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Atrial septal defect and exercise capacity: value of cardio-pulmonary exercise test in assessment and follow-up

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Abstract: Nearly four decades ago, the World Health Organization stated that functional capacity explorations best reflected the impact of a chronic disease on quality of life. Today, cardio-pulmonary exercise test (CPET) is recommended in the follow-up of patients with congenital heart diseases (CHDs). Indeed, the maximum oxygen uptake (VO_{2max}) and the ventilatory efficiency (VE/VCO_2 slope) correlate with both the prognosis and the quality of life in this population. Atrial septal defects (ASDs) represent the second most frequent CHD and are usually considered as simple CHDs. However, the exercise capacity of ASD patients may be impaired. Therefore, the CPET provides important information in assessment and follow-up of patients with ASDs, for both children and adults. Exercise capacity of patients with unrepaired ASDs depends on the importance of the shunt, the right ventricular (RV) function and volume overload, the level of pulmonary arterial pressure, and the occurrence of arrhythmias. For repaired ASDs, exercise capacity also depends on the delay before closure and the type of procedure (catheter or surgery). In most cases, the exercise capacity is nearly normal and CPET contributes to promote sports participation. In addition, a regular CPET follow-up is necessary to evaluate the occurrence, severity and physiological mechanisms of comorbidities, i.e., heart failure, pulmonary hypertension and arrhythmia. Furthermore, CPET follow-up in patients with ASDs may detect early onset of muscular deconditioning, for which cardiac rehabilitation may be considered.

Keywords: Atrial septal defect (ASD); cardio-pulmonary exercise test (CPET); VO_2; maximum oxygen uptake; congenital heart defect

Introduction

Nearly four decades ago, the World Health Organization stated that functional capacity explorations best reflected the impact of a chronic disease on quality of life (1). In chronic heart failure, several studies have demonstrated a correlation between maximal oxygen uptake (VO_{2max}) and both quality of life and prognosis (2-4). Similar results have also been found in patients with congenital heart diseases (CHDs) (5-9) and cardio-pulmonary exercise test (CPET) is now recommended in the follow-up of this population (10).

Atrial septal defects (ASDs) represent the second most frequent CHD, with a worldwide reported birth prevalence of 2.6 per 1,000 live births (11). Undiagnosed ASDs remain significant in paediatrics (12) and their incidence in adulthood reaches the rates of 1 in 5,000–10,000 (13). Before the 90's, cardiac surgical repair was the only option for ASD; therefore, only large defects with significantly increased pulmonary blood flow (Qp/Qs >2) underwent heart surgery. Nowadays, percutaneous catheter closure is the first line therapy for most patients with ostium secundum ASDs (10). Indications of ASD closure have been progressively extended to smaller defects, ASDs with moderate pulmonary hypertension, elderly patients, and younger children (14).

Exercise capacity of patients with unrepaired ASDs depends on the importance of the shunt, the right ventricular (RV) function and volume overload, the level of pulmonary arterial pressure, and the occurrence of arrhythmias. For repaired ASDs, exercise capacity also depends on the delay before closure and the type of procedure (catheter or surgery) (15).

This review focuses on the value of CPET in assessment and follow-up of patients with repaired and unrepaired ASDs.

Methods

We searched three electronic databases on October 2017 (PubMed, EMBASE, and Web of Science) by using a combination of the terms "atrial septal defect" and "exercise test". We also used the terms "cardio-pulmonary exercise test" "CPET", "VO_2" "maximum oxygen uptake" "ASD" "peak VO_2" "VO_{2max}" in combination. The selection criteria were as follows: CPET assessment at diagnosis, CPET follow-up after ASD device closure or surgical procedure, CPET follow-up of complications (pulmonary hypertension, arrhythmia, and heart failure) and articles written in English. We did not set any restriction to study setting, era, or locale. Paediatric and adult patients were eligible. In title and abstract screening, two reviewers (P.A. and A.G.) independently reviewed articles identified by the search. Studies identified in title or abstract screening were included for full-text review.

Results

We selected 32 original studies and 2 review articles. One article in Polish and one in German were not selected (16,17). Most studies did not detail the maximum exercise test criteria and/or the existence of a plateau of VO_2. Therefore we purposely referred to "peak VO_2" in this review. The main CPET parameters are reported and explained in *Table 1* (18). The value of these parameters in repaired and unrepaired ADS are summarized in *Table 2*.

CPET in unrepaired ASDs

In most reported studies, patients with ASDs have an impaired exercise capacity and their VO_{2max} is reduced until 60% of predicted values and decreases with age (19-24), including minor reduction even for asymptomatic patients (25). Despite the lack of longitudinal cohort CPET studies among ASD patients, it is well established that symptoms usually appear during adulthood and may compromise exercise capacity in older patients (26).

However, the link between peak VO_2 and invasive haemodynamic evaluation at rest [mean pulmonary arterial pressure (mPAP), Qp/Qs ratio] remains unclear (27-30). Some studies found a correlation between Qp/Qs and peak VO_2 (21,22,29), whereas some others did not (20,25,31).

In ASD patients, RV function may also represent a limiting factor. Indeed, physiologically, the RV mean power is defined as the product of RV cardiac output by mPAP) and is linearly correlated to peak VO_2. Van De Bruaene *et al.* have shown that, compared to healthy controls, the workload of the RV in patients with an open ASD was higher at rest, due to a left-to-right shunt, and at peak exercise, due to an additional increase in mPAP (32). Therefore, during exercise, a higher increase in RV afterload may affect its function, even in asymptomatic ASD without volumetric overload and normal RV function evaluated at rest (33).

Other CPET parameters may be altered in ASDs. The ventilatory efficiency measured by the VE/VCO_2 slope increases in ASDs associated with heart failure, RV dysfunction, pulmonary hypertension and/or lung disease (18,20,21,23). The VE/VCO_2 slope correlates to prognosis in heart failure (34) and needs to be monitored in the follow-up of CHD patients, as now recommended (10).

The ventilatory anaerobic threshold (AT) may also be impaired in ASDs, as a result of muscular deconditioning, like many patients with simple and complex CHD (8). The "vicious circle" of deconditioning includes dyspnoea at exercise, sedentary lifestyle, overweight and a lack of motivation for sports and exercise. Yet, physical activity and sports are in most cases authorized and even recommended in ASDs (35). Restrictions only concern scuba diving in the presence of a small shunt (risk of paradoxical air emboli), competitive sports in case of symptomatic atrial or ventricular arrhythmias and high intensity sports in case of pulmonary arterial hypertension (PAH) (pulmonary

Table 1 CPET parameters: interpretation of the main variables

CPET parameters	Interpretation
Oxygen uptake (VO_2, mL/kg/min)	VO2 is defined as the volume of O_2 extracted from inspired air in a given period of time. It can be expressed by the Fick equation: VO_2 = Qc x C(a-v)O_2
Peak VO_2	Maximum level of oxygen consumption measured during an incremental exercise test. Usually expressed as % of predicted VO_{2max}
VO2_{max}	Plateau of VO_2 obtained despite the increasing exercise intensity. Similar to peak VO2 if effort is maximal but usually rarely achieved by patients. Usually expressed as % of predicted VO_{2max} (age- and gender-matched standards)
Maximum heart rate (HR_{max}, beats per minute-bpm)	Theoretical value usually estimated through the 220-age formula
Anaerobic threshold (AT, mL/kg/min)	Also named ventilator anaerobic threshold, the AT corresponds to the value of VO2 above which aerobic energy production is supplemented by anaerobic mechanisms, causing a sustained increase in lactate and metabolic acidosis. The AT is commonly expressed as % of predicted $VO_{2max.}$ Using the V-slope method, the AT is the breaking point of the VCO_2 versus VO_2 curve. Alternately, the AT is the point at which VE/VO_2 increases without an increase in VE/VCO_2
Minute ventilation (VE, L/min)	Ventilation (based on tidal volume and respiratory rate) during exercise. In healthy individuals, there is more than sufficient VE capacity to maintain $PaCO_2$ at any achievable workload. In heart failure, lung perfusion is altered and VE increases, which is correlated to prognosis.
VE/VO_2	Oxygen respiratory equivalent: corresponds to the number of liters of air that are being breathed for each liter of O2 uptake
VE/VCO2	Carbon dioxide respiratory equivalent: corresponds to the number of liters of air that are being breathed to eliminate 1 liter of CO_2. Normal values are usually <30
VE/VCO_2 slope	During normal incremental exercise testing, VE correlates linearly with VCO_2. The VE/VCO_2 slope in normal subjects ≈25–30. Also named ventilatory efficiency, it increases in heart failure, pulmonary hypertension, and/or intrinsic lung diseases and correlates to the prognosis
Oxygen uptake efficiency slope (OUES)	Logarithmic relation between VO_2 and VE during an incremental exercise (VO_2 = a log VE + b, where a = OUES). The more pronounced is the slope, the better is the ventilatory efficiency
Oxygen pulse (VO_2/HR, mL)	The O2 pulse is defined as: VO_2/HR=stroke volume x C (a-v)O_2. The basic profile for the O_2 pulse is to initially increase in a hyperbolically fashion, followed by a slow approach to an asymptotic value. A low, unchanging or flat O_2 pulse, with increasing work rate may be interpreted as resulting from a reduced stroke volume. The normal absolute value of O_2 pulse is >80%
Respiratory exchange ratio (RER)	Ratio VCO2/VO_2, which rises during anaerobic metabolism. The RER usually increases >1.1 during a maximal exercise test
Pulse oximetry (SpO_2, %)	Should be >95% throughout exercise test. The decline in haemoglobin oxygenation levels <90% indicates impaired ability to adequately increase alveolar-pulmonary capillary oxygen transfer during exercise
VO2/Work rate relationship (ΔVO2/ΔWR, mL/min/watt)	This slope reflects the ability of exercising muscle to extract O_2 and to aerobically generate ATP. Its reduction (<10 mL/min/w) throughout the exercise test or an acute flattening at a given point during exercise suggests a problem in O transport
Dead space to tidal volume ratio (VD/VT)	Index of gas exchange efficiency (normally value ≈0.30–0.40 at rest). An increase in VD/VT reflects an increased inefficiency of ventilation, due to V/Q mismatching or a right-to-left shunt. The ratio typically decreases initially with increasing exercise intensity due to increasing VT
Partial pressure of end-tidal CO_2 ($PetCO_2$, mmHg)	Level of CO_2 in the air exhaled from the body (normal value at rest ≈36 and 44 mm Hg ≈ arterial PCO_2). During exercise, $PetCO_2$ increases 3 to 8 mm Hg from rest to VT, and then slightly declines at maximal exercise secondary to the anaerobically induced increase in VE. Reduced values indicate V/Q mismatching, and are consistent with worsening cardiac or pulmonary disease severity, and worse prognosis

V/Q, ventilation/perfusion; CPET, cardio-pulmonary exercise test; VE, ventilatory efficiency; AT, anaerobic threshold; VD, dead space; VT, tidal volume.

Table 2 CPET parameters in ASD

CPET parameters	Unrepaired ASD	Repaired ASD
Maximum oxygen uptake (VO_2, mL/kg/min)	Decrease (adults); major decrease if PAH, HF; Normal (children); unless muscular deconditioning	Normal (children, adults) >6 months post closure; unless muscular deconditioning
Maximum heart rate (HR_{max}, beats per minute-bpm)	Normal; unless NKX 2.5 mutation (rare)	Normal; chronotropic incompetence (rare), after surgery or if NKX2.5 mutation
Anaerobic threshold (AT, mL/kg/min)	Decrease in muscular deconditioning, PH, HF; normal in children unless muscular deconditioning	Decrease in muscular deconditioning, PAH, HF; normal in children unless muscular deconditioning
Minute ventilation (VE, L/min)	Increase	Normal; unless PAH, HF
VE/VO_2	Increase	Normal; unless PAH, HF
VE/VCO_2	Increase	Normal; unless PAH, HF
VE/VCO_2 slope	Increase if PAH, HF	Normal; Increase if PAH, HF
Oxygen uptake efficiency slope (OUES)	No data	No data
Oxygen pulse (VO_2/HR, mL)	Normal; decrease if HF	Normal; decrease if HF
Respiratory exchange ratio (RER)	Increase	Normal
Pulse oxymetry (SaO_2, %)	Decrease if right-to-left shunt, PAH	Normal, unless residual shunt with PAH
VO2/Work rate relationship ($\Delta VO_2/\Delta WR$, mL/min/watt)	No data	No data
Dead space to tidal volume ratio (VD/VT)	No data	No data
Partial pressure of end-tidal CO2 ($PetCO_2$, mmHg)	Normal; decrease if right-to-left shunt	Normal; decrease if residual right-to-left shunt

PAH, pulmonary arterial hypertension; HF, heart failure; CPET, cardio-pulmonary exercise test; ASD, atrial septal defect; HR, hazard ratio; VE, ventilatory efficiency; NKX2.5, NK2 homeobox 5; VD, dead space; VT, tidal volume.

arterial systolic pressure >40 mmHg) (36). Therefore, in the situation of muscular deconditioning diagnosed by CPET, cardiac rehabilitation may be considered for ASD patients (4,37,38).

CPET in repaired ASDs

The large majority of reported studies found a significant improvement in exercise capacity after ASD closure, with both surgical and catheter procedures (15,39). The peak VO2 gradually improves after the procedure (30,40-42), and sometimes reaches normal values in the long term (31). Only one study found no improvement of peak VO2, anaerobic threshold and oxygen pulse after ASD catheter closure, but the cohort was small (N=9) and the delay after procedure was limited, between 1 and 7 months (28).

Once the ASD is closed, the reduction of volumetric overload is associated with a rapid RV remodelling (≅1 month after the procedure) and a significant exercise capacity improvement (≅6 months after the procedure) (40,41,43,44). Along with the peak VO_2, the anaerobic threshold, the ventilatory parameters and the oxygen pulse also improve after ASD closure (42,45). At exercise, the stress-induced pulmonary hypertension reduces, the RV means power increases and the RV strain improves (32,46,47). The improvement in terms of exercise capacity after ASD closure concerns patients of all ages, even elderly ones (40,43,48), but is more marked when the procedure occurs at an early stage during childhood (49). However, even when ASD closure is performed in childhood, some patients may have RV strain anomalies more than three decades after the procedure (50). Therefore, CPET remains useful in the long-term follow-up for all patients with a history of ASD.

The haemodynamic status before ASD closure stands as a main determinant for the exercise capacity improvement after the procedure. Indeed, exercise capacity in patients with large left-to-right shunt increases after ASD closure regardless of whether they had high pulmonary arterial pressure (30).

Interestingly, even asymptomatic patients and patients with sub-normal peak VO_2 before ASD closure seem to improve their exercise capacity after the procedure (22,25). Similarly, some patients with insignificant shunt (Qp/Qs <1.5) may also benefit from ASD closure in terms of peak VO_2, oxygen pulse, ventilatory efficiency and quality of life (45). Indeed, a normal haemodynamic status at rest in patients with ASDs might not be predictable of a normal haemodynamic adaptation at exercise.

No randomized trial compared catheter and surgical ASD closures in terms of CPET parameters' variation. However, the observational study from Suchon *et al.* reported a higher decrease in VE/VCO_2 slope after catheter than after surgical closure, at 1-year follow-up (39). Similarly, Van De Bruaene *et al.* showed a gap of 18% in terms of ventilatory efficiency between surgically treated patients and healthy controls, more than 7 years after surgery (23). Physiologically, pulmonary hyper perfusion may deteriorate the lung viscoelastic properties, resulting in remodelling of the lung parenchyma and fibrotic changes (51-53). In this context, the age at cardiac surgery appears to be determinant for the lungs' ability to preserve or regain their compliance (49).

CPET and comorbidities related to ASDs

As discussed in the previous paragraph, heart failure, PAH and arrhythmia are the main complications of repaired or unrepaired ASDs, for which CPET may be useful.

The existence of an impaired exercise capacity after ASD closure may be associated with RV dysfunction and/or abnormal vascular pulmonary response to exercise (54). For instance, patients with a moderate left-to-right shunt (Qp/Qs <3) associated with elevated pulmonary arterial pressure (systolic PAP >50 mmHg) have an impaired peak VO_2, which might not improve after ASD closure (30).

In patients with mild tricuspid insufficiency observed after ASD closure, the exercise capacity is more reduced. Mild tricuspid insufficiency occurs more frequently in older patients and in patients with higher mPAP at peak exercise (55). It could be considered as a marker of subclinical persistent diastolic pressure load on the right ventricle, even after ASD closure.

The exercise capacity is impaired in case of RV dysfunction, as a result of early and/or prolonged RV volume overload, but possibly also as sequel of surgery (50).

A right-to-left shunt at exercise will lead to desaturation and decrease in $PetCO_2$. Therefore, CPET may identify patients who would benefit or not from ASD closure, regarding the risk of developing pulmonary arterial vasculopathy (15). Indeed, the deoxygenated venous blood shunting to the systemic circulation causes a disproportionate rise in CO_2 levels and a reflex increase in ventilation (18). This condition commonly occurs in PAH with patent foramen ovale (PFO). Patients with PAH associated with ASD have an important decrease of exercise capacity associated with hyperventilation, attested by a VE/VCO$_2$ ratio increase. Indeed, in the most severe physiology, i.e., the Eisenmenger syndrome, the peak VO$_2$ is the lowest and the VE/VCO$_2$ slope the highest among all CHDs (8). As a result, the quality of life of these patients is significantly impaired, especially in the physical well-being, with a strong correlation to their NYHA functional class (56).

For patients in the "grey zone" of PAH, i.e., pulmonary vascular resistance between 2.3 and 4.6 Wood Units (57), ASD closure remains under debate. Some patients have been successfully treated with sildenafil, bosentan or intravenous prostacyclin allowing for defect closure (58-60). However, randomized-controlled trials on vasodilator therapy before and after ASD closure in such physiological conditions are lacking. Therefore, CPET parameters (VO$_{2\text{max}}$, VE/VCO$_2$ slope) would probably be useful as primary or secondary outcomes in future clinical trials.

Atrial fibrillation (AF) is the most common arrhythmia associated with ASD. In a large cohort of 1,111 ASD patients diagnosed during childhood, Karunanithi *et al.* showed an significantly increased risk of AF; both with closure [adjusted hazard ratio (HR) 18.5; 95% CI: 7.8–44.1, P<0.0001] and without closure (HR 16.4; 95% CI: 6.8–39.8; P<0.0001), in comparison with controls. A comparison of surgical closure with transcatheter closure found no difference in terms of risk of AF (61). Classically, the AF needs to be reduced before CPET is performed. However, in case of chronic AF associated with ASD, CPET parameters are not specific, showing deterioration of peak VO$_2$, oxygen pulse, VE/VCO$_2$ slope, and heart rate response (62).

Abnormal heart rate response during exercise is uncommon in ASDs, however, chronotropic incompetence may occur after surgical repair and therefore be diagnosed by CPET (63). Moreover, ASDs may be associated to progressive atrioventricular block, related to NK2 homeobox 5 (NKX2.5) mutations (64).

Heart failure in ASDs may also be related to left ventricular (LV) dysfunction. Indeed, some studies have reported deterioration of systolic or diastolic LV function after ASD closure. An acute rise in the volume and filling pressure of both the left atrium and LV may cause left-sided heart failure, even without evident LV dysfunction prior to the intervention (65-67). This rare condition mostly concerns elderly patients and/or patients with a large shunt, for which impairment of LV contractility may occur until 6 months after closure (68). CPET results for LV dysfunction after ASD closure are not specific: decrease in peak VO$_2$, oxygen pulse and anaerobic threshold, and increase in heart rate response and VE/VCO$_2$ slope. Therefore, close long-term observation is required after ASD closure, especially in older patients with a large shunt. In a recent study, the absolute ASD shunt volume per minute remained unchanged under dobutamine stress test compared to values at rest, and the peak VO$_2$ correlated to cardiac output but not to RV volume, suggesting abnormal LV compliance as a limiting factor for exercise capacity (69).

CPET in paediatric patients with ASDs

Exercise intolerance is uncommon in young children with an isolated ASD (28). However, pulmonary function is often impaired in this age group and improves after ASD closure (70). Although exercise capacity seems to insidiously decrease with age, serial CPET studies starting from paediatric age are clearly missing (24). In a small paediatric cohort (N=16), CPET parameters in children with ASD only slightly differ from those in normal children (71). Another small cohort (N=10) found no differences in terms of VO$_{2\text{max}}$ between children with ASD and controls (72). Similarly, in a study of 22 children with ASD surgical repair (N=22), Rosenthal *et al.* found that exercise performance was unaffected by age at repair (73).

Although peak VO$_2$ correlates with the quality of life of children with CHDs (9), the follow-up of paediatric CHD patients with CPET is not yet recommended as it is in adults with CHDs (10). Nevertheless, a normal or sub-normal peak VO$_2$ in such a simple CHD may participate in promoting self-confidence to the child, reassuring his or her family, and motivating them to engage the young patient in physical activity (74). Indeed, although physical activity and sports are in almost all cases authorized in children with ASDs (75), CHD children are often hovered over by their parents, stigmatized by their teachers, and eventually remain on the side-lines (74,76). Consequently, their quality of life is significantly reduced (9,77). Therefore, CPET follow-up in children with ASDs may detect early onset of muscular deconditioning, for which cardiac rehabilitation may be considered (75,78).

Conclusions

The CPET provides important information in assessment and follow-up of patients with ASDs, for both children and adults. In most cases, the exercise capacity is fairly normal and CPET contributes to promote sports participation. Furthermore, a regular CPET follow-up is necessary to evaluate the occurrence, severity and physiological mechanisms of comorbities, i.e., heart failure, pulmonary hypertension and arrhythmia. Finally, CPET follow-up in patients with ASDs may detect early onset of muscular deconditioning, for which cardiac rehabilitation may be considered.

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Footnote

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