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NEW APPLICATIONS OF CARDIOPULMONARY EXERCISE TESTING AND TRAINING IN PAEDIATRIC HEART DISEASE

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1. BACKGROUND
Congenital heart defects have a reported incidence of 4 to 8 per 1000 live births and encompass a broad spectrum of disorders. Exercise capacity is reduced across the spectrum of patients with congenital heart defects (CHD), both in natural history and after surgical and interventional treatment. Due to advances in cardiac surgery and cardiology care, most children born with CHD are now surviving into adulthood and there are currently more adults with congenital heart disease than children. Despite these advances, many young adults with CHD are at risk for premature death with heart failure being one of the leading causes of death. It is well recognised that exercise capacity is impaired across the broad spectrum of congenital heart lesions. This is clearly expected in complex anatomies that go down the univentricular palliation pathways but also milder lesions have been demonstrated to lead to exercise limitation.

Two percent of children with CHD have a single functioning ventricle. Single ventricle hearts comprise a heterogeneous group of defects which are not suited for a two ventricle repair. The Fontan procedure, originally described by Fontan and Baudet in 1971, has been a major contribution in improving the quality of life and survival of children and adolescents with cyanotic congenital heart disease who were limited in their physical activities and at high risk of premature death. The primary indication of this procedure was to palliate tricuspid atresia. The procedure was designed to deviate the venous return from the superior and inferior vena cavae through the pulmonary arteries, with the right atrium being used to propel the venous return through the lungs. Thus, partial restoration of the pulmonary blood flow was achieved, alleviating the mixed arterial and venous blood characteristic of this malformation. This was introduced to obtain normal oxygenation and to avoid volume overloading. Several modifications of the Fontan procedure have been developed to address the single functional ventricle in general. The ‘Fontan circulation’ procedure connects the systemic venous return to the pulmonary arteries without the interposition of an adequate ventricle and all shunts at the venous, atrial, ventricular and arterial level are interrupted. Patients with a Fontan circulation possess a unique physiological response to exercise. This procedure confers a significant survival benefit, relief of cyanosis and improvement of approximately 20% in exercise tolerance. In fact, patients have a 30% to 40% lower exercise tolerance than that of healthy, age-matched controls. Patients who have had a Fontan procedure constitute an heterogeneous group. Indeed, there are significant hemodynamic differences between the different Fontan procedures (for example, a classic Fontan procedure compared with an extracardiac Fontan procedure).
single left ventricle Fontan patient cannot be compared with a single right ventricle Fontan patient. Several limitations of the cardiorespiratory functions may explain this reduced exercise tolerance. Although the population of patients with a Fontan procedure is heterogeneous, they share similar physiological and metabolic adaptations during exercise.

Among the different screening tools employed during periodic follow-up, cardiopulmonary exercise testing (CPET) has emerged as one of the most valuable. It is non-invasive, enables risk stratification with regard to morbidity and mortality, and helps deciding on the need and timing of therapeutic interventions. Previous studies have suggested that exercise intolerance is a powerful prognostic marker in patients with CHD establishing an association between exercise intolerance and increased morbidity and mortality. More recently studies have shown the prognostic value of parameters of cardiopulmonary testing in patients with a systemic right ventricle or corrected Tetralogy of Fallot.

Reduced exercise capacity (peak oxygen uptake (VO$_2$)) can be related to abnormal cardiovascular haemodynamics during exercise (inappropriate increase in stroke volume or heart rate to exercise), abnormal perfusion of the exercising muscles, abnormal extraction of O$_2$ from the exercise muscles, and abnormal O$_2$ content (hypoxemia or anemia).

However, these variables alone often do not fully explain the exercise limitations found in this young population. Data collected in patients with heart failure from acquired cardiomyopathy (ischemic or dilated) suggest exercise limitation is often due also to a generalized myopathy. The cause of this myopathy is not well understood and is thought to be multifactorial. The myopathy can involve the peripheral skeletal muscles and the respiratory muscles, particularly the diaphragm, and can have an impact on aerobic capacity and on respiratory response to exercise.

In the last decade it has been recognized that adults with CHD suffer a heart failure syndrome which is identical to the one observed in patients with acquired heart disease. There is evidence that patients with CHD have reduced skeletal and respiratory muscle strength, as assessed by maximal inspiratory and expiratory pressures at rest and 10 minutes after maximal exercise. This evidence exists for patients with repaired tetralogy of Fallot, Fontan operation and Musterd/Senning operation. Furthermore it is noteworthy that CHD patients suffer from a life-long detraining as exercise limitations are often imposed since childhood independently of the pathology as a remnant of clinical and social fears.
Decreased skeletal and respiratory muscle strength is associated with poor outcomes in patients with heart failure and is a target for specific treatment with aerobic exercise and respiratory muscle training to improve functional capacity and quality of life. In recent years an effort has been made to understand to which extent the exercise intolerance observed in CHD patients is due to skeletal and respiratory muscle weakness and if exercise and respiratory training may help improving quality of life and survival.

2. AIMS
The aim of this project was to better understand exercise limitations and safety/usefulness of exercise training in young patients (children and young adults) with heart diseases across a broad spectrum of diagnosis and in particular we focused on left to right shunts, systemic right ventricular physiology, univentricular physiology with Fontan palliation and dilated cardiomyopathy.

Looking at future perspective we are currently exploring new ways of engaging teenagers with univentricular palliation in systemic and respiratory muscle training. Also, in collaboration with biomedical engineers we are modelling the univentricular circulation looking at outcomes on the basis of the anatomical shape and their haemodynamic repercussion on the cavopulmonary connection.

Similarities exist in the physiological changes observed during exercise and pregnancy and the final goal is to implement the model with these physiological variables to gain in depth understanding of this physiology and how we can achieve better clinical outcome in this growing population of young adults with complex lesions and limited exercise and child-bearing potential.

2.1 EXERCISE CAPACITY IN LEFT TO RIGHT SHUNTS
2.1.1 INTRODUCTION
A left-to-right shunt lesion exists when blood from the left atrium, left ventricle, or aorta transits to the right atrium or its tributaries, the right ventricle, or the pulmonary artery. In these conditions blood from the systemic arterial circulation mixes with systemic venous blood. The presence of a left-to-right shunt results in a volume overload of one or more cardiovascular chambers or structures. Multiple factors influence the extent of flow through the shunt and its physiologic effects. If the shunt is significant, blood flow and pressure in the pulmonary circulation become abnormally high. At the same time the amount of blood which reaches the systemic circulation (cardiac output) can be reduced, particularly during exercise. Over time, there is progressive damage to the pulmonary vasculature endothelium and gradual development of irreversible pulmonary vascular changes and pulmonary
hypertension. The resistance in the pulmonary circulation may ultimately exceed the systemic resistance with reversal of blood flow from the right side of the circulation to the left (Eisenmenger syndrome) evident as cyanosis either at rest or during exercise. Lesions resulting in left to right shunts include: (1) Atrial septal defect (ASD); (2) Ventricular septal defect (VSD); (3) Patent ductus arteriosus (PDA); (4) Large coronary artery fistulas. While wide consensus exists in the management of significant shunts, it is not always clear when and how it is time to intervene on smaller defects. We will review the evidence supporting a role of exercise testing in the assessment of children and adults with left-to-right shunt and the effect of abolishing left-to-right shunt on exercise.

2.1.2 ATRIAL SEPTAL DEFECTS
Atrial septal defects are the most common form of congenital heart defect and occur in 1 child in 1,500 live births. Of the various types classified in base of the anatomic location, ostium secundum ASDs represent 6% to 10% of all cardiac anomalies. In the setting of a large inter-atrial communication, a chronic left-to-right shunt creates a volume overload on the right-sided cardiac structures and results in dilation of the right atrium and right ventricle. The chronic volume overload causes dilation of the entire pulmonary vascular bed. Pulmonary blood flow is increased, often up to three to four times normal. However, the pulmonary artery pressure is only slightly increased, and in most patients, pulmonary resistance remains in the normal range.

Most infants and children with ASDs are asymptomatic. Rarely, ASDs are associated with poor growth, recurrent lower respiratory tract infection, and heart failure. Children with large left-to-right shunts are likely to complain of some fatigue and dyspnea. The natural course of ASDs is relatively benign except for those with persistent significant left-right shunt. Typically, patients with smaller ASDs remain active and asymptomatic through early childhood, and many patients have lived into their fourth, fifth, sixth, and even seventh decades with ASDs of moderate size before symptoms developed. Congestive heart failure rarely is found in the first decades of life, but it becomes more common with advancing age. The same can be said for the incidence of atrial arrhythmias with the associated risk of stroke and paradoxical embolism. In a few patients (5-10%) with a secundum ASD, severe and irreversible hypertensive pulmonary vascular disease may develop. As cardiac catheterisation used to performed as a diagnostic step in many patients with an ASD, indication on closure was predominantly based on haemodynamic data, particularly the extent of the ratio between pulmonary blood flow and systemic blood flow (Qp/Qs).

It is generally accepted that elective closure of ASD is the treatment of choice if
pulmonary-to-systemic blood flow ratio is >1.5. However, many children now do no undergo cardiac catheterisation as a diagnostic step and invasive criteria have been replaced by echocardiographic criteria. The main criteria for posing the indication to ASD closure is the presence of more than mild right heart dilatation or signs of increased right ventricular systolic pressure in the face of significant left-right shunt (which can also measured by echocardiography). Additional qualitative criteria are the presence of increased venous return from the pulmonary veins and dilatation of the main pulmonary artery. Elective surgical repair of ASDs has been a safe and simple operation in the hands of an experienced surgical team. It has been the first treatment of choice for children with large defects in the last 50 years and there is a large body of medical research covering long term results. Since most ASDs are well tolerated in infancy and may spontaneously close, elective repair frequently has been deferred until the child is at least 4 years of age.

Trans-catheter techniques for closure of ostium secundum ASDs have been available for several years. In 1976, King et al reported the first trans-catheter closure of a secundum ASD in humans with a double-umbrella device. The availability of non-surgical ASD closure has led to an increase in the number of the defects being closed[5] and has perhaps also lowered the bar for some defects to be considered for closure. Trans-catheter closure has the advantage of avoiding the need for sternotomy, cardiopulmonary bypass and intensive care stay and facilitates rapid patient recovery when the anatomy of the defect is suitable. However still nowadays younger patients or those with very large defects or small/absent defect margins require surgical closure.

2.1.2.1 EXERCISE TOLERANCE IN CHILDREN TREATED FOR ASD

Data are now available on long term follow-up of patients who underwent surgical ASD closure during childhood. Despite a clear improvement in the morbidity of these patients, there is still ongoing debate on whether children with ASD which undergo surgical closure can achieve the same life expectancy of healthy peers if treated timely. Cuypers et al recently published very long-term (30-41 years) outcome after surgical ASD closure in childhood and showed excellent survival and low morbidity. The general health and exercise capacity of the patients reported were comparable to the healthy Dutch population. They reported no pulmonary hypertension but persistent right ventricular dilation at magnetic resonance imaging despite a long follow-up from closure. In the recent study by de Koning et al, exercise testing did not reveal differences between patients who underwent surgical ASD closure in childhood and healthy reference population. In line with Cuypers et al they found right ventricular end-systolic volume remained increased in the long term after surgical closure without any impact on exercise capacity or onset of arrhythmias.
Only one study, by Massin et al, compared the outcome of children who underwent percutaneous ASD closure versus open surgery. The study showed no difference in peak VO$_2$ but underlined a higher prevalence of chronotropic incompetence in the surgical group, even though this didn’t affect overall exercise capacity $^{32}$. In this setting chronotropic incompetence is thought to be secondary to the effect of the cannulation used to establish cardiopulmonary bypass. Previous studies showed a significant reduction in exercise tolerance in children with ASD $^{33}$ and failed to show a significant improvement after trans-catheter closure $^{33,34}$. Reasons for that might be the fact that study cohorts were small and that the follow up was limited to 3 months, when research in young adults suggests that the process of normalisation of exercise capacity can take significantly longer than 3 months $^{35}$. No data is currently available on long term outcome of percutaneous closure in children.

2.1.2.2 EXERCISE TOLERANCE IN ADULT PATIENTS TREATED FOR ASD

At present ASDs accounts for up to 40% of congenital heart lesions detected in adults 40 years of age and older $^{36}$. Despite high pulmonary blood flow and right heart volume overload, patients with uncomplicated ASD often report only minor subjective complaints and do not recognise their reduced exercise tolerance. This is evident from the fact that several studies have shown reduced exercise capacity even in asymptomatic patients $^{37,38}$. Nakanishi and colleagues tested 18 adult ASD patients and found their peakVO$_2$ was impaired (21.6±5.6 mL/min/kg or 63.5±16.2% of predicted). They also observed that higher PAPm and higher Qp/Qs were related to lower exercise capacity $^{36}$. Oelberg et al tested 10 adults with ASD and compared them to 10 matched healthy controls. Their patients were found to have reduced exercise performance, which could be associated with an abnormal increase in pulmonary artery pressure during exercise $^{39}$. In the past when only surgical procedures were available, only large ASDs would be advised for closure because they were considered likely to result over time in shunt reversal or heart failure. Adults with significant ASDs are advised to undergo surgical repair before the onset of pulmonary hypertension in order to increase longevity and limit the deterioration of functional capacity. Once pulmonary hypertension develops, irreversible right ventricular failure may result. However, it can be difficult to detect early stages of pulmonary vascular damage when pulmonary arterial pressures and pulmonary vascular resistance are still normal at rest but they can rise, instead of physiologically decrease, during exertion $^{40}$. Surgical series have shown discordant results on functional status following surgical ASD closure in adult patients, giving rise to concerns on the appropriate timing of intervention and patients selection. Fredriksen et al. compared exercise capacity in adults with congenital heart disease with healthy subjects and found that even patients with closed ASDs did not do as
well as controls in the long term. However, Helber et al showed a lack of improvement in exercise capacity early after surgical ASD closure in patients over the age of 40 years, but they suggested that the improvement in exercise capacity took place later as demonstrated by the complete normalisation observed 10 years after shunt closure. They observed that the improvement in exercise tolerance didn’t correlate with the size of the shunt but it correlated inversely with mean pulmonary pressure before closure. Kobayashi et al reported a larger cohort and stratified patients on the basis of the size of the shunt and the degree of pulmonary arterial hypertension. No peak VO2 improvement was shown in the group of patients with PAPm>30 mmHg, while those patients with significant shunts and lower pulmonary artery pressure did improve their exercise capacity following closure. The importance of finding abnormal and possibly exercise-limiting elevations in pulmonary artery pressure during exercise in ASD might also be important in the decision making regarding the timing of surgical closure. Van de Bruaene et al demonstrated older patients who underwent closure later on in life had a good overall cardiopulmonary capacity but didn’t normalise pulmonary haemodynamics, which was shown by the lack of physiological decrease of pulmonary vascular resistance on exertion.

In recent years trans-catheter closure has become widely available and the results have proven to be at least as good as surgical closure in terms of mortality and functional capacity. Suchon et al compared the two techniques in an effort to demonstrate that, when dealing with favourable anatomy, percutaneous closure is a less costly option and guarantees the same results in the midterm. They demonstrated a low exercise capacity at baseline and a significant increase in oxygen uptake after both surgical and trans-catheter closure, as well as a significant decrease in minute ventilation/CO2 dioxide output. Their patients improved significantly their exercise capacity, irrespective of the actual method of closure, but patients with elevated right ventricular systolic pressures failed to normalise their peak VO2. Brochu et al assessed the effect of percutaneous ASD closure in 37 asymptomatic or mildly symptomatic adults showing a significant and rapid improvement of exercise capacity and regression of right ventricular dilatation at 6 months. The improvement in exercise capacity was irrespective of age, functional class, right ventricular enlargement, or baseline exercise capacity. Jategaonkar et al reported a significant decrease in right ventricular end-diastolic diameter and significant improvements of NYHA functional class and peak VO2 at 3 months from ASD device closure in all age groups, even in patients over 60 years old. However, little is known about long-term results in those patients. Our group evaluated the impact of trans-catheter ASD closure on right ventricular remodelling and exercise
capacity in asymptomatic adult patients with the aim of identifying the factors associated with a change in exercise capacity. We demonstrated that the improvement in peak VO$_2$ is due to an improvement in peak O$_2$ pulse. We also demonstrated that an increase in both left ventricular stroke volume and cardiac output due to a positive ventricular interaction is the mechanism leading to increased peak O$_2$ pulse and peak VO$_2$ \textsuperscript{37}. We also demonstrated that the improvement is not limited to the 6 months period as a further cardiac remodelling and improvement in exercise capacity can be expected in the midterm\textsuperscript{35,37}. Another observation from our group is that device ASD closure can quicken the time taken to recover from maximal exercise, which might also have positive implications for patients.

2.1.3 VENTRICULAR SEPTAL DEFECTS

Ventricular septal defects account for approximately a third of the congenital cardiac defects diagnosed at birth. The magnitude of the left-to-right shunt is related directly to the size of the defect and pulmonary vascular resistance. Small VSDs are those less than one third the size of the aortic root and which impose a high resistance to flow with a resultant large pressure drop between the left and the right ventricle. In this case, the left-to-right shunt is small, right ventricular systolic pressure is normal, and there is no tendency for an increase in pulmonary vascular resistance. With large VSDs, a gradual decline of pulmonary vascular resistance usually occurs in the first few months of life, resulting in augmentation of the left-to-right shunt. The large blood volume handled by the left atrium results in left atrial and pulmonary venous hypertension. The increased return to the left side of the heart results in an enlarged left atrium and left ventricle as well as an increase in the left ventricular muscle mass. With the marked volume overload of the left ventricle, congestive heart failure is particularly likely to occur between the ages of 2 and 8 weeks. Compensatory mechanisms that allow the infant to adapt to this volume load include the Frank Starling effect, increased sympathetic cardiac stimulation, and myocardial hypertrophy. The rapidity of the development of myocardial hypertrophy is one of the major factors in the ability of an infant to compensate adequately for a VSD with a large left-to-right shunt. Excessive and high pressure pulmonary blood flow is associated with progressive pulmonary arterial vessel injury. Chronic injury associated with a large un-repaired VSD can result in a thickened adventitia, medial hypertrophy, and intimal injury resulting in pulmonary vascular obstrctive disease \textsuperscript{25}. Therefore, large VSDs with left-to-right shunt should undergo surgical repair within 1 year of age to prevent pulmonary vascular changes. Smaller defects can be followed up in time and a considerable portion is found to decrease in size and eventually spontaneously close \textsuperscript{46,47}. The long term outcome of this latter group
seems benign. When children with surgically closed VSDs or those with haemodynamically insignificant defects have undergone ECG exercise testing results have generally showed normal exercise capacity. A small number of studies concentrated on cardiopulmonary exercise testing in patients with VSDs. Binkhorst et al. showed no difference in peak VO2 in patients after surgical VSD closure, small VSDs left untreated and healthy controls. Perrault et al. compared a small cohort of repaired VSD patients to patients with repaired tetralogy of Fallot, patients with repaired ASD and healthy controls and found peak VO2 values were within the normal range in patients with closed VSDs. In both the previously mentioned studies, peak heart rate was found to be lower in surgical treated VSD patients, which is consistent with previous evidence of chronotropic limitations after cardiopulmonary bypass surgery in different types of congenital cardiac defects. Moller et al. described 44 patients (17 surgically closed ASD, 11 surgically closed VSD, 16 restrictive VSD considered haemodynamically not significant and thus left open) who underwent cardiopulmonary exercise testing and exercise echocardiography. They found reduced exercise capacity in all patients groups when compared to a control group comprising 88 healthy subjects. The authors observed an abnormal right ventricular systolic pressure response to exercise even in those patients who did not have any signs of increased pulmonary artery pressure at rest before closure. This finding was confined to VSD patients alone, either closed (5/11 patients) or open (4/16 patients), whereas no ASD patients showed increased pulmonary pressure during exercise.
### Table 1: Studies testing cardiopulmonary capacity in children with ASDs.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age at closure (years)</th>
<th>QpQs</th>
<th>PAPm (mmHg)</th>
<th>RVSP (mmHg)</th>
<th>Age at CPET (years)</th>
<th>Fup CPET</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuyyem [2] 2011</td>
<td>63</td>
<td>-</td>
<td>S</td>
<td>7.5±3.5</td>
<td>2.3</td>
<td>-</td>
<td>43±3.8</td>
<td>35±2.7</td>
</tr>
<tr>
<td>deKeunen [3] 2013</td>
<td>38</td>
<td>-</td>
<td>S</td>
<td>4.6±2.8</td>
<td>-</td>
<td>-</td>
<td>16±2.9</td>
<td>38±7.7</td>
</tr>
<tr>
<td>Massin [4] 2009</td>
<td>20</td>
<td>-</td>
<td>S</td>
<td>7.8±2.8</td>
<td>2.8±0.5</td>
<td>-</td>
<td>2.9±2.7</td>
<td>-</td>
</tr>
<tr>
<td>Rhodes [5] 2012</td>
<td>9</td>
<td>-</td>
<td>P</td>
<td>8.3±2.8</td>
<td>2.6±0.4</td>
<td>-</td>
<td>2.6±2.4</td>
<td>-</td>
</tr>
<tr>
<td>Pianameter [7] 2002</td>
<td>15</td>
<td>4.3 (3.0-9.2)</td>
<td>C</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>VO: within the normal range.</td>
</tr>
</tbody>
</table>

Legend: pts: patients; VO: oxygen consumption; group: kind of treatment; QpQs: pulmonary flow/systemic flow; PAPm: mean pulmonary arterial pressure; RVSP: right ventricle systolic pressure; CPET: cardiopulmonary exercise test. * 63 pts underwent CPET of the 332 pts cohort described. * 38 pts underwent CPET of the 96 pts cohort described. ** 24 pts underwent CPET of the 59 pts cohort described.

### Table 2: Studies testing cardiopulmonary capacity in adults with ASDs.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age at closure (years)</th>
<th>QpQs</th>
<th>PAPm (mmHg)</th>
<th>RVSP (mmHg)</th>
<th>Age at CPET (years)</th>
<th>Fup CPET</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helber [9] 1997</td>
<td>31</td>
<td>13.1</td>
<td>S</td>
<td>9.9±11.5</td>
<td>2.8±1.2</td>
<td>18.9±6.2</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>Kobayashi [10] 1997</td>
<td>28</td>
<td>27±6±5</td>
<td>S</td>
<td>42.3±5.9</td>
<td>2.5±0.4</td>
<td>26±8.6</td>
<td>-</td>
<td>3.7±1.4</td>
</tr>
<tr>
<td>Kobayashi [11] 1997</td>
<td>28</td>
<td>19±3.5</td>
<td>S</td>
<td>47±9±5</td>
<td>3.9±1.8</td>
<td>35±9±1</td>
<td>-</td>
<td>4.4±2.0</td>
</tr>
<tr>
<td>Nishimura [12] 1999</td>
<td>20</td>
<td>17±6.3</td>
<td>S</td>
<td>46±7.2</td>
<td>1.7±0.4</td>
<td>74±8±4</td>
<td>5.6±2.4</td>
<td>17±4.2</td>
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<tr>
<td>Suehokai [13] 2002</td>
<td>17</td>
<td>43±10.9</td>
<td>0±11.0</td>
<td>2.6±0.7</td>
<td>-</td>
<td>36±7±1</td>
<td>1</td>
<td>29±7.1</td>
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<tr>
<td>Van Vianen [14] 2002</td>
<td>18</td>
<td>26±7±16</td>
<td>7±11.9</td>
<td>P</td>
<td>39±11.9</td>
<td>1.6±0.9</td>
<td>25±1.7</td>
<td>39±11.9</td>
</tr>
<tr>
<td>Brochu [15] 2003</td>
<td>37</td>
<td>23±6±4</td>
<td>1±6</td>
<td>P</td>
<td>49±19.7</td>
<td>2.1±3.4</td>
<td>5</td>
<td>26±6.9</td>
</tr>
<tr>
<td>Fukaya [16] 2003</td>
<td>120</td>
<td>15±6±5</td>
<td>3±6±6</td>
<td>P</td>
<td>54±10.9</td>
<td>2±6±6</td>
<td>1</td>
<td>17±8.5</td>
</tr>
<tr>
<td>Jangzonquee 2010 [17]</td>
<td>54</td>
<td>20±5.6</td>
<td>P</td>
<td>28±7.2</td>
<td>49±11.9</td>
<td>5.6±8.6</td>
<td>3</td>
<td>27±7.2</td>
</tr>
<tr>
<td>Jangzonquee [18] 2010</td>
<td>47</td>
<td>16±8.3</td>
<td>P</td>
<td>70±35.4</td>
<td>69±12.9</td>
<td>25±7.5</td>
<td>3</td>
<td>17±5.5</td>
</tr>
<tr>
<td>Jangzonquee 2010 [19]</td>
<td>35</td>
<td>17±5.5</td>
<td>P</td>
<td>69±3.8</td>
<td>68±2.6</td>
<td>-</td>
<td>33±6±2</td>
<td>18±8.5</td>
</tr>
<tr>
<td>Lange [20] 2010</td>
<td>24</td>
<td>23±6±2</td>
<td>P</td>
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<td>-</td>
<td>24±5</td>
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<td>12</td>
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<td>P</td>
<td>42±14.7</td>
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<td>6</td>
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<td>P</td>
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<td>52±11.2</td>
<td>2±4±5</td>
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<td>No closure</td>
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<td>2±4±5</td>
<td>-</td>
<td>-</td>
<td>31±8</td>
</tr>
</tbody>
</table>

Legend: pts: patients; VO: oxygen consumption; group: kind of treatment; QpQs: pulmonary flow/systemic flow; PAPm: mean pulmonary arterial pressure; RVSP: right ventricle systolic pressure; CPET: cardiopulmonary exercise test. * 93 pts underwent CPET of the 136 pts cohort described. * 38 pts underwent CPET of the 96 pts cohort described. ** 24 pts underwent CPET of the 59 pts cohort described.
2.2 EXERCISE TRAINING IN SYSTEMIC RIGHT VENTRICLE

2.2.1 INTRODUCTION
The estimated prevalence of congenital heart disease (CHD) is 3 per1000 live births, and the number of these patients that survive until adulthood is steadily increasing. A substantial portion of these patients has a morphological right ventricle that sustains the systemic circulation, for instance patients with a transposition of the great arteries (TGA) after a Mustard or Senning operation, and patients with a congenitally corrected transposition of the great arteries (ccTGA). The large majority of adult patients with a systemic right ventricle is faced with deteriorating right ventricular function, and decreased exercise capacity. In patients with acquired congestive heart failure the European Society of Cardiology recommends patient's participation in a multidisciplinary care program, which includes exercise training, to reduce the risk of heart failure hospitalization. A study by O'Connor et al. showed an 11% reduction in all-cause mortality or all-cause hospitalization at 30 months of follow-up of a 3 month supervised training program, followed by a home-based training program. In our own study, ten weeks of exercise training improved exercise capacity in patients with a systemic right ventricle. In patients with acquired heart disease beneficial effects of exercise training are known to diminish as time from the training program progresses. However, it remains unclear whether the effects of exercise training in adult patients with a systemic right ventricle is only temporary or whether it constitutes a permanent effect, possibly due to lifestyle changes. Therefore, the primary objective of this study is to determine the long-term effects of a ten-week exercise training program in adult patients with a systemic right ventricle.
2.2.2 METHODS

Study design
The present study was a one-time cross-sectional re-evaluation at three years follow up of participants of the 2009 study “The effect of exercise in adult patients with a systemic right ventricle” (http://trialregister.nl id. NTR1909) 58.

Participants
All patients who participated in the 2009 study were eligible. These were adults with a systemic right ventricle due to congenitally or surgically corrected TGA. Patients who were mentally or physically incapable to participate in a home-based exercise program had been excluded, as were patients with experienced exercise-induced arrhythmia, symptomatic myocardial ischemia, a resting systolic blood pressure ≥200 mm Hg and/or diastolic blood pressure ≥110 mm Hg, New York Heart Association (NYHA) class III or IV, pregnancy during the training period, and non-cardiac co-morbidity that could affect exercise performance or that could aggravate by exercise.

Study settings
The study was conducted in the Netherlands (three sites) and Italy (one site). The study complies with the Declaration of Helsinki and was approved by the locally appointed Ethics Committee of all participating centers. Renewed informed consent was obtained from all participants prior to participation in the present re-evaluation.

Interventions
In 2009 consenting patients were randomized using unmarked opaque envelopes to an intervention group with three aerobics step training sessions per week for 10 consecutive weeks, and a control group. The detailed exercise training protocol has been published previously 58.

Sports participation
Patients were asked to indicate 1) whether they currently participated in sports or physical exercise, 2) how many times they participated in sports or exercise and 3) with what intensity (light, medium, heavy). The answers were compared to the data of the original trial. Patients who participated in sports or those who exercised at least 1 weekly in an activity that scored 5 METS or more according to the Compendium of Physical Activities 60, were considered to be active in sports, while patients who scored below this threshold were not considered active in sports or exercise.

Outcomes
  
  Cardiopulmonary exercise testing
Exercise testing was performed on an upright bicycle ergometer. After an initial calibration period of 2 min, workload was increased by 5–15 W/min in a stepwise
manner. The exercise protocol was identical to the tests performed in 2009. Breath-by-breath analysis of minute ventilation, oxygen uptake (VO$_2$), carbon dioxide elimination (VCO$_2$), heart rate, blood pressure and electrocardiography was made.

Serum N-terminal pro-hormone of brain natriuretic peptide
Samples were analyzed locally and in a standardized fashion. N-terminal prohormone brain natriuretic peptide assessment kits differed between participating centers, although the same kit was used for the same patient.

Quality of life
Health-related quality of life was assessed by means of the Dutch and Italian translations of the Medical Outcomes Study Short Form 36 item(SF-36) health survey. The SF-36 is a generic multi-item questionnaire comprising of 36 questions on eight domains (physical functioning, role functioning physical, bodily pain, general health perception, vitality, social functioning, role functioning emotional, and mental health). Scores range from 0 to 100, with higher scores representing better quality of life. Patients' SF-36 scores were analyzed in comparison to published age- and gender-matched reference population norms, after which the eight domains were combined into two higher ordered clusters; the physical component summary and the mental component summary. In addition, the quality of life was assessed by means of the Dutch and Italian translations of the CHD-TNO/AZL Adult Quality of Life (CHD-TAAQOL) questionnaire. The CHD-TAAQOL was developed as a disease specific tool for measuring health-related quality of life in adults with congenital heart defects. Scores were transformed to a 0–100 scale, with higher scores representing better quality of life.

Statistical analysis
Data are expressed as numbers with percentage, as mean with standard deviation, or median with interquartile range (IQR) as appropriate. Analysis was intention-to-treat. Chi-square and Students independent t-test were performed to evaluate whether the re-recruitment process might have imbalanced the study groups, the original grouping being the result of randomization. Changes from baseline in each group were evaluated using a two-tailed paired t-test or Wilcoxon matched pairs signed ranks test where appropriate. Significance and size of the treatment effect (intervention vs control) were determined by analysis of covariance. The analysis was adjusted for baseline values and participating center (to account for stratification). In addition, a sensitivity analysis including only those patients who completed the protocol in both 2009 and 2013 was performed. A 2-tailed p-value of <0.05 was used as a criterion for statistical significance. An exploratory multivariate analysis of covariance was performed to assess whether any determinants at baseline were associated with exercise capacity at follow-up.
Moreover, a composite endpoint of clinical events was defined similar to a previous publication \(^6^1\). This included any arrhythmia, reoperation, thromboembolism, myocardial infarction, worsening heart failure, and death. Event-free survival was estimated using all available data (including chart review of non-participating patients). In patients with multiple events only the first event was used in survival analysis. Differences in the occurrence of complications were assessed using a log rank test.

2.2.3 RESULTS

Recruitment

Between January and September 2013 all but 2 (one could not be reached, one had died) of the original 54 participants were contacted by telephone. Of the remaining 52 original study entrants who were contacted 12 did not consent to the full cardiopulmonary exercise test protocol (the primary outcome), citing no time and the distance to their tertiary referral center as the main reason. Of these 12 patients, 3 participated partly by filling out the quality of life questionnaires only. Consequently, 40 patients completed the full cardiopulmonary exercise test protocol. Of these 40 participants, 4 patients had not completed the full protocol in 2009. Consequently, 22 patients who were originally assigned to the intervention group and 18 patients who were assigned to the control group were analyzed in the assessment of the primary endpoint. There were no differences in baseline parameters (age, Peak VO\(_2\), NT proBNP, medication, NYHA class) or event-rate between the 40 participants of the current follow-up study and the 14 non-participants. In 50 of the original 54 participants medical charts with complete follow-up were available leaving 50 patients for survival analysis.

Baseline data

Table 1 outlines the baseline characteristics of all patients who participated in the follow-up analysis. The study groups were reasonably well balanced at the present re-evaluation, although patients with Senning operation were overrepresented in the intervention group, without reaching statistical significance.
Outcomes and estimations

Cardiopulmonary exercise testing

In the overall group (n=40), Peak VO\textsubscript{2} showed no significant change from baseline to three years of follow-up (\(-0.7\) ml/kg/min 95% CI \(-2.6\) ml/kg/min to 1.1 ml/kg/min, \(p=.43\)), nor were there significant changes in the two treatment groups (intervention \(-0.1\) ml/kg/min 95%, CI \(-2.7\) ml/kg/min to 2.8 ml/kg/min, \(p=.96\); control \(-1.6\) ml/kg/min, 95% CI \(-4.2\) ml/kg/min to 0.9 ml/kg/min, \(p=.18\)). At three year follow-up, there were no differences in change in cardiopulmonary or hemodynamic parameters between the intervention and control groups (Table 2). A sensitivity analysis that included only patients who completed in the protocol in both 2009 and 2013 (control n=15, intervention n = 21) yielded similar results (Peak VO\textsubscript{2} 1.8 mg/kg/min (\(-1.8\) mg/kg/min to 5.5 mg/kg/min, \(p=.311\)).

Sports habits

Patients in the intervention group were not more likely to change their exercise habits than patients in the control group (increase in habitual exercise: intervention 37% vs controls 24%, \(p=.38\)).

Serum N-terminal pro-hormone of brain natriuretic peptide

There was no significant change from baseline in NT-proBNP. Moreover, at three year follow-up there was no effect of the ten week exercise program on serum NT-proBNP (Table 2).

Quality of life

As can be seen in Table 2, no effect of the ten week exercise program on the quality of life-scores remained at three year follow-up.
Ancillary analysis

An exploratory univariate analysis of baseline characteristics yielded an association between change in exercise capacity and the use of β-blockers, RAAS inhibitors, and participation in sports. In multivariate analysis, RAAS inhibitors and sports participation remained independent predictors of change in exercise capacity at follow-up (Table 3).

When compared to patients who did not exercise regularly (no sports group), patients who habitually exercised (sports group) had higher Peak VO\textsubscript{2}, although this effect was no longer significant when corrected for age and sex (Peak VO\textsubscript{2} as percentage of predicted, Tables 4 and 5).
Sports participation at baseline was associated with an increase of 13% (95% CI 4% to 23%) of predicted Peak VO₂ and a decrease of 62% (95% CI −115% to 10%) in NT-proBNP, when compared to patients who did not exercise (Table 5 and Fig. 2).
During follow-up 22 clinical events occurred in 13 patients (11 supraventricular arrhythmias, 4 episodes of worsening heart failure, 6 reoperations, 1 pulmonary embolism, 1 non-sustained VT and 1 sudden cardiac death). Whereas the 10-week exercise program had no effect on the occurrence of clinical events, patients in the sports group had better event-free survival than patients in the no-sports group (Fig. 3).
2.3 EXERCISE CAPACITY IN CYANOTIC CONGENITAL HEART DISEASE
Predicting survival of patients with cyanotic congenital heart disease: The value of cardiopulmonary exercise testing. Results from an international multicentre study.

2.3.1 INTRODUCTION
Patients with cyanotic congenital heart disease (CHD) are at risk of increased mortality. Few predictors of adverse outcome exist. Cardiopulmonary exercise testing (CPET) has been established as a prognostic tool in CHD patients – in general, but the value in cyanotic patients remains unclear. We analyzed the prognostic value of CPET in a large cohort of cyanotic patients.

2.3.2 METHODS
Cyanotic patients who underwent CPX at five major centres were included. Cyanosis was defined as oxygen saturation <90% during exercise or at rest. Cox proportional-hazards analyses were performed to identify predictors of all cause mortality.

2.3.3 RESULTS
582 patients were included (52% males, age 27.3±14.2 years, 39% cyanosis at rest). During a follow-up of 4.6 years, 69 patients died. Univariate predictors were older age (HR 1.25, p=0.003), NYHA-class >1 (HR 4.0, p=0.0002), lower peak VO₂ (HR 0.90, p<0.0001), lower anaerobic threshold (HR 0.90, p=0.0005), higher VE/VCO₂ slope (HR 1.02, p<0.0001), lower resting O₂-saturation (HR 0.95, p<0.0001), lower heart rate increase during exercise (HR 0.84 /10 bpm, p<0.0001), and lower O₂-saturation during exercise (HR 0.97, p=0.0001). On multivariable analysis, peak VO₂ was the only significant predictor (HR 0.88, p<0.0001). The figure below shows survival by quartiles of peak VO₂. In patients with resting cyanosis, lower peak VO₂ (HR 0.92, p=0.002), higher VE/VCO₂-slope (HR 1.02, p=0.01), lower anaerobic threshold (HR 0.90, p=0.02) and lower heart rate increase (HR 0.82 /10 bpm, p=0.001) were predictive. On multivariable analysis lower peak VO₂ was the only predictor.
2.4 EXERCISE CAPACITY IN UNIVENTRICULAR PHYSIOLOGY

Children born with a single ventricle represent 2% of patients with congenital heart disease. Single ventricle hearts comprise a heterogeneous group of defects which are not suited for a two ventricle repair. Since 1971 they have been palliated with a Fontan operation and subsequent modifications. Patients with a total cavo-pulmonary connection can nowadays look forward to significantly improved life expectancy, exercise tolerance and quality of life, still they face impaired physical capacity and increased mortality compared to their peers.

Previous studies suggested that exercise intolerance is a powerful prognostic marker in patients with CHD establishing an association between exercise intolerance and increased morbidity and mortality. Among the different screening tools employed during periodic follow-up, cardiopulmonary exercise testing (CPET) has emerged as one of the most valuable. It is non-invasive, enables risk stratification with regard to morbidity and mortality, and helps deciding on the need and timing of therapeutic interventions. Patients with a Fontan circulation exhibit a
novel and unique artificial physiology both at rest and on exertion, which is considered responsible for the 30% to 40% lower exercise tolerance than that of healthy, age-matched controls. A number of different exercise test parameters have been used to try and predict outcome or to better evaluate exercise capacity in this population. It can be difficult to obtain maximal exercise levels, both for intrinsic physiological reasons and the specific population young age, which often prevents them to be fully cooperating. For this reason some groups concentrated their work on submaximal parameters, nonetheless some that proved useful in adult populations with acquired cardiac disease are not reliable for evaluation in the Fontan circulation. Of particular concern is that exercise capacity seems to further lower during follow-up.

2.4.1 EXERCISE CAPACITY IN UNIVENTRICULAR PALLIATION: METAREGRESSION OF PREVIOUS STUDIES

2.4.1.1 SEARCH STRATEGY
A literature search on the Medline database covering from 1971 to January 2014 was performed. Search terms used were “Fontan” OR “univentricular heart” AND “exercise” OR “exercise testing” OR “exercise capacity” OR “exercise tolerance” (349 papers). The search was performed by one of the authors. The abstracts of relevant articles were screened on the basis of the following criteria: the study population or part of the study population had to have a Fontan circulation and exercise testing had to be a CPET (cycloergometry or treadmill test with gas exchange evaluation). If data reported in the abstract met the inclusion criteria, the full-text paper was studied. References of the selected publications were tracked to find additional publications on this subject.

To be included in our analysis publications had to include a description of the patients characteristics (at least mean age at CPET and gender) and exercise stress test variables (VO$_2$ max in mL/min/kg or percent of predicted VO$_2$ max value for age and sex). Where feasible we asked the authors for missing data. This left us with 123 papers that matched our criteria. When more than one paper was reported from the same exercise laboratory we chose either the latest or the largest which satisfied the criteria. Exceptions were made when different papers from the same center described patients that were not included in the previously reported cohorts. We excluded from our analysis cohort consisting of 10 patients or less. A flow-chart of the search strategy and result is shown in figure 1.
Figure 1. Flowchart of the search strategy

2.4.1.2 RESULTS
We considered for our meta-regression analysis a total of 39 papers shown in table 170-108.
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<th>Pulse (bpm)</th>
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<th>Temperature (°C)</th>
<th>Temperature (°F)</th>
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Table 1. Type of exercise: C: cycloergometer; T: treadmill. RER: respiratory exchange ratio (if mentioned in the paper). Diagnosis: All: mixed diagnosis; LV: univentricular heart with left morphology; RV: univentricular heart with right morphology; TA: tricuspid atresia. TCPC: total cavopulmonary connection. ECC: extracardiac conduit. Fen: patent fenestration at time of CPET (if mentioned in the paper or provided by the author). peak VO$_2$%: percent of predicted VO$_2$. HR: heart rate. WL: workload. HRR: heart rate reserve (peak HR-rest HR). VE/VCO$_2$: ventilatory equivalent for carbon dioxide; *:slope; °: ratio.

Our analysis considered a total of 2247 patients, data come from a broad time window and this gives reason for the different surgical approach (classic Fontan, intra-atrial tunnel, extracardiac conduit) and age at final palliation. Meta-regression analysis was performed on VO$_2$ max in mL/min/kg or percent of predicted VO$_2$ max value for age and sex or both depending an data provided by the authors and results are shown in the figure below.

![Graph showing peak VO$_2$ vs age at test](image)

It is clearly shown that peak VO$_2$, either considering absolute and percent of predicted values, declines with age. This is consistent with what Anderson et al. $^{109}$ and Fernandes et al. $^{110}$ previously reported in smaller cohorts. In the vast population considered this trend is well-rendered despite surgical techniques improvements over the last three decades.
2.4.2 ANALYSIS OF EXERCISE TOLERANCE IN A LARGE FONTAN POPULATION

2.4.2.1 METHODS

Data for analyses described here were obtained from the two largest databases on exercise tolerance in patients with a Fontan circulation. The NIH/NHLBI Pediatric Heart Network Fontan Cross-Sectional Study dataset was used in preparation of this work together with the dataset of patients analysed by Diller and colleagues. Data were downloaded from https://pediatricheartnetwork.com/pud_login.asp?study_id=FSCD. Subjects in this study were survivors of multistage surgical palliation for functional single ventricle ending with a Fontan procedure. Periodic exercise testing is standard for Fontan patients capable of performing CPET at the institutions involved.

Cardiopulmonary exercise test

Exercise tests were performed on an electronically braked cycloergometer or on a treadmill. Carbon dioxide elimination, VO$_2$, and minute ventilation were measured with a computerized breath-by-breath analyser. Patients performed a symptom-limited maximal exercise test using an incremental protocol that allowed reaching exhaustion in ≈10 min of exercise. A 12-lead electrocardiogram and transcutaneous oxygen saturation were also continuously monitored throughout the study, and blood pressure was determined manually every 2 min. The technical details of measurement of peak VO$_2$ and VE/VCO$_2$-slope have been published. Resting heart rate was measured after at least 2 min of complete rest in a seated position, whereas peak heart rate was defined as the maximal heart rate achieved during exercise. Heart rate reserve was calculated as the difference between peak and resting heart rates. Standard equations were used to generate predicted values for peak exercise parameters. Because of age-related differences of normal peak VO$_2$ when expressed in mL/kg/min, peak VO$_2$ was also expressed as % of predicted value. Anaerobic threshold was determined according to Beaver et al.

Statistical Analysis

Continuous variables are summarized by mean±standard deviation or median and interquartile range, depending on normality of distribution. Categorical variables are represented by frequencies and percentages. Wilcoxon rank sum tests and χ-squared tests were used, as appropriate, to compare clinical and demographic features of patients. T-tests were used to test for differences in mean CPET parameters between groups. Statistical significance was achieved with a two-sided
\textit{P}-value < 0.05. All analyses were performed using SPSS, Version 22 for Mac (SPSSStatystics software, IBM/SPSS, Inc., Chicago, IL, USA).

2.4.2.2.RESULTS

A total of 732 Fontan patients who underwent CPET were identified. From this population we excluded CPET performed on a treadmill (85 patients) to exclude variabilities due to differences in the test methodology. Our cohort consisted of 647 patients who performed the CPET on a cycloergometer. Among those we chose to study those who achieved maximal effort, considered to be RER$\geq$1.09 at peak exercise. Details of the 301 patients (41.2\% of the initial cohort) that performed a maximal effort cicloergometer CPET are shown in table 2. 171 patients were male (56.8\%), the patients’ median age at the time of CPET was 15.4 years (range 7.2-44.8, IQR 12.5–18.1). Ventricle morphology was left in 218 (72.4\%), Fontan type is shown in table 2.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Maximal effort</th>
<th>Sub Maximal effort</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients no.</td>
<td>647</td>
<td>301</td>
<td>346</td>
<td>-</td>
</tr>
<tr>
<td>Age at evaluation (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>13.6</td>
<td>15.4</td>
<td>11.6</td>
<td>0.000*</td>
</tr>
<tr>
<td>IQR</td>
<td>10.5-17.3</td>
<td>12.5-18.1</td>
<td>9.5-15.5</td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>379 (58.6%)</td>
<td>171 (56.8%)</td>
<td>208 (60.1%)</td>
<td>0.378*</td>
</tr>
<tr>
<td>Age at Fontan (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>0.845*</td>
</tr>
<tr>
<td>IQR</td>
<td>2.3-5.5</td>
<td>2.3-5.7</td>
<td>2.3-5.4</td>
<td></td>
</tr>
<tr>
<td>Time since Fontan (years)</td>
<td>mean±SD</td>
<td>9.5±4.8</td>
<td>11.1±4.6</td>
<td>8.2±4.5</td>
</tr>
<tr>
<td>LV morphology</td>
<td>465 (71.9%)</td>
<td>218 (72.4%)</td>
<td>247 (71.4%)</td>
<td>0.762°</td>
</tr>
<tr>
<td>Surgery palliation</td>
<td>classic/modified Fontan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lateral tunnel TCPC</td>
<td>156 (24.1%)</td>
<td>85 (28.2%)</td>
<td>71 (20.5%)</td>
<td>0.352*</td>
</tr>
<tr>
<td>ECC TCPC</td>
<td>350 (54.1%)</td>
<td>157 (52.2%)</td>
<td>193 (55.8%)</td>
<td>0.403*</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>141 (40.6%)</td>
<td>59 (19.6%)</td>
<td>82 (23.7%)</td>
<td>0.223*</td>
</tr>
</tbody>
</table>

Table 2. clinical details of the whole cohort and comparison between the maximal and sub-maximal effort subgroups. TCPC: total cavo-pulmonary connection; ECC: extracardiac conduit. *: Mann-Whitney U test; °: Independent samples T test; ^: Pearson \( \chi \)-squared.
The peak VO$_2$ in the whole population was 25.2±7.3 mL/kg/min, 60.7±19.9% and in the maximal effort group was 26.3±6.9 mL/kg/min, 63.3±17.1% predicted.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Maximal effort</th>
<th>Sub Maximal effort</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients no.</td>
<td>647</td>
<td>301</td>
<td>346</td>
<td>-</td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>mean±SD</td>
<td>81±17</td>
<td>80±18</td>
<td>82±17</td>
</tr>
<tr>
<td>Resting SatO$_2$ (%)</td>
<td>mean±SD</td>
<td>92.7±10.6</td>
<td>93.1±8.5</td>
<td>92.3±12.2</td>
</tr>
<tr>
<td>Resting SBP (mmHg)</td>
<td>mean±SD</td>
<td>106±14</td>
<td>108±14</td>
<td>104±14</td>
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<tr>
<td>FEV1 (L)</td>
<td>median</td>
<td>1.93</td>
<td>2.26</td>
<td>1.73</td>
</tr>
<tr>
<td></td>
<td>IQR</td>
<td>1.43-2.56</td>
<td>1.75-2.97</td>
<td>1.27-2.20</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>median</td>
<td>2.23</td>
<td>2.59</td>
<td>1.85</td>
</tr>
<tr>
<td></td>
<td>IQR</td>
<td>1.62-2.99</td>
<td>2.04-3.41</td>
<td>1.38-2.53</td>
</tr>
<tr>
<td>MVV (L/min)</td>
<td>mean±SD</td>
<td>62.9±30.8</td>
<td>74.0±33.7</td>
<td>54.0±24.9</td>
</tr>
<tr>
<td>AT VO$_2$ (mL/kg/min)</td>
<td>mean±SD</td>
<td>17.5±6.2</td>
<td>17.6±5.8</td>
<td>17.6±6.7</td>
</tr>
<tr>
<td>Peak VO$_2$ (mL/kg/min)</td>
<td>mean±SD</td>
<td>25.2±7.3</td>
<td>26.3±6.9</td>
<td>24.2±7.5</td>
</tr>
<tr>
<td>Peak VO$_2$</td>
<td>mean±SD</td>
<td>60.7±19.9</td>
<td>63.3±17.1</td>
<td>58.4±21.8</td>
</tr>
<tr>
<td>(% of predicted value)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRR (bpm)</td>
<td>mean±SD</td>
<td>71±31</td>
<td>79±32</td>
<td>65±29</td>
</tr>
<tr>
<td>Peak HR (bpm)</td>
<td>mean±SD</td>
<td>149±29</td>
<td>154±24</td>
<td>147±27</td>
</tr>
<tr>
<td>Peak SatO$_2$ (%)</td>
<td>mean±SD</td>
<td>83.9±23.8</td>
<td>87.7±16.1</td>
<td>83.2±25.6</td>
</tr>
<tr>
<td>Peak SBP (mmHg)</td>
<td>mean±SD</td>
<td>132±31</td>
<td>142±24</td>
<td>134±23</td>
</tr>
<tr>
<td>Peak RER</td>
<td>mean±SD</td>
<td>1.06±0.10</td>
<td>1.15±0.05</td>
<td>0.95±0.19</td>
</tr>
<tr>
<td></td>
<td>min-max</td>
<td>0.66-1.37</td>
<td>1.09-1.37</td>
<td>0.66-1.08</td>
</tr>
<tr>
<td>Peak workload (watts)</td>
<td>mean±SD</td>
<td>80.7±41.0</td>
<td>99.7±43.0</td>
<td>64.8±29.2</td>
</tr>
<tr>
<td>peak VE/VCO$_2$ ratio</td>
<td>mean±SD</td>
<td>44.5±9.9 (403pts)</td>
<td>43.0±8.5 (188pts)</td>
<td>45.8±10.6 (215 pts)</td>
</tr>
</tbody>
</table>

Table 3. CPET parameters of the whole cohort and comparison between the maximal and sub-maximal effort subgroups. HR: heart rate; SatO$_2$: oxygen saturation; SBP: systolic blood pressure; FEV1: forced expiratory volume; FVC: forced vital capacity; MVV: Maximal Voluntary Ventilation; AT: aerobic threshold; VO$_2$: oxygen consumption; HRR: heart rate reserve; RER: respiratory exchange ratio; VE/VCO$_2$: ventilatory equivalent ratio for carbon dioxide. *: Mann-Whitney U test; °: Independent samples T test.
2.5 EXERCISE CAPACITY IN PAEDIATRIC DILATED CARDIOMYOPATHY

2.5.1 BACKGROUND

Dilated cardiomyopathy (DCM) is the final common phenotypic pathway for multiple pathological processes that are characterized by left ventricular (LV) chamber dilation and systolic dysfunction, and clinically manifested by congestive heart failure\textsuperscript{117}. Etiologies may include antecedent viral myocarditis and generalized myopathies, along with a broad spectrum of sarcomeric, sarcolemmal, cytoskeletal, or nuclear protein abnormalities. However, etiology remains idiopathic in approximately two-thirds of cases\textsuperscript{118}. Epidemiological studies have estimated the incidence of newly diagnosed DCM to be between 0.57 and 0.73 cases per 100,000 per year among infants and children <18 years of age\textsuperscript{119,120}. Despite advances in the medical management of congestive heart failure, the prognosis of children with DCM remains poor, with a 5-year transplantation-free survival of approximately 50\%\textsuperscript{121}. Conventionally, maximal oxygen uptake (peak VO\textsubscript{2}), assessed during cardiopulmonary exercise testing (CPET), has been used for risk stratification in HF patients with non-ischemic DC\textsuperscript{117}. The clinical management of outpatient children with heart failure secondary to dilated cardiomyopathy (DCM) has been greatly improved by the routine monitoring of biomarkers (natriuretic peptides) and exercise tolerance (cardiopulmonary exercise test, CPET). They offer useful advice in monitoring the progression of the disease. The aim of the study was to determine their usefulness in the timing for transplant listing in the paediatric population and their potential value as predictors of outcome (death and transplant) in outpatient children with DCM.
2.5.2 METHODS
This study was designed as single-center and retrospective, the need for consent was waived due to the study design. DCM was diagnosed based on 2006 definitions and classification of cardiomyopathies by the American Heart Association. DCM was defined as left ventricular end-diastolic diameter Z score -2.0 and a left ventricular shortening fraction (LVSF) <30%. Forty-eight patients were enrolled in this study according to the inclusion criteria: (1) paediatric DCM patients aged <18 years, (2) availability of complete data for serial measurements of NT-proBNP and exercise test, and (3) a follow-up duration >6 months.
All children enrolled were outpatients and considered stable on oral medical therapy alone. None had been hospitalized in the month before assessment. Their clinical assessment included physiological data, medications prescribed, echocardiography. All children at least 120 cm tall and able to exercise on a bicycle underwent a cardiopulmonary exercise test as part of their functional capacity. Serum biomarkers, first available at our institution as BNP and later as NT pro-BNP, were requested when signs and symptoms of worsening heart failure manifested despite medical therapy, with clinical suggestion of deterioration and progression to medical refractory decompensation requiring assessment for non medical management. Most of the investigations were performed on the same date, when that was not possible sets of investigations performed within 6 months have been considered.
Follow-Up and Survival
All the children enrolled have remained under continued clinical follow up at our institution, so that all events in the cohort were captured. Medical records were reviewed to obtain relevant data, including survival status. Survival was taken as the time from initial exercise testing. The study end point was the combination of death and transplant, where criteria for elective listing were based on the presence and magnitude of symptoms and deterioration despite optimal medical therapy. Criteria for urgent listing were mechanical ventilation, high-dose intravenous inotropic agents, or need for bridging with an extracorporeal membrane oxygenator or ventricular assist device.
Echocardiography
Echocardiography was performed using a GE Vivid series (General Electric Healthcare, Buckinghamshire, UK). In the echocardiographic data, we investigated left ventricular (LV) diastolic dimension, LV systolic dimension, LV ejection fraction (EF), and LV fractional shortening (FS. M-mode measurements for LV diastolic dimension, LV systolic dimension, LVEF, and LVFS were obtained from the parasternal long-axis view. Body surface area normalized z scores for LV systolic dimension and LV diastolic dimension were then calculated. Although
extrapolation of EF from linear LV minor-axis diameters can be inaccurate because of the geometric assumptions, acceptable ventricular geometry was observed supporting the linear relation between LVFS and LVEF based on volumetric measurements. Because of incomplete data on LVEF, LVFS was consistently used instead.

. Cardiopulmonary Exercise Test

Exercise tests were performed on an electronically braked cycloergometer. Carbon dioxide elimination (VCO$_2$), VO$_2$ and minute ventilation (VE) were measured with a computerized breath-by-breath analyzer (Medgraphics, St. Paul, MN). Patients performed a symptom-limited maximal exercise test using a continuous incremental bicycle protocol with a work rate increment between 5 and 20 W/min, with the aim of completing the test within 10 to 12 minutes of exercise. Criterion for test ending was considered patient exhaustion with a respiratory exchange ratio >1.09. A 12-lead ECG and transcutaneous oxygen saturation were also monitored continuously throughout the study, and cuff blood pressure was determined manually every 2 minutes. Resting heart rate (HR) was measured after at least 2 minutes of complete rest in a seated position, and peak HR was defined as the maximal HR achieved during exercise. Predicted maximum HR was estimated according to the following formula: 200-age in years. Chronotropic incompetence was described as a ratio of peak HR to predicted peak HR of <0.85. None of the patients had known coronary artery disease or inability to exercise for other reasons. Standard equations were used to generate predicted values for baseline spirometric and peak exercise parameters. Because of age-related differences in normal peak VO$_2$ when expressed in milliliters per kilogram per minute in a pediatric patient cohort with a large age range, peak VO$_2$ was expressed as percent of predicted value based on sex and age. Z scores for peak exercise systolic blood pressure were calculated from the normative data of Alpert et al.

. Biomarkers

BNP and NT pro-BNP samples were all obtained by venipuncture and processed by our biochemistry laboratory. BNP measurements were carried out on a point of care on blood samples collected in EDTA tubes with a fluorescence immunoassay (Triage Meter, Biosite). Scarce data is available in literature on normal values in children, we used the cut off suggested by Koch and Singer. NT pro-BNP measurements were performed on heparinised plasma with a chemiluminescent immunoassay (IMMULITE 2000 NTproBNP, Siemens). Our laboratory validated the reference values in children that we are currently using.
For both biomarkers it is recognised normal values vary impressively in children being extremely high in neonates, decreasing rapidly in the first weeks of life to then normalise and stabilise to adult values at puberty.

### Statistical Analysis

Data distribution was tested for normality with the Shapiro-Wilk test. Normally distributed continuous variables data are reported as mean±standard deviation, not normally distributed continuous variables as median (25° percentile-75° percentile). Categorical variables are reported as number and percentage. Patients were divided into two groups depending on their clinical outcome. Patients who died during follow up or underwent urgent or elective orthotopic heart transplant were grouped in the “Events” group. Patient who were alive with no transplant at their last follow up are described in the “No events” group.

The two groups were compared for differences on major demographic, echocardiographic, exercise parameters and biomarkers using independent samples T-test, Mann-Whitney U test and Pearson’s χ² test as appropriate. A 2-tailed value of p≤0.05 was used as the criterion for statistical significance. Kaplan-Meier curves were plotted for all events (death and transplant) and groups were compared. First grouping variable was biomarkers (normal vs. abnormal values), then an empirical cutoff value of peak VO₂ (62%) was selected to define groups.¹⁴⁵

All analyses were performed using SPSS, Version 22 for Mac (SPSSStatystics software, IBM/ SPSS, Inc., Chicago, IL, USA).

### 2.5.3 RESULTS

Between 2003 and 2013 we enrolled 48 consecutive patients with DCM in this study, the baseline characteristics are presented in Table 1. DCM was idiopathic in 37 (77.1%), induced by anthracycline in 5 (10.4%), and secondary to Duchenne muscular dystrophy in 1 (2.1%), mitochondrial disease in 1 (2.1%) and post-myocarditis in 1 (2.1%).

All children completed a symptom-limited CPET at a mean age of 14.2±2.1 years (range 9.4-17.9 years), with a peak exercise respiratory exchange ratio of 1.12 ±0.8. Overall, LVSF was 17.9±7.2%. Exercise capacity was 24.9±10.3 mL/kg/min (range 11.1-46.9 mL/kg/min), which corresponded to 65.8% of predicted (IQR 39.5%-86.9% and range 30.7%-108.9%). Peak HR in the overall study cohort was 155.6±22.5 bpm (range, 114–207 bpm), which corresponded to 83.8±12.2% of predicted (range, 60.7%–111.5%). Peak exercise systolic blood pressure was 120 mmHg (IQR 100-130), with Z-score of -4.4±3.5. Twenty-eight patients (58.3%) had chronotropic incompetence. Biomarkers were tested in all the patients: twenty-seven
patients had BNP tested and this was 346.9±470.4 pg/mL (range 4-1580 pg/mL), 21 patients had NT pro-BNP measured and this was 3537.6±5367.3 pg/mL (range 24-21784 pg/mL).

Thirty patients (62.5%) were receiving β-blockers at the time of the CPET, and forty patients (83.3%) were receiving angiotensin-converting enzyme inhibitors. All children were in sinus rhythm with 5 patients on antiarrhythmic prophylaxis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Study Cohort (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology, n (%)</td>
<td></td>
</tr>
<tr>
<td>idiopathic</td>
<td>31 (64.6)</td>
</tr>
<tr>
<td>familial</td>
<td>6 (12.5)</td>
</tr>
<tr>
<td>anthracyclines induced</td>
<td>5 (10.4)</td>
</tr>
<tr>
<td>DMD</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>mitochondrial</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>post-myocarditis</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Age at CPET, y</td>
<td>14.2±2.1</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>29 (60.4)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>55.4 (44.0-67.3)</td>
</tr>
<tr>
<td>Body surface area, m2</td>
<td>1.58±0.31</td>
</tr>
<tr>
<td>Body mass index, kg/m2</td>
<td>20.0 (17.8-23.4)</td>
</tr>
<tr>
<td>LVSF, %</td>
<td>17.9±7.2</td>
</tr>
<tr>
<td>Peak workload, W</td>
<td>103.0 (69.3-140.5)</td>
</tr>
<tr>
<td>Peak SPB, mmHg</td>
<td>120 (100-130)</td>
</tr>
<tr>
<td>z score</td>
<td>-4.4±3.5</td>
</tr>
<tr>
<td>Peak heart rate, bpm</td>
<td>155.6±22.5</td>
</tr>
<tr>
<td>% of predicted</td>
<td>83.8±12.2</td>
</tr>
<tr>
<td>Prevalence of chronotropic incompetence, n (%)</td>
<td>28 (58.3)</td>
</tr>
<tr>
<td>Peak VO₂, mL/kg/min</td>
<td>24.9±10.3</td>
</tr>
<tr>
<td>% of predicted</td>
<td>65.8 (39.5-86.9)</td>
</tr>
<tr>
<td>VE/VO₂ slope</td>
<td>31.1 (26.2-35.1)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Peak respiratory exchange ratio</td>
<td>1.12 ±0.8</td>
</tr>
<tr>
<td>BNP, pg/mL (27 pts)</td>
<td>346.9±470.4</td>
</tr>
<tr>
<td>NT pro-BNP, pg/mL (21 pts)</td>
<td>3537.6±5367.3</td>
</tr>
</tbody>
</table>

Medications, n(%)

- **Diuretics** 25 (52.1)
- **K-sparing diuretics** 13 (27.1)
- **β-blockers** 30 (62.5)
- **ACE-inhibitors** 40 (83.3)
- **Digoxin** 16 (33.3)
- **Amiodarone** 5 (10.4)
- **Aspirin** 16 (33.3)
- **Warfarin** 13 (27.1)

DMD: Duchenne muscular dystrophy; CPET: cardiopulmonary exercise test; LVSF: left ventricular shortening fraction; SBP: systolic blood pressure; VO₂: oxygen uptake; VE/VCO₂: ventilatory efficiency; BNP: brain natriuretic peptide; NT pro-BNP: amino-terminal of the prohormone brain natriuretic peptide

**Outcome**

All patients had complete follow-up until December 2014. At an average follow-up (time from CPET to first event) of 14.2±18.5 months (range, 0.3 [early transplantation] to 83.4 months), 25 patients reached the end point of death or heart transplant. In detail, 7 patients died (1 died after heart transplant and 1 on the list), 19 patients were listed for transplant either electively (12) or needed urgent listing (7) because of severe clinical deterioration and were bridged to HTx on high-dose intravenous inotropic support ventricular assistance/ECMO.

At univariate analysis echocardiographic and exercise parameters, biomarkers and use of diuretics and ACE-i were all associated with a higher rate of death or need for HTx, whereas sex, age at CPX and body size were not.

In the multivariable analysis that included peak VO₂% and LVSF as independent variables, peak VO₂% was the only variable associated with the composite end point. Kaplan-Meier curves plotted for abnormality of biomarkers values (BNP and NT pro-BNP) showed none of the children with normal biomarkes died or were listed for urgent HTx. Using the empirical peak VO₂ cutoff point of 62% of predicted, Kaplan-Meier survival curves showed a higher rate of death/listing for urgent HTx in.
patients with a peak VO$_2$ 62%. Kaplan-Meier curves are also showns for the composite end point comprising all events (death, urgent and elective HTx).

<table>
<thead>
<tr>
<th>Variable</th>
<th>No events (n=23)</th>
<th>Events (n=25)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at CPET, y</td>
<td>14.6±2.3</td>
<td>13.9±1.8</td>
<td>0.222*</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>13 (57)</td>
<td>16 (64)</td>
<td>0.597^</td>
</tr>
<tr>
<td>Height, cm</td>
<td>162.0±16.0</td>
<td>159.1±12.9</td>
<td>0.505*</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>57.8</td>
<td>50.0</td>
<td>0.358°</td>
</tr>
<tr>
<td>(42.5-73.7)</td>
<td>(44.0-64.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body surface area, m$^2$</td>
<td>1.62±0.36</td>
<td>1.53±0.27</td>
<td>0.328*</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>20.9</td>
<td>19.9</td>
<td>0.516°</td>
</tr>
<tr>
<td>(17.9-24.5)</td>
<td>(18.1-22.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVSF, %</td>
<td>22.5±5.7</td>
<td>13.6±5.7</td>
<td>0.000*</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>57.7±10.5</td>
<td>68.3±9.9</td>
<td>0.001*</td>
</tr>
<tr>
<td>LVEDD/BSA, mm/m$^2$</td>
<td>36.6±7.6</td>
<td>45.5±7.8</td>
<td>0.000*</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>45.1±10.3</td>
<td>58.5±9.2</td>
<td>0.000*</td>
</tr>
<tr>
<td>LVESD/BSA, mm/m$^2$</td>
<td>28.4±6.5</td>
<td>39.0±8.0</td>
<td>0.000*</td>
</tr>
<tr>
<td>Peak workload, W</td>
<td>133.0</td>
<td>80.0</td>
<td>0.002°</td>
</tr>
<tr>
<td>(100.5-153.5)</td>
<td>(57.0-108.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak SPB, mmHg</td>
<td>128</td>
<td>104</td>
<td>0.000°</td>
</tr>
<tr>
<td>(120-142)</td>
<td>(94-118)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>z score</td>
<td>-2.3±2.6</td>
<td>-6.3±3.1</td>
<td>0.000*</td>
</tr>
<tr>
<td>Peak heart rate, bpm</td>
<td>165.2±23.0</td>
<td>146.7±18.3</td>
<td>0.004*</td>
</tr>
<tr>
<td>% of predicted</td>
<td>89.1±12.4</td>
<td>78.8±10.0</td>
<td>0.003*</td>
</tr>
<tr>
<td>Peak VO$_2$, mL/kg/min</td>
<td>29.8±11.3</td>
<td>20.4±6.8</td>
<td>0.001*</td>
</tr>
<tr>
<td>% of predicted</td>
<td>76.4</td>
<td>54.9</td>
<td>0.001°</td>
</tr>
<tr>
<td>(65.2-104.4)</td>
<td>(32.7-73.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VE/VCO$_2$ slope</td>
<td>27.9</td>
<td>32.5</td>
<td>0.001°</td>
</tr>
<tr>
<td>(25.6-29.8)</td>
<td>(31.1-37.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomarker</td>
<td>Mean (Range)</td>
<td>(n)</td>
<td>Mean (Range)</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------------</td>
<td>-----</td>
<td>--------------</td>
</tr>
<tr>
<td>BNP, pg/mL (27 pts)</td>
<td>11.2 (6.5-26.4)</td>
<td>(n=13)</td>
<td>496.0 (301.8-1013.0)</td>
</tr>
<tr>
<td>NT pro-BNP, pg/mL (21 pts)</td>
<td>118.5 (62.8-581.5)</td>
<td>(n=10)</td>
<td>4754.0 (2525.5-5844.5)</td>
</tr>
<tr>
<td>Abnormal biomarkers, xULN</td>
<td>0.5 (6.5-26.4)</td>
<td>(n=10)</td>
<td>19.2 (12.1-34.6)</td>
</tr>
</tbody>
</table>

**Medications, n(%)**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Count (%)</th>
<th>Count (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>6 (23.1)</td>
<td>19 (76.0)</td>
<td>0.001^</td>
</tr>
<tr>
<td>K-sparing diuretics</td>
<td>4 (17.4)</td>
<td>9 (36.0)</td>
<td>0.147^</td>
</tr>
<tr>
<td>β-blockers</td>
<td>13 (56.5)</td>
<td>17 (68.0)</td>
<td>0.412^</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>16 (69.6)</td>
<td>24 (96.0)</td>
<td>0.014^</td>
</tr>
<tr>
<td>Digoxin</td>
<td>5 (21.7)</td>
<td>11 (44.0)</td>
<td>0.102^</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>2 (8.7)</td>
<td>3 (12.0)</td>
<td>0.708^</td>
</tr>
<tr>
<td>Aspirin</td>
<td>6 (26.1)</td>
<td>10 (40.0)</td>
<td>0.307^</td>
</tr>
<tr>
<td>Warfarin</td>
<td>3 (13.0)</td>
<td>10 (40.0)</td>
<td>0.036^</td>
</tr>
</tbody>
</table>

*: independent samples T-test; °: Mann-Whitney U test; ^: Pearson’s χ-squared test

Univariate analysis for patients reaching endpoint (death or heart transplant, urgent or elective) during the study.
We also grouped biomarkers, peak V02 and VE/VC02 slope in tertiles and tested their concordance in predicting outcomes. The results are shown in the tables below and plot biomarkers against CPET parameters separately to assess the while children with normal biomarkers had no events peak V02 was in the upper tertile (>76.4%) in 5 children who had a negative outcome, nonetheless concordance of the two (i.e. normal biomarkers and high peak V02 or severely abnormal biomarkers and peak V02) was effective in predicting outcome. The same considerations apply to the comparison between biomarkers and VE/VC02 slope underlying how better prediction of outcome is possible when the two tests are assessed together as compared to using exercise test alone. Biomarkers showed excellent predictive value even when considered alone with no events in children with biomarkers in the lower tertile and adverse outcome in all the patients with biomarkers in the higher tertile.

<table>
<thead>
<tr>
<th>Biomarkers (xULN)</th>
<th>3° tertile (13.4-116.1)</th>
<th>2° tertile (1.1-13.4)</th>
<th>1° tertile (&lt;1.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of predicted VO2</td>
<td>1° tertile (≤53.0)</td>
<td>2° tertile (53.0-76.4)</td>
<td>3° tertile (76.4-150.5)</td>
</tr>
<tr>
<td>10/10</td>
<td>2/5</td>
<td>0/1</td>
<td></td>
</tr>
<tr>
<td>3/3</td>
<td>5/8</td>
<td>0/4</td>
<td></td>
</tr>
<tr>
<td>3/3</td>
<td>2/3</td>
<td>0/10</td>
<td></td>
</tr>
</tbody>
</table>

○: event; ○no event
<table>
<thead>
<tr>
<th>VENCO₂ slope</th>
<th>3° tertile (32.6-55.0)</th>
<th>2° tertile (28.0-32.6)</th>
<th>1° tertile (&lt;28.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3° tertile</td>
<td>9/9</td>
<td>3/5</td>
<td>0/2</td>
</tr>
<tr>
<td>2° tertile</td>
<td>0/3</td>
<td>0/6</td>
<td>0/10</td>
</tr>
<tr>
<td>1° tertile</td>
<td>0/5</td>
<td>0/7</td>
<td>0/10</td>
</tr>
</tbody>
</table>

○: event; ◯: no event

### Biomarkers (xULN)

<table>
<thead>
<tr>
<th>3° tertile</th>
<th>2° tertile</th>
<th>1° tertile</th>
</tr>
</thead>
<tbody>
<tr>
<td>(13.4-116.1)</td>
<td>(1.1-13.4)</td>
<td>(&lt;1.1)</td>
</tr>
</tbody>
</table>
Kaplan-Meier for death/urgent Htx according to abnormal biomarkers

Kaplan-Meier for death/urgent and elective Htx according to abnormal biomarkers
Kaplan-Meier for death/urgent Htx according to peak V02 > 62%

Kaplan-Meier for death/urgent and elective Htx according to peak V02 > 62%
3. FUTURE PERSPECTIVES

3.1 SKELETAL AND RESPIRATORY MUSCLE TRAINING IN TCPC PATIENTS

Patients with congenital heart defects present with reduced exercise capacity and this has prognostic implications.

Reduced exercise capacity is multifactorial in this group and mainly related to abnormal cardiovascular haemodynamics during exercise (inappropriate increase in stroke volume or heart rate to exercise), abnormal perfusion of the exercising muscles, abnormal extraction of \( O_2 \) from the exercise muscles, and abnormal \( O_2 \) content (hypoxemia or anemia).

There is evidence that patients with CHD have reduced skeletal and respiratory muscle strength, as assessed by maximal inspiratory and expiratory pressures at rest and 10 minutes after maximal exercise. This evidence exists for patients with repaired tetralogy of Fallot, Fontan operation and Mustard/Senning operation. Reduced respiratory muscle strength can be important in patients with CHD for several reasons:

1. Patients with CHD need to hyperventilate during exercise because of hyperstimulation form chemo and metaboreceptors, with potential for premature interruption of exercise because of dyspnoea (high Borg scale).
2. Hyperventilation is particularly increased in patients with hypoxemia (Eisenmenger, Fontan)
3. Respiratory muscle fatigue related to reduced respiratory muscle strength causes an increase in adrenergic stimulation, which produces a vasocostriction in the skeletal muscles arteries, compromising perfusion of exercising muscles (quadriceps in bicycle ergometry).
4. Some patients, like those with TCPC heavily rely on ventilation (and therefore respiratory muscle strength and their tolerance to progressive exercise) to increase their cardiac output during exercise.

Studies in adults with heart failure have shown that respiratory muscle training can improve exercise tolerance and peak \( VO_2 \), by means which differ from those of standard aerobic exercise training.

Skeletal muscle deconditioning have an additional role in decreased exercise capacity and patients with CHD are frequently discouraged from participating in any kind of physical activities for social/psychological reasons in fear of increased risk of adverse events. Recently a relevant body of literature has become available to confirm these patients, even with complex conditions palliated with univentricular
circulation, are safe in undertaking mild to moderate aerobic exercise and evidence is emerging regarding the benefit of regular training in their overall health and prognosis.

We are recruiting teenager patients with univentricular physiology in two pilot studies regarding exercise training, one is focusing on skeletal muscle training with a computer based exercise programme (Nintendo Wii) and the second focuses on respiratory muscles training.

3.2 MULTISCALE MODELLING OF UNIVENTRICULAR HEARTS

Developed in the 1930s and 1940s to study hydraulic problems, computational fluid dynamics (CFD) has become a practical modelling tool to solve and analyse physical phenomena that involve fluid flows. In congenital cardiac surgery, where the objective of the operative reconstruction is to reshape the blood flow within the heart and great vessels to achieve the best dynamics and tissue oxygen delivery, CFD is a natural tool to uncover suboptimal circulations and improve surgical techniques. However, a lack of a common language and mutual understanding of each other’s expertise have often stymied this logical collaboration between cardiac surgeons and engineers. Advances in computational methods have led to numerous contributions in the field of congenital heart diseases and surgery, including assist device development, studying of valvular and aortic pathologies, modifications to the Fontan operation and the continuing efforts to understand the modified physiologies in single ventricular circulations.

While these advances have shed light into some of the altered flow dynamic phenomena that are unique in congenital heart surgery, there has been an increased recognition that modelling approaches that only focus on the local or the surgical domain will miss or underrepresent the overall effects on the entire cardiovascular and pulmonary physiology. In effect, the haemodynamics of the operative reconstruction site are dynamically coupled to the rest of the cardiovascular system. New multiscale modelling methods have been developed to provide a computationally efficient approach to correctly model both local and systems-level behaviour. Without going into the mathematical background, a multiscale model of the cardiovascular system combines the detailed 3D, anatomically accurate CFD model of the desired surgical reconstruction with a zero-dimensional (0D) hydraulic lumped-parameter network (LPN) representation of the rest of the cardiovascular circulation system. Computationally, the flow and pressure output values from the 3D CFD model become the input pressure and flow values to the 0D LPN and, in turn, these same outputs from the LPN model become the input values to the CFD model of the surgical domain. This multiscale approach, such as shown for a TCPC model (Fig. 1), allows for closed-loop circulatory modelling. The
initiating conditions set by the user put into motion a set of calculations that iteratively arrive at flow and pressure solutions anywhere in the circulation. In a multiscale TCPC model, not only would shear stress and power loss within the TCPC be calculated, but also would a host of clinically relevant physiological variables, such as Fontan pressures, pressure–volume relationship of the single ventricle and cerebral perfusion. And when combined with fundamental oxygen equations, systemic and end organ, such as cerebral and myocardial, oxygen delivery can be assessed. Further adjustments to these models allow for simulations under exercise and growth effects. The aim is to establish a new investigative paradigm in which patient-specific anatomy and physiology are used in an engineering model to predict surgical outcomes, better understand hemodynamic changes related to the physiological changes induced by exercise and supplement patient management. Such a process involves virtual surgery and computational/experimental simulations using clinical data acquired from echocardiography, computed tomography, magnetic resonance imaging and cardiac catheterization. Multiscale models were constructed to assess the surgically altered flow dynamics, as well as the overall physiological effect in a clinically relevant manner.

We are currently working on projects that aim to explore the importance of anatomical shape in determining the hemodynamic efficiency of the circuit, in particular the aortic arch shape after Norwood reconstruction and the pulmonary artery anatomy. Furthermore we are implementing LPN models to predict physiological response of the TCPC circuit in conditions that require increase in cardiac output and namely exercise and pregnancy. Both this physiological changes in TCPC pose great difficulties to clinicians. Major differences can be observed from in response to exercise as outlined previously and poor outcome is well recognised in pregnancy in this cohort with very high rate of miscarriages, low birth weight and prematurity. We hope further development of these computational models will shed some light on our understanding of this artificial physiology.
Multiscale model coupling a patient-specific, realistic 3D extracardiac conduit total cavopulmonary connection with the 0D hydraulic lumped parameter network of entire cardiovascular system, including a single-ventricle heart and pulmonary circulation.

4. DISCUSSION

4.1 EXERCISE CAPACITY IN LEFT TO RIGHT SHUNTS
Patients with significant left-to-right shunt, particularly ASD patients, even if asymptomatic, have a significant exercise capacity limitation when compared to healthy controls. Patients who are symptomatic, those with larger shunts and those with increased pulmonary artery pressure can be particularly limited. Patients with ASD, like many other children with congenital heart defects, generally adapt to their limitation which is present since early infancy and describe themselves as asymptomatic, even when their exercise capacity is clearly reduced \[^{37,53,131}\].
Therefore, indication for closure can not rely on symptoms which are generally late, when complications have already developing. There are no available longitudinal data on exercise capacity in untreated ASD patients but early cross-sectional evaluations suggested symptoms usually develop during adulthood and the natural history of the disease is not benign in the long term 27. While we agree on ASD closure when a large shunt is detected during childhood, debate is still ongoing in older patients with smaller shunts or large shunts that eventually caused borderline pulmonary vascular damage with slight and/or reversible raise in pulmonary arterial pressures. Age does not seem a determinant of the response to ASD closure as over 40 years old seem to improve their peak VO₂ in a similar fashion to those patients below 40 years of age 27,28. Even though there is an association between change in peak VO₂ and size of the left-to-right shunt, patients with smaller shunts (like those with a Qp/Qs <2) also show some clinically significant improvements in their exercise capacity after closure. After surgical closure right ventricular dimensions change dramatically and exercise capacity greatly improves. However, whereas in children exercise capacity gradually reaches normal values in the long term 31, peak VO₂ fails to reach predicted values in adult patients with preoperative signs of pulmonary hypertension 44. Due to its less invasive nature with short recovery time and low morbidity and mortality, percutaneous closure has becoming the first choice treatment in older children and adults with a suitable anatomy. The first small studies on trans-catheter closure showed no significant difference in peak VO₂ after closure 33,34. Larger subsequent studies showed that percutaneous ASD closure led to an improvement in exercise capacity regardless of age at ASD closure 45 and symptoms, but proportional to the amount of left-to-right shunt and pulmonary artery pressure 35,43. Data from our lab 37 have shown that the left to right shunting of blood does not only cause pulmonary overcirculation (both at rest and during exercise) but also causes a reduction in systemic perfusion, both at rest and during exercise. We also showed that the improvement in peak VO₂ after ASD closure is a consequence of increased left ventricular stroke volume and cardiac output. ASD closure augments left ventricular filling, thereby increasing left ventricular preload, left ventricular end-diastolic diameter and ultimately left ventricular stroke volume. At the same time the right ventricle decreases in size, paradoxical septal motion disappears and ventricular interaction improves. Peak VO₂ improvement was observed with both surgical and percutaneous closure series 32,44. Improvements were as early as 3 months post-op, particularly after percutaneous closure because of the reduced recovery time, but they appear to continue over time with further increase in exercise capacity in the mid-term 31,35. However, postoperative exercise capacity was reported lower than in normal subjects 131 presumably because of low
cardiac output during exercise due to reduced heart rate response during exercise \(^{132}\), or a low level of daily physical activity after surgical closure of ASD which is observed also in children with other types of congenital heart disease. Furthermore an inappropriate response of the pulmonary vasculature to exercise may also have a large influence on postoperative exercise capacity. Studies looking at cardiopulmonary responses to exercise in VSD patients have shown mixed results with some studies showing some limitation in peak VO\(_2\) related to increased right ventricular systolic pressure during exercise whereas other studies have shown no evidence of significantly reduced exercise tolerance either when considering large VSDs after closure or small VSDs in natural history. However, all studies were of small size and therefore no generalization can be made for the overall VSD population. Children with Down’s syndrome and congenital heart defects have a higher predisposition to develop pulmonary hypertension \(^{91}\) and this is due to many different factors that can be controlled or modified only to a minor extent \(^{133}\). Therefore, exposure to long-standing increased left-to-right shunt flow where shear stress on endothelium induces endothelial dysfunction followed by irreversible remodelling of pulmonary arteries, may have a worse effect in subjects with Down syndrome compared to non-syndromic children \(^{134}\). These children and young adults are therefore more likely to have their exercise capacity affected by changes in the pulmonary vasculature and should receive early treatment \(^{53}\).

4.2 EXERCISE TRAINING IN SYSTEMIC RIGHT VENTRICLE
This follow-up analysis of our randomized controlled trial on the effect of exercise training in adult patients with a systemic right ventricle, demonstrates that the beneficial effects found after a 10-week exercise program do not persist over time. peak VO\(_2\), NT-proBNP levels, and quality of life remained stable in both patients who had participated in exercise training, as well as in those who had not. On the other hand, patients who were already involved in sports at baseline, regardless of their study group, had an increase in exercise capacity, a decrease in NT-proBNP, and, more importantly, better event-free survival, as compared to those with a more sedentary lifestyle.

Current guidelines appreciate the fact that physicians have been over-conservative in their advice on sports participation, despite the growing evidence that regular exercise has a positive impact on a patient’s current status, as well as on the risk of future acquired heart disease \(^{135}\). Indeed, a recent systematic review by Duppen et al. stressed the improved fitness in a large number of children and young adults with congenital heart disease who participated in an exercise training program. Moreover, in all reviewed articles the training programs had been performed without incidents \(^{136}\). More specifically, two other recent studies demonstrated safety and efficacy of
exercise in adult congenital heart disease patients. Westhoff-Bleck et al. found an improvement in exercise capacity and NYHA classification in patients with a systemic right ventricle after a 24-week training program. They found no change in right ventricular function, which could be due to small patient numbers, and short follow-up \(^{137}\). In 146 patients with congenital heart disease, Tikkanen et al., found improved Peak VO\(_2\) in patients involved in regular exercise, as compared to those with a more sedentary lifestyle \(^{138}\). Unfortunately, long-term effects of exercise could not be derived from these studies.

Our finding that beneficial effects of exercise training are short-lived in adult patients with congenital heart disease is in line with previous results published on the long-term effect of rehabilitation programs in adult patients with acquired heart disease. In patients after myocardial infarction who participated in an eight-week training program, Dorn et al. reported a diminishing effect on cardiovascular mortality as time since participation increased \(^{59}\). Willich et al. published his findings in 2441 patients who were enrolled in a rehabilitation program after myocardial infarction, coronary artery bypass grafting, or percutaneous intervention. After an initial improvement in cardiovascular risk factors during the rehabilitation program, risk factors deteriorated in the following 12 months \(^{139}\). In contrast, in patients with congestive heart failure, a five-year follow-up study showed less deterioration in walking distance in those patients who had participated in a 24 week rehabilitation program, compared to controls. It has to be noted, however, that the intervention group remained more physically active during follow-up. This could indicate that favorable outcome in the intervention group is not a primary result from the rehabilitation program per se, but a secondary result, as patients involved in such programs seem inclined to increase their participation in habitual exercise \(^{60}\). These findings were confirmed by Mueller et al., who also found superior engagement in physical activity in patients with congestive heart failure who had participated in cardiac rehabilitation, compared to controls, after a six-year follow-up period \(^{140}\). As short-term exercise programs are no guaranty for long-term benefit, the question remains if long-term intervention is the answer for long-term improvement. Recently, Belardinelli et al., indeed found decreased deterioration of peak VO\(_2\), and NT-proBNP levels in patients with chronic heart failure after a 10-year exercise-training program.

More importantly, although the study was not powered for the purpose, patients who were involved in the training program had lower rates of hospital readmission, and cardiac mortality \(^{141}\). Whether such longterm sports participation would be associated with improvement of peak VO\(_2\), and NT-proBNP, and better event-free survival in our patients remains unclear. Although follow-up is relatively long, power
is insufficient to draw definite conclusions. Hence, it seems highly likely that physical exercise in itself, more than the actual intervention, results in improvement in peak VO₂, and decreased hospitality and mortality in patients with heart disease, independent of the etiology. The European Society of Cardiology (ESC) guidelines on the prevention of cardiovascular disease recommend physical exercise as primary and secondary prevention, as it lowers the risk of hypertension and diabetes mellitus type II, and increases HDL cholesterol. ESC guidelines state that exercise decreases cardiovascular mortality in both patients with cardiovascular disease, as well as in healthy individuals. Unfortunately, less than 50% of Europeans are involved in regular exercise, which is less than in our study population (61%). Guidelines on exercise and sports in adult patients with congenital heart disease are less straightforward. As the patient group is very heterogeneous, recommendations should be based on the patient's ability, hemodynamic status, and the risk of decompensation and arrhythmias. In our patients, the exercise-training program was executed without significant incidents. Moreover, there seems to exist a beneficial effect of habitual sports participation. Therefore, keeping patient's ability in mind, our reticence to advice in favor of sports participation might be counterproductive.

As with many studies on adult patients with congenital heart disease, our study population was relatively small. This makes the generalizability of our results limited. However, large-scale studies do not seem feasible in this patient group. In addition, only 40 out of the original 54 patients (74%) consented to participate in the current study, as 14 patients could not participate for a variety of reasons. Consequently, there is a possibility of a type 2 error. However, clinical events could be evaluated in 50 patients. Moreover, there were no differences in baseline parameters or event rate compared to the participating patients. The current study was not powered to evaluate the effect of habitual sports participation on exercise capacity, neurohormone levels, or event-free survival.

This follow-up analysis on long-term effect of a 10-week exercise training intervention in adult patients with a systemic right ventricle, demonstrates that short-term beneficial effects of exercise training do not persist over a three-year follow-up period. On the other hand, regular sports participation at baseline was associated with better exercise capacity, lower neurohormone levels, and increased event-free survival.

4.3 EXERCISE CAPACITY IN CYANOTIC CONGENITAL HEART DISEASE

Our study confirms the predictive value of peak VO₂ in cyanotic patients with CHD and suggest that CPET can be used for risk stratification independently of cyanosis as previously reported in smaller cohorts.
4.4 EXERCISE CAPACITY IN UNIVENTRICULAR PHYSIOLOGY
The prognostic value of exercise test has been inconsistent in Fontan patients with recently published large cohorts. Diller at al. demonstrated that exercise intolerance is prevalent amongst patients with a Fontan palliation and relates to increased short-term morbidity but not increased mortality or need for cardiac transplantation in their cohort. Non-TCPC type of Fontan palliation, a history of clinically relevant arrhythmia, and signs and symptoms of heart failure were identified as strong prognosticators of morbidity and mortality. A combination of these factors was strongly related to risk of death or transplantation and was far superior to any measure of CPET. On the contrary Ohuchi and colleagues found peak VO$_2$, Heart rate response and peak VE/VCO$_2$ were good predictors of mortality in their cohort and concluded general skeletal muscle weakness, endothelial dysfunction, and glucose intolerance play a role in morbidity and mortality and can be improved through lifestyle modification. They suggest resistance exercise training may benefit Fontan patients with the focus of maintaining levels of peak VO2 during follow up in view of the rapid decline observed during adolescence. Our study clearly showed that peak VO$_2$, either considering absolute or percent of predicted values, declines with age. This is consistent with what Anderson et al. and Fernandes et al. previously reported in smaller cohorts. In the vast population considered this trend is well-rendered despite surgical techniques improvements over the last three decades.

4.5 EXERCISE CAPACITY IN PAEDIATRIC DILATED CARDIOMYOPATHY
Exercise capacity measured as peak VO$_2$ on cardiopulmonary exercise test and serum biomarkers levels correlate with the severity of the disease in paediatric DCM and showed good predictive value in terms of disease progression on the composite endpoint death and heart transplantation. Exercise testing, echocardiography and serum biomarkers are easy and widely available tests that prove valuable and dependable also in the follow up of children with DCM as already shown in the adult population. In our study biomarkers proved excellent correlation to outcome and when considered together peak VO$_2$ and abnormal biomarkers recognised all patients with good outcome (low biomarkers and high peak VO$_2$) and adverse outcome (high biomarkers and low peak VO$_2$).

5. CONCLUSIONS
Most patients born with congenital heart disease are expected to reach adulthood in the current era. Owing to the frequent late complications, however, many of them require and will benefit from life-long cardiac follow-up. Among the different screening tools employed during such periodic follow-up, cardiopulmonary exercise testing (CPET) has emerged as one of the most valuable. It is non-invasive, enables
risk stratification with regard to morbidity and mortality, and helps deciding on the need and timing of therapeutic interventions. The interpretation of CPET results in patients with congenital heart disease remains challenging, however. It is well known that exercise capacity is reduced in these patients. Relating exercise capacity to normal values obtained in healthy volunteers may, however, not tell the whole story in CHD patients. It is obvious that one cannot expect an Eisenmenger patient to achieve a similar peak oxygen uptake (peak VO$_2$) as a patient with a simple cardiac lesion. As some level of impairment in peak VO$_2$ is to be expected it may be more helpful to interpret the achieved level of exercise capacity in comparison with what would be usual/expected given the patient's age, gender, and underlying diagnosis. Comparing an individual patient to his/her peer patients may inform clinicians if this represents a ‘good’ or ‘bad’ exercise capacity for a given patient group.

Exercise capacity has been assessed in many studies both in adult and paediatric patients with congenital heart disease. Protocols differ between centres and, thus, the results cannot be generalized to all patients with this disease. Ideally, every centre should develop its own database and reference values. Given the wide anatomic spectrum of CHD patients and the variable patient volume attached to different centres, this may not be practicable for most centres. In recent years many reviews of literature and large cohorts have been reported and offer an extremely helpful frame within which the clinician can interpret the exercise capacity of single patients given the specific anatomy, gender and kind of repair.

Across the whole spectrum of CHD varying degrees of exercise limitation is observed even in the most simple lesions (i.e. left to right shunts due to atrial septal defect). Many patients with CHD have unnecessary restrictions placed upon them regarding physical activity and sport participation by well-meaning parents and physicians. As a result, many children with CHD lead sedentary lifestyles that persist into adulthood and present with lower levels of physical activity than optimum for general cardiovascular fitness. These sedentary lifestyles increase their risk for secondary mordialities such as hypertension, obesity, diabetes and acquired heart disease. The American Heart Association recently published a statement on the promotion of physical activity to individuals with CHD following the publication of a substantive body of literature regarding safety and beneficial impact on overall health and quality of life. Current guidelines appreciate the fact that physicians have been over-conservative in their advice on sports participation, despite the growing evidence that regular exercise has a positive impact on a patient's current status, as well as on the risk of future acquired heart disease. Indeed, a recent systematic review by Duppen et al. stressed the improved fitness in a large number
of children and young adults with congenital heart disease who participated in an exercise training program. Moreover, in all reviewed articles the training programs had been performed without incidents. The series we presented confirm exercise capacity is impaired, albeit at different levels, in every group assessed, important prognostic information can be assessed through exercise testing in all the diseases considered. Furthermore the benefits of exercise training, namely in systemic right ventricle, were evident soon after the exercise programme was completed but did not last in the long term as previously observed in long term outcomes of rehabilitation programs after myocardial infarction and heart failure, data on long term outcome in CHD are lacking at present.

Looking at future perspectives the population of adults with CHD continues to grow in size but also evolves in anatomic and complexity case composition. Most patients with significant CHD are nowadays diagnosed prenatally, which often enables safe delivery and even occasionally intrauterine therapy. There has been ongoing innovation and improvement of surgical and percutaneous interventions matched with better long-term follow-up and, with it, better understanding and treatment of late sequelae. The resulting survival benefit is most striking in patients with complex lesions, such as those born with a ‘single ventricle’. Survival prospects in patients with single ventricle have changed dramatically over the last four decades due to the advent of better and earlier diagnosis and advances in cardiac surgery. Clinical research, aided by advanced haemodynamic computer simulations, enabled optimisation of this surgical approach. The modern version of the ‘Fontan circulation’ (total cavopulmonary connection, TCPC) is established by routing the inferior vena cava flow to the pulmonary artery with a rigid conduit, whereas the superior vena cava is anastomosed to the right pulmonary artery using a Glenn shunt.

Despite the success of this radical concept of the Fontan circulation, surgery for single-ventricle physiology remains palliative and not reparative, and it is inevitably associated with increasing long-term morbidity and mortality. Complications and late sequelae include progressive ventricular dysfunction, arrhythmia, thromboembolism, protein loosing enteropathy, liver cirrhosis, renal dysfunction and bleeding requiring frequent hospitalisations and interventions. Exercise performance and quality of life are significantly reduced in many.

While TCPC conversion might be considered in selected cases of older generation of Fontan circulation most of these patients are better managed with medical therapy, education on risk factors and physical conditioning. Transplantation
remains the only definitive solution when comorbidities do not pose absolute contraindications. From recent estimates in the UK, it appears that the overall adult population with single ventricle will increase within 2023 by almost 60%, and over 45% of these patients will be above 30 years of age, adding to the complexity of care. This underline how important it is to have structured follow up pathways that include functional assessment and physical conditioning or rehabilitation were appropriate in this cohort as well as in the general population to improve their prognosis.

Exercise testing and training are becoming more and more relevant in this scenario to guide therapy and management but also to assess the ability in daily activities that play an important role in many aspects of life that have not been addressed specifically until now. The increasing data available enable physicians to give adequate advice and counseling regarding vocational or professional choices, suitable leisure activities and family planning according to the levels of activity considered safe and sustainable in the specific physiology. Further studies regarding exercise training and peculiar physiological changes in the univentricular circulation, also through modeling, will warrant further understanding and knowledge of issues that are specific to these patients and will help us to target interventions can help in improving quantity and quality of life.

6. REFERENCES


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