

Exercise Tolerance in Children with a Left to Right Shunt

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ABSTRACT

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

capacity, both early and late after closure. No data is available in the literature on exercise capacity in patients with PDA or coronary artery fistulas. Therefore our work will focus on ASDs, which have been widely studied, and, to a lesser extent, VSDs.

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Key words: Exercise tolerance; children; Left-to-right shunt; Atrial septal defect (ASD); Ventricular septal defect (VSD); Patent ductus arteriosus (PDA); Large coronary artery fistulas

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ATRIAL SEPTAL DEFECTS PROPOSED

Atrial septal defects are the most common form of congenital heart defect and occur in 1 child in 1,500 live births^[1]. 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^[2].

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^[1]. In a few patients (5-10%) with a secundum ASD, severe and irreversible hypertensive pulmonary vascular disease may develop^[3].

As cardiac catheterisation used to be 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 not 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 be 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^[4]. 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.

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^[6]. 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^[7].

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 VO₂ but underlined a higher prevalence of chronotropic incompetence in the surgical group, even though this didn't affect overall exercise capacity^[8]. 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^[9] and failed to show a significant improvement after trans-catheter closure^[9,10]. 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^[11]. No data is currently available on long term outcome of percutaneous closure in children.

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^[12]. 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^[13,14]. Nakanishi and colleagues tested 18 adult ASD patients and found their peakVO₂ 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^[12]. 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^[15].

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^[16].

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^[17]. 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^[18]. 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

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Table 1 Studies testing cardiopulmonary capacity in children with ASDs.

Study	Pts	Pre closure peak VO ₂ (mL/kg/min)	Pre closure peak VO ₂ (% of predicted)	Group	Age at closure (years)	Qp/Qs	PAPm (mmHg)	RVSP (mmHg)	Age at CPET (years)	Fup CPET	F post closure peak VO ₂ (mL/kg/min)	post closure peak VO ₂ (% of predicted)	Comment
Cuyppers ^[6]	63*	-	-	S	7.5±3.5	2.3	-	-	43±4.8	35±2.7 y	-	96	VO ₂ : within the normal range
de Koning 2013 ^[9]	38^	-	-	S	4.6±2.8	-	-	-	16.7±2.9	-	38.8±7.7	-	VO ₂ : within the normal range
Massin 2009 ^[7]	18	41±13	-	C	7.8±2.8	2.8±0.5	-	-	16.3±3.7	2.9±2.7 y	-	-	No difference between surgical and percutaneous closure, VO ₂ was within the normal range
Rhodes 2002 ^[8]	20	-	-	P	8.3±2.8	2.6±0.4	-	-	-	2.6±2.4 y	-	-	No significant difference pre-post ASD closure VO ₂ : was within the normal range
Plammatter 2002 ^[9]	16	40.8 (27.8-44.9)	-	S/P	13 (7-48)	1.9±0.7	16.8±3	-	-	2 (1-7) m	37.8 (28.5-48.6)	90±18	ASD pts had a significantly reduced VO ₂ : which didn't improve after closure irrespectively of shunt relevance

Legend, pts: patients; VO₂: oxygen consumption; group: kind of treatment; Qp/Qs: pulmonary flow / systemic flow; PAPm: mean pulmonary arterial pressure; RVSP: right ventricle systolic pressure; CPET: cardiopulmonary exercise test. * 63 pts underwent CPET of the 135 pts cohort described; ^ 38 pts underwent CPET of the 42 pts cohort described.

Table 2 Studies testing cardiopulmonary capacity in adults with ASDs.

Study	Pts	Pre closure peak VO ₂ (mL/kg/min)	Pre closure peak VO ₂ (% of predicted)	Group	Age at closure (years)	Qp/Qs	PAPm (mmHg)	RVSP (mmHg)	Age at CPET (years)	Fup CPET	F post closure peak VO ₂ (mL/kg/min)	post closure peak VO ₂ (% of predicted)	Comment
Fredriksen 2001 ^[13]	93	-	-	S	25 (1-72)	-	-	-	41 (17-71)	-	19.8±7.3	-	Adult pts with closed ASDs have a significant VO ₂ reduction compared to controls
Helber 1997 ^[14]	31	13.1	-	S	39.9±11.5	2.8±1.2	18.2±6.2	-	-	10 y	27.0	-	Significant VO ₂ improvement at 10y (not significant at 4m fup), Improvement was not correlated to Qp:Qs but inversely correlated to PAPm
Kobayashi 1997 ^[15]	28	27.6±6.3	-	S: Qp:Qs<3 PAPm<30	42.3±15.9	2.5±0.4	26.8±6.1	-	-	3.7±1.4 m	31.1±5.1	-	No VO ₂ improvement observed in the group with high PAPm
Suchon 2009 ^[16]	14	17.6±3.6	-	S: Qp:Qs>3 any PAPm	47.3±9.7	3.9±0.8	35.9±11.7	-	-	4.4±2.0 m	21.5±2.1	-	Significant VO ₂ improvement in the other groups
Van De Bruene 10/18	52	23.4±8.9	64.3±18.0	S	38.6±15.0	2.6±0.7	-	36.7±11.3	-	1 y	29.7±10.2	83.1±20.3	Significant improvement in VO ₂ at 1 y, no difference in the surgical/percutaneous closure; VO ₂ : didn't normalize in patients with RVSP>30 mmHg
Brochu 10/18	48	26.7±10.6	79±19	P	42.4±13.0	2.4±0.7	-	33.3±10.7	-	1 y	31.7±8.3	86.6±13.5	VO ₂ : within normal range after closure
Takaya 20	37	23.5±6.4	-	No closure	39±19	1.6±0.9	24.1±6.7	-	41±17	-	-	-	Significant VO ₂ improvement
Jategaonkar 2010 ^[20]	53*	25.5±6.7	53.6±6.5	P	49.4 (19-76)	2.1 (1.2-3.4)	-	-	-	6 m	26.9±6.9	-	Significant VO ₂ improvement in pts>40 yo
Lange 2010 ^[21]	54*	20.9±5.6	-	P: 16-40 yo	54.5±10.9	2.6±0.6	-	-	-	1 y	17.5±3.5	61.8±9.7	Significant VO ₂ improvement
Giardini 2010 ^[21]	29	16.8±5.3	-	P: 41-60yo	28.7±7.3	4.9±1.9%	15.8±4.6	-	-	3 m	27.7±7.0	-	Significant VO ₂ improvement in pts>40yo and Qp:Qs>2
J. 2009 ^[21]	35^	17.1±5.5	-	P: 61- 85 yo	50.7±5.5	51.2±11.8	21.1±5.4	-	-	3 m	23.0±6.2	-	Significant VO ₂ improvement at 3 months in all age groups if Qp:Qs>2
Lange 2010 ^[21]	24**	23.6±2.1	-	P	70.3±5.4	49.4±12.9	25.3±7.5	-	-	3 m	18.8±5.1	-	In 60-84 yo pts VO ₂ improvement is more significant if Qp:Qs>2
Giardini 2010 ^[21]	32	21.9±10.3	-	P	42.6±16.7	2.0±0.5	15.8±4.2	-	-	24 m	23.2±2.3	-	VO ₂ : within normal range, no significant VO ₂ improvement
Trojnaraska 2009 ^[21]	26	24.6±4.8	-	No closure	42.3±16.4	2.0±0.5	16±4	-	-	6 m	25.6±9.9	-	Significant VO ₂ improvement in pts<40yo and Qp:Qs>2
Oelberg 1998 ^[12]	39	33.6±9.3	88.9±14.8	Healthy controls	43.2±8.9	-	-	-	-	3.7±0.4 y	-	88.8±12.4	Further remodeling and VO ₂ : improvement in the long term
	10	17.3±4.2	-	No closure	35.8±9.3	-	-	-	-	-	-	-	Significant VO ₂ impairment compared to healthy controls
	10	22.9±5.4	-	Healthy controls	52.3±10.9	1.0±0.2	-	-	-	-	-	-	Significant VO ₂ impairment compared to healthy controls

Legend, pts: patients; VO₂: oxygen consumption; group: kind of treatment; Qp/Qs: pulmonary flow / systemic flow; PAPm: mean pulmonary arterial pressure; RVSP: right ventricle systolic pressure; fup: follow up; CPET: cardiopulmonary exercise test. * 154 pts underwent CPET of the 332 pts cohort described; ^ 35 pts underwent CPET of the 96 pts cohort described; ** 24 pts underwent CPET of the 59 pts cohort described.

stratified patients on the basis of the size of the shunt and the degree of pulmonary arterial hypertension. No peak VO_2 improvement was shown in the group of patients with $\text{PAPm} > 30$ mmHg, while those patients with significant shunts and lower pulmonary artery pressure did improve their exercise capacity following closure^[19].

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^[16].

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 mid term. 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/ CO_2 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 VO_2 ^[20].

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^[14].

Jategaonkar *et al* reported a significant decrease in right ventricular end-diastolic diameter and significant improvements of NYHA functional class and peak VO_2 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^[21].

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 ^[13]. 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 mid term^[11,13]. 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.

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 obstructive disease^[1]. 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^[22,23]. 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^[23-26]. A small number of studies concentrated on cardiopulmonary exercise testing in patients with VSDs. Binkhorst *et al.* showed no difference in peak VO_2 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 VO_2 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^[27,28].

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^[29].

DISCUSSION

Patients with significant left-to-right shunt, particularly ASD patients, even if asymptomatic, have a significant exercise capacity limitation when compared to healthy controls^[9,15]. 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^[13,29,30]. 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^[3].

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^[13,14]. 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^[13,14].

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^[7], peak VO₂ fails to reach predicted values in adult patients with preoperative signs of pulmonary hypertension^[20].

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^[9,10]. Larger subsequent studies showed that percutaneous ASD closure led to an improvement in exercise capacity regardless of age at ASD closure^[21] and symptoms, but proportional to the amount of left-to-right shunt and pulmonary artery pressure^[11,19]. Data from our lab^[13] have shown that the left-to-right shunting of blood does not only cause pulmonary over-circulation (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^[8,20]. 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^[7,11]. However, postoperative exercise capacity was reported lower than in normal subjects^[31] presumably because of low cardiac output during exercise due to reduced heart rate response during exercise^[32], 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 VO₂ 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 generalisation 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^[33] and this is due to many different factors that can be controlled or modified only to a minor extent^[34]. Therefore, exposure to long-standing increased left-to-right shunt flow where sheer 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^[35]. 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^[29].

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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