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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.

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