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Factors associated with exercise capacity in patients with a systemic right ventricle☆

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ABSTRACT

Background: Systemic right ventricle (RV) is a rare and complex congenital heart disease (CHD). Patients with a systemic RV present with a significant decrease of their exercise capacity. We aimed at identifying clinical and paraclinical factors associated with maximum oxygen uptake ($VO2_{max}$) in adults with a systemic RV.
Methods: This multicentre cross-sectional study was performed in 2017 in three French tertiary care CHD centres. Adult patients with a D-transposition of the great artery (d-TGA) or a congenitally corrected TGA (cc-TGA) were included. Demographic, clinical, laboratory and imaging data were collected. Univariate and multivariate analyses were performed to identify predictors of impaired $VO2_{max}$, as measured by cardiopulmonary exercise test (CPET).
Results: A total of 111 patients were included in the study (85% d-TGA, median age 37.2 ± 8.2 years). Most patients presented with impaired physical capacity (mean $VO2_{max}$ of 23.3 ± 6.9 ml/kg/min, representing 68.4 ± 16.6% of predicted values) and ventilatory anaerobic threshold (VAT) impaired (mean VAT of 32.7 ± 10.9% of the predicted values). In univariate analysis, $VO2_{max}$ correlated with professional status, NYHA functional class, BNP level, the type of systemic RV, decreased RV function values in cardiac imaging, the severity of tricuspid regurgitation, the presence of a pacemaker or an implantable defibrillator, the VAT, the maximum load, and the maximal heart rate during exercise. In multivariate analysis, the $VO2_{max}$ remained associated with the NYHA functional class. The final multivariate model explained 49% of the variability of $VO2_{max}$.
Conclusion: NYHA functional class and RV function are predictors of impaired exercise capacity in adult patients with systemic RV.

1. Introduction

In the spectrum of congenital heart diseases (CHD), the systemic right ventricle (RV) represents a poorly understood physiological model, accounting for approximately 10% of all CHD [1]. In a normal heart, the RV is a compliant pump providing the low-pressure pulmonary output, whereas the systemic RV provides, by definition, the high-pressure systemic output. Therefore, the systemic RV is observed in two situations, when considering patients with two ventricles: D-looped transposition of the great arteries (d-TGA) after atrial switch procedure (Mustard, Senning) and congenitally corrected TGA (cc-TGA) [1].

Despite various adaptive mechanisms, patients with a systemic RV often present with a reduced exercise capacity, as evaluated by the maximum oxygen uptake ($VO2_{max}$), measured during a cardio-pulmonary exercise test (CPET) [2–5]. In the current guidelines, the follow-up of patients with CHD includes a CPET, and their $VO2_{max}$ correlates with both functional class (NYHA) and health-related quality of life [6,7]. The existence of an impaired exercise capacity in patients with a complex CHD

Abbreviations: BMI, body mass index; CHD, congenital heart disease; CPET, cardiorespiratory exercise test; ECG, electrocardiogram; CMR, cardiac magnetic resonance imaging; M3C, French National Reference Centre for Complex Congenital Heart Diseases; RV, right ventricle; TGA, transposition of the great arteries; VO2, oxygen uptake.

☆ The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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usually involves multifactorial mechanisms: hemodynamic changes, electrical abnormalities, ventricular pressure and/or volume increases, decreased preload, chronotropic insufficiency, desaturation, alterations of the sympathetic system, deconditioning, and/or increased neurohormonal activity [8–10].

In patients with a systemic RV, detailed mechanisms causing an impaired exercise capacity have been scarcely reported and the existing link between cardiopulmonary fitness and RV function remains controversial [11–13]. As a result, the current approach to systemic RV management is an on-going challenge. Indeed, systemic RV dysfunction is often subclinical, pharmacological therapy is empirical, patients eligible to cardiac rehabilitation are not clearly defined, and new techniques such as resynchronization are still being evaluated [1,14–16].

Therefore, assessing the determinants of the cardiopulmonary fitness in patients with a systemic RV would provide a better understanding of the pathophysiology of exercise limitation and ultimately improve management. This study aimed to identify the clinical and paraclinical characteristics associated with the maximum oxygen uptake in adult patients with a systemic RV.

2. Methods

2.1. Study design and population

This multicentre cross-sectional study was carried out from January to December 2017 in three tertiary care CHD centres in France (Montpellier University Hospital, Bordeaux University Hospital, and Georges Pompidou European Hospital in Paris). National health authorities have labelled these 3 institutions as referral centres for complex CHD (e.g. the "M3C" network).

Adult patients (≥18 years) with a systemic RV were screened. Patients with a single ventricle physiology were not eligible (double inlet right ventricle with previous Fontan palliation, and hypoplastic left heart syndrome palliated with the Norwood-Fontan protocol). Therefore, two types of systemic RV were included in the study: D-looped transposition of the great arteries (d-TGA) after atrial switch procedure (Mustard, Senning) and congenitally corrected TGA (cc-TGA). Patients followed in one of the three centres were offered to participate in the study during their annual cardiac follow-up, including at least a physical examination, an ECG, an echocardiography and a CPET, as recommended [6].

2.2. CPET variables

The main outcome of this study was the exercise capacity, as measured by the maximum oxygen uptake ($VO2_{max}$). Indeed, $VO2_{max}$ correlates with prognosis and health-related quality of life in chronic heart failure, including in patients with CHD [10,17,18].

As in our previous CPET studies [18–20], all centres used a cycle ergometer triangular protocol to obtain a homogeneous incremental overall duration between 10 and 15 min: a 1-minute rest; a 3-minute warm-up (10 to 20 W) in increments of 10, 15, or 20 watts each minute; a pedalling rate of 60 to 80 rpm; a 3-minute active recovery (20 watts); and a 2-minute rest. The following CPET variables were measured: oxygen uptake (VO2), carbon dioxide production (VCO2), heart rate, maximum load, minute ventilation (VE), ventilatory anaerobic threshold (VAT) using Beaver's method [21], ventilation efficiency (VE/VCO2 slope with $VE = slope \times VCO2 + b$), and pulse oximetry (SpO2) at rest and during exercise.

The CPET was considered as maximal when 3 out of the 4 following criteria were reached: respiratory exchange ratio ($RER = VCO2/VO2$) ≥ 1.1, maximum heart rate ≫85% of maximal age-predicted heart rate, limit of the patient's tolerance despite verbal encouragement, plateau of VO2 ($VO2_{max}$) despite the increasing exercise intensity. When the oxygen uptake did not reach a plateau, the peak VO2 was informed. $VO2_{max}$ and VAT values were normalized in a percentage of the predicted $VO2_{max}$ using reference values for cycle ergometer test in the general adult population (named as percent-predicted VO2max and percent-predicted VAT, respectively) [22,23].

2.3. Clinical and paraclinical variables

The following clinical variables were collected: gender, age, socio-professional status, weight, height, body mass index (BMI), NYHA functional class, cardiac medications, the type of systemic RV (d-TGA or cc-TGA), and the number and type of cardiac surgery or catheter procedures. We also collected the information about patients for which RV assistance or cardiac transplantation was considered. The electrocardiographic status (arrhythmia, atrio-ventricular block, pacemaker, implantable defibrillator, and age at implantation of cardiovascular devices), and the biology report (liver function, renal function, brain natriuretic peptide (BNP)) were collected.

2.4. Cardiac imaging data

The following echocardiography variables were collected, according to the current guidelines [24], and adapted to systemic RV [25]: S wave by tissue Doppler imaging (TDI), TEI index of myocardial performance using TDI, TAPSE (M-mode from the tricuspid lateral annulus), systolic longitudinal 2D strain of the RV free wall, existence and degree of tricuspid regurgitation, tricuspid dP/dt, existence and degree of pulmonary stenosis, RV surface shortening fraction, existence of any pathway obstruction (Mustard or Senning), left ventricle ejection fraction (Simpson), and RV outflow tract velocity time integral (VTI).

When the cardiovascular magnetic resonance (CMR) was performed during the same annual follow-up, the systemic RV ejection fraction (RVEF, %), using axial slice orientation, was also collected [26].

2.5. Formal aspects

The study was conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles and approved by the Ethics Committee Nord-Ouest II (2017-A01515-48). Informed consent to participate in the study was obtained from all patients.

2.6. Statistics

The study population was described using means and standard deviations (SD) for quantitative variables. For qualitative variables, frequencies and their associated percentage were used. The normal distribution of continuous variables was explored graphically. Quantitative variables were compared using Student's *t*-test when the distribution was Gaussian and using the Mann-Whitney test otherwise. For qualitative variables, groups were compared using the chi-squared test or Fisher's exact test.

The statistical analysis used the ratio of $VO2_{max}$ over predicted $VO2_{max}$, e.g. the percent-predicted $VO2_{max}$ using age, gender and weight-adjusted reference values for cycle ergometer test in the general adult population [22,23].

The association between the percent-predicted $VO2_{max}$ and other variables was explored by the Pearson correlation coefficient for normal quantitative variables, the Spearman correlation coefficient for other quantitative variables, the Kruskal Wallis test for qualitative variables with ≫2 modalities and the Student's test for the binary qualitative variables.

A multiple linear regression was used to identify the factors associated with the percent-predicted $VO2_{max}$. The relevant variables with a P value ≤ 0.2 in the univariate analysis were included in the model. The final model was obtained using an upward selection based on the Akaïke information criterion (AIC) and with an exit threshold of 0.10. The normality of residues in the final model was assessed graphically.

The statistical significance was set at 0.05 and analysed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Demographic and clinical characteristics (Table 1)

A total of 111 patients with a systemic RV were included in the study (mean age 37.2 ± 8.2 years; sex ratio of 2.2). No patients refused to participate. The most common diagnosis was d-TGA (n = 94, 85%), including 74 Mustard and 20 Senning procedures. Only 15% patients had a cc-TGA (n = 17).

A majority of patients were clinically asymptomatic (68.5% in NYHA 1 functional class), with a normal mean level of BNP. More than half (n = 60) of the patients were under at least one cardiac medication. A RV assistance or cardiac transplantation project was considered in 10 patients. Most patients were able to work full-time.

Patients with a pacemaker (n = 20; 18%) or an implantable defibrillator (n = 7; 6%) were implanted at a mean age of 20.1 ± 12.3 or 33.6 ± 5.6 years, respectively.

3.2. ECG and imaging data (Table 2)

Nearly 2/3 of patients (n = 70) presented with various conduction disorders: sinus node dysfunction (n = 24; 22%), right bundle branch block (n = 24; 22%) and complete atrioventricular block (n = 10; 9%). Supraventricular tachycardia was reported in 34 (31%) patients, including atrial flutter (n = 10; 9%) and atrial fibrillation (n = 9; 8%).

All echocardiography parameters used in this study (TAPSE, S wave, TEI index, RV surface shortening fraction, global longitudinal 2D Strain) were impaired and suggested the existence of a systemic RV systolic dysfunction. Only 17% patients presented with a severe tricuspid

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regurgitation. Atrial pathway obstruction was rare in this population. A total of 41 patients (36%) underwent CMR during the study period, reporting a mean systemic RV ejection fraction of 47 ± 9.6%.

3.3. CPET variables (Table 3)

Overall, the exercise capacity in patients with a systemic RV included in the study was impaired, with a mean $VO2_{max}$ of 23.3 ± 6.9 ml/kg/min, representing 68.4% ± 16.6% of the predicted values. Moreover, the VAT was impaired with a mean value of 13.7 ± 5 ml/kg/min, representing 32.7% ± 10.9% of the predicted $VO2_{max}$. The ventilatory efficiency was moderately impaired with a mean VE/VCO2 slope of 34 ± 8. A desaturation during exercise was found in 13 (19%) patients.

3.4. Factors associated with the $VO2_{max}$ (Table 4)

The following variables correlated with the percent-predicted $VO2_{max}$ in the univariate analysis: professional status, NYHA functional class, BNP level, the type of systemic RV, decreased RV function values in cardiac imaging, the severity of tricuspid regurgitation, the presence of a pacemaker or an implantable defibrillator, the VAT, the maximum load, and the maximal heart rate during exercise.

The percent-predicted $VO2_{max}$ was more impaired in patients with ccTGA than with atrial switch (60.0% ± 19.9% vs. 69.9% ± 15.6%, respectively, $P = 0.03$). The VE/VCO2 slope did not correlate with the percent-predicted $VO2_{max}$ ($r = -0.26$, $P = 0.16$). In this cohort, CPET was performed in 8 patients in the perspective of RV assistance or cardiac transplantation. Their $VO2_{max}$ was severely more impaired than in the other patients (37.5% ± 3.8% vs. 70.6% ± 14.8%, respectively, $P \ll 0.001$). Desaturation during exercise was reported in nearly one fifth of the patients, however this was not associated with a significant impact on exercise capacity.

All right ventricular function echocardiography parameters evaluated in this study were significantly and moderately correlated with exercise capacity (coefficients of correlation ≈ 0.3 to 0.5). In greater detail, among all these echocardiography parameters, the 2D global longitudinal strain analysis provided the best correlation level with percent-predicted $VO2_{max}$ ($r = -0.46$, $P \ll 0.01$). With a higher level of

Table 1
Socio-demographic and clinical characteristics.

Socio-demographic data		
N		111
Age (year, mean ± SD)		37.2 ± 8.2
BMI (kg/m², mean ± SD)		23 ± 3.9
Gender, N (%)	Male	76 (68.5)
	Female	35 (31.5)
Employment, N (%)	Unemployed/disability	19 (17)
	Part-time work	13 (12)
	Full-time work	79 (71)
Family circumstances, N (%)	Single	50 (45)
	Married/in a relationship	61 (55)
Clinical data		
Type of systemic RV, N (%)	D-TGA with atrial switch	94 (85)
	Cc-TGA	17 (15)
Type of atrial switch, N (%)	Senning	74 (67)
	Mustard	20 (18)
Number of cardiac surgeries, N (%)	0	7 (10)
	1	45 (67)
	≥2	15 (23)
Number of interventional catheterization procedures, N (%)	0	41 (63)
	1	13 (20)
	≥2	11 (16.9)
NYHA functional status, N (%)	I	76 (68.5)
	II	16 (14.5)
	III	17 (15)
	IV	2 (2)
Saturation (%, mean ± SD)		97.4 ± 1.4
BNP (ng/l, median [min, max])		58.5 [10, 995]
Comorbidities, N (%)	Liver insufficiency	4 (4)
	Renal insufficiency	2 (2)
	Stroke	4 (3.5)
Cardiovascular devices, N (%)	Pacemaker	22 (19.5)
	Implantable defibrillator	7 (6)
Cardiac medications, N (%)	Beta-blockers	39 (34.5)
	Other antiarrhythmic drugs	19 (16.8)
	ACE inhibitor, angiotensin II receptor blockers, sacubitril/valsartan	40 (35.4)
	Furosemide	20 (17.7)
	Anticoagulants (VKA, NOAC)	18 (15.9)
RV assistance/cardiac transplantation considered, N (%)		10 (8.9)

Values are mean ± standard deviation (SD) or N (%). Legend: ACE, angiotensin converting enzyme; BMI, body mass index; BNP, brain natriuretic peptide; NOAC, Non-vitamin k antagonist Oral Anti-Coagulants; RV, right ventricle; VKA, vitamin K antagonist.

Table 2
Electrocardiogram and imaging data.

Electrocardiogram		
Cardiac conduction disorders, N (%)	Complete atrioventricular block	10 (9)
	Sinus dysfunction	24 (22)
	Other conduction disorders[a]	36 (32.4)
	Absence of disorders	41 (37)
Cardiac rhythm disorders, N (%)	Atrial fibrillation and/or atrial flutter	19 (17)
	Other rhythmic disorders[b]	15 (13.5)
	Absence of disorders	77 (69.4)
Echocardiogram		
Systemic RV function	TAPSE (mm, mean ± SD)	12.2 ± 3.3
	S wave (cm/s, mean ± SD)	7.9 ± 2.3
	TEI index (mean ± SD)	0.50 ± 0.24
	RV Surface shortening fraction (%, mean ± SD)	33.2 ± 9.9
	Global longitudinal 2D Strain (%, mean ± SD)	−12.3 ± 4.2
	Outflow tract VTI (cm, mean ± SD)	19.4 ± 5
Tricuspid valve	Tricuspid dP/dT (mmHg/s, mean ± SD)	1065 ± 501
	Mechanic valve, N (%)	4 (3.5)
Tricuspid regurgitation	Mild, N (%)	85 (77)
	Moderate, N (%)	7 (6)
	Severe, N (%)	19 (17)
LVEF (%, mean ± SD)		66.8 ± 11.1
Atrial pathway obstruction, N (%)		7 (6)
CMR		
RVEF (%, mean ± SD)		47 ± 9.6

Values are mean ± standard deviation or N (%). Legend: AV block, Atrioventricular Block; CMR: cardiovascular magnetic resonance; LVEF, left ventricle ejection fraction; RV, right ventricle; RVEF, right ventricle ejection fraction; SD, standard deviation; RV, right ventricle; VTI, velocity time integral.

[a] Other conduction disorders: first-degree atrioventricular block, right bundle branch block, and left bundle branch block.

[b] Other rhythmic disorders: atrial ectopic tachycardia, accessory pathway, and atrial premature complexes.

Table 3
CPET data.

Variables	
$VO2_{max}$ (ml/kg/min, mean ± SD)	23.3 ± 6.9
Percent-predicted $VO2_{max}$ (%, mean ± SD)	68.4 ± 16.6
Desaturation ≫3% at exercise, N (%)	13 (19)
Percentage of predicted maximum heart rate (%, mean ± SD)	80 ± 13
Maximum systolic arterial pressure (mmHg, mean ± SD)	153 ± 23
Maximum load (Watt, mean ± SD)	120 ± 36
VAT (ml/kg/min, mean ± SD)	13.7 ± 5
Percent-predicted VAT (%, mean ± SD)	32.7 ± 10.9
VE/VCO2 slope (mean ± SD)	34 ± 8

Values are mean ± standard deviation (SD) or N (%). Legend: VAT, ventilatory anaerobic threshold; VO2max, maximum oxygen uptake; VE/VCO2 slope, the minute ventilation/carbon dioxide production slope.

correlation, systemic RV ejection fraction evaluated by CMR was associated with exercise capacity ($r = 0.56$, $P \ll 0.01$).

$VO2_{max}$ was similar in patients with or without PMK (67% ± 13% vs. 71% ± 16%, respectively, $P = 0.42$), but was lower in patients with an implantable defibrillator compared to patients without any implantable defibrillator (42% ± 8% vs. 70% ± 15%, respectively, $P \ll 0.001$).

In multivariate analysis, the $VO2_{max}$ remained affected by the NYHA functional class. The final multivariate model explained 49% of the percent-predicted $VO2_{max}$ variability.

4. Discussion

This multicentre cross-sectional study included 111 patients and appeared to be representative of the overall adult systemic RV population, in terms of physical capacity impairment, with a magnitude of $VO2_{max}$ values similar to previous reports from the literature [8,11].

In this cohort of patients with a systemic RV, the strongest predictor of impaired exercise capacity was the NYHA functional class. In adult heart failure among patients with a normal cardiac anatomy, NYHA functional class also stands as a major prognosis parameter, which strongly correlates with exercise capacity and mortality [17,27,28]. Assessment of NYHA functional class in routine clinical practice has long been neglected by congenital cardiologists, claiming that it might not reflect the wide spectrum of anatomic and physiological conditions in patients with complex CHD. Yet, NYHA functional class currently stands as an important tool to assess heart failure severity in the overall adult CHD population [29]. Nevertheless, few studies have specifically focused on heart failure and exercise capacity in patients with a systemic RV. In a cohort of 51 patients with a systemic RV, Book et al. found an association between NYHA functional class and 6-minute walk test [30], but did not use CPET parameters, as it is now recommended in the follow-up of patients with a CHD [6,31].

Despite high prevalence of associated haemodynamic lesions, previous cardiac surgeries and underlying conduction disorders, most patients in this study remained subjectively well and reported minimal

Table 4
Factors associated with exercise capacity (percent-predicted $VO2_{max}$).

Qualitative variable		Description Percent-predicted $VO2_{max}$ (% ± SD)	Univariate analysis *P*-value	Multivariate analysis *P*-value
Gender	Female	71.0 ± 13.2	0.51	–
	Male	67.1 ± 16.7		
	Unemployed/disability	59.6 ± 15.8	0.04	0.9
Professional status[a]	Part-time work	66.5 ± 16.6		
	Full-time work	70.8 ± 16.2		
NYHA functional class[a]	I	75.1 ± 13.0	≤0.0001	0.0004
	II	59.2 ± 14.1		
	II	46.6 ± 8.6		
	IV	43.1 ± 6.2		
Type of systemic RV[a]	cc-TGA	60.0 ± 19.9	0.05	0.8
	D-TGA Mustard repair	66.9 ± 18.3		
	D-TGA Senning repair	70.7 ± 14.8		
Tricuspid regurgitation[a]	Mild and moderate	71.1 ± 15.1	0.0004	0.2
	Severe	54.1 ± 17.0		
Cardiac conduction disorders[a]	Complete atrioventricular block and sinus dysfunction	65.7 ± 16.1	0.3	0.9
	Absence and low degree conduction disorders[b]	69.4 ± 16.8		
Pacemaker or implantable defibrillator[a]	Yes	59.3 ± 16.6	0.004	0.8
	No	70.9 ± 15.8		

Quantitative variables		Description r^c (percent-predicted $VO2_{max}$)	Univariate analysis *P* value	Multivariate analysis *P* value
Biology	BNP[a]	−0.37	0.0002	0.9
CPET	VAT	0.68	≪0.0001	–
	Maximum load	0.43	≪0.0001	–
	Maximal Heart rate	0.48	≪0.0001	–
Imaging	RVEF (CMR)	0.55	0.0002	–
	TAPSE	0.40	0.0003	–
	S wave	0.28	0.004	–
	TEI index	−0.40	≪0.0001	–
	RV surface shortening fraction	0.37	0.0001	–
	Global longitudinal 2D Strain	−0.46	≪0.0001	–

Legend: BNP, brain natriuretic peptide; cc-TGA, congenitally corrected transposition of the great arteries; CMR, cardiovascular magnetic resonance; D-TGA, dextro-transposition of the great arteries; NYHA, New York Heart Association functional classification; RVEF, right ventricle ejection fraction; S wave, secondary wave; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; VAT, ventilator anaerobic threshold; $VO2_{max}$, maximum oxygen uptake.

[a] Candidate variables for multivariate analysis.

[b] Low degree conduction disorders: first degree atrioventricular block, right bundle branch block, and left bundle branch block.

[c] Spearman correlation coefficient.

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or no exertional symptoms, with ≫80% patients in NYHA functional class 1 or 2. Consequently, NYHA functional class remains a major tool in the follow up of systemic RV patients and may participate in identifying patients at risk of cardiac events, and therefore those who could benefit from specific treatments. Unsurprisingly, BNP levels were also related to decreased exercise capacity. Indeed, BNP has been shown to be a strong predictor of heart failure and mortality in this population because of right ventricle sensitivity to dilatation, hence the secretion of natriuretic peptide [2,12].

In this study, all patients presented with decreased parameters of systolic RV function, as assessed by echocardiography and CMR, and these parameters moderately correlated with exercise capacity. Among all echocardiography RV function parameters, the systemic RV global longitudinal 2D strain best correlated with exercise capacity, as recently reported by Ladouceur et al. [12]. With another approach, Helsen et al. compared RV function parameters at rest (echocardiography and CMR) in terms of $VO2_{max}$ severity groups, found no significant difference, and concluded that right ventricular systolic dysfunction at rest was not related to decreased exercise capacity in patients with a systemic RV [11]. As a result, RV function assessment with cardiac imaging in systemic RV patients remains challenging, especially when considering the high number of patients with pacemaker or implantable defibrillator (e.g. 25% in our cohort) and potential contraindication for CMR. Moreover, in our study, the severity of the tricuspid regurgitation related to decreased exercise capacity. Tricuspid regurgitation determines prognosis and need for intervention in systemic RV [32,33]. In significant tricuspid regurgitation, tricuspid valve surgical repair has been suggested if RV ejection fraction is above 40% [33,34]. However, patients with severe tricuspid regurgitation may often present with significant RV dysfunction and intervention on the valve is then contraindicated. It is currently challenging to define the appropriate surgical timing for intervention on the tricuspid valve versus need for transplantation, as recurrent tricuspid regurgitation was observed in 60% of patients with systemic RV [33]. Therefore, regular CPET in the follow-up of patients with systemic RV may provide additional help, when considering the evolution of $VO2_{max}$ and VE/VCO2 slope.

Nearly half of the patients presented with chronotropic incompetence because of conduction disorders and/or bradycardic treatments. Moreover, the presence of a pacemaker or an implantable defibrillator was associated with decreased exercise capacity. In systemic RV, chronotropic incompetence is associated with impaired exercise tolerance and poor prognosis, due to decreased cardiac output [35]. Moreover, as previously reported, high-grade conduction disorders, so as long-term pacing, have an impact on cardiac function, desynchrony and clinical performance [36,37].

In this study, the existence of a low ventilatory anaerobic threshold and its association with a decreased exercise capacity, suggest that many systemic RV patients might be affected by physical deconditioning. Similarly, the association between employment status and exercise capacity reported in this study may also be indicative of muscular conditioning. Nevertheless, further research should clarify whether unemployment or part-time employment are due to physical impairment, or if, conversely, full-time employment is beneficial for muscular conditioning. Patients with a systemic RV, as in most CHD, are prone to physical deconditioning from an early age [19] and should be offered to participate in cardiac rehabilitation programs from an early age [20].

4.1. Study limitations

This multicentre cross sectional study included a significant number of systemic RV patients, but the absence of relation between exercise capacity and some clinical or paraclinical parameters in multivariate analysis may result from a lack of statistical power. Moreover, patient-related outcomes were not evaluated in this study.

End-systolic and end-diastolic RV volumes have not been routinely measured in this study; yet, recent reviews have highlighted the value of RV dimension measurement when assessing systolic function in systemic RV [38,39]. Therefore, we recently started the QUALISYTEMIC study, assessing health-related quality of life, extensive RV function measures, and exercise capacity, in a large nationwide prospective cohort of patients with a systemic RV (NCT03379831).

5. Conclusion

NYHA functional class and RV function appear to be strong predictors of exercise capacity in adults with a systemic RV, as measured by the maximum oxygen uptake. Assessing the determinants of cardiopulmonary fitness in patients with a systemic RV contributes to a better understanding of the pathophysiology of exercise limitation, and should ultimately help improving their management. Further research should evaluate the impact of cardiac rehabilitation on exercise capacity and quality of life of patients with a systemic right ventricle.

Declaration of Competing Interest

The authors have no competing interests to declare.

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