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Right ventricular systolic dysfunction at rest is not related to decreased exercise capacity in patients with a systemic right ventricle☆

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ABSTRACT

Background: To evaluate the relationship between right ventricular (RV) systolic dysfunction at rest and reduced exercise capacity in patients with a systemic RV (sRV).

Methods: All patients with congenitally corrected transposition of the great arteries (ccTGA) or complete TGA after atrial switch (TGA-Mustard/Senning) followed in our institution between July 2011 and September 2017 who underwent cardiac imaging within a six-month time period of cardiopulmonary exercise testing (CPET) were analyzed. We assessed sRV systolic function with TAPSE and fractional area change on echocardiogram and, if possible, with ejection fraction, global longitudinal and circumferential strain on cardiac magnetic resonance (CMR) imaging.

Results: We studied 105 patients with an sRV (median age 34 [IQR 28–42] years, 29% ccTGA and 71% TGA-Mustard/Senning) of which 39% had either a pacemaker (n = 17), Eisenmenger physiology (n = 6), severe systemic atrioventricular valve regurgitation (n = 14), or peak exercise arterial oxygen saturation < 92% (n = 17). Most patients were asymptomatic or mildly symptomatic (NYHA class I/II/III in 71/23/6%). Sixty-four percent had evidence of moderate or severe sRV dysfunction on cardiac imaging. Mean peak oxygen uptake (pVO2) was 24.1 ± 7.4 mL/kg/min, corresponding to a percentage of predicted pVO2 (%ppVO2) of 69 ± 17%. No parameter of sRV systolic function as evaluated on echocardiography (n = 105) or CMR (n = 46) was correlated with the %ppVO2, even after adjusting for associated cardiac defects or pacemakers.

Conclusions: In adults with an sRV, there is no relation between echocardiographic or CMR-derived sRV systolic function parameters at rest and peak oxygen uptake. Exercise imaging may be superior to evaluate whether sRV contractility limits exercise capacity.

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1. Introduction

Both in congenitally corrected transposition of the great arteries (ccTGA) and complete TGA after atrial switch procedure (TGA-Mustard/Senning), the morphological right ventricle acts as the systemic ventricle (sRV). A progressive decline in sRV systolic function with development of heart failure is a major concern in adults with an sRV [1–4]. Current standard of care prescribes annual follow-up in a specialized Adult Congenital Heart Disease center with clinical examination, electrocardiogram and echocardiogram at rest [5]. If heart failure is suspected, natriuretic peptides and cardiopulmonary exercise testing (CPET) have additional value in the assessment of those patients [6]. However, it remains unclear whether a certain degree of sRV dysfunction at rest in a patient without clinical signs or subjective symptoms of heart failure should lead to a further diagnostic work-up. This study aimed to investigate the association between echocardiographic or

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cardiac magnetic resonance (CMR)-derived parameters of sRV systolic function at rest and peak oxygen consumption.

2. Methods

2.1. Study population

The records of all patients with an sRV were retrieved from the CPET database of the University Hospitals Leuven (Belgium). All files between July 2011 and September 2017 were reviewed. Exclusion criteria were patients with a functionally univentricular heart, a ventricular assist device, or a submaximal CPET. Baseline clinical, electrocardiographic and echocardiographic variables were documented at the day of the CPET. CMR data of those patients with a CMR within six months of the CPET were also analyzed.

The study was conducted in compliance with the principles of the Declaration of Helsinki. The local institutional ethical review committee approved the study and waived informed consent. All authors had direct access to the raw and derived datasets.

2.2. Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) with continuous monitoring of expiratory gases was performed on an upright cycle ergometer (ER900 and Oxycon Alpha, Jaeger, Germany) using a continuous ramp protocol until exhaustion [7]. Maximal power output in Watts (P_{max}), peak oxygen consumption (pVO_2), ventilatory equivalent for carbon dioxide (VE/VCO_2), heart rate (HR), systolic blood pressure (SBP) and peak exercise arterial oxygen saturation were recorded. We calculated the predicted pVO_2 (%$ppVO_2$) with the Wasserman equation as a measure for peak exercise capacity. The first ventilatory anaerobic threshold was determined according to Binder [8] and expressed as a percentage of pVO_2. Heart rate reserve (HHR) was defined by the formula (peak exercise HR − resting HR). Age-adjusted HRR was calculated as (HRR / [220 − age − resting HR]). Peak oxygen pulse (POP), a surrogate for stroke volume, was calculated as (pVO_2 / peak HR). All patients with a respiratory exchange ratio (RER) at peak exercise ≥1.10, or a RER ≥1.01 while reaching the second ventilatory threshold, or a RER ≥1.04 at a Borg score ≥ 15, or a peak exercise oxygen saturation ≤ 60%, were considered to have performed a maximal CPET. A resting 12-lead ECG was analyzed for the presence of fragmented QRS complexes [9].

2.3. Cardiac resting imaging

Experienced sonographers performed comprehensive 2-dimensional and color Doppler echocardiographic examinations. All digital loops were retrieved from the hospital files and reanalyzed offline using dedicated software (EchoPAC PC Version 113, General Electric Vingmed Ultrasound, Horten, Norway). Quantification of systolic sRV function was done qualitatively using an integrative multi-view approach and quantitatively with tricuspid annular plane systolic excursion (TAPSE) and sRV fractional area change (sRV FAC) [10]. Severity of systemic atrioventricular valve (SAVV) regurgitation was semi quantitatively assessed by color flow Doppler and was graded as none-to-mild, moderate, or severe [11].

CMR studies were performed using a 1.5 T scanner (Achieva, Philips Medical Systems, Best, the Netherlands). Steady-state free precession end-inspiratory breath hold cine-images were acquired in approximated horizontal and vertical long-axis planes to reach the best orientation for obtaining a stack of short-axis slices covering the ventricular cavities. All CMR studies were retrieved from the hospital files and reanalyzed. The sRV ejection fraction (EF) was quantified on an in-house developed software program (RightVol, Leuven, Belgium) [12]. Global longitudinal strain (GLS) and global circumferential strain (GCS) of the sRV were quantified using the strain analysis module in Segment v2.0 R5557 (Medviso, Lund, Sweden) [13]. This analysis consisted of contouring the sRV myocardium and triggering the automatic computation. We contoured the sRV myocardium on two or more long axis slices for the GLS and on all short axis slices for the GCS. If necessary, the contouring was repeated until the visually assessed tracking consistency was optimal.

2.4. Statistical analysis

Categorical variables are expressed as numbers and percentages. Continuous data are presented as mean ± standard deviation (SD) or as median (25 and 75% percentile [IQR]). Data were tested for normal distribution with the Shapiro-Wilk test. Differences between groups for continuous variables were analyzed using unpaired *t*-test, Kruskal-Wallis H test, Wilcoxon-Mann-Whitney test or one-way ANOVA, as appropriate; Pearson's chi-square test or Fisher's exact test was performed for categorical variables. For multivariable analyses, linear regression models were constructed. All statistical tests were 2-sided, and a P-value <0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics, version 24.

3. Results

3.1. Patient characteristics

In our institutional database, 111 individual patients with an sRV underwent CPET between July 2011 and September 2017. We excluded six patients: one with a Fontan circulation, two with a ventricular assist device and three with a submaximal CPET. The remaining 105 patients were studied (Table 1). Median age was 34 (IQR 28–42) years; 32% were female; 71% were in NYHA functional class I. Thirty (29%) patients had ccTGA, five of them had previous physiologic repair (consisting of VSD closure [patient 1–4], left ventricular outflow tract patch augmentation [patient 1], subpulmonary stenosis resection [patient 3], implantation of a prosthetic SAVV [patient 3–4], and SAVV repair [patient 5]) and two had undergone pulmonary artery banding. Of the 75 TGA-Mustard/Senning patients studied, 67% had undergone Senning repair. They were significantly younger than the patients after Mustard repair (the mean age ± SD was 30 ± 4 vs. 41 ± 4 years). Six TGA-Mustard/Senning patients had Eisenmenger physiology (five due to a large ventricular septal defect, one due to a long-standing baffle leak). TGA-Mustard/Senning patients were significantly younger than ccTGA patients and were less likely to have QRS fragmentation and a pacemaker. The indication for pacemaker implantation in TGA-Mustard/Senning patients was sick sinus syndrome, His bundle ablation or high-grade AV-block in respectively 71.4, 14.3 and 14.3%. All pacemakers in the ccTGA patients were implanted for a high-grade AV-block; four of them received cardiac resynchronization therapy in the setting of heart failure. Three patients had an Implantable Cardioverter Defibrillator, one in primary and two for secondary prevention.

3.2. Cardiac resting imaging

sRV systolic function was moderately or severely impaired in 67 (64%) patients. Quantitative measures of sRV function are noted in Table 1. There was no correlation between TAPSE and GCS values (P = 0.940). All other cardiac resting imaging parameters correlated with each other (the absolute correlation coefficient ranged from 0.317 to 0.665, P ≤ 0.044). About two-thirds of patients showed moderate or severe systemic atrioventricular valve (SAVV) regurgitation; three patients (3%) had a prosthetic SAVV. An open ventricular septal defect (VSD) was present in 16 patients (31% of them had a small perimembranous defect and 69% a large VSD). All five TGA-Mustard/Senning patients with a large VSD had Eisenmenger physiology; all six ccTGA patients with a large VSD had a balanced circulation with concomitant pulmonary outflow tract obstruction.

3.3. Cardiopulmonary exercise testing

Mean $pV0_2$ was 24.1 ± 7.4 mL/kg/min, corresponding to a %$ppVO_2$ of 69 ± 17%. Oxygen saturation at peak exercise below 92% was present in 17 patients. Median peak heart rate and heart rate reserve was significantly lower in ccTGA patients, even after correcting for the older age of these patients. Median peak oxygen pulse was higher in ccTGA patients.

Patient characteristics were assessed according to tertiles of the %$ppVO_2$ (Table 2), which resulted in categories of %ppVO2 ≥ 75 (upper), 62 to 74 (middle), and ≤61% (lower). The median %$ppVO_2$ in the three tertiles were 86, 67 and 55%, respectively. Patients with lower %$ppVO_2$ had a higher NYHA class and were more likely to receive beta-blockers, aldosterone antagonists and loop diuretics. There was also a higher incidence of pacemakers. There were clear and consistent differences across the tertiles in chronotropic competence, peak systolic blood pressure, peak oxygen pulse, the anaerobic threshold and VE/VCO_2 slope. No significant differences in resting parameters of systolic sRV function were found across the tertiles.

3.4. Factors associated with exercise capacity

In the total cohort of sRV patients, there was no significant correlation between resting parameters of systolic sRV function and the %$ppVO_2$ (all P-values ≥0.241) (Fig. 1). This result did not change when we assessed ccTGA and TGA-Mustard/Senning patients separately, nor

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Table 1
Patient characteristics.

	Total (N = 105)	ccTGA (N = 30)	TGA-Mustard/Senning (N = 75)	P-value
Age, years	33.9 (27.6–41.8)	40.4 (28.2–49.3)	33.3 (27.3–38.2)	**0.016**
Female gender	33 (32)	7 (23)	26 (35)	0.258
Pacemaker	17 (16)	10 (33)	7 (9)	**0.006**
NYHA functional class, I/II/III/IV	75 (71)/24 (23)/6 (6)	21 (70)/7 (23)/2 (7)	54 (72)/17 (23)/4 (5)	0.959
Medication				
Beta blocker	31 (29.5)	12 (40)	19 (25)	0.137
ACE-I/ARB	27 (26)	10 (30)	17 (23)	0.259
Aldosterone antagonist	8 (8)	3 (10)	5 (7)	0.686
Loop diuretic	9 (9)	4 (13)	5 (7)	0.272
fQRS	50 (48)	19 (63)	31 (41)	**0.041**
Echocardiographic characteristics				
Systemic RV dysfunction, mild/moderate/severe	38 (36)/54 (51.5)/13 (12.5)	13 (43)/12 (40)/5 (17)	25 (33)/42 (56)/8 (11)	0.320
TAPSE, mm	12 (10–15)	15 (12–17)	11 (10–15)	**0.001**
RV FAC, %	23 ± 7	23 ± 9	23 ± 7	0.850
SAVV regurgitation, mild/moderate/severe/prosthetic valve	36 (34)/52 (50)/14 (13)/3 (3)	2 (7)/16 (53)/10 (33)/2 (7)	34 (45.3)/36 (48)/4 (5.3)/1 (1.3)	<**0.001**
VSD	16 (15)	9 (30)	7 (9)	**0.014**
CMR characteristics				
RV EF, %	42 ± 10 (N = 46)	44 ± 10 (N = 13)	41 ± 10 (N = 33)	0.406
GLS	−12.2 ± 3.0 (N = 46)	−11.7 ± 3.6 (N = 13)	−12.4 ± 2.7 (N = 33)	0.510
GCS	−15.2 ± 5.5 (N = 41)	−11.4 ± 4.8 (N = 11)	−16.6 ± 5.1 (N = 30)	**0.005**
CPET characteristics				
Peak power output, W	161 ± 51	152 ± 47	164 ± 52	0.269
Peak VO_2, mL/kg/min	24.1 ± 7.4	22.5 ± 6.5	24.8 ± 7.7	0.146
Peak VO_2, % of predicted peak VO_2	69 ± 17	67 ± 19	70 ± 16	0.441
Peak heart rate, bpm	164 (139–176)	140 (98–171)	169 (150–179)	**0.001**
HRR, bpm	82 (63–95)	67 (33–89)	88 (76–99)	<**0.001**
Age-adjusted HRR, %	60 (46–69)	50 (22–65)	62 (53–70)	<**0.001**
Peak SBP, mm Hg	159 ± 25	155 ± 29	161 ± 24	0.342
Peak O2 saturation < 92%	17 (17) (N = 102)	3 (10) (N = 28)	14 (19) (N = 74)	0.388
VE/VCO_2 slope	29.8 (26.9–34.8)	29.9 (27.6–36.4)	29.6 (26.4–34.0)	0.561
Peak oxygen pulse, mL/beat	11.4 (8.8–13.8)	13.0 (11.7–16.0)	11.0 (8.4–13.0)	**0.003**
Anaerobic threshold, % of peak VO_2	48 ± 13	48 ± 14	49 ± 13	0.896

Values are mean ± SD, median (IQR) or number (%). Bold text highlights significant comparisons (P value <0.05).
ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise testing; EF, ejection fraction; FAC, fractional area change; GLS, global longitudinal strain; GCS, global circumferential strain; HRR, heart rate reserve; n, number of patients; RV, right ventricular; SAVV, systemic atrioventricular valve; SBP, systolic blood pressure; VSD, ventricular septal defect.

when we excluded patients with Eisenmenger physiology, a pacemaker, severe SAVV regurgitation, or arterial oxygen saturation at peak exercise <92%.

The HRR and the anaerobic threshold explained 64% of the variance in the %ppV0_2. In the subgroup of patients with a peak exercise arterial oxygen saturation ≥ 92% and no PM, the HRR stayed a significant contributor to the variance in the %ppV0_2. The peak exercise SBP and VE/VCO_2 slope were correlated with peak oxygen consumption. However, they did not significantly impact the variance in the %ppV0_2 after adjusting for the HRR and the anaerobic threshold.

4. Discussion

The key finding of this study is that there is no association of resting parameters of systolic sRV function with peak oxygen consumption. This suggests that a follow-up with resting imaging alone is insufficient and that a more comprehensive evaluation of a patient with a systemic RV is needed.

4.1. Systemic RV function assessment

The gold standard for ventricular function assessment is CMR-derived EF [14]. However, the EF is an expression of the ratio of stroke volume to end-diastolic volume and not of intrinsic myocardial contractility. Strain potentially better reflects systolic ventricular function because it examines the myocardial deformation that occurs during ventricular contraction. Some studies assessed GLS in patients with a sRV, indicating a correlation with sRV FAC [15], sRV EF [16] and an association with adverse outcome [17]. With our study results we can corroborate these findings. Another component of myocardial strain that we measured is the GCS. Although it is infrequently reported in patients with a sRV, it is probably a better marker of systolic sRV dysfunction as there is a shift to predominant circumferential over longitudinal free wall shortening in the sRV compared with the normal RV [18]. All strain measurements in our series were based on CMR data to be less dependent on patient echogenicity and acoustic windows [19].

4.2. Systemic RV function at rest and its impact on exercise capacity

Reduced exercise capacity is common in adults with congenital heart disease, even if they consider themselves asymptomatic [20] [21]. In the past, investigators have tried to study the possible impact of sRV dysfunction on exercise capacity. These studies yielded conflicting results (Table 3).

In TGA-Mustard patients, two older studies found a moderated to high degree of correlation between pVO2 and a single quantitative parameter of sRV function (respectively TAPSE [22] and the Tei index [23]). However, both studies are limited by low patient numbers. Studies focusing on CMR-based EF either point towards a low degree of correlation [24] or a complete lack of correlation [19,25,26]. A more novel way to assess sRV systolic function is by deformation imaging in which patterns of features/irregularities are tracked in successive images during a cardiac cycle, either with speckle tracking echocardiography or by CMR feature tracking [27]. Generally there is a good

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Table 2
Patients divided in tertiles of %ppVO$_2$.

	Lower %ppVO$_2$ tertile	Middle %ppVO$_2$ tertile	Upper %ppVO$_2$ tertile	P-value
	N = 35	N = 35	N = 35	
Peak VO$_2$, % of predicted peak VO$_2$	55 (45–59)	67 (65–70)	86 (81–92)	**<0.001**
Age, years	35.9 (27.7–42.9)	34.5 (27.3–42.6)	32.0 (27.2–39.2)	0.405
ccTGA/TGA-Mustard/TGA-Senning	13 (37)/10 (29)/12 (34)	8 (23)/9 (26)/18 (51)	9 (26)/6 (17)/20 (57)	0.340
Female gender	10 (29)	9 (26)	14 (40)	0.395
Pacemaker	10 (29)	5 (14)	2 (6)	**0.032**
NYHA functional class, I/II/III/IV	12 (34.3)/18 (51.4)/5 (14.3)	29 (83)/5 (14)/1 (3)	34 (97)/1 (3)/0	**<0.001**
Medication				
Beta blocker	14 (40)	12 (34)	5 (14)	**0.047**
ACE-I/ARB	10 (29)	12 (34)	5 (14)	0.143
Aldosterone antagonist	6 (17)	2 (6)	0	**0.023**
Loop diuretic	6 (17)	3 (9)	0	**0.038**
fQRS	16 (46)	16 (46)	18 (51)	0.858
Echocardiographic characteristics				
Systemic RV dysfunction, mild/moderate/severe	15 (43)/15 (43)/5 (14)	10 (29)/20 (57)/5 (14)	13 (37)/19 (54)/3 (9)	0.664
TAPSE, mm	12 ± 4	13 ± 4	13 ± 3	0.871
RV FAC, %	23 ± 8	22 ± 7	23 ± 8	0.635
SAVV regurgitation, mild/moderate/severe/prosthetic valve	11 (31)/17 (49)/4 (11)/3 (9)	13 (37)/16 (46)/6 (17)/0	12 (34.3)/19 (54.3)/4 (11.4)/0	0.320
Eisenmenger physiology	6 (17)	0	0	**0.002**
CMR characteristics				
RV EF, %	44 ± 8 N = 13	39 ± 10 N = 14	43 ± 11 N = 19	0.352
GLS	−12.2 ± 2.7 N = 13	−12.0 ± 3.6 N = 14	−12.3 ± 2.8 N = 19	0.949
GCS	−15.1 ± 5.4 N = 13	−15.3 ± 6.1 N = 14	−15.2 ± 5.5 N = 14	0.997
CPET characteristics				
Peak power output, W	120 (90–140)	160 (120–180)	200 (160–240)	**<0.001**
Peak VO$_2$, mL/kg/min	18.2 ± 4.7	24.1 ± 5.1	30.1 ± 6.9	**<0.001**
Peak heart rate, bpm	136 (100–164)	164 (142–179)	173 (171–181)	**<0.001**
HRR, bpm	57 (32–79)	82 (71–94)	94 (89–106)	**<0.001**
Age-adjusted HRR, %	45 (20–58)	59 (52–69)	67 (62–73)	**<0.001**
Peak SBP, mmHg	150 ± 24	161 ± 24	168 ± 25	**0.011**
Peak O2 saturation<92%	14 (41) N = 34	3 (9) N = 33	0 N = 35	**<0.001**
VE/VCO$_2$ slope	32.5 (27.4–39.3)	28.6 (26.5–32.9)	29.6 (26.4–33.0)	**0.049**
Peak oxygen pulse, mL/beat	10.7 (6.9–12.4)	11.2 (9.3–13.4)	12.6 (9.7–14.4)	**0.037**
Anaerobic threshold, % of peak VO$_2$	39 ± 10	46 ± 9	60 ± 11	**<0.001**

Values are mean ± SD, median (IQR) or number (%). Bold text highlights significant comparisons (P value <0.05).
CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise testing; EF, ejection fraction; FAC, fractional area change; GLS, global longitudinal strain; GCS, global circumferential strain; HRR, heart rate reserve; n, number of patients; RV, right ventricular; SAVV, systemic atrioventricular valve; SBP, systolic blood pressure; VSD, ventricular septal defect.

correlation between strain measurements obtained by echocardiography and CMR [28,29]. In TGA-Mustard/Senning patients, Ladouceur et al. [26] found a low-to-moderate correlation between exercise capacity and GLS measured by speckle tracking echocardiography. Unfortunately, they did not report GCS values. In contrast, our study and the study of Tutarel et al. [19] fail to reproduce this correlation using CMR feature tracking. This could be related to differences in patient characteristics as the series of Ladouceur had a skewed distribution towards some patients with a very low peak oxygen uptake. Data specific in ccTGA patients is even scarcer. Grewal et al. found no difference between sRV function at rest in ccTGA patients with a normal versus impaired %ppV02 [30]. In a study were ccTGA and TGA-Mustard/Senning patients were pooled, there was a low degree of correlation between the %ppVO2 and sRV EF or the Tei index [24]. Although we examined a large series of sRV patients, we could not find a correlation between any cardiac resting imaging parameters and peak oxygen uptake. Although both ccTGA and TGA-Mustard/Senning patients have a RV in systemic position, one might wonder if it would not be more prudent to assess them separately as mechanisms to achieve cardiac output augmentation differ [31]. However, even when adjusting for the type of sRV and other possible confounders, we could not identify a significant correlation between systolic sRV function at rest and peak oxygen uptake.

Because none of sRV systolic function parameters correlated with the peak oxygen uptake, we tried to identify other parameters that might predict peak oxygen uptake. In this sub analysis we could identify the HRR and the physical fitness level (anaerobic threshold) as the two main determinants. Effectively, the peak heart rate is an important determinant of the cardiac output and hence peak oxygen uptake. An abnormal HRR is also an independent predictor of survival in congenital heart disease and in heart failure [32,33]. Second, there is a relatively high incidence of a sedentary lifestyle and physical deconditioning in patients with chronic conditions influencing peak exercise capacity. Randomized trials have shown that a training protocol could improve peak oxygen consumption in this population [34,35].

This series complements the current literature, by reporting both echocardiography and CMR-derived measures of sRV function in a large cohort of patients with sRV, by assessing circumferential strain in the whole ventricle, and by accounting for possible confounders.

4.3. Limitations

This study has some limitations. First, this was a retrospective, single-institution cohort study. Adults with TGA comprise approximately 1.6% of all grown-up congenital patients [36], making large studies and subgroup analyses difficult. Second, the echocardiographic assessment of sRV function is challenging. Therefore, we added CMR measures of sRV function whenever possible. Besides EF we also assessed GLS and GCS [13]. Third, we do not have systematically assessed NT-proBNP or other biomarkers at the time of CPET. Last, in this study we could not look in depth to the role of loading conditions and baffle related problems, fibrosis, myocardial contractile reserve and systemic RV geometry, although these are

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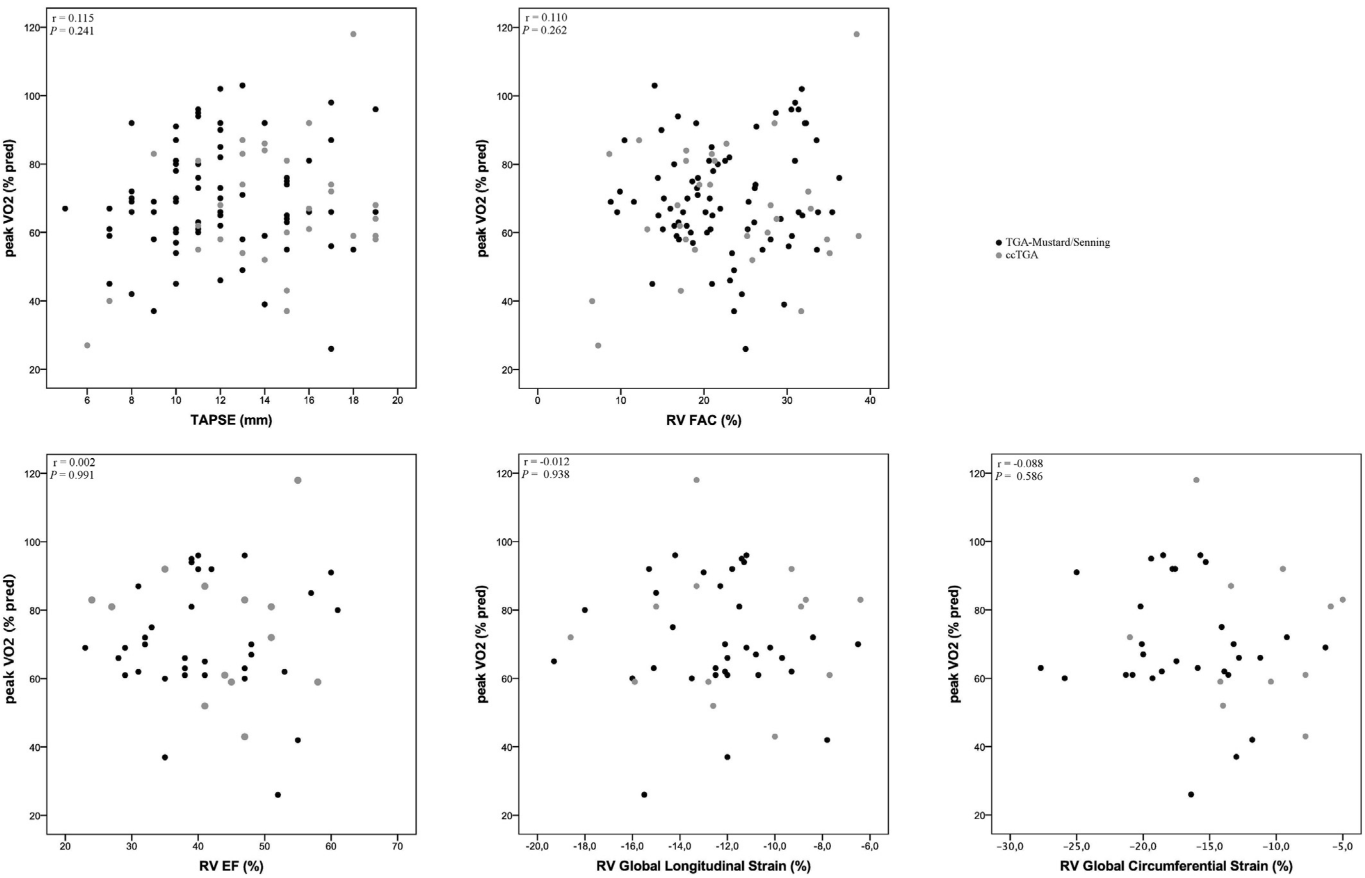

Fig. 1. There is no relation between systolic right ventricular function at rest and peak oxygen uptake in adults with a systemic right ventricle. ccTGA, congenitally corrected transposition of the great arteries (grey dots); TGA-Mustard/Senning, complete transposition of the great arteries after atrial switch procedure (black dots).

important factors to consider. Further studies with cardiac stress imaging, fibrosis imaging and biomarker analysis – preferably in a longitudinal manner – are warranted in this population.

5. Conclusions

Based on our findings, the value of imaging the sRV at rest - whether it is by echocardiography or CMR - to understand exercise intolerance is limited. Exercise testing could provide a better understanding of the interplay between cardiac filling and contractility, chronotropy, pulmonary function, oxygen extraction and peripheral muscle strength in both conditions.

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Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

Table 3
Previous studies examining the association between quantitative parameters of sRV function and peak oxygen uptake.

	n	Type of sRV	Quantitative parameter(s) of sRV function	Correlations with peak oxygen uptake
Grewal J. et al. [30]	26	ccTGA	CMR: EF	x
			TTE: longitudinal strain (free wall & septum), circumferential strain (mid free wall), Tei index	x
Tutarel O. et al. [19]	91	TGA-Mustard/Senning	CMR: EF, GLS, GCS, GRS	x
Roentgen P. et al. [25]	21	TGA-Mustard	CMR: EF	x
Norozi K. et al. [23]	33	TGA-Mustard	TTE: Tei index	Tei index ($r = -0.83$)
Li W. et al. [22]	27	TGA-Mustard	TTE: TAPSE, S′	TAPSE ($r = 0.66$)
Shafer KM et al. [24]	69	ccTGA + TGA-Mustard/Senning	CMR: EF	EF ($r = 0.29$)
			TTE: TAPSE, Tei index, dP/dT	Tei index ($r = -0.22$)
Ladouceur M. et al. [26]	47	TGA-Mustard/Senning	CMR: EF	x
			TTE: FAC, dP/dT, TAPSE, S′, Tei index, GLS, GTS	GLS ($r = 0.42$)

ccTGA, congenitally corrected transposition of the great arteries; CMR, cardiovascular magnetic resonance imaging; EF, ejection fraction; GLS, global longitudinal strain; GTS, global transverse strain; n, number of individual patients; sRV, systemic right ventricle; TGA, complete transposition of the great arteries; TTE, transthoracic echocardiogram.

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References

[1] T.P. Graham, Y.D. Bernard, B.G. Mellen, D. Celermajer, H. Baumgartner, F. Cetta, et al., Long-term outcome in congenitally corrected transposition of the great arteries: a multi-institutional study, J. Am. Coll. Cardiol. 36 (2000) 255–261.

[2] J.A. Cuypers, J.A. Eindhoven, M.A. Slager, P. Opić, E.M. Utens, W.A. Helbing, et al., The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years, Eur. Heart J. 35 (2014) 1666–1674.

[3] S. Piran, G. Veldtman, S. Siu, G.D. Webb, P.P. Liu, Heart failure and ventricular dysfunction in patients with single or systemic right ventricles, Circulation 105 (2002) 1189–1194.

[4] A. Van De Bruaene, E.J. Hickey, A.H. Kovacs, A.M. Crean, R.M. Wald, C.K. Silversides, et al., Phenotype, management and predictors of outcome in a large cohort of adult congenital heart disease patients with heart failure, Int. J. Cardiol. 252 (2017) 80–87.

[5] H. Baumgartner, P. Bonhoeffer, N.M. De Groot, F. de Haan, J.E. Deanfield, N. Galie, et al., ESC guidelines for the management of grown-up congenital heart disease (new version 2010), Eur. Heart J. 31 (2010) 2915–2957.

[6] W. Budts, J. Roos-Hesselink, T. Rädle-Hurst, A. Eicken, T.A. McDonagh, E. Lambrinou, et al., Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology, Eur. Heart J. 37 (2016) 1419–1427.

[7] Society AT, Physicians ACoC, ATS/ACCP statement on cardiopulmonary exercise testing, Am. J. Respir. Crit. Care Med. 167 (2003) 211–277.

[8] R.K. Binder, M. Wonisch, U. Corra, A. Cohen-Solal, L. Vanhees, H. Saner, et al., Methodological approach to the first and second lactate threshold in incremental cardiopulmonary exercise testing, Eur. J. Cardiovasc. Prev. Rehabil. 15 (2008) 726–734.

[9] F. Helsen, B. Vandenberk, P. De Meester, A. Van De Bruaene, C. Gabriels, E. Troost, et al., Appearance of QRS fragmentation late after Mustard/Senning repair is associated with adverse outcome, Heart 103 (2017) 1036–1042.

[10] R.M. Lang, L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging, J. Am. Soc. Echocardiogr. 28 (2015), 1-39.e14.

[11] P. Lancellotti, L. Moura, L.A. Pierard, E. Agricola, B.A. Popescu, C. Tribouilloy, et al., European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease), Eur. J. Echocardiogr. 11 (2010) 307–332.

[12] A. La Gerche, G. Claessen, A. Van de Bruaene, N. Pattyn, J. Van Cleemput, M. Gewillig, et al., Cardiac MRI: a new gold standard for ventricular volume quantification during high-intensity exercise, Circ. Cardiovasc. Imaging 6 (2013) 329–338.

[13] P. Morais, A. Marchi, J.A. Bogaert, T. Dresselaers, B. Heyde, J. D'hooge, et al., Cardiovascular magnetic resonance myocardial feature tracking using a non-rigid, elastic image registration algorithm: assessment of variability in a real-life clinical setting, J. Cardiovasc. Magn. Reson. 19 (2017) 24.

[14] S. Orwat, G.P. Diller, H. Baumgartner, Imaging of congenital heart disease in adults: choice of modalities, Eur. Heart J. Cardiovasc. Imaging 15 (2014) 6–17.

[15] J.A. Eindhoven, M.E. Menting, A.E. van den Bosch, J.S. McGhie, M. Witsenburg, J.A. Cuypers, et al., Quantitative assessment of systolic right ventricular function using myocardial deformation in patients with a systemic right ventricle, Eur. Heart J. Cardiovasc. Imaging 16 (2015) 380–388.

[16] M. Lipczyńska, P. Szymański, M. Kumor, A. Klisiewicz, Ł. Mazurkiewicz, P. Hoffman, Global longitudinal strain may identify preserved systolic function of the systemic right ventricle, Can. J. Cardiol. 31 (6) (2015) 760.

[17] G.P. Diller, J. Radojevic, A. Kempny, R. Alonso-Gonzalez, L. Emmanouil, S. Orwat, et al., Systemic right ventricular longitudinal strain is reduced in adults with transposition of the great arteries, relates to subpulmonary ventricular function, and predicts adverse clinical outcome, Am. Heart J. 163 (2012) 859–866.

[18] E. Pettersen, T. Helle-Valle, T. Edvardsen, H. Lindberg, H.J. Smith, B. Smevik, et al., Contraction pattern of the systemic right ventricle shift from longitudinal to circumferential shortening and absent global ventricular torsion, J. Am. Coll. Cardiol. 49 (2007) 2450–2456.

[19] O. Tutarel, S. Orwat, R.M. Radke, M. Westhoff-Bleck, C. Vossler, C. Schülke, et al., Assessment of myocardial function using MRI-based feature tracking in adults after atrial repair of transposition of the great arteries: reference values and clinical utility, Int. J. Cardiol. 220 (2016) 246–250.

[20] G.P. Diller, K. Dimopoulos, D. Okonko, W. Li, S.V. Babu-Narayan, C.S. Broberg, et al., Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication, Circulation 112 (2005) 828–835.

[21] A. Kempny, K. Dimopoulos, A. Uebing, P. Moceri, L. Swan, M.A. Gatzoulis, et al., Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life–single centre experience and review of published data, Eur. Heart J. 33 (2012) 1386–1396.

[22] W. Li, T.S. Hornung, D.P. Francis, C. O'Sullivan, A. Duncan, M. Gatzoulis, et al., Relation of biventricular function quantified by stress echocardiography to cardiopulmonary exercise capacity in adults with Mustard (atrial switch) procedure for transposition of the great arteries, Circulation 110 (2004) 1380–1386.

[23] K. Norozi, R. Buchhorn, V. Alpers, J.O. Arnhold, S. Schoof, M. Zoege, et al., Relation of systemic ventricular function quantified by myocardial performance index (Tei) to cardiopulmonary exercise capacity in adults after mustard procedure for transposition of the great arteries, Am. J. Cardiol. 96 (2005) 1721–1725.

[24] K.M. Shafer, N. Mann, R. Hehn, A. Ubeda Tikkanen, A.M. Valente, T. Geva, et al., Relationship between exercise parameters and noninvasive indices of right ventricular function in patients with biventricular circulation and systemic right ventricle, Congenit. Heart Dis. 10 (2015) 457–465.

[25] P. Roentgen, M. Kaan, O. Tutarel, G.P. Meyer, M. Westhoff-Bleck, Declining cardiopulmonary exercise capacity is not associated with worsening systolic systemic ventricular dysfunction in adults with transposition of great arteries after atrial switch operation, Congenit. Heart Dis. 9 (2014) 259–265.

[26] M. Ladouceur, A. Redheuil, G. Soulat, C. Delclaux, M. Azizi, M. Patel, et al., Longitudinal strain of systemic right ventricle correlates with exercise capacity in adult with transposition of the great arteries after atrial switch, Int. J. Cardiol. 217 (2016) 28–34.

[27] G. Pedrizzetti, P. Claus, P.J. Kilner, E. Nagel, Principles of cardiovascular magnetic resonance feature tracking and echocardiographic speckle tracking for informed clinical use, J. Cardiovasc. Magn. Reson. 18 (2016) 51.

[28] M. Obokata, Y. Nagata, V.C. Wu, Y. Kado, M. Kurabayashi, Y. Otsuji, et al., Direct comparison of cardiac magnetic resonance feature tracking and 2D/3D echocardiography speckle tracking for evaluation of global left ventricular strain, Eur. Heart J. Cardiovasc. Imaging 17 (2016) 525–532.

[29] P. Claus, A.M.S. Omar, G. Pedrizzetti, P.P. Sengupta, E. Nagel, Tissue tracking technology for assessing cardiac mechanics: principles, normal values, and clinical applications, JACC Cardiovasc. Imaging 8 (2015) 1444–1460.

[30] J. Grewal, A. Crean, P. Garceau, R. Wald, A. Woo, H. Rakowski, et al., Subaortic right ventricular characteristics and relationship to exercise capacity in congenitally corrected transposition of the great arteries, J. Am. Soc. Echocardiogr. 25 (2012) 1215–1221.

[31] M.M. Winter, M.N. van der Plas, B.J. Bouma, M. Groenink, P. Bresser, B.J. Mulder, Mechanisms for cardiac output augmentation in patients with a systemic right ventricle, Int. J. Cardiol. 143 (2010) 141–146.

[32] J. Benes, M. Kotrc, B.A. Borlaug, K. Lefflerova, P. Jarolim, B. Bendlova, et al., Resting heart rate and heart rate reserve in advanced heart failure have distinct pathophysiologic correlates and prognostic impact: a prospective pilot study, JACC Heart Fail. 1 (2013) 259–266.

[33] G.P. Diller, K. Dimopoulos, D. Okonko, A. Uebing, C.S. Broberg, S. Babu-Narayan, et al., Heart rate response during exercise predicts survival in adults with congenital heart disease, J. Am. Coll. Cardiol. 48 (6) (2006) 1250.

[34] M.M. Winter, T. van der Bom, L.C. de Vries, A. Balducci, B.J. Bouma, P.G. Pieper, et al., Exercise training improves exercise capacity in adult patients with a systemic right ventricle: a randomized clinical trial, Eur. Heart J. 33 (2012) 1378–1385.

[35] M. Westhoff-Bleck, B. Schieffer, U. Tegtbur, G.P. Meyer, L. Hoy, A. Schaefer, et al., Aerobic training in adults after atrial switch procedure for transposition of the great arteries improves exercise capacity without impairing systemic right ventricular function, Int. J. Cardiol. 170 (2013) 24–29.

[36] A.J. Marelli, R. Ionescu-Ittu, A.S. Mackie, L. Guo, N. Dendukuri, M. Kaouache, Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010, Circulation 130 (2014) 749–756.

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