walk test in healthy children between 6 and 12 years of age.

2. Methods

Healthy children were recruited in a French-speaking Belgian elementary school between June 2015 and March 2016. The inclusion criteria were participation in the national physical education program at school after the annual medical investigation, Caucasian, and between 6 and 12 years old. The exclusion criteria were to have acute or chronic lung, cardiac, or neuromuscular disease, to be over- weight (body mass index >85th percentile for children of the same age and sex)[135], and to have a cognitive disorder or a motor disability based on parent answer to a standardized questionnaire. The subjects were free of physical activity for 1 hour preceding the study. They participated only in 1 part of the study.

The study was approved by the regional Ethic Committee in Cliniques universitaires Saint-Luc and Université Catholique de Louvain in Brussels in 2015 (BE403201524763- BE403201524845) and registered with ClinicalTrials.gov (NCT03276299). Parents of the children and children provided their written informed consent before the experiment.

The study included 2 parts and 2 distinct samples of children were recruited. The children performed two 6-minute walk test in both parts of the study separated by a 10-minute resting period. In part 1, the 6-

minute walk test was repeated twice under the same conditions to evaluate the learning effect. In part 2, a stimulating standardized, and repetitive encouragement to maintain the same walking pace was randomly added to one of the tests (www.randomizer.org) to evaluate the encouragement effect.

All 6-minute walk tests were carried out in a straight, un- obstructed, flat corridor using the protocol validated in healthy children by Li et al[31]. Children were instructed to walk as far as possible for 6 minutes between 2 marks separated by 30 m. During all tests, standardized sentences were pronounced to give time indications every minute. During the 6-minute walk test with encouragement, sentences such as "Just keep going," "It is good," "Continue like this," and "You are doing well" were played every 15 seconds. All tests were performed by a trained examiner, independent of the analysis.

Walking distance was measured as main outcome and ex- pressed in absolute and in relative values based on Goemans' equation[136]. Measurements of oxygen saturation and heart rate (HR) were measured with a finger pulse oximeter (Onyx, Nonin, Plymouth, MN). Change in HR was calculated by the difference between initial and final values divided by the initial value. Dyspnea was evaluated through the visual analog scale at rest, immediately after the test and after a 2-minute recovery. Age, weight, and height were recorded.

Statistical Analyses

The sample size determination was based on the detection of a 0.70

correlation coefficient between 2 field tests with a power of 80% and an alpha level of 0.05. The number of participants required for the study was determined to be ≥52.

Data were computed using SPSS 24.0 (IBM software, Chicago, IL) for Windows. Descriptive analysis was performed for anthropometric variables and for results of both tests. Variables were presented as mean, SD, and CI, or median and minimum and maximum after verifying the normality of the distribution by Kolmogorov-Smirnov test. The variability was calculated by the coefficient of variation. Intraclass correlation coefficient (ICC) was calculated using a 2-way mixed effects model for absolute agreement from a single measurement to verify the learning effect and using a 2-way random effects model for absolute agreement from a single measurement to verify the encouragement effect. ICC was expressed by absolute value and 95% CI. Reliability was interpreted from the ICC as poor (ICC of <0.50), moderate (ICC from 0.50 to 0.75), good (ICC from 0.75 to 0.90), or excellent (ICC of >0.90)[137]. Agreement between the first and second tests and between the tests with and without encouragement was calculated by paired Student *t* test and Bland-Altman method for distance and HR change. Bias (mean of the differences) and limits of agreement were calculated[138]. $P < .05$ was considered significant. When a difference between both tests was found, Pearson coefficient of correlation was calculated between age and changes in distance to verify the effect of age.

3. Results

One hundred two children were eligible, 2 declined to participate, and 5 were excluded (Figure 1) for musculoskeletal disorders (n = 2), acute rhinitis (n = 1), and overweight (n = 2). Ninety-five children were recruited. The sample to evaluate the learning effect included 57 girls and 38 boys. Both tests were performed by all the recruited children. The results of both tests are presented in Table 1.

Figure 1: Consort flow diagram

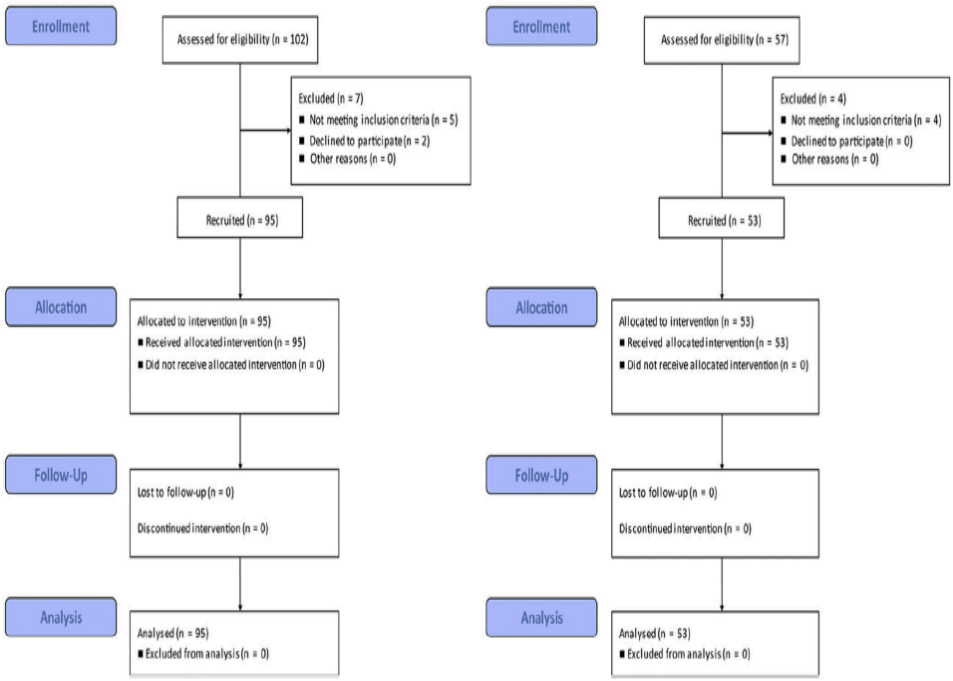


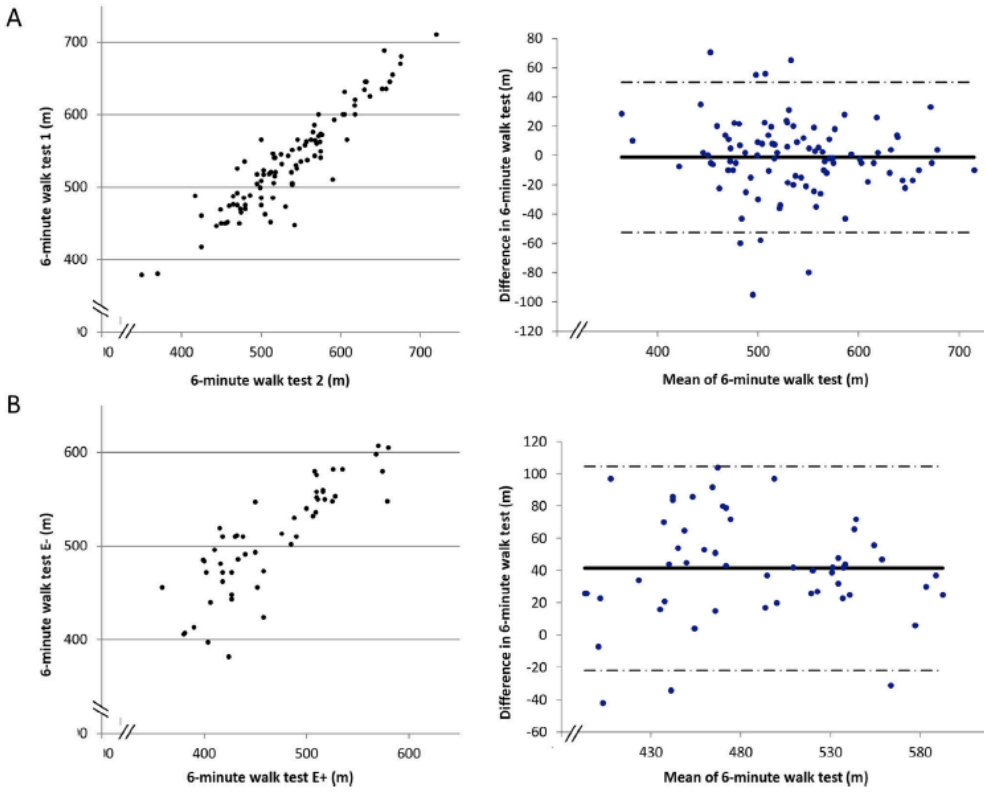
Table 1: Characteristics of the children and results of the 6-minute walk tests 1 and 2

Outcomes	6-Minute walk test 1 (n= 95)		6-Minute walk test 2 (n= 95)		P value
Age (y)	8.7 ± 19	8.3 - 9.1			
Weight (kg)	31.0 ± 7.9	29.4 - 32.6			
Height (cm)	131 ± 11	130 - 134			
BMI (kg/m2)	17.6 ± 2.4	17.1 - 18.1			
Distance (m)	537 ± 70	523 - 551	536 ± 68	520 - 548	0.679
Distance (% of predicted)	93 ± 11	90 - 95			
HR_i (bpm)	93 ± 12	91 - 96	96 ± 12	94 - 99	0.010*
HR_f (bpm)	124 ± 19	120 - 128	122 ± 21	118 - 127	0.347
HR_r (bpm)	94 ± 13	91 - 97	95 ± 14	93 - 98	0.172
$SpO2_i$ (%)	98 ± 1	99 - 99	99 ± 1	99 - 99	0.123
$SpO2_f$ (%)	99 ± 1	99 - 99	99 ± 1	99 - 99	0.857
$SPO2_r$ (%)	99 ± 1	99 - 99	99 ± 2	98 - 99	0.188
$Dyspnea_i$ (/10)	0.3 ± 1	0.1 - 0.5	0.3 ± 0.6	0.1 - 0.4	0.745
$Dyspnea_f$ (/10)	1.2 ± 1.6	0.8 - 1.5	1.1 ± 1.5	0.8 - 1.5	0.858
$Dyspnea_r$ (/10)	0.6 ± 1.1	0.4 - 0.9	0.6 ± 1	0.4 - 0.8	0.832
$Fatigue_i$ (/10)	0.8 ± 1.1	0.5 - 1.0	0.4 ± 0.7	0.2 - 0.5	0.001*
$Fatiguei_f$ (/10)	1.4 ± 1.4	1.2 - 1.7	1.3 ± 1.4	1 - 1.6	0.202
$Fatigue_r$ (/10)	0.7 ± 1.1	0.5 - 0.9	0.7 ± 1.2	0.5 - 1.0	0.863

The mean walked distance corresponded to 93% of the predicted values. The ICC estimate was 0.927 (95% CI, 0.893-0.951; Figure 2, A, left). The test-retest agreement was verified for distance (537 ± 69 m vs 536 ± 67 m; *P* = .679; Figure 2, A, right). Bias was 1.1 m (95% CI, −4 to 6) and limits of agreement were −52 and +50 m. The coefficient of variation for the walked dis- tance was similar in both tests (12.8% vs 12.5%). In contrast with distance, HR change showed a learning effect (33 ± 21% vs 28 ± 21%;

P = .011). Bias was 5% (95% CI, −9 to −1) and limits of agreement were −44% and 34%.

Figure2: Relationship between A, first and second 6-minute walk test (left) and Bland-Altman plots for distance between these tests (right) and B, between 6-minute walk test with and without encouragement (left) and Bland-Altman plots for distance between these tests (right).



Fifty-seven children were eligible and 53 were recruited (Figure 1, right). Four children were excluded for over- weight (n = 2), broken

foot (n = 1), and a cognitive disorder (n = 1). The sample to evaluate the encouragement effect included 30 girls and 23 boys. All recruited children performed both tests.

The results of both tests are presented in Table 2.

Table 2: Characteristics of the children and results of the 6-minute walk test

Outcomes	6-Minute walk test E- (n= 53)		6-Minute walk test E+ (n= 53)		P value
Age (y)	8.9 ± 2.1	8.4 - 9.5			
Weight (kg)	34.9 ± 11.3	31.8 - 38.0			
Height (cm)	137 ± 15	134 - 142			
BMI (kg/m2)	17.9 ± 3.1	17.1 - 18.8			
Distance (m)	466 ± 59	450 - 482	507 ± 57	491 - 523	<0.001*
HR_i (bpm)	95 ± 15	91 - 100	94 ± 14	90 - 98	0.616
HR_f (bpm)	117 ± 15	113 - 121	123 ± 15	118 - 127	0.031*
HR_r (bpm)	100 ± 13	96 - 104	98 ± 15	94 - 102	0.434
$SpO2_i$ (%)	99 ± 1	98 - 99	99 ± 1	99 - 99	0.020*
$SpO2_f$ (%)	98 ± 2	98 - 99	98 ± 1	94 - 102	0.764
$SPO2_r$ (%)	99 ± 1	98 - 99	99 ± 1	99 - 99	0.177
$Dyspnea_i$ (/10)	0.0 ± 1	0.0 - 0.1	0.0 ± 0.1	0.0 - 0.1	0.322
$Dyspnea_f$ (/10)	2.2 ± 0.7	2.0 - 2.4	2.3 ± 0.7	2.1 - 2.5	0.348
$Dyspnea_r$ (/10)	1.2 ± 0.4	1.1 - 1.3	1.1 ± 0.2	1.0 - 1.1	0.033*

E+, with encouragement; E-, without encouragement.
Data are expressed by mean ± SD and 95% CI.
**P* <0.05

The ICC estimate was 0.844 (95% CI, 0.744-0.907; Figure 2, B, left). The distance increased when encouragement was given to the children (466 ± 58m vs 507 ± 57 m; *P* < .001; Figure 2, B, right). The coefficients of variation were around 12% for both tests. Bias was 41 m (95% CI, 33-50) and limits of agreement were −22 and +105 m. The encouragement tended to increase the HR change even if it was not significant (25 ± 22% vs 32 ± 22%; *P* = .07). Bias was 7% (95% CI, −1 to 15) and limits of

agreement were −48% and 62%. Age was not associated with the change in distance related to the encouragement (r = −0.196; *P* =0 .160)

4. Discussion

Repeatability and reliability are two of the fundamental properties of a test and are influenced by many factors. They represent the extent to which a test provides the same result on repeated testing occasions. The reproducibility of the 6-minute walk test has been evaluated in children in different studies with test–retest intervals varying from 4 days[139] to 4 weeks[31]. They showed intertest differences up to 15 m, but lower than the differences found in adults (>20 m) and highlighted the influence of the time on the result. Because of the time between tests, these studies cannot evaluate the learning effect. In contrast, the repeatability has been evaluated previously in children with chronic heart disease[140], with cystic fibrosis[122,123], and in healthy children[52,140]. The children in these studies were not representative due to small sample size (<30 children), heterogeneity of age (mean age of >10 years), inclusion criteria variability from the current guidelines for the 6-minute walk test, or the repetition of 2 tests by 2 evaluators.

Owing to the reliability (ICC of >0.90) and the agreement between both repetitions of the walked distance by children (around 1 m) found in our study, there may be no need to repeat this test in children, unlike what is required in adults[51]. There was no evidence for a learning effect for the 6-minute walk test in children <12 years of age. When the distance in- creases between 2 conditions or after a

treatment, our results suggest it is not related to a learning effect and is likely due to the intervention.

However, if the evaluation of HR change during exercise is the main objective of the test, a learning effect would have to be taken into account. The observed change in HR is probably not clinically relevant. Because the HR was lower for a similar walked distance, we hypothesize that the test was less stressful. It could be explained by a training effect or a better effort management by the children with benefit on the cardiorespiratory demand.

Encouragement has been demonstrated to improve endurance performance[141]. For such a long duration as for the 6-minute walk test, the time perception could be more difficult in children and encouragement is sometimes used to maintain attention during such a task.

It is useful to evaluate encouragement in children. First, most children fail to demonstrate consistent accuracy at judging relative durations before age of 11 or 12 years[142], especially for tasks with a longer duration[143]. Second, intrinsic motivation varies with age increasing until 15 years of age and stabilizes after this age[131]. Although the reliability between the tests was good, an improvement in walked distance related to encouragement was observed in our study. This improvement was greater in children than reported in adults (40 m vs 30 m)[144]. The variability of walked distance was not influenced by encouragement. Indeed, there was no difference in the coefficient of variation when encouragement was given to the children. Moreover, there was no

correlation between age and the improvement. Both findings suggest that the effect was similar for all children.

Because the absence of learning effect was demonstrated in the first part of the study, we postulate that the observed improvement is only explained by encouragement. Thus, the effect of encouragement must be taken in account in children, similar to in adults, because the improvement was twice as high as the smallest bias found in the studies of reproducibility (Table 3) and 40 times higher than the bias related to the repeatability of the test.

Table 3: Test-retest differences found in children in previously published studies

Authors	Year	Interval	n and disease	Age	6-minute walk distance 1 (m)	6-minute walk distance 2 (m)	Bias (m)	ICC
Cunha et al.	2006	30 min to 12h	16, CF	11	582	598	-15.9	NA
Li et al.	2005	2 to 4 wk	52, healthy	14	622	677	15	0.94
Gulmans et al.	1996	1 wk	23, CF	11	737	742	NA	0.90 (r)
Martins et al.	2014	30 min	29, healthy	10.5	570	564	5.5	0.742
Moalla et al.	2005	<12h	14, healthy	13	549	NA	-1.4	NA
Moalla et al.	2005	<12h	12, CHD	13.5	473	NA	-1.3	Na
Morinder et al.	2009	4 d	49, obese	13	571	574	2.8	0.85

CF, Cystic fibrosis; CHD, chronic heart disease; NA, not available

Some limitations need to be addressed to the study. First, only healthy subjects were recruited. It could be argued that, in contrast with healthy subjects in our study, patients could walk a shorter distance in the second 6-minute walk test owing to fatigue related to the disease. This phenomenon was not observed in the studies comparing the reproducibility in walking tests between healthy subjects and patients[140]. Moreover, the longer distance observed in the second 6-minute walk test in patients with cystic fibrosis does not suggest this effect, despite patients having potentially greater physical limitations[122]. Second, the 10-minute interval for resting between both tests could be too short to complete the recovery in patients with cardiorespiratory diseases. In patients with chronic obstructive pulmonary disease, the variability was more pronounced when repeated walks were performed over short intervals[145]. In our healthy subjects, we postulate that this interval was sufficient, as illustrated by the similar initial heart and respiratory rate at the initial evaluation of both tests. That factor should be examined in a different population of patients.

We showed that no training was required for the 6-minute walk test in children, in contrast with adults, but there was an encouragement effect on the walked distance during the test in these children. Further guidelines should take into account these results in children under 12 years of age to standardize the use of encouragement during the 6-minute walk test in this population.

Assessment of Validity and Reliability of the 1-Minute Sit-to-Stand Test to Measure the Heart Rate Response to Exercise in Healthy Children

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Abstract

This study examines the concurrent validity and reliability of the sit-to-stand test to quantify heart rate response during submaximal exercise in healthy Belgian children.

1. Introduction

The importance of physical activity is gaining recognition in children with cardiac or respiratory diseases, and the measurement of heart rate (HR) response during exercise is required[146]. The 6-minute walking test (6MWT), which has been verified for validity and reliability in children[31], is the reference field test to measure functional exercise capacity. New field tests are emerging to counteract the practical drawbacks associated with the 6MWT. The 1-minute sit-to-stand test (STST) is easy to implement and has already been validated in adults[147], but not yet in children. Moreover, to our knowledge, the physiological response associated with this test is unknown in children. The aims of this study were to evaluate the concurrent validity and reliability of the STST in measuring the HR response to submaximal exercise and functional exercise capacity in children.

2. Methods

After ethical approval from the Comité d'Ethique Hospitalo-Facultaire at Cliniques universitaires St-Luc, registration (NCT03670511), and written informed consent were provided, healthy children aged 8 to 18 years were recruited. The only inclusion criterion was participation in the mandatory medical investigation at school. The exclusion criteria were a diagnosis of chronic lung, cardiac, or neuromuscular disease, motor disability, or being overweight.

Children performed 2 1-minute STSTs[148] (STST1 and STST2) with a 1-week interval. Concomitantly to STST1, children performed a 6MWT as a reference test[31]. The number of sit-to-stands, walked distance, HR, and HR response (ΔHR initial to final [i-f] and ΔHR final to rest [f-r]) during the test were recorded. The STST concurrent validity (association with the 6MWT), inter-STST agreement (Cohenκ), reliability (intra class correlation coefficient [ICC]), and repeatability (paired t test after checking for normality [learning effect] and the Bland-Altman method) were verified.

Statistical analyses were performed with SPSS, version25.0 (IMB) and statistical significance was set at $P< 0.05$.

3. Results

Fifty-two children (mean [SD] age, 12.8 [2.4] years) were recruited. All children completed the tests.

Concurrent Validity. The HR and HRresponses were similar for both tests (Table 4). However, HRrecovery (ΔHRf-r) was faster for the STST than for the 6MWT. The HRf was lower than the theoretical maximal HR for all children and tests (STST1, 70%; 95%CI, 67-73 and6MWT, 69%; 95%CI, 65-72). The HR

changes (ΔHRi-f) in the STST1 and the 6MWT were moderately and significantly associated with one another (ρ = 0.522; P < .001). The distance was not associated with the number of sit-to-stands (ρ = 0.178; P = .21) (Table 4). No anthropometric parameter was associated with the number of sit-to-stands, unlike age (ρ = 0.294; P = .03).

Table 4: Concurrent validity of the functional exercise capacity and the HR responses measured by STST and the 6MWT in children

	Mean (SD)						
Measure	6MWT	STST1	Difference between STST1 and 6MWT	Difference (95% CI)	*P* Value	*p*	*P* Value
Distance, m/STS	646 (55)	40 (6)	NA	...	...	0.178	0.21
HR_i, bpm	92 (15)	94 (15)	-2 (10)	(-4 to 1)	0.18	0.785	<0.001
HR_f, bpm	139 (24)	141 (20)	-2 (17)	(-7 to 3)	0.38	0.698	< 0.001
ΔHR_{i-f}%	51 (24)	51 (22)	-0.3 (23.8)	(-6.9 to 6.3)	0.93	0.522	< 0.001
ΔHR_{f-r}%	19 (8)	22 (9)	-3.5 (8.7)	(-5.8 to -1.1)	0.006	-0.298	0.03

f, final; ΔHR_{f-r}, HR, heart rate; HR recovery; ΔHR_{i-f}, HR change; i, initial; NA, not applicable; r, rest (2' posteffort); STS, sit-to-stand, STST, sit-to-stand test

Reliability and Repeatability. The inter-STST agreement regarding the HR response was weak but statistically significant (κ = 0.24; P = .006). The reliability (ICC) of the HR response (ΔHRi-f and ΔHRf-r) was verified without

a learning effect (t test) (Table 5). The bias was −5% (95%CI, −12 to 2) and the limits of agreement were −55% (lower) and 44% (upper).

The reliability (ICC) of the number of sit-to-stands was excellent, but a learning effect (t test) was observed (Table 5).The number of repetitions was greater in STST2 than in STST1 in 43 patients (83%). The repeatability of the number of sit-to-stands was verified with a bias of 2.5 (95% CI, 1.5-3.5) and limits of agreement of −4.9% (lower) and 9.9% (upper).

Table 5: Repeatability and reliability of the functional exercise capacity and the HR responses measured by STSTs in children

	Mean (SD)		**Repeatability**			**Reliability**		
Measure	**STST1**	**STST2**	**Difference between STST1 and STST2, Mean (SD)**	**Difference 95% CI**	***P* Value**	**ICC, STST1 and STST2**	**Difference 95% CI**	***P* Value**
Distance, m/STS	40 (6)	42 (6)	2 (4)	1 to 4	< 0.001	0.90	0.832 - 0.945	< 0.001
HR_i bpm	94 (15)	91 (15)	-2 (11)	-5.4 to 0.9	0.16	0.83	0.708 - 0.903	< 0.001
HR_f bpm	141 (20)	142 (21)	1 (17)	-3.9 to 5.7	0.71	0.78	0.622 - 0.875	< 0.001
ΔHR_{i-r}%	51 (22)	56 (28)	5.2 (25.2)	1.8 to 12	0.14	0.68	0.434- 0.814	< 0.001
ΔHR_{f-r}%	22 (9)	25 (11)	2.4 (10.3)	-0.4 to 5.3	0.10	0.66	0.413 - 0.807	< 0.001

f, final; ΔHR_{f-r}, HR, heart rate; HR recovery; ΔHR_{i-f}, HR change; i, initial; NA, not applicable; r, rest (2' posteffort); STS, sit-to-stand, STST, sit-to-stand test; ICC, interclass coefficent; r, rest (2' posteffort)

4. Discussion

To our knowledge, this study demonstrated for the first time the concurrent validity and reliability of the STST to quantify the HR response during submaximal exercise in healthy children. Indeed, the cardiorespiratory responses to the STST and the 6MWT were similar and associated in the sample of healthy children. This result means that the STST is a good alternative field test to the 6MWT to evaluate cardiorespiratory demand. The STST is interesting because its submaximal exercise is similar to the 6MWT, but it is less time consuming while also requiring fewer resources and no long hallway.

Moreover, the reliability of the cardiorespiratory response measured by the STST at a 1-week interval was verified. Although we cannot consider the STST as a surrogate for the 6MWT for measuring the functional exercise capacity in children because of the lack of association with the walked distance, the STST was reliable for the number of repetitions measurement. The associated learning effect observed for the number of sit-to-stands, which contrasted with the adult results, could be explained by the differences in intrinsic motivation[131] and time perception[133] between adults and children. The STST could be used complementarily with the maximum incremental cardiopulmonary exercise test or when that test cannot be performed.

Chapter V: Test validation in the congenital heart disease pediatric patients: STST

Use of 1-minute Sit-to-Stand test to predict exercise capacity in pediatric patients with congenital heart disease

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Abstract

Introduction: Field tests are commonly used as complements of Cardiopulmonary Exercise test (CPET) to evaluate the functional exercise capacity. The aims of this study were to validate the one-minute Sit-to-Stand test (STST) in Congenital Heart Disease (CHD) children and to evaluate the possibility of predicting the peakVO_2 using the STST in this pediatric population.

Methods: Children (8 to 18 year old) followed for a CHD and performing CPET were recruited prospectively. Concomitantly, they performed STST. The heart rate (HR), oxygen saturation (SpO_2), muscular fatigue and dyspnea were recorded before (t0), immediately after (t1) and one minute after the end of the STST (t2).

Results: We observed a low but significant correlation between the STST and the peakVO_2 ($r=0.306$; $p=0.013$). A significant difference between girls and boys were observed for peakVO_2 ($p<0.001$), HR t0 ($p=0.030$), HR t1 ($p=0.002$) and HR t2 ($p<0.001$). The proposed model of prediction, including the

number of STST, weight, height and age explains 37% of the predicted peakVO_2 variance.

Conclusion: The STST can assess the physical capacity in CHD children. When CPET cannot be performed, we propose an alternative equation using the STST as a surrogate of peakVO_2 in CHD children.

1. Introduction

Maximal or peak oxygen uptake (peakVO_2 or VO_2max) reflects the body's maximal capacity to generate energy through aerobic metabolism[149]. It represents maximal aerobic capacity and its measurement is used to appraise health and performance as well as develop exercise prescriptions[150]. In a medical setting, the measurement of this peakVO_2 explores cardiac, respiratory and muscular functions[16].

The cardiorespiratory data are relevant health indicators in children with heart diseases[41]. The peakVO_2 such as other parameters (i.e. blood pressure, anaerobic threshold, heart rate, oxygen saturation, lung function) is measured during a cardiopulmonary exercise test (CPET). The CPET in Congenital Heart Disease (CHD) children provides important information for diagnostic (differential), prognostic and evaluation of the effects of a therapeutic intervention[16,41]. The peakVO_2 is an indicator of physical performance and allows optimizing the prescription of exercises and revalidation in cardiac patients. The CPET is performed on a cycloergometer or a treadmill and the volumes of inspired and expired gaz are analyzed

during the test and compared with the normal data available from the literature[16].

This expensive and time-consuming test is not always available because it requires specific equipment and a qualified team. Alternatives to estimate the physical performance are the submaximal fields tests such as the Six Minutes Walk test (6MWT)[151] or Incremental Shuttle Walking test (ISWT)[152]. Indeed, the peakVO_2 and the walked distance in the 6MWT[31,151] as well as the ISWT[152] were already shown to be correlated in healthy children and adolescents. These tests offer a simplest way to obtain a good estimate of the peakVO_2.

Unfortunately, the 6MWT and the ISWT both require time and space, and are not always realistic approaches in the routine follow-up. The 1-minute Sit-to-stand test (STST) however is easy to implement and has been validated in adults[147]. Moreover, a predictive equation was derived from the 6MWT to estimate the peakVO_2 in adults with cardiopulmonary disorders[153]. The STST can also be used as complement to CPET (or when it cannot be performed) to determine the HR response during a submaximal exercise in children[33]. Our hypothesis is that the STST could also be used to estimate peakVO_2 appropriately in children, in particular with underlying CHD.

The primary objective of this study was to validate the STST in CHD children as alternative and complement to CPET. The secondary objective was to verify if the combination of STST repetitions and some descriptive/anthropometric data (i.e. age, weight, height, BMI, sex and CHD severity) can be used to predict the peakVO_2 in children with CHD.

2. Methods

Study design

Children aged between 8 and 18 years, with a CHD diagnosis were prospectively included. All children with an appointment for a CPET in our Pediatric Cardiology Department from May to September 2019 were recruited for this study. The children underwent (1) their regular appointment with a pediatric cardiologist, (2) the CPET and (3) the STST. Anthropometric data were recorded just before to perform the STST. The experiments were carried out at Cliniques universitaires Saint-Luc in Brussels. All CHD children who had previously undergo a CPET and all children with contra-indication(s) to physical activity were excluded

The study was performed in accordance with the Helsinki declaration and was approved by the institutional medical Ethics Committee form the Catholic University of Louvain (B403201629869). Before any experiment, the subjects and their parents received a letter explaining the processes of the study and signed the consent form. In addition, the aim of the study and its objective were explained to children and their parents.

CPET protocol

The children performed a maximal CPET with a paediatric face mask (Hans Rudolph), a calibrated gas analyser (Oxycon Pro, Jaeger), a breath-to-breath measurements software (Windows 98, Jaeger), a 12-lead ECG monitoring (Cardiosoft, GE Healthcare), a pulse oxymeter (Nellcor), and an automated sphygmomanometer with adapted paediatric cuffs. All CPET were performed on the same treadmill following a standardized modified Bruce

protocol[41]: 1-min rest, 3-min warm-up (1 km/h, slope 0%), and then 2-min increments in speed (from 2.5 to 10.5 km/h) and slope (from 3 to 18%), and finally a 3-min active recovery (2.5 km/h, 0% slope) then 2-min rest. Exercise was pursued until the limit of the child's tolerance was reached, with active verbal encouragements. The following variables were measured: oxygen uptake (VO_2; ml/kg/min), carbon dioxide production (VCO_2; ml/kg/min), respiratory exchange ratio (RER = VCO_2/VO_2), minute ventilation (VE; breaths/min), ventilatory equivalent for oxygen (VE/VO_2), ventilatory equivalent for carbon dioxide (VE/VCO2), dead space-to-tidal volume ratio (VD/VT), heart rate (HR; beats per minute - bpm), maximum workload (Watts and METS), and oxygen pulse (VO_2/HR; ml). From all performed CPET, the investigator manually established the peak oxygen uptake (peakVO_2), the ventilatory anaerobic threshold (AT) using Beaver's method[42], the ventilation efficiency (VE/VCO_2 slope with VE = slope × VCO_2 + b), and the oxygen uptake efficiency slope (OUES with VO_2 = OUES × log10 VE + b)[43–45]. The VO_2max and AT were normalized in percentage of predicted peakVO_2 using normal values published by Wasserman and Cooper[46–48].

STST Protocol

For a reproductible protocol, the child should sit on a chair with his or her back firmly on the back and then stand up with full extension of the legs. This "sit-to-stand" has to be complete. The child must repeat this movement as often as possible over a period of 1 minute. Throughout the experience, the child must keep his arms crossed on his chest. The height of the chair was 37 cm for the short (<135cm) children (S) and 46 cm for the tall children

(T). Before the experiment, a demonstration was performed in front of the child to make sure she/he had a full understanding of the test.

Evaluation and Outcomes

The same senior qualified and blinded physiotherapist (NM) performed all the data collection and STST. An experienced paediatric cardiologist blindly performed the CPET. Anthropometric data and CHD characteristics were collected from the medical records of the patients. The heart rate (HR) and the pulsed oxygen saturation (SpO_2) were measured three times with a pulse oxymeter (NONIN Onyx): before and at the end of the test and after 1 minute of recovery. The difference between initial and final values (DeltaHR and DeltaSpO_2) was calculated in the STST. The dyspnea and muscular fatigue were quantified using the visual analogue scale (VAS) graduated from 0 to 10 (0=no dyspnea or muscle fatigue, 10=extreme dyspnea or maximal muscle fatigue). The collected data from CPET for this study was the peakVO_2.

Statistical Analysis

A descriptive analysis was performed for all parameters of the study with SPSS software (25.0). The descriptive data are expressed as mean, standard deviation (SD) and confidence interval (CI). The validity of the STST was verified by the correlation with CPET parameters by Pearson's or Spearman's correlation coefficient.

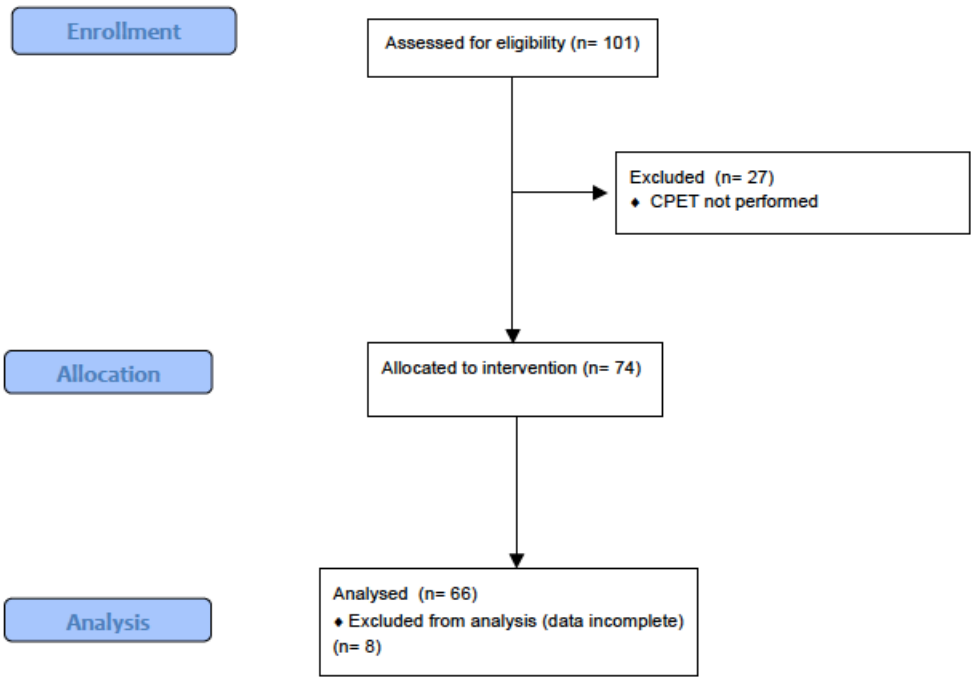
The Pearson or Spearman correlation coefficients were also calculated to highlight any correlations between peakVO_2 and independent variables

(age, height, weight, BMI, HR, SpO_2 and number of repetitions during STST). Correlation coefficients (r) higher than 0.70 were considered high, between 0.70-0.50 good, between 0.50-0.30 fair and <0.30 weak [154]. The comparison between girls and boys was made using the unpaired Student test. Multiple linear regression was used to create a peakVO_2 regression equation using independent variables as predictor variables. In the statistical analysis, the threshold considered "significant" was $p<0.05$.

3. Results

Sixty-six children were recruited (32 girls and 34 boys; Figure 1).

Figure 1: Consort flow diagram



The characteristics of the population and results of data collection are summarized in Table 1. The measured value of peakVO_2 was in the normal range of predicted values for most cases, but not in severe cases as detailed below (93.8 ± 26.4%). No significant differences were found between girls and boys (91.2 ± 25.9% vs 96.1 ± 27.1% respectively). However, we observed a significant difference between girls and boys in: peakVO_2 expressed by mL/Kg/min (33.8 ± 9.0ml/kg/min and 42.7 ± 10.4ml/kg/min respectively) ($p<0.001$), and the HR before (91.2 ± 18.5bpm and 81.5 ± 18.4bpm respectively) ($p=0.03$), after the STST (124.5 ± 22.2bpm and 112.6 ± 19.7bpm respectively ($p= 0.02$) and after one minute of recovery after the end of the STST (95.0 ± 22.5bpm and 80.5 ± 18.1bpm respectively) ($p<0.001$).

Table 1: Characteristics of the sample and descriptive outcomes

	All (n= 66)	Female (n= 32)	Male (n= 34)	P value
Age (years)	13.2 ± 2.9 (12.5 ; 13.9)	13.7 ± 2.3 (12.9 ; 14.6)	12.7 ± 3.4 (11.5 ; 13.9)	0.16
BMI	19.8 ± 4.5 (18.6 ; 20.9)	20.1 ± 4.4 (18.5 ; 21.6)	19.5 ± 4.8 (17.8 ; 21.2)	0.61
Weigh (kg)	48.9 ± 17.1 (44.7 ; 53.2)	48.2 ± 13.6 (43.3 ; 53.1)	49.7 ± 20.1 (42.6 ; 56.7)	0.72
Height (m)	1.5 ± 0.1 (1.5 ; 1.5)	1.5 ± 0.1 (1.4 ; 1.5)	1.5 ± 0.1 (1.4 ; 1.6)	0.53
SpO2 t0	97.5 ± 2.5 (96.9 ; 98.1)	97.1 ± 2.8 (96.0 ; 98.1)	97.9 ± 2.1 (97.2 ; 98.6)	0.19
HR t0 (bpm)	86.2 ± 18.9 (81.5 ; 90.9)	91.2 ± 18.5 (84.5 ; 97.9)	81.5 ± 18.4 (75.1 ; 88.0)	0.03*
SpO2 t1	97.0 ± 3.0 (96.3 ; 97.8)	96.6 ± 3.8 (95.2 ; 98.0)	97.5 ± 1.9 (96.8 ; 98.1)	0.25
HR t1	118.2 ± 21.6 (112.9 ; 123.6)	124.5 ± 22.2 (116.2 ; 132.2)	112.6 ± 19.7 (105.8 ; 119.5)	0.02*
STST	32.4 ± 5.4 (31.0 ; 33.7)	31.3 ± 4.5 (29.7 ; 33.0)	33.3 ± 6.0 (31.2 ; 35.4)	0.13
SpO_2 t2	97.5 ± 2.8 (96.7 ; 98.2)	97.0 ± 3.5 (95.7 ; 98.3)	97.9 ± 2.0 (97.2 ; 98.6)	0.21
HR t2	87.5 ± 21.5 (82.2 ; 92.8)	95.0 ± 22.5 (86.8 ; 103.1)	80.5 ± 18.1 (74.2 ; 86.9)	0.00*
Delta Spo_2	-0.4 ± 2.1 (-1.0 ; 0.6)	-0.5 ± 2.5 (-1.4 ; 0.4)	-0.4 ± 1.8 (-1.0 ; 0.1)	0.91
Delta HR	0.4 ± 0.2 (0.3 ; 0.4)	0.3 ± 0.1 (0.3 ; 0.4)	0.4 ± 0.2 (0.3 ; 0.5)	0.49
Delta SpO_2 t2	0.4 ± 1.4 (0.6 ; 0.7)	0.4 ± 1.6 (-0.2 ; 1.0)	0.4 ± 1.2 (0.0 ; 0.8)	0.92
Delta FC t2	-0.2 ± 0.1 (-0.3 ; -0.2)	-0.2 ± 0.1 (-0.2; 0.1)	-0.2 ± 0.1 (-0.3 ; -0.2)	0.31
Dyspnea	4.1 ± 2.2 (3.5 ; 4.6)	4.5 ± 1.7 (3.8 ; 5.1)	3.7 ± 2.6 (2.7 ; 4.6)	0.17
Muscular fatigue	3.2 ± 2.2 (2.6 ; 3.7)	3.2 ± 2.1 (2.4 ; 4.0)	3.2 ± 2.3 (2.4 ; 4.0)	0.93
$PeakVO_2$ (ml/kg/min)	38.4 ± 10.7 (35.8 ; 41.1)	33.8 ± 9.0 (30.6 ; 37.1)	42.7 ± 10.4 (39.1 ; 46.4)	0.00*
$PeakVO_2$ (%PV)	93.8 ± 26.4 (87.1 ; 100.4)	91.2 ± 25.9 (81.5 ; 100.8	96.1 ± 27.1 (86.6 ; 105.6)	0.46

BMI: body mass index; SpO_2: peripheral capillary oxygen; HR: heart rate; STST: sit-to-stand test; $PeakVO_2$: maximum oxygen consumption during an exercise; PV: predicted value; *: significant $p< 0.05$; t0: before STST; t1: after STST; t2: one minute after end the STST

We observed a rather low but significant correlation between the number of STS and the peakVO_2 (r=0.306; p=0.013) (Figure 2) and weak correlation between the dyspnea and the muscular fatigue (r=0.277; p=0.024). A fair correlation was observed between SpO_2 at t0 and t2 (r=0.461; p<0.001). Good correlations between HR at t0 and at t1 (r=0.629; p<0.001) and at t2 (r=0.786; p<0.001), and a fair correlation between HR at t0 and DeltaHR (r=0.488; p<0.001) were observed. A significant and fair correlation was observed between DeltaHR and STST (r=0.329; p=0.007). As expected, a negative correlation was observed between the peakVO_2 and the age (r=-0.374; p=0.002), the weight (r=-0.387; p=0.001) and the height (r=-0.219; p=0.077). We also observed a decreased peakVO_2 in the most severe patients (Figure 3).

Figure 2: Correlation between number of STST repetitions and peakVO_2 by CPET

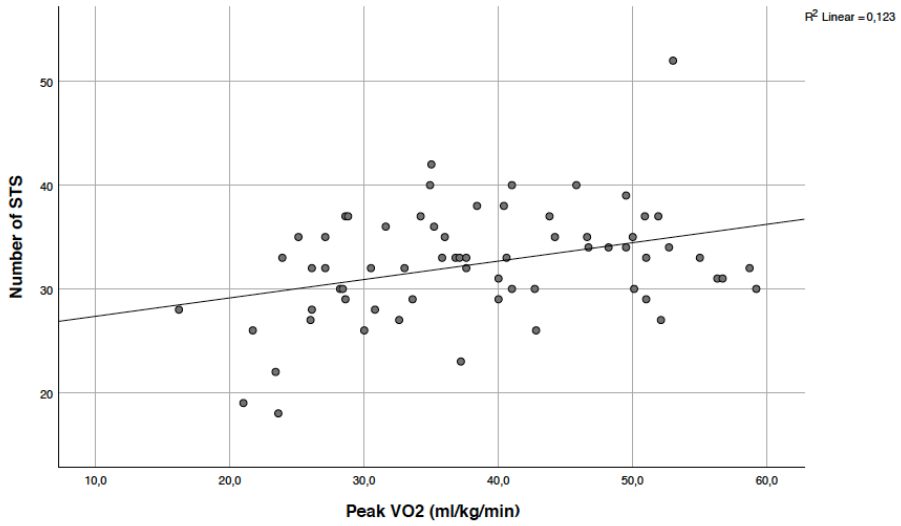
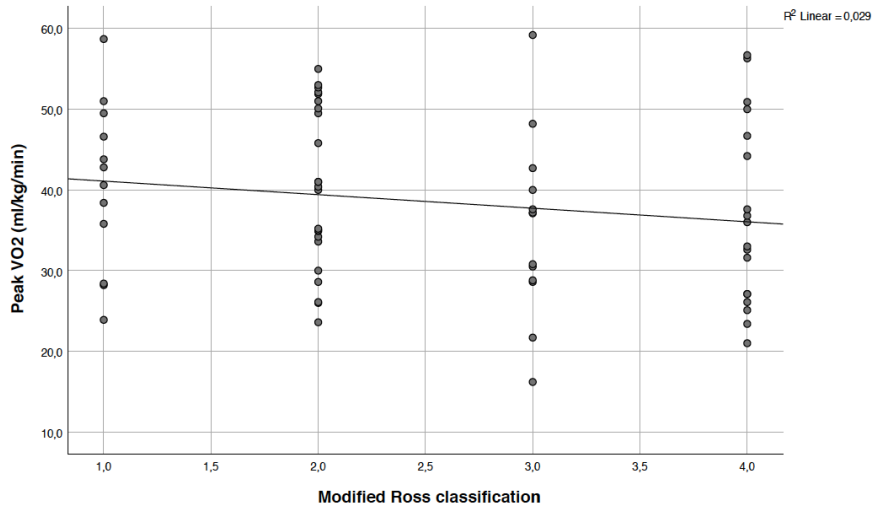


Figure 3: Correlation between the peakVO_2 from CPET and CHD severity by modified Ross classification



The best predictive model selected for CHD children includes the age (years), the weight (kg), the height (m) and the number of STS repetitions (Table 2). This model explains the 37% of peakVO_2 variance. The predicted equation for peakVO_2 in CHD children was:

PeakVO_2 (pred.)= -2.243 + 46.595 x (height in cm) - 1.999 x (age in years) - 0.344 x (weight in Kg) + 0.368 x (number of STST).

Table 2: Regression analysis for the prediction of peakVO_2 thought the STST

	R^2	Beta	Standard error	Beta standardised	p value
Model	0.377				0.000
Height		46.595	15.092	0.692	0.003
Age		-1.999	0.649	-0.556	0.003
Weight		-0.344	0.122	-0.551	0.006
Nb STST		0.368	0.213	0.186	0.089

4. Discussion

The purpose of this study was, on the one hand, to verify the validation of the STST in CHD children, and on the other hand, to define the appropriate equation to estimate the predicted value peakVO_2 in CHD children from basic data obtained during the STST. Although in healthy children the STST can be used to determine the chronotropic reserve (HR response) during a submaximal test[33], our study showed that in CHD children, STST may give additional information about the patient's physical capacity. Indeed, our new algorithm helped to estimate the peakVO_2 using a combination of the STST and anthropological data (age, weight and height) with 37% of confidence.

In our cohort, there was no difference between girls and boys in any of the anthropological data at rest. However, the HR measured after the test and after one minute of recovery, as well as the peakVO_2 was significantly different. Nevertheless, the peakVO_2, expressed as a percentage of the predicted value, was similar between girls and boys (p= 0.46) and the measured values were, for most patients, in the normal range (Table 1). As previously demonstrated, the girls have usually a lower peakVO_2 levels compared to boys, especially at the onset of puberty[155]. This difference in peakVO_2 is related to the stroke volume of the heart, which is greater in boys [155].

Field tests were created as alternatives or complements to CPET which remains the gold standard to evaluate the physical capacity[16]. The most widely used test in the clinical setting is the 6MWT which was demonstrated to be reliable to assess the functional capacity in healthy children[31].

Currently, there are many equations to verify if the walked distance (6MWD) is in the normal range for children[50,136,156,157]. These equations take into account the age and the height of the children[50,136,153], and can be used to estimate the mean peakVO_2[151,153]. The main limitation of the 6MWT is the required infrastructure and time needed to perform the test. The recommended hallway's length (30 m) can indeed be a limiting factor in many clinical settings. Hence, other field tests such as the STST began to emerge. In adults, the STST was already validated and increasingly used as alternative to 6MWT[147,158]. In healthy children, STST has been demonstrated to be valid and reliable to quantify the HR response during a submaximal exercise[33] but it cannot be considered as a valid test to assess the functional exercise capacity in healthy children due to the lack of correlation with the 6MWD. In our study, we observed fair but significant correlations between the STST and the peakVO_2 ($r=0.306$; $p=0.013$) and between the STST and DeltaHR ($r=0.329$; $p=0.007$). Therefore, it means that the STST highlight the HR response during a submaximal effort in healthy children[33] but not in CHD children. With our results, we can state that the STST is useful to assess the physical capacity in CHD children.

Here, we can estimate the peakVO_2 combined with other parameters (age, weight and height). Our work suggested an original linear model, which explains the 37% of peakVO_2 variance using the STST in CHD children, when a CPET cannot be performed.

Similar to other pediatrics models (i.e. estimation peakVO_2 with 6MWT[153]) our model included simple parameters (age, height, weight and number of

STST). The aforementioned parameters (BMI, CHD severity and sex) were actually not adding additional value, with a lower R^2 coefficient.

In adult model, to determine the reference values for the STST, there is a confidence of 28%[158]. In contrast, in our study we obtained 37% of confidence, which is higher. A similar equation was proposed in adults with cardiopulmonary disorders but the authors reported that 6MWD alone does not accurately predict the peakVO_2, confirming the need to include other parameters like in our model[153].

As an example, for a 12-year-old CHD child (weight 55kg, height 1.57m) who performs 42 repetitions of STST, we predicted a peakVO_2 value of 43.46 ml/kg/min. According to reference values of peakVO_2 reported by Takken in healthy children[16,159], our measured value (38.4 ± 10.7 [35.8 ; 41.1]) is close to the median value (43.46ml/kg/min) for this age.

One study limitation in our pediatric cohort was the height of the chair. In adults, the recommended height is 46cm[158]. However, in some children (<1,35m) this height was too high and we used a not validated alternative of 37cm (n=14). Another factor, which could impact our results, is that proportion (25%) of our patients were treated with beta-blockers, a medication limiting their chronotropic response during exercise.

In conclusion, the STST can provide relevant data on a physical capacity of children with CHD. In this work we proposed an equation based on the STST and anthropometric parameters (age, weight and height) to estimate the peakVO_2 when CPET is not available.

Chapter VI: Questionnaire validation in healthy pediatric population: PAQ-C and PAQ-A

Reliability and validity of French version of Physical Activity Questionnaire for children and adolescents

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Abstract

Background: The aim of this study was to validate the French version of the Physical Activity Questionnaire for Children (PAQ-C) and Adolescents (PAQ-A) as a tool to assess their participation in various types of physical activities and sports.

Methods: The validation process followed the Guidelines for the Process of Cross-Cultural Adaptation of Self-Report Measures. First, the PAQ was translated from English to French and a linguistic validation was performed. To verify the criterion validity, all children completed the French version of PAQ (VfPAQ) and the French version of the International Physical Activity Questionnaire (IPAQ), considered as the reference tool. The internal consistency was verified by the Cronbach's alpha. To assess the test-retest reliability, the same children completed again the VfPAQ after one month.

Results: 53 children and 59 adolescents completed the questionnaires. The validity was weak for the children ($r= 0.279$, $p< 0.05$) and moderate for the adolescents ($r= 0.497$, $p< 0.01$). The internal consistency was adequate ($\alpha=$

0.713 in children and α= 0.755 in adolescents), the test-retest reliability was good (ICC= 0.75, p= 0.05 in children and ICC = 0.84, p= 0.05 in adolescents). Conclusion: Criterion validity results suggest that VfPAQ is valid to assess the physical activity level in adolescents but not in children. Moreover, test-retest reliability was good for both groups.

1. Introduction

Physical activity (PA) is highly recommended in many chronic diseases, including in Congenital Heart Disease (CHD)[25]. The evaluation of the level of PA permits to detect the first symptoms of sedentary or the need to improve the functional capacity of the patient. Moreover, the PA level during the adolescence is correlated with the health status in adulthood, and it is inversely correlated to overweight and cardiovascular risks[25,160]. A systematic evaluation of PA level needs to be performed regularly in clinical routine. Valid instruments to assess the PA level are therefore essential to the clinicians to know the lifestyle of the patients.

The questionnaires offer a low cost approach to investigate the self-defined patient's participation in sports or other physical activities. Self-reported questionnaires also give information not available through objective measurements[161]. The *International Physical Activity Questionnaire* (IPAQ) is the most commonly used either in the general population or in disease[162]. However, specific questionnaires may be useful for the patients with chronic diseases. The *Physical Activity Questionnaire - Children/Adolescent* (PAQ-C and PAQ-A) was developed in English[163] and was validated to assess the PA levels in CHD children and adolescents[164]. The PAQ-C/A is self-recorded during 7-day to measure the moderate and vigorous physical activity levels during the school year, and has proven to be a low cost, reliable and valid tool to assess the physical activity level from childhood to adolescence[165]. Unfortunately, this specific questionnaire is not available in many languages. To date, no French version has been developed, although the French-speaking population around the world represent 40% (about 300 million

people) of the global worldwide population. Although it has been already validated for Dutch-speaking belgian children (living in Flanders, North of Belgium)[166], it was not done for those living in the French-speaking part of the country.

The aims of this study were to validate such French version of PAQ-C/A and to assess its validity, the internal consistency and the reliability of the test-retest in a specific population of children with CHD.

2. Methods

Sample

Children and adolescents aged between 6 and 18 years were randomly recruited from 3 different Belgian schools (province of Brabant Wallon) in November 2018. Children with chronic diseases (neuromuscular, neurologic, cardiac, respiratory and musculoskeletal), difficulties of understanding and non French speaker were excluded.

The institutional medical Ethics Committee of Catholic University of Louvain previously approved the study (2018/04JUL/274). Before any experiment, the subjects and their parents received a letter explaining the process of the study and signed the consent form. In addition, the aim of the test and its objectives were explained to the children and their parents.

Study design

This prospective study was based on the English speaking version of the PAQ-C/A[164].

- Translation

The method used to translate the questionnaire was based on the "Guidelines for the Process of Cross-Cultural Adaptation of Self-Report Measures"[167].

First of all, we performed a forward translation. Two independent translators translated the original questionnaire to French. The translators were native English speakers. After comparing the two translated versions, the differences in vocabulary were resolved by a third impartial bilingual translator. Secondly, a backward translation from French to the English was done by a fourth bilingual translator to ensure the accuracy of this French version[167]. A linguistic validation was done on 5 French-speaking children to ensure that the translated words have the same meaning as the original words and to avoid any confusion concerning the translated questionnaire. After processing these three steps, the French version of the PAQ-C/A (VfPAQ-C/A) was obtained.

- Validation procedure

Before completing both questionnaires (IPAQ and VfPAQ-C/A), the examiner emphasized that there were no right or wrong answers to favour response as honest and as precise as possible. The administration and scoring of PAQ-C/A and IPAQ are described elsewhere[162,165]. After the explanations and information given by the examiner, the participants completed the VfPAQ-C followed by the IPAQ. The questionnaire had to be completed within 20 minutes. To ensure that every child had a good understanding, the investigator read each question to the children between 6 and 8 year old.

The ten questions of VfPAQ-C and nine of VfPAQ-A (the question about recreation is not included for adolescents) were asked in order to collect information on participation in various types of activities and sport, effort during physical education at school, activity during lunch pause or after school, evening and weekend during the last 7 days. When the questionnaire was completed, each child or adolescent received a score. In the PAQ each item is scored between 1 (low physical activity level) and 5 (very high physical activity level) and the average score made it possible to have a final score[168]. For the IPAQ-short form score, each item was quantified by minutes per day or per week. Then, the final score (minutes/week) was calculated by adding each item and converted to METs at the end. From this result, the subjects were classified in low (no activity or some activity but not enough), moderate (3 or more days of vigorous activity during 20min or 5 days of combination moderate and low activity at least 30min per day or 5 or more days of low and moderate/vigorous activity 600 MET-min/week) or high level of PA (3 days of vigorous intensity accumulating at least 1500 MET-min/week or 7 days accumulating 3000 MET-min/week).

- Reliability procedure

One month after the first assessment, the same children and adolescents only responded to French version of PAQ-C and PAQ-A, respectively, in the same conditions than for the first evaluation.

Statistical Analysis

The statistical program SPSS 25.0 was used to perform all statistical analysis. The minimum sample size was previously calculated and set at 52.

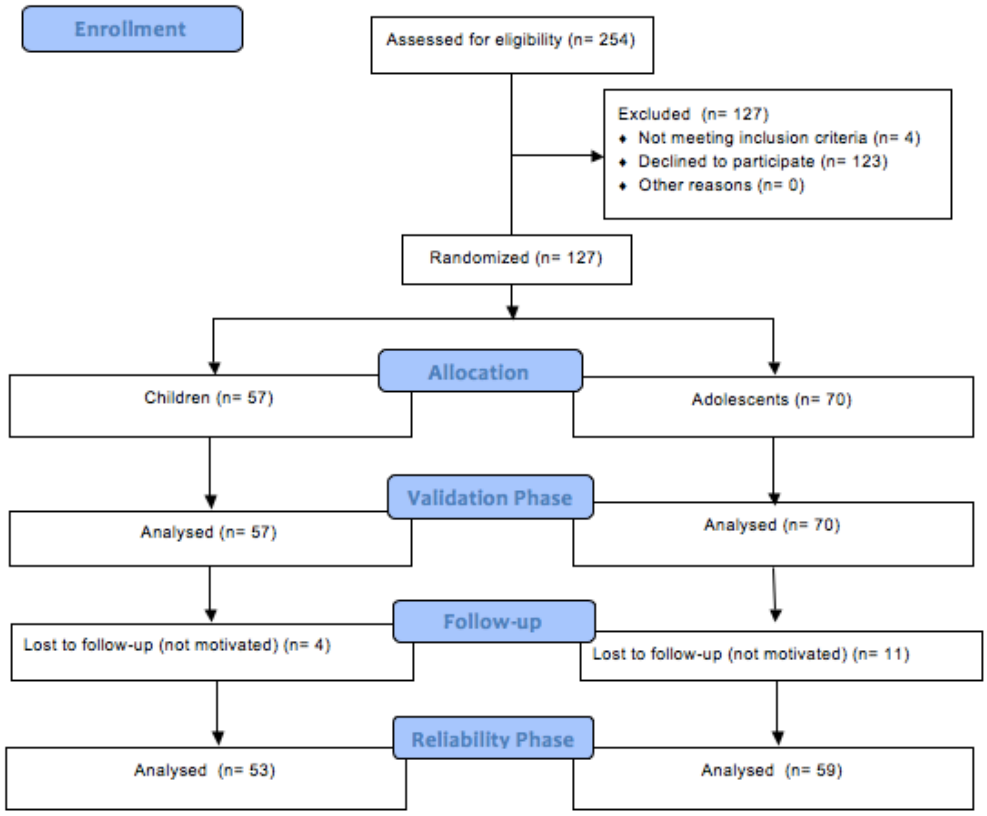
Descriptive statistics (mean ± SD) were calculated for each variable. The concurrent validity of VfPAQ was evaluated by the Spearman's correlation coefficient[10] (rho) interpreted as: weak for 0.1, moderate for 0.3, important for 0.5 and stronger closer to 1[167]. An analysis of variance (ANOVA) and Tukey post-hoc were used to compare the VfPAQ-C/A between the three categories obtained with IPAQ (level of PA).

The internal consistency was evaluated by the Cronbach's alpha coefficient[169] (α). Values greater than 0.70 were considered acceptable for general research purposes[161]. The reliability of the VfPAQ was verified by the intraclass correlation coefficient (ICC) (two-way random model) to determine the test-retest reliability. Values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively[170]. The relationship between items were analyzed by corrected item total correlations, which are the sum of all the final scores and correlations coefficients. This corrected item total correlations had to be over 0.20 to indicate a homogeneous scale[161]. A Bland & Altman method was used to determine the concordance of the total scores between the test and retest[138]. The significance level has been set at $p<0.05$.

3. Results

One hundred and twelve subjects were recruited : 53 children (9.1 ± 1.4 years) and 59 adolescents (14.7 ± 1.8 years) as shown in Figure 1. There were more girls than boys in both groups (54% in children, 57% in adolescents).

Figure 1: Consort flow diagram



The total VfPAQ score was 2.97 ± 0.60 and 2.66 ± 0.56 for children and adolescents, respectively. There were no difference between girls and boys (p= 0.051 in children and p= 0.350 in adolescents).

Concurrent validity and internal consistency

The correlation between the scores of VfPAQ-C and IPAQ was weak but significant (rho= 0.28; p< 0.05), and moderate and highly significant between scores of VfPAQ-A and IPAQ (rho= 0.50; p< 0.01). In post-hoc analysis of ANOVA, we observed a difference (p= 0.001) between VfPAQ scores depending on the level of PA measured by IPAQ in children and adolescents (Table 1).

Table 1: Correlation between the scores obtained by IPAQ and French version of PAQ-C and PAQ-A

	IPAQ PA level score (mean ± SD)			**p Value**
	Low	**Moderate**	**High**	
VfPAQ-C	2.76 ± 0.43	2.96 ± 0.58	3.18 ± 0.66	0.04*
VfPAQ-A	2.14 ± 0.66	2.37 ± 0.47	2.88 ± 0.47	0.001**

PA: physical activity
SD: standard deviation
p: p value corresponding to the comparison between total score from questionnaires
*: significant correlation p< 0.05
**: significant correlation p< 0.01

Internal consistency of the questionnaire was adequate for VfPAQ-C (α= 0.713) and VfPAQ-A (α= 0.755), as shown in Table 2 for each question (Q). For the VfPAQ-C the lowest α value was for the Q9 (α= 0.64). In VfPAQ-A, the lowest value was for the Q4 (0.70).

Table 2: Internal consistency and intraclass correlation coefficient in each item of the questionnaire in children and adolescents

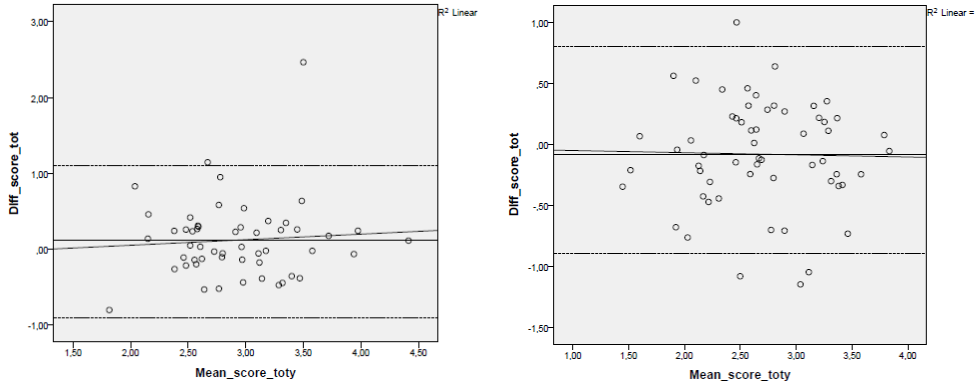
	Internal Consistency (α)		**Intraclass Correlation Coefficient (ICC)**	
	Children (n= 57) α	**Adolescent (n=70) α**	**Children (n= 53)**	**Adolescent (n=59)**
Item 1	0.715	0.759	0.399*	0.112
Item 2	0.685	0.751	0.509***	0.543**
Item 3	0.701	-	0.457*	-
Item 4	0.709	0.794	0.224	0.655***
Item 5	0.725	0.679	0.409*	0.806***
Item 6	0.672	0.713	0.503***	0.675***
Item 7	0.650	0.717	0.589***	0.649***
Item 8	0.682	0.698	0.640***	0.768***
Item 9	0.646	0.691	0.475**	0.806***
Total Score	0.713	0.755	0.749***	0.840***

*: significant correlation p< 0.05
**: significant correlation p< 0.01
***: significant correlation p< 0.001

Reliability

The reliability between the test and retest of the VfPAQ total score was good and significant in both groups (ICC= 0.75; p= 0.05 in VfPAQ-C, ICC= 0.84; p= 0.05 in VfPAQ-A). A good concordance between the scores for both questionnaires is shown Figure 2.

Figure 2: Bland and Altman for difference between both assessments (children on the left panel and adolescents on the right panel)



4. Discussion

This study verified the validity and reliability of the French version of the PAQ questionnaire in healthy French-speaking children and adolescents (VfPAQ-C/A). Our results showed a weak validity in children and moderate in adolescents, an adequate internal consistency and good reliability between the test and retest whatever the age category.

These results are comparable to other validation studies for this questionnaire carried out with Spanish children[171], Flemish children and adolescents[166], Chinese children[161] and Turkish children[172] as shown in Table 3.

Table 3: Comparison of results from validation studies for PAQ in healthy children and adolescents

	PAQ-C/A (Morales Mestre et al., 2020)	**PAQ-C (Kowalski et al., 1997)**	**PAQ-C (Benítez-Porres et al. 2016)**	**PAQ (Bervoets et al., 2014)**	**PAQ-C (Erdim et al., 2019)**	**PAQ-C (Wang et al., 2016)**
Validity (rho Sprearman, r Pearson)	PAQ-C: rho= 0.28; p< 0.05 PAQ-A: rho= 0.50; p< 0.01	rho between 0.28 and 0.57 p< 0.05 (n= 89)	rho= 0.23 p< 0.05 (n= 83)	rho= 0.52 p< 0.001	rho between 0.41 and 0.80 p< 0.01	r= 0.33 r= -0.18
Internal Consistency (Cronbach's α coefficient)	PAQ-C: α= 0.71 PAQ-A: α= 0.75	-	α= 0.76	PAQ-C: α= 0.77 (n=192) PAQ-A: α= 0.77	α= 0.77	α= 0.79
Test-retest reliability (Intraclass correlation coefficient, ICC)	PAQ-C: Good (ICC= 0.75) PAQ-A: Good (ICC= 0.84)	Moderate	Excellent (ICC= 0.96)	-	Excellent (ICC= 0.91)	Good (ICC= 0.88)

The validity of the VfPAQ-C/A was assessed by correlating the total score of this test with the results of the IPAQ[173] considered as the reference to assess the physical activity level[162] and related to the measurements obtained form a pedometer[173]. In our study, the correlation between the VfPAQ score and the IPAQ score was weak and significant for children (VfPAQ-C) but moderate and highly significant for the adolescents (VfPAQ-A). The concurrent validity of VfPAQ-C was poor but slightly better than in Spanish children[171]. However, it was lower than with the original PAQ-C version[164], as well as the versions for Chinese [161] and Turkish [172] and Flemish children[166](Table 3). In our population, the correlation of VfPAQ-C with IPAQ

was moderate (rho= 0.28) and similar to the other studies, however in the Flemish children it was higher (rho= 0.52)[166]. Our poor and moderate validity could be explained by the fact that IPAQ is not as well suited to children younger than 14 years than the older children[174]. In general, the self-report instruments in younger patients are difficult to complete due to the subjectivity and variable recall ability of young children[163].

Analyzing the internal consistency question by question, we observed that Q9 had little interdependence with the other questions in VfPAQ-C. For the VfPAQ-A, Q4 had little interdependence with the other questions. These Q4 and Q5 are two questions related to the physical education at school, recreation, and activities after school, evenings and weekend[165]. This fact could explain the internal consistency of this questions because depending on age, PA is done in various moments of the day. Indeed, PA during the evening (like in Q5) was less appropriate for the majority of children.

This questionnaire has already been validated before using an accelerometer in Chinese[161] and Spanish children[171]. Similary, IPAQ was also already validated with objective tools, such as a pedometers for Tunisian overweight and obese adolescents[160] and an accelerometer in the Spanish general population.

The reliability between test-retest was good for both questionnaires (ICC= 0.75, ICC= 0.85 in children and adolescents, respectively). These results are comparable to the initial version of the PAQ-C[164] but lower than the results achieved in Spanish[171] (ICC= 0.96), Chinese[161] (ICC= 0.88) and Turkish[172] (ICC= 0.91) pediatric population (Table 3). These differences could be explained by the difference in time between test and retest. Indeed,

participants completed the PAQ on the same day[171] or 7[161], 10[172] and 15[164] days later in other studies. The time between test and retest is clearly an important parameter to assess the reproducibility of the test. When the time between the two assessments is too short, the participant may be more likely to remember his first answers. Moreover, physical activity may changes overtime (even a week) in children and adolescents[175]. In this case, the reproducibility could be overestimated[167]. On the other hand, if the interval between the two assessments is too long, the participant's responses could be influenced by external factors[10] such as the occurrence of a rainy period, holidays or school deadlines. All these factors differently affected the estimation of test-retest reliability in the previous studies, depending on the test-retest interval. In our case, the second assessment corresponded to a pre-school exam period for the adolescents. Despite this element, the test-retest reliability was verified, although with greater difference than in previous studies.

Some limitation must be taken into account when analyzing the validity of the VfPAQ and IPAQ. The IPAQ can estimate the metabolic expenditure and the intensity of the activities. However, in young children it is difficult to have an accurate measure by self-report[176]. The PAQ evaluates the general physical activity, one of the strengths of this questionnaire[165]. The self-filling principle appeared unsuitable for younger children (6 and 7 years old, n= 10) due to their limited skills in reading and listening to instructions. This observation was also made for Flemish-speaking children[166]. The examiner also observed that social desirability was higher in young children (6 to 8 years old, n= 15).

5. Conclusion

Our study is the first to assess the validity and reliability of a French-speaking version of the PAQ-C and PAQ-A questionnaire with healthy children and adolescents (6 to 18 years).

As the validity is weak for children and moderate for adolescents, our finding indicates that it is possible to assess the PA level in adolescents with this self-reporting tool but further studies are required to determine what the VfPAQ-C truly evaluates. We suggest the use of this questionnaire as a complement to another objective tool to assess the PA level and investigate the self-feeling of children and adolescents during sport or other physical activities.

The VfPAQ-C/A questionnaire is easy, cost-effective and fast to apply. However, even if the French-speaking pediatric population may use this approach to quantify the physical activity, caution is necessary when studying younger children (6 to 8 tears).

Thesis discussion

Functional exercise capacity evaluation and lung function in congenital heart disease children have evolved over the years. The main aims of our work were to describe the specific tools available to assess the FEC and to describe the LF pattern in this specific population of patients. As we refined our work other objectives appeared, such as the validation of new tools to evaluate the FEC using the healthy children and the CHD adult population, known as grow-up congenital heart disease (GUCH) patients as references. On one hand, we validated specific tools to evaluate the FEC in CHD children, and on the other hand we showed the clear relationship between the FEC, the LF and the peak VO_2 in a pediatric cohort of paediatric patients with CHD.

First of all, one of the main observation that caught our attention during the elaboration of this manuscript was the evolution in the patient's profiles over the last 20 years[177]. Nowadays, the medical and surgical managements of CHD patients are indeed very different than 20 years ago. Until quite recently, the vast majority of CHD patients was strongly advised against practicing physical activity[27]. On the opposite, regular physical activity is now part of the holistic therapeutic approach of most congenital heart diseases[25,178]. Most cardiologists encourage patients to live a healthy lifestyle, in which physical activity has a fundamental role. Apart from medical treatments, the environment of these patients has also changed. The former overprotection by the parents was well documented as a source of sedentarity, obesity and psychosocial disorders. Although there is still room for improvement, overprotection is not the rule anymore, and does

not impact on the quality of life, previously shown to be lower than in healthy children[19,38]. In the general population, it is also well documented that the lack of physical activities leads to sedentary lifestyle[23]. Currently, sedentary behaviour is also becoming a problem in healthy children[179], and - as in children with chronic diseases - is clearly a risk factor when their outcome is evaluated in terms of morbidity and mortality[180].

In patients with congenital heart disease, where physiological and physical limitations are mainly caused by a cardiovascular impairment, a systematic FEC evaluation is essential. Currently, various tools are available to assess objectively or subjectively the FEC. One example of objective assessment, considered as the gold standard, is the cardiopulmonary exercise test (CPET) or other field tests used as surrogates, such as the 6-minute walk test (6MWT) or the 1-minute sit-to-stand test (STST).

Self-reported questionnaires such as PAQ or IPAQ are subjective tools available for the evaluation of PA.

Some guidelines were already published using some of the objective field tests such as the the flamingo balance test, the standing long jump test (lower-limb explosive strength) or the 40m sprint test (speed)[181]. However, these tests are not adapted for adult cardiac patients, and even less appropriate for the evaluation of CHD children. When using subjective tools like questionnaires, an important limitation derives from the linguistic barriers. For instance, we have found that some of these questionnaires were not even translated to French. We therefore proposed a french translation and validation in healthy children. For these reasons, we believed

that the development of appropriate evaluation tools was of vital importance to perform a representative evaluation of our paediatric patients. The tools needed to be adapted and validated before considering their use in research protocols.. Then, the evaluation of the FEC will allow to determine the physical status, the evolution and status of patients with heart diseases, healthy controls, or if physically deconditioned patients.

One parameter with a close relationship with the FEC is the LF[64], which has been studied for years[182]. As we have previously mentioned, children's profiles have drastically changed over the last decades, mostly because the medical and surgical management of their condition benefited for major advances. In our work, one of the first things we wanted to define was the LF pattern in CHD pediatric population. However, as shown in our systematic review, all the previous studies struggled with the heterogeneity of the reference values used to describe the LF. In 2012, the European Respiratory Society finally proposed a set of reference values for the main population, known as the Global Lung function Initiative, or GLI)[53]. These are currently the most recent normative data available. One remaining limitation of this reference values though, is that there is not reference values for young children because a valid testing is difficult to obtain under the age of 4-5 years. In our systematic review we analyzed all the studies published up to 2019. Theoretically, the studies from 2012 to 2019 should have used the 2012 GLI values as a reference. However, this was not the case and this was a bias when assessing the lung pattern among CHD children. However, observing our results we can conclude that vascular damage and the

different number of surgeries have an impact on their impaired LF. In our work, we showed that these children have a tendency towards the restrictive pattern. Lung damage had a direct impact on daily activities and, in general, on the FEC. One marker to know the FEC is the peakVO_2 as measured by a CPET, and well known to be decreased in CHD children compared to their healthy pairs[21].

In our systematic review, we wanted to evaluate the relationship between the LF, CHD severity and CPET[80]. Our hypothesis was that children with a more severe or complex heart disease had the most altered LF and therefore a lower FEC. To our surprise, the sickest children had a lower tolerance to effort (decrease peakVO_2) but LF was preserved in the vast majority of cases. We have previously reported that the LF in CHD children was altered and followed a restrictive pattern. However, in this study we observed that the LF is mostly within normal limits. This may be due to several factors such as the use of the 2012 GLI reference values, which prevent the comparison it with other studies based on other reference values such as Zapletal or Chang. This unexpected observation may also be due to the fact that the studied population was more active than the average. Indeed, in our pediatric cardiology unit most cardiologists encourage patients to practice sport and to have an active lifestyle. For these reasons we might think that LF is normal in our study group. It would be relevant to assess the same parameters in other countries, using GLI reference values.

Most children with CHD perform at least one CPET per year in order to evaluate their cardiopulmonary status, its evolution overtime, and their

overall physical condition. Many times the CPET cannot be done. In some hospitals, the equipment is not always available or it represents an expensive testing procedure that is not always acceptable to family's budget or in terms of Public Health. That is why field tests were developed as an alternative. One of the most widely used field tests is the 6MWT, already studied in both adults and children[31]. In adults, this test must always be performed twice because there is a training effect[32]. However, it was not clear if this training effect was also observed in healthy children, and if there was an encouragement effect influencing the distance walked by the patients. Interestingly, we observed that unlike in adults, there is no training effect in children, allowing clinicians and researchers to perform the test once. In addition we also observed that there was a stimulating effect, meaning that the more we stimulated the child with verbal encoragements, the better she/he performed in terms of walked distance[183]. This lead us to think that when this test is done on children, stimulation should be performed in a very consistent way (standardized protocol) between the tests, using always the same vocabulary, and with a previous training of the evaluator.

In adult population, there is a correlation between the walked distance during the 6MWT and the peakVO_2 as measured on the CPET[153]. This means that the 6MWT gives us a decent evaluation of the peakVO_2 without the need to do a classic CPET. This opened the door to introduce the 6MWT as an alternative to the CPET in a pediatric population. However, since the 6MWT required time and space were not always available during the clinic

visits, we decided to investigate how the STST could be used as a surrogate to the 6MWT. In adults, this has been validated and is still used to assess the lower body muscular strength and endurance[158]. This test was also reproducible and showed a high correlation with the 6MWT[158]. However, in healthy children it has not been studied yet, even less so in CHD children. When trying to validate this test in healthy children, we found that, to our surprise, the STST did not yield the same results than in adults. Indeed, we observed that with the STST there was no correlation between the walking distance using the 6MWT and the number of STST[33]. In other words, we cannot assess the FEC in children by the STST as done in adults. As there is a correlation between the 6MWT and the peakVO_2[153] we proposed a new algorithm to determine peakVO_2 with the STST, when the CPET is not available.

At this point, we know that the children with CHD have an altered LF with a restrictive pattern. They have a lower peakVO_2 compared to healthy pairs[21] of the same age. In order to accurately evaluate the FEC, the appropriate tools must be able to extract the information over the physical state of the child, but it is also important to know how the child experiences the effort. Since these children tend to have a decreased quality of life due to their chronic disease, we believe that this evaluation should be obtained with a multidisciplinary approach, which could follow the International Classification of Functioning, Disability and Health (ICF). Most children suffering a chronic disease like CHD have health issues and also multifactorial limitations to participate in several activities of daily life[38]. We

believe this multidisciplinary evaluation (physician, physiotherapist, psychologist,...) would be of great help to detect the various issues that have been raised in the literature over the last few years. In CHD children in particular, there may be a cardiac limitation and/or a pulmonary limitation. With the panel of tests currently available (such as CPET, field test, questionnaires and also LF assessment) we can define the child's profile and detect the main origin of her/his limitations. Of note, in many patients there is no physiological limitation but rather physical deconditioning due to a sedentary lifestyle. All these tests are therefore very useful in physiotherapy since they help us to not only determine the children physical state, but also how the disease affects their daily life. It is also useful to evaluate the evolution of the disease or the results of some interventions, such as surgical procedure or a physical activity program. In other chronic diseases such as Cystic Fibrosis, COPD or Bronchopulmonary Dysplasia[184], these tests have similarly been used before and after a physical activity program to objective its efficacy on the evolution of underlying disease. We believe that all physical activity programs should be done with a systematic pre- and post-evaluation of the FEC as well as a follow-up of the LF.

PERSPECTIVES

As mentioned in the discussion, FEC and LF assessments are essential and should be performed at least annually in most CHD children. Once we have assessed the patients' physical status (using objective or subjective tools), the lung function and self-regulation feelings, we believe that in many instances it would be very useful to propose some solutions to improve their limitations. For instance, some children have a significant physical deconditioning (low Peak VO_2) which affects their participation in sports and exercises, while cardiac rehabilitation programs lead to significant peak VO_2 improvements after participation for only a few weeks[20].

However, we do not want to focus only on structured exercise programs. As we mentioned earlier, we believe that it is crucial to improve the education of the healthcare workers and their multidisciplinary teams. The psychological aspect of children should also be included and it can help to improve the motivation to practice sports or physical activity. Another aspect to take into account is that cardiac rehabilitation programs may need some adaptations when applied to children compared to adults. Indeed, adults can perform cardiac rehabilitation for years, whereas this could not be compatible with the children lifestyle. In the pediatric population, cardiac rehabilitation can be seen as a useful way to reach the optimal functional exercise capacity (similar or equal to healthy pairs) and to be able to later participate in normal physical activities with other healthy children. In our opinion, a child could have more fun playing with his friends or practicing

the sports that she/he likes the most in contrast to other prescribed activities that the child would see as another therapeutic option. We also believe that the role of the parents is crucial and justifies including them in the program, as frequently done with the partner for older patients. As we already mentioned, overprotection of sick children may limit their normal participation in physical activities. On the contrary, parents who give self-confidence and serenity to their children will clearly facilitate the relationship between CHD children and their healthy pairs. In addition, most children with a chronic disease but can still live a so-called 'normal' life.

The ability to recognize a physiological or abnormal cardiorespiratory response to an effort is not so easy. When a child performs an exercise, the recognition of her/his typical physiological reactions (such as heart rate and blood pressure increases) is not always appropriate. Not being used to those feelings or not being able to recognize them as limiting factors can preclude a normal participation in various physical activities. Indeed, while this might seem straightforward for whom regularly practices physical activity, it is not necessarily obvious for a child who has never experienced it, especially when affected by a heart disease, with chronotropic or inotropic impairments. For this reason, physiotherapists must perform training sessions with the aim of guiding cardiac children towards the correct recognition of their cardiorespiratory adaptation to exercise. It is also important to train them to recognize a potential red flag during an effort, in order to stop it when necessary, for example when dizziness or chest pain is experienced by the patient.

In conclusion, we believe that a standardized cardiac rehabilitation program

for children should be similar but adapted to the pulmonary rehabilitation program proposed for COPD patients[185]. This model consists of a multidisciplinary approach, with the aim of giving autonomy and confidence to the patient, accompanying and encouraging him to participate in various physical activities, thereby promoting an active lifestyle.

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