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1 **Heart rate response during exercise predicts exercise**
2 **tolerance in adults with transposition of the great arteries**
3 **and atrial switch operation**
4
5

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25

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27 Echocardiography; Exercise tolerance; Chronotropic incompetence; Transposition of the great
28 arteries
29
30

31 **Conflicts of interest** - None

32 **1. INTRODUCTION**

33

34 Transposition of the Great Arteries (TGA) is one of the most common cyanotic heart defects
35 accounting for ~5% of all congenital heart diseases [1]. The Senning or the Mustard repair
36 provides a condition where the RV pumps through the systemic circulation resulting in the
37 morphological right ventricle being called systemic right ventricle (sRV). Senning and
38 Mustard surgery provides excellent results, with the large majority of patients with sRV
39 surviving until adulthood [2–6]. There are however a number of concerns regarding the long-
40 term results [2][7], including exercise intolerance in a vast majority of those affected [8–11].
41 Contradictory results have been observed regarding the correlation between sRV function
42 evaluated by echocardiography or Cardiac Magnetic Resonance Imaging (CMRI) and
43 exercise intolerance [12–19]. Inadequate heart rate response to exercise (chronotropic
44 incompetence) is prevalent in this population and may play a role in this intolerance [20].

45 The aim of the present study was to assess the relationship between heart rate response with
46 exercise capacity in adults with TGA after atrial repair operation in addition to the other
47 parameters obtained by the cardiopulmonary exercise test (CPET).

48

49 **2. MATERIAL AND METHODS**

50

51 This study was designed as a single-center retrospective analysis of data collected at a referral
52 center of adult congenital heart disease (ACHD) at the Bordeaux Heart University Hospital,
53 France. Data were collected retrospectively for all patients with sRV after atrial repair for
54 TGA who underwent a CPET between 2015 and 2018. Clinical, electrocardiographic and
55 laboratory data were documented at the day of the CPET. Cardiac imaging data, including
56 transthoracic echocardiography or Magnetic resonance imaging (MRI) performed within a
57 six-month time period of the CPET, were also collected.

58 Complex TGA was defined by associated intracardiac anomalies including ventricular
59 septal defect (VSD), left ventricular (pulmonary) outflow tract obstruction (LVOTO) or
60 coarctation of the aorta, as opposed to simple TGA. The study was performed in accordance
61 with the principles outlined in the declaration of Helsinki and was approved by the
62 Institutional Ethics Committee. All patients provided informed consent.

63

64 **2.1 Cardiopulmonary exercise test protocol**

65 All CPETs were performed on an upright cycle ergometer (Ergo Card, Medisoft,
66 Soriennes, Belgium) to assess maximal exercise capacity and maximal heart rate (HR) with
67 continuous monitoring of expiratory gases. Work load was increased by 10W/min or
68 30W/2min in a stepwise manner, depending on the individually predicted maximum exercise
69 capacity and in such a way that the calculated maximal effort was attained in ~10–15 min.
70 Oxygen consumption (VO_2), ventilatory equivalent for O_2 (VE/VO_2 ratio) and ventilatory
71 equivalent for CO_2 (VE/VCO_2), peak expiratory exchange ratio (VCO_2/VO_2), O_2 pulse,
72 ratio of physiological dead space to tidal volume (VD/VT), ventilatory reserve (VR) and end-
73 tidal CO_2 tension ($\text{P}_{\text{ET CO}_2}$) were measured with a computerized breath-by-breath analyzer.
74 Patient's maximal power output in watts, HR and systolic blood pressure (SBP) were also
75 recorded. The « circulatory power » (CP) was measured as the product of oxygen uptake and
76 arterial pressure following the Cohen-Solal method [21]. Exercise intolerance (functional
77 aerobic impairment) was defined as a peak oxygen uptake ($\%pp\text{VO}_2$) < 70% of predicted
78 value. The VE/VCO_2 slope was calculated as a linear regression function, excluding the non-
79 linear portion after the ventilatory compensation point. HR was measured by continuous
80 electrocardiography. Arterial blood pressure was recorded manually at 2-minutes intervals by
81 sphygmomanometry. Patients were verbally encouraged to expend a maximal effort. All
82 parameters were expressed as a percentage of the Wasserman predicted normal values [22].

83 The first ventilatory anaerobic threshold (VAT) was determined according to the Wasserman
84 method [23] and expressed as a percentage of pVO₂ and ppVO₂. Age-predicted maximal HR
85 was calculated as (220 – age) [24]. Chronotropic responses were evaluated by heart rate
86 reserve (HRR), calculated as the difference between peak exercise HR and resting HR (peak
87 exercise HR – resting HR) and the age-adjusted HRR, calculated as the difference between
88 peak exercise HR and resting HR, divided by the difference of age-predicted maximal and
89 resting HR (HRR / [220–age–resting HR]). Chronotropic incompetence was defined using
90 established criteria as an age-adjusted HRR <80% or <62% on beta-blocker regimen [20].
91 Forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) were
92 performed prior to exercise testing and are expressed as percentages of predicted values.
93 Patients in whom respiratory exchange ratio at peak exercise was < 1.1 were excluded from
94 the study.

95 96 **2.2 Echocardiography**

97 All transthoracic echocardiographies (TTE) were performed with a Siemens SC2000
98 (Siemens Mountain View, USA) using a 4v1c probe (phased array 1.5 to 4.3 MHz).
99 Assessment of RV function, pulmonary arterial hypertension and baffle status were assessed
100 semi quantitatively by an experienced echocardiographer. Systemic RV function was
101 evaluated by qualitative assessment of echocardiograms. Severity of systemic atrioventricular
102 valve (SAVV) regurgitation were graded by experienced physicians as trivial/mild, moderate
103 or severe.

104 The 2D area in systole and diastole was traced. Fractional area change (FAC) was
105 calculated as $FAC = 100 \times [(End\ diastolic\ area - end\ systolic\ area) / end\ diastolic\ area]$.
106 Tricuspid annular plain systolic excursion (TAPSE) was measured in the apical 4-chamber
107 view. Tricuspid annular plane systolic velocity (TAPSV) wave was measured using pulsed
108 Doppler Tissue Imaging, with the Doppler sample volume placed in the tricuspid annulus of

109 the RV free wall. Systemic RV global longitudinal strain (GLS) was quantified when
110 conditions allowed. Left-Right or Right-Left shunt in the intra-atrial baffle obstruction to
111 systemic venous and/or pulmonary venous drainage were diagnosed either with TTE with the
112 use of Doppler techniques and contrast agents or CMR.

113 Systemic venous baffle obstruction was diagnosed as low flow velocity (<0.5 m/s) in
114 either the inferior vena cava or superior vena cava with flow >1.0 m/s in the baffle.
115 Pulmonary venous baffle obstruction was diagnosed if the peak velocity at the narrowest point
116 of the baffle was greater than 1.5 m/s [5]. LVOTO was determined using continuous wave
117 Doppler from the apical and 3- and 5-chamber views and was defined as peak aortic outflow
118 velocity > 2m/s.

119

120 **2.3 Cardiac Magnetic Resonance**

121

122 CMR studies were conducted on a 1.5 Tesla system (MAGNETOM Avanto,
123 SiemensHealthineers, Erlangen, Germany) equipped with a 32-channel cardiac coil. Cine
124 imaging was applied in a stack of contiguous slices encompassing both ventricles in short axis
125 using a retrospectively gated cine steady state free precession pulse sequence with the
126 following parameters: TR/TE 20/1.4ms, flip angle 60°, slice thickness 6 mm, pixel size 1.6
127 mm x 1.4 mm, and 30 frames per cardiac cycle. High resolution LGE imaging was performed
128 approximately 17 min after contrast injection, using a 3-dimensional, inversion-recovery-
129 prepared, ECG-gated, respiration-navigated gradient-echo pulse sequence with fat-saturation.
130 Typical imaging parameters were: TR/TE, 6.1/2.4 ms; flip angle, 22°; voxel size, 1.25 Å~
131 1.25 Å~ 2.5 mm; inversion time, 260–320 ms depending on the results of a TI scout scan
132 performed immediately before acquisition; parallel imaging using GRAPPA technique with R
133 = 2; 42 reference lines; acquisition time, 5–10 minutes depending on the patient's heart and
134 breath rate. The processing of cine images was performed using Argus software (Siemens
135 Healthineers, Erlangen, Germany). An observer with 15 years' experience in CMR performed

136 all measurements. Ventricular end-diastolic volume (EDV), end-systolic volume (ESV) and
137 ejection fraction (EF) were derived from the segmentation of short axis images for the LV and
138 the RV.

139 140 **2.4 Statistical analysis**

141 Quantitative variables are expressed as means and standard deviations or as medians
142 and quartiles depending on their distribution. Analysis for quantitative variables was carried
143 out with the non-parametric Mann-Whitney test. Qualitative variables are expressed as
144 amounts and percentages. Nominal variables were analyzed with Fisher's exact test. Patients
145 were ranked in tertiles according to %ppVO₂, due to the current lack of validated or
146 consensual cut-off values for %ppVO₂ and given the limited number of patients expected to
147 be included. Differences between groups were analyzed using one-way ANOVA followed by
148 a Bonferroni post-hoc test or Fisher's exact test. Statistical analysis was carried out comparing
149 these 3 groups (lower, middle, higher %ppVO₂ tertiles). Logistic regression testing with
150 forward and backward selection and Spearman rank correlation coefficient was applied in the
151 univariate analysis. All statistical tests were 2-sided and a p value < 0.05 was considered
152 statistically significant.

153

154 **3. RESULTS**

155

156 **3.1 Patient characteristics**

157 Ninety-eight patients with a sRV for TGA after atrial switch repair were identified in
158 our institutional database during the study period. Twenty-eight patients were excluded due to
159 unavailable CPET data or were non-interpretable for technical reasons or because respiratory
160 exchange ratio at peak exercise was < 1.1, resulting in 70 patients being ultimately studied

161 (mean of age 32.4 ± 7.6 years old, 51 males). The baseline data for the study cohort are
162 presented in Table A.

163

164 **3.2 Cardiac resting imaging**

165 All patients had a TTE and a CMR was performed in 56 patients. The mean CMR RV
166 Ejection Fraction (RVEF) was $49.1 \pm 9.8\%$, mean RV FAC was $34.6 \pm 7.4\%$ and mean GLS
167 was $-11.9 \pm 2.2\%$. Two patients had severe systemic atrioventricular valve (SAVV)
168 regurgitation, ten had moderate regurgitation and the remainder had trivial to mild
169 regurgitation. Leak baffle was found in 4 patients and baffle stenosis in 4 patients. Twenty-
170 two patients had LVOTO. No significant differences in resting parameters of systolic sRV
171 function were observed across the tertiles and there was no correlation between resting
172 cardiac function and ppVO₂% (CMR RV EF: $r=0.124$, $p=0.362$; TAPSV: $r=0.178$, $p=0.56$;
173 FAC: $r=0.282$, $p=0.124$; Strain: $r=-0.077$, $p=0.639$). Quantitative measurements of sRV
174 function assessed by TEE and MRI and late gadolinium enhancement data are shown in Table
175 B.

176

177 **3.3 Cardiopulmonary exercise testing**

178 Patient characteristics were assessed according to tertiles of the % ppVO₂ (Tables C)
179 which resulted in categories of %ppVO₂ > 62% (upper tertile, 22 patients, group 3), 52 to
180 62% (middle tertile, 22 patients, group 2) and ≤ 51% (lower tertile, 26 patients, group 1).

181 All data of CPET are presented in appendix 1 (supplemental data). Mean pVO₂ was
182 21.5 ± 5.8 mL/kg/min, corresponding to a $57 \pm 14.1\%$ of predicted values. The median
183 %ppVO₂ in the three tertiles were 72.7, 57.2 and 43.4%, respectively for groups 3, 2 and 1.
184 Mean % of predicted peak oxygen pulse was $63.9 \pm 18.2\%$ for a normal > 70% and was
185 significantly different between the 1st and 3rd tertiles. There was no significant correlation

186 between % of predicted peak O₂ pulse and the %ppVO₂ (r=0.23; p=0.148). The oxygen pulse
187 coefficient was significantly different between the 3rd tertile and the other two tertiles and
188 there was a moderate correlation with %ppVO₂ (r=0.494; p<0.001). A significant exaggerated
189 hyperventilation was observed in the study population with a VE/VCO₂ slope of 37.1. Peak
190 circulatory power was 3536.9 ± 1227.5 mmHg.ml O₂.min⁻¹.kg⁻². No reference values were
191 validated, although a prognostic cut-off of < 1476 mm Hg mlO₂.min⁻¹.kg⁻² was proposed by
192 Giardini et al. as this cut-off was associated with a 15.4-fold increase in the 4-year risk of
193 death in adult congenital heart disease [25].

194 Peak SBP was considered normal without significant differences across tertiles
195 whereas the peak to resting SBP gradient was significantly different between the 1st tertile and
196 the other two tertiles. Peak SBP and SBP gradient were correlated with %ppVO₂ (r=0.284,
197 p=0.018 and r=0.382, p=0.001 respectively).

198 None of the patients had electrocardiographic changes suggestive of myocardial
199 ischemia during exercise or recovery. One patient had transient exercise-induced high degree
200 atrioventricular block and subsequently underwent a pacemaker implantation.

201 NYHA functional class was correlated with %ppVO₂ (r=-0.49, p<0.001) and was
202 significantly different across tertiles.

203 FEV₁ was > 80% of predicted values as was the FEV₁/FCV ratio, indicating that these
204 patients had no pulmonary obstructive disease.

205 Although patients had a slightly decreased mean FCV (78,6 ± 14.2%, normal > 80%
206 predicted value), the data showed no correlation between FCV and peak VO₂.

207 VD/VT ratio decreased at stress while Ventilatory reserve was > 30% in the 3 tertiles
208 with no significant difference between the three groups. There was a significant difference in P_{ET}
209 CO₂ at VAT between group 1 and 3 (p = 0.044) and in VD/VT at peak between the same
210 groups (p = 0.009).

211 Mean VE/VCO₂ slope was 37.1 ± 8.2 whereas a VE/VCO₂ slope < 30 is considered
212 normal without modification for age and sex [26].

213 VAT was determined for 67 patients and was decreased throughout the cohort,
214 reaching $5'10'' \pm 2'$. Mean value was 13.4 ± 3.6 mL/min/kg, with 61.8 ± 13.4 % of pVO₂ and
215 35.4 ± 10.8 % of ppVO₂. A value < 40% of predicted peak VO₂ generally suggests muscle
216 deconditioning and was correlated with %ppVO₂ ($r=0.571$; $p<0.001$). VAT was > 40% only
217 in group 3.

218

219 **3.4 Impact of cardiac rhythm on exercise capacity**

220 The mean heart rate reserve value was 84.7 ± 25.4 and mean age-adjusted HRR was
221 68.5 ± 19 . Peak heart rate was 148.6 ± 26.2 bpm.

222 Chronotropic incompetence (CI) was found in 65.7% of patients as a whole, with
223 76.9% in group 1, 77.3% in group 2 and 38.1% in group 3.

224 CI was associated with lower %ppVO₂ (statistical difference between 1st or 2nd and 3rd
225 tertile) and age-adjusted HRR was correlated with %ppVO₂ ($r=0.482$; $p<0,001$) as was peak
226 heart rate ($r=0.457$, $p<0.001$) (Tables C).

227 Seventeen patients treated with beta-blockers (77%) and 13 patients having a
228 pacemaker (86.6%) showed chronotropic incompetence. Beta-blocker treatment and the
229 presence of a pacemaker appeared to be associated with a limitation in %ppVO₂ (significant
230 difference between 1st and 3rd tertiles).

231

232 **4. DISCUSSION**

233

234 Exercise capacity is known to be impaired in adults with sRV after a TGA atrial repair
235 [8–11]. Aerobic functional performance requires integrated cardiovascular, pulmonary and

236 skeletal muscle physiology. Abnormal function in any one of these systems diminishes pVO_2
237 and increases ventilatory equivalents [27]. The Fick equation states that oxygen uptake equals
238 cardiac output times the arterial minus mixed venous oxygen content ($C(A-V) O_2$). Exercise
239 intolerance could hence be related to one or both of these factors and to the variables that
240 influence them.

241

242 **4.1 Involvement of limited HRR to exercise intolerance**

243 Chronotropic incompetence defined by age-adjusted HRR was directly correlated with
244 $\%ppVO_2$. The degree of chronotropic incompetence was a major determinant of exercise
245 intolerance in this population.

246 In healthy humans, the increase in VO_2 is achieved by a 2.5 to 3.2-fold increase in
247 cardiac output and a 1.5 to 2.5-fold increase in $C(A-V) O_2$. The increase in cardiac output
248 results from a 2.2 to 2.5-fold increase in heart rate and a 0.3 to 1.4-fold increase in stroke
249 volume [28–30]. Thus, the increase in HR is the strongest contributor to the ability to perform
250 sustained aerobic exercise. It is therefore not surprising that chronotropic incompetence can
251 be the primary cause or a significant contributor to severe, symptomatic exercise intolerance
252 [24][31][32].

253 In adults with sRV after TGA atrial redirection, various causes may explain
254 chronotropic incompetence. Sinus node dysfunction after atrial switch procedures is common
255 (prevalence ~ 60% at 20 years of follow-up) [33]. It is seemingly caused by sinus node/atrial
256 conduction tissue damage or interruption of sinus node blood flow during surgery [34]. This
257 could be of major importance since treatment optimization, as well as pacemaker parameter
258 adjustment, could benefit these patients. The inability to reach an age-adjusted HRR > 80% in
259 the study was associated with antiarrhythmic or beta-blocker therapy in parallel with a

260 decrease in %ppVO₂. These drugs have been poorly studied in this population and their
261 beneficial effects remain equivocal [35][36]. The present study findings suggest that they may
262 have a negative effect on exercise capacity while their effects on mortality and morbidity are
263 yet to be well established. In adults with CHD and frequent recurrent symptomatic
264 supraventricular tachycardia, ablation strategy may be preferable to a long-term
265 pharmacologic therapy as stated by the PACES/HRS Expert Consensus Statement on the
266 Recognition and Management of Arrhythmias in Adult Congenital Heart Disease [33][37]

267

268 **4.2 Involvement of stroke volume augmentation to exercise intolerance**

269 O₂ pulse is the instantaneous ratio of VO₂ and HR. It reflects the stroke volume and
270 peripheral oxygen extraction response to increasing workload during exercise. The present
271 findings showed a correlation between the increase in oxygen pulse and ppVO₂% suggesting
272 that a part of exercise limitation was also due to an inadequate response of stroke volume to
273 effort in addition to the peripheral limitation.

274 Ventricular stroke output is regulated by three factors: preload, the contractile state of
275 the myocardium and afterload stress [29]. Preload might play a role since ventricular filling
276 may be inadequate through the atrial baffle and further worsened by abnormal sRV
277 compliance secondary to chronic RV hypertrophy. Furthermore, atrial blood redirection after
278 surgery can be modified by baffle leaks or baffle obstruction. Derrick et al. suggested that the
279 major limiting factor of stroke volume augmentation during exercise was an impaired
280 ventricular filling in adults with TGA after atrial redirection [38].

281 sRV inotropic response to exercise is another main determinant of cardiac output
282 augmentation at exercise. Systemic RV exhibits unique myocardial mechanics, with a shift
283 toward a more predominant circumferential free wall shortening compared to subpulmonary
284 RV, but with lack of normal torsion [16]. It may also be affected by ischemia and fibrosis. RV

285 myocardial ischemia is common in this particular setting, the reason likely being
286 multifactorial. The branching pattern of the major coronary vessels is often abnormal in this
287 condition. In addition, ischemia may be further increased [39] by a metabolic imbalance given
288 that the right coronary arterial system may not supply adequate flow to the hypertrophied
289 systemic RV, thus providing a substrate for the development of progressive ischemic damage
290 [39][40]. Fibrosis may additionally be a consequence of ischemia but also of preoperative
291 cyanosis as well as of the surgery itself. Younger patients have been reported to exhibit a
292 lower degree of myocardial fibrosis, possibly as a result of improvements in cardiothoracic
293 surgery, including the advent of cold cardioplegia and cardiopulmonary bypass [41].
294 Notwithstanding, this study showed no association between resting systolic sRV function and
295 exercise capacity. Neither CMR RV Ejection Fraction nor other TTE-measured parameters
296 were correlated with %ppVO₂. Reported data on the relationship between resting RVEF and
297 exercise capacity in patients with sRV are inconsistent. Indeed, whereas Ladouceur et al.
298 reported a low to moderate correlation between longitudinal strain and exercise capacity [17],
299 recent studies with advanced CMR techniques including longitudinal and circumferential
300 strain showed poor to absence of correlation [13–18] between function resting parameters and
301 exercise capacity. This suggests that a resting imaging follow-up alone may be insufficient to
302 explore exercise intolerance [19]. Moreover, afterload did not appear of critical importance in
303 the present population since patients were relatively young and did not present resting or
304 exercise arterial hypertension.

305

306 **4.3 Ventilatory response and lung function**

307 We did not find evidence of ventilatory or pulmonary vascular limitation in our study
308 cohort. Mean FVC was slightly decreased ($78.6 \pm 14.2\%$) and 57.3% of patients had a FVC

309 <80%. A diminished FVC could be predictive of a restrictive respiratory pattern, although the
310 diagnosis was made by the Total Lung Capacity which was not measured.

311

312 **4.4 Peripheral vascular and skeletal muscle bulk and functions**

313 Peak VO₂ is also determined by peripheral factors [42]. VAT usually occurs at
314 approximately 45% to 65% of peak VO₂ in healthy untrained subjects [43]. In the present
315 study, 73.5% of our patients had a VAT < 40% of predicted peak VO₂ and was statistically
316 associated with VO₂ limitation. It has been shown that decreased exercise cardiac output
317 probably causes skeletal muscle hypoperfusion, which is a potent stimulus for early anaerobic
318 metabolism, and subsequent generation of muscle lactate and other metabolites that can
319 produce the sensation of peripheral and central fatigue [44]. There is also a relatively high
320 incidence of a sedentary lifestyle and physical deconditioning in this population resulting in
321 their peripheral large muscles being unable to maximize extraction of oxygen and influencing
322 peak exercise capacity [45]. Randomized trials have shown that a training protocol could
323 improve peak oxygen consumption in this adult population with sRV / TGA [42] [46].

324

325 **4.5 Strengths and limitations**

326 This study has several limitations inherent to any retrospective study. Adults with
327 TGA comprise approximately only 1.6% of all adult congenital patients. Given the single-
328 center nature of this study, its power was limited by the small number of included patients, as
329 could its generalizability. Despite this latter drawback, the present study population
330 represented one of the largest cohorts on TGA after atrial redirection.

331 A selection bias may have occurred as patients were recruited at a tertiary center.
332 Therefore, we cannot exclude the possibility that it represented a biased sample, favoring
333 patients with more symptoms and lower perceived functional capacity.

334 A registry search with IC10 codes could also have led to a selection bias by missing
335 some patients classified under other codes. In order to limit this bias, an extensive list of IC10
336 codes was used after which medical records were meticulously analyzed by the same
337 researcher.

338 Finally, it could be argued that chronotropic incompetence is the main factor of exercise
339 intolerance as long as the cardiac function of the ventricle is relatively preserved, which is the
340 case in our relatively young population, and we cannot exclude that progressive weakening of
341 systemic ventricle function may play a larger role as the population ages.

342 **5. CONCLUSION**

343 Adults with TGA after atrial redirection had exercise intolerance due to a limitation of
344 cardiac output augmentation at exercise which was multifactorial, including chronotropic
345 intolerance, muscle deconditioning and impaired cardiac hemodynamics throughout exercise
346 testing. Resting imaging data were not predictive of the hemodynamic adaptation to exercise.
347 The inability to increase cardiac output during exercise was notably due to incompetent
348 chronotropic response which is predominant in this population.

349

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351 This research did not receive any specific grant from funding agencies in the public,
352 commercial, or not-for-profit sectors.

353

354 **7. CONFLICTS OF INTEREST**

355 None.

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Tables

Table A: Patient characteristics

N = 70	
Age, years	32,4 +/- 7,6
Male gender	51 (72,9)
Senning procedure	57 (81,4)
Mustard procedure	13 (18,6)
Complexe TGA	19 (27,1)
Age repair, month	7,3 +/- 5,4
Body Mass Index, kg.m-2	24,8 +/-5,5
NYHA functional class	1,4 +/- 0,7
O2 saturation, %	97,3 +/- 2,1
<u>Medication</u>	
Beta-blockers	22 (31,4)
ACE-I/ARBs/ARNI/Aldosterone antagonist	21 (30)
Loop diuretic	6 (8,6)
Antiarrhythmic	13 (18,6)
Pacemaker (Dual chamber or CRT)	15 (21,4)
<u>Rhythm history</u>	
Sinus node dysfunction	27 (38,6)
Atrioventricular block	8 (11,4)
Ventricular arrhythmias	14 (20)
Supraventricular arrhythmias	31 (44,3)
BNP, ng/L	78,1 +/- 80,7

Data are mean ± standard deviation or number (%) unless otherwise specified.
ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker;
ARNI: angiotensin receptor neprilysin inhibitor; BNP: B-type natriuretic peptide; NYHA: New York Heart Association; TGA: Transposition of Great Artery

Table B: Resting imaging data

Echocardiography	N = 70
TAPSE, mm	12,5 +/- 3,4
S', cm/s	7,3 +/- 1,9
RV FAC, %	34,6 +/- 7,4
GLS RV, %	-11,9 +/- 2,9
SAVV Trivial-mild/moderate/severe	57 (81,4) / 10 (14,5) / 2 (2,9)
LVOTO	22 (31,4)

Cardiac Magnetic Resonance	N = 56
RV EF, %	49,1 +/- 9,8
RV EDV, mL/m ²	107,1 +/- 28,8
RV ESV, mL/m ²	57,9 +/- 29,6
LV EF, %	59,4 +/- 7,9
LV EDV, mL/m ²	64,6 +/- 17,5
LV ESV, mL/m ²	26,9 +/- 10
Late Gadolinium Enhancement	10 (27)
Baffle leaks	4 (5,7)
Baffle stenosis	4 (5,7)

Data are mean ± standard deviation or number (%) unless otherwise specified. EDV: End-diastolic Volume; EF: Ejection Fraction; ESV: End-systolic Volume; FAC: Fractional area change; GLS: Global Longitudinal Strain; LV: Left Ventricle; LVOTO: Left Ventricular Outflow Trac Obstruction; RV: Right Ventricle; S': Tricuspid annular plane systolic velocity; SAVV: Systemic AtrioVentricular Valve; TAPSE: Tricuspid annular plain systolic excursion

Table C.1: Patient demographics and resting imaging data according to % ppVO2 tertiles

	Lower tertile (N = 26)	Middle tertile (N = 22)	Upper tertile (N = 22)	p for Bonferroni <i>post-hoc</i> test or Fisher's exact test		
				1 vs. 2	1 vs. 3	2 vs. 3
ppVO2%	43.4 +/- 9.2	57.2 +/- 3.4	72.7	<0.001	<0.001	<0.001
Age, years	32.9 +/-9	32.1 +/- 7	32 +/- 6.8	1.0000	1.0000	1.0000
Male gender	18 (69.2)	17 (77.3)	16 (72.7)	0.7460	1.0000	1.0000
TGA complex	8 (30.8)	5 (22.7)	6 (27.3)	0.7460	1.0000	1.0000
Age at repair, month	6.4 (5.2)	8.1 +/-5.4	7.5 +/-5.7	1.0000	1.0000	1.0000
NYHA functional class	1.8 +/- 0.8	1.4 +/- 0.6	1 +/- 0.2	0.0713	<0.001	0.2458
Antiarrhythmic therapy	8 (30.8)	3 (13.6)	2 (9.1)	0.1890	0.0840	1.0000
Beta-blocker	13 (50)	6 (27.3)	3 (13.6)	0.1440	0.0130	0.4570
Pacemaker	9 (34.6)	4 (18.2)	2 (9.1)	0.3290	0.0450	0.6640
History of SND	12 (46.2)	7 (31.8)	8 (36.4)	0.3820	0.5650	1.0000
<u>Echocardiography</u>						
TAPSE, mm	12.5 +/- 3.6	12.2 +/- 2.6	12.6 +/- 4.1	1.0000	1.0000	1.0000
S', cm/s	6.78 +/- 1.8	7.5 +/- 1.7	7.7 +/- 2.1	0.5714	0.3275	1.0000
RV FAC, %	36.2 +/- 9	30.8 +/- 6	35.6 +/- 5.9	0.1603	1.0000	0.2254
Strain VD Global	-11.3 +/- 3.5	-12.8 +/- 2.7	-11.22 +/- 1.5	0.9001	1.0000	1.0000
<u>CMR</u>						
RV EF, %	48.2 +/- 10.9	48 +/- 8.7	51 +/- 10.1	1.0000	1.0000	1.0000
RV EDV (mL/m ²)	102.9 +/- 34.8	112.8 +/- 28.2	105.5 +/- 23.4	0.9245	1.0000	1.0000
RV ESV (mL/m ²)	55.1 +/- 28	64.6 +/- 38.9	53.8 +/- 18.8	1.0000	1.0000	0.8030

Data are expressed as mean ± standard deviation or n (%) unless specified otherwise.

CMR: Cardiac Magnetic Resonance; EDV: End-diastolic Volume; EF: Ejection Fraction; ESV: End-systolic Volume; FAC: Fractional area change; GLS: Global Longitudinal Strain; LV: Left Ventricle; NYHA: New York Heart Association; ppVO2 = peak VO2 of predicted VO2 %; RV: Right Ventricle; S': Tricuspid annular plane systolic velocity; SAVV: Systemic AtrioVentricular Valve; SND: Sinus Node Dysfunction; TAPSE: Tricuspid annular plain systolic excursion; TTE: Transthoracic Echocardiography

Table C.2: CPET characteristics according to % ppVO2 tertiles

	Lower tertile (N = 26)	Middle tertile (N = 22)	Upper tertile (N = 22)	p for Bonferroni <i>post-hoc</i> test or Fisher's exact test		
				1 vs. 2	1 vs. 3	2 vs. 3
Sinus rhythm	18 (69.2)	16 (72.7)	15 (68.2)	0.4847	0.2823	0.2434
Peak power output, Watt	101.12 +/- 24.1	121.9 +/- 22.7	136.8 +/- 36.8	0.0459	<0.001	0.2700
Peak SBP, mm Hg	151.6 +/- 20	163.4 +/- 25.7	166.8 +/- 19.2	0.2033	0.0587	1.0000
Peak heart rate, bpm	134.4 +/- 29.2	150.3 +/- 19.6	164.4 +/- 19.5	0.0697	<0.001	0.1673
HRR, bpm	71.9 +/- 26.9	85.5 +/- 19.8	99.3 +/- 21.8	0.1430	0.0003	0.1700
Age-adjusted HRR, %	57.7 +/- 20.7	69.5 +/- 13.4	80.7 +/- 14.6	0.0570	<0.001	0.0990
Chronotropic incompetence	20 (76.9)	17 (77.3)	8 (38.1)	1.0000	0.0160	0.0140
Peak VO2, mL/kg/min	17.1 +/- 4.5	22.1 +/- 4.2	26.1 +/- 4.7	<0.001	<0.001	0.0124
VE/VCO2 slope	39.3 +/- 7.5	37.5 +/- 7.5	34.1 +/- 9	1.0000	0.0933	0.5165
Peak Circulatory power, mmHg.mL.min-1.kg-2	2585.4 +/- 767.1	3687.5 +/- 939.4	4424.3 +/- 1182	<0.001	<0.001	0.0432
Peak O2 pulse, % of predicted	56.9 +/- 20.8	63.2 +/- 14.4	72.9 +/- 15.3	0.6853	0.0106	0.2323
Coefficient of increase O2 pulse	2.11 +/- 0.6	2.24 +/- 0.6	3.07 +/- 1.16	1.0000	0.0010	0.0050
VAT, % of peak VO2	66.4 +/- 11.1	59 +/- 13.4	59.6 +/- 15	0.1797	0.2594	1.0000
VAT, % of ppVO2	29.2 +/- 7.5	35.1 +/- 7.1	42.9 +/- 12.7	0.1030	<0.001	0.0225
<u>Pulmonary parameters</u>						
FVC	74 +/- 17.7	79 +/- 8.9	83.9 +/- 12.3	0.6714	0.0512	0.7515
FEV1	80.1 +/- 16.9	80.6 +/- 9.6	82.4 +/- 12.9	1.0000	1.0000	1.0000
FEV1/FVC	106.1 +/- 8.3	105.4 +/- 7.5	101.7 +/- 10.9	1.0000	0.3367	0.6178
Respiratory Rate at peak	36.7 +/- 7.9	36.6 +/- 8.9	37.5 +/- 10.3	1.0000	1.0000	1.0000
VD/VT at rest	0.32 +/- 0.05	0.31 +/- 0.08	0.36 +/- 0.07	0.6728	0.3130	0.0209
VD/VT at peak	0.267 +/- 0.05	0.23 +/- 0.05	0.21 +/- 0.05	0.0693	0.0095	1.0000
Ventilatory Reserve at peak, %	42.4 +/- 11.1	30.2 +/- 13.5	24.4 +/- 17.1	0.0183	<0.001	0.5825

Data are expressed as mean ± standard deviation or n (%) unless specified otherwise.

FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; PetCO2: End-tidal CO2 tension; VCO2: Carbon dioxide output; VE: Minute ventilation; VO2: Oxygen uptake; VE/VCO2:

Ventilatory equivalent of carbon dioxide; VE/VO₂: Ventilatory equivalent of oxygen; VAT: Ventilatory Anaerobic threshold; VD/VT: Volume of dead space / Tidal volume ratio

Supplemental data

Appendix: CPET data

N = 70	
<u>Rhythm at CPET</u>	
Heart rate at rest, bpm	63.9 +/- 12.7
Sinus rhythm	49 (70%)
Sinus node dysfunction	13 (18.6%)
Atrial paced rhythm	6 (8.6%)
<u>CPET characteristics</u>	
Peak power output, Watt	118.8 +/- 31.8
Peak SBP, mm Hg	160.2 +/- 22.4
RQ at peak VO ₂	1.2 +/- 0.1
Peak heart rate, bpm	148.6 +/- 26.2
Maximum heart rate, % Age predicted	78.9 +/- 12.4
HRR, bpm	84.6 +/- 25.4
Age-adjusted HRR, %	68.5 +/- 19.1
Chronotropic incompetence	46.0 (65.7)
Peak VO ₂ , mL/kg/min	21.51 +/- 5.81
Peak VO ₂ , % of predicted peak VO ₂	56.95 +/- 14.13
Peak VO ₂ , L/min	1.511 +/- 0.512
VE/VCO ₂ slope	37.1 +/- 8.2
Circulatory power, mmHg.mL.min ⁻¹ .kg ⁻²	3536.9 +/- 1227.5
Oxygen pulse at rest, mL/beat	4.5 +/- 1.4
Peak oxygen pulse, mL/beat	10.4 +/- 3.6
Peak oxygen pulse, % of predicted	63.9 +/- 18.2
Coefficient of increase O ₂ pulse	2.46 +/- 0.9
VAT, min	5.1 +/- 2
VAT, mL/kg/min	13.4 +/- 3.9
VAT, % of peak VO ₂	61.8 +/- 13.4
VAT, % of predicted peak VO ₂	35.4 +/- 10.8

Data are expressed as mean ± standard deviation or n (%) unless specified otherwise.

<u>Pulmonary parameters</u>	N = 70
FVC	78.6 +/- 14.2
FEV1	81.0 +/- 13.6
FEV1/FVC	104.4 +/- 9.1
Respiratory Rate at rest	17.2 +/- 5.6
Respiratory Rate at peak Vo2	36.9 +/- 8.9
PetCO2 at rest, mmHg	31.0 +/- 3.7
PetCO2 at VAT, mmHg	36.5 +/- 4.9
PetCo2 at peak VO2, mmHg	30.1 +/- 4.6
VE/VCO2 at VAT	34.4 +/- 5.5
VE/VO2 at VAT	32.3 +/- 6.9
VE/VO2 at peak VO2	48.3 +/- 11.3
VD/VT at rest	0.33 +/- 0.07
VD/VT at peak	0.24 +/- 0.06
VE at rest, L/min	11.9 +/- 3
VE at peak VO2, L/min	70.2 +/- 18.4
Ventilatory reserve at rest, %	87.8 +/- 5.8
Ventilatory reserve at peak VO2, %	33.0 +/- 15.8

HRR: Heart Rate Reserve; RQ: Respiratory Quotient; SBP: Systolic Blood Pressure; VAT: Ventilatory Anaerobic Threshold; VE/VCO2: Ventilatory equivalent of carbon dioxide; VO2: Oxygen uptake

Data are expressed as mean \pm standard deviation or n (%) unless specified otherwise.

FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; PetCO2: End-tidal CO2 tension; VCO2: Carbon dioxide output; VE: Minute ventilation; VO2: Oxygen uptake; VE/VCO2: Ventilatory equivalent of carbon dioxide; VE/VO2: Ventilatory equivalent of oxygen; VAT: Ventilatory Anaerobic threshold; VD/VT: Volume of dead space / Tidal volume ratio