JACC: ADVANCES VOL. 1, NO. 2, 2022

ORIGINAL RESEARCH

CONGENITAL HEART DISEASE

Determinants of Aerobic Capacity After Tricuspid Valve Replacement in Congenitally Corrected Transposition of Great Arteries

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ABSTRACT

BACKGROUND Systemic tricuspid regurgitation and impaired aerobic capacity are common in adults with congenitally corrected transposition of great arteries (cc-TGA), but it is unknown whether systemic tricuspid valve replacement (sTVR) is associated with improvement in aerobic capacity.

OBJECTIVES The purpose of this study was to determine whether sTVR was associated with postoperative improvement in aerobic capacity as measured by peak oxygen consumption (VO_2).

METHODS This is a retrospective cohort study of adults with cc-TGA and ≥moderate tricuspid regurgitation that underwent sTVR and exercise test pre- and post-sTVR (2003-2019). We selected a propensity-matched control group of patients with cc-TGA and ≥moderate tricuspid regurgitation that did not undergo sTVR between exercise tests. Improvement in aerobic capacity was calculated as the difference between baseline and follow-up exercise tests.

RESULTS The study comprised 48 patients in each group, and both groups had similar peak VO_2 at baseline. Compared to the baseline exercise test, the sTVR group had more improvement in peak VO_2 ($6 \pm 4\%$ vs $-8 \pm 3\%$-predicted, $P = 0.001$), and the factors associated with postoperative improvement in peak VO_2 were baseline systolic blood pressure (<120 mm Hg), systemic right ventricular global longitudinal strain (<−16%), and preoperative peak VO_2 (>60%-predicted).

CONCLUSIONS There was an improvement in aerobic capacity after sTVR in patients with cc-TGA and severe tricuspid regurgitation. The determinants of improvement in aerobic capacity were baseline systolic blood pressure, systemic right ventricular global longitudinal strain, and preoperative peak VO_2. Further studies are required to determine whether strict blood pressure control and optimal timing of sTVR based on these indices would result in improved clinical outcomes in this population. (JACC Adv 2022;1:100027) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 8, 2022; revised manuscript received March 25, 2022, accepted April 5, 2022.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2022.100027

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

cc-TGA = congenitally corrected transposition of great arteries

CI = confidence interval

dP/dtic = mean rate of pressure rise during isovolumetric contraction

NYHA = New York Heart Association

OR = odds ratio

RAAS = renin angiotensin aldosterone system

sRV = systemic right ventricle

sTVR = systemic tricuspid valve replacement

VCO_2 = carbon dioxide output

VE = minute ventilation

VE/VCO_2 = ventilatory equivalent of carbon dioxide

VO_2 = oxygen consumption

About 90% of patients with congenitally corrected transposition of great arteries (cc-TGA) have morphologically abnormal systemic tricuspid valves (tricuspid valve dysplasia), and as a result, tricuspid regurgitation is 1 of the most common hemodynamic lesions in this population.[1,2] Chronic volume overload from systemic tricuspid regurgitation, coupled with systemic afterload, results in a high prevalence of systemic right ventricular (sRV) systolic dysfunction and heart failure in this population.[3-7] Similarly, progressive sRV dilation and dysfunction can lead to tricuspid valve annular dilation and malcoaptation of the tricuspid valve leaflet, which, in turn, will exacerbate the severity of tricuspid regurgitation. Systemic tricuspid valve replacement (sTVR) is an effective therapy for the management of tricuspid regurgitation in this population, and it is associated with improvement in sRV systolic function especially when performed prior to the onset of significant sRV systolic dysfunction.[4]

Aerobic capacity, as measured by peak oxygen consumptions (VO_2), is an important prognostic metric in patients with cardiovascular disease, and interventions that improve peak VO_2 are associated with improved clinical outcomes.[8-11] Adults with cc-TGA have impaired aerobic capacity (reduced peak VO_2) because of impaired heart rate and stroke volume at peak exercise.[6,12,13] However, the relationship between sRV indices (tricuspid valve regurgitation and sRV systolic function) and peak VO_2 has been inconsistent across studies.[6,12,14-16] More importantly, it is unknown whether sTVR is associated with improvement in peak VO_2 (an important prognostic marker) and what the mechanism of response might be. The purpose of this study was to determine whether sTVR was associated with postoperative improvement in peak VO_2. We hypothesized that sTVR would be associated with improved peak VO_2.

METHODS

STUDY POPULATION. To test the above hypothesis, we conducted a retrospective cohort study of adults (≥18 years of age) with cc-TGA and ≥moderate systemic tricuspid regurgitation that underwent cardiopulmonary exercise tests pre- and post-sTVR at the Mayo Clinic from January 1, 2003, to December 31, 2019. The last exercise test performed prior to sTVR was considered as the baseline test while the first exercise test performed >12 months after sTVR was considered as the follow-up test.

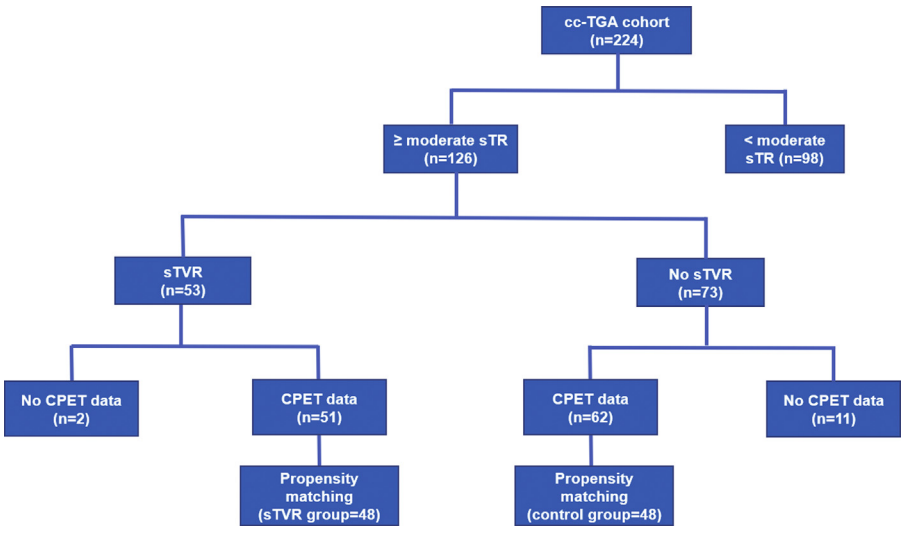
For the control group, we selected consecutive patients with cc-TGA and ≥moderate systemic tricuspid regurgitation that underwent ≥2 cardiopulmonary exercise tests without sTVR between studies. The first exercise test performed within the study period was considered as the baseline test while the next exercise test performed >12 months after the baseline test was considered as the follow-up test. In order to minimize differences in baseline characteristics between the sTVR and control groups, we performed a 1:1 propensity matching of both groups based on age, sex, body mass index, and cardiac implantable electronic devices at the time of baseline exercise test. The patients were identified through the Mayo Adult Congenital Heart Disease Registry, and the institutional review board approved this study.

CARDIOPULMONARY EXERCISE TEST. Cardiopulmonary exercise test was performed with treadmill ergometer using the modified Bruce protocol, and only patients who took a symptom-limited maximum effect test (defined as respiratory exchange ratio of >1.1) were included in the study. VO_2 was directly measured by expired gas analysis (MedGraphics) and expressed as percent of predicted values (%-predicted) to account for differences in age and sex.[17-19] Temporal change in aerobic capacity was calculated as %-predicted peak VO_2 at follow-up exercise test minus %-predicted peak VO_2 at baseline exercise test, and improvement in aerobic capacity was defined as follow-up peak VO_2 > baseline peak VO_2.[18] Oxygen pulse (O_2 pulse) was used as surrogate for sRV stroke volume and calculated as VO_2 (mL/min) divided by heart rate.[19,20] Breath-by-breath measurement of VO_2, carbon dioxide output (VCO_2), and minute ventilation (VE) were measured throughout the test until the end of exercise, and ventilatory equivalent of carbon dioxide (VE/VCO_2) slope, which is a measure of ventilatory efficiency, was calculated from the start of incremental exercise to the ventilatory compensation point.[21,22]

ECHOCARDIOGRAPHY. Echocardiograms performed within 3 months of the exercise tests were reviewed, and offline image analyses were performed by a single research sonographer.

Systemic tricuspid regurgitation severity and sRV cardiac index were assessed using qualitative and quantitative Doppler echocardiography, respectively, while left atrial function and sRV systolic function were assessed by speckle tracking imaging.[23,24]

FIGURE 1 Flowchart Showing Patient Selection



Of the 51 eligible patients with sTVR and CPET data and 62 without, 48 propensity-matched patients in each group were used for all analyses. cc-TGA = congenitally corrected transposition of great arteries; CPET = cardiopulmonary exercise test; sTR = systemic tricuspid regurgitation; sTVR = systemic tricuspid valve replacement.

Additionally, we assessed the mean rate of pressure rise during isovolumetric contraction (dP/dtic) as a secondary measure of sRV systolic function because it less preload-dependent (unlike sRV global longitudinal strain). dP/dtic Was calculated as ([aortic diastolic pressure − sRV end-diastolic pressure]/isovolumetric contraction time), using an assumed sRV end-diastolic pressures of 10 mm Hg as described by Joyce et al.[25] Right atrial pressure was estimated based on respirophasic changes in the diameter of the inferior vena cava.[26] Left ventricular systolic pressure was estimated using the mitral regurgitation peak velocity and estimated right atrial pressure.[26]

STATISTICAL ANALYSIS. A propensity score, which is the probability of being in the case group, was estimated using logistic regression based on age, sex, body mass index, and history of cardiac implantable electronic device implantation. One-to-one nearest neighbor caliper matching was used to match patients based on the logit of the propensity score using a caliper equal to 0.2 of the standard deviation of the logit of the propensity score.[27] The balance of covariates after matching was assessed using unpaired *t*-test and Fisher exact test as appropriate. We were unable to assess right ventricle (RV) strain in 3 patients (1 in the sTVR group and 2 in the control group), and we addressed the issue of missing data with imputation. Longitudinal improvements in exercise and echocardiographic indices were assessed using paired *t*-test and McNemar tests for continuous and binary variables, respectively. The correlations between continuous variables were assessed using Pearson correlation.

The relationship between preoperative variables (demographic, echocardiographic, and exercise indices) and postoperative change in aerobic capacity was assessed using multivariable linear regression analysis with stepwise backwards selection. First, we created a univariable model for each variable, a P value of <0.25 in the univariable model was required for entry into the multivariable model, and a P value <0.10 was required for the variable to remain in the multivariable model. The stability of the models was assessed using 1,000 bootstrap samples (accuracy 0.87, kappa 0.59). Receiver operating characteristic curve and maximum Youden index were used to determine the optimal cutoff point for the variables associated with postoperative improvement in aerobic capacity. A $P < 0.05$ was considered statistically significant. All statistical analyses were performed with JMP and SAS software (versions 14.1 and 9.4 respectively, SAS Institute Inc).

RESULTS

BASELINE ECHOCARDIOGRAM AND EXERCISE TEST. Based on prespecified inclusion criteria, we

TABLE 1 Baseline Characteristics

	sTVR (n = 48)	Control (n = 48)	*P* Value	Standardized Diff
Age, y	41 ± 12	41 ± 10	0.80	0.052
Male	25 (52%)	25 (52%)	0.90	0.206
Body mass index, kg/m^2	27 ± 6	26 ± 5	0.80	0.052
CIED implantation	21 (44%)	21 (44%)	0.90	0.206
Systolic blood pressure, mm Hg	124 ± 12	119 ± 10	0.80	0.052
NT-proBNP, pg/mL	316 (58-867)	263 (69-716)	0.60	0.107
Ebstein malformation of tricuspid valve	23 (48%)	21 (44%)	0.70	0.079
Prior cardiac procedures				
Tricuspid valve repair	2 (4%)	6 (13%)	0.20	0.264
Ventricular septal defect closure	5 (10%)	11 (23%)	0.10	0.341
PVR/RV-PA conduit placement	3 (6%)	7 (15%)	0.30	0.213
Palliative shunts	2 (4%)	1 (2%)	0.60	0.107
Pulmonary artery band	0	1 (2%)	–	
Comorbidities				
Hypertension	6 (12%)	4 (8%)	0.40	0.172
Prior atrial fibrillation	9 (19%)	11 (23%)	0.30	0.213
Medications				
Beta-blockers	13 (27%)	10 (21%)	0.30	0.213
ACEI/ARB	31 (65%)	37 (77%)	0.20	0.264
Spironolactone	6 (13%)	4 (8%)	0.60	0.107
Loop diuretics	16 (33%)	14 (29%)	0.20	0.213
NYHA functional class				
I	28 (58%)	33 (69%)	0.30	0.213
II	16 (33%)	14 (29%)	0.50	0.138
III	4 (8%)	1 (2%)	0.80	0.052
Systemic indices				
LA volume index, mL/m^2 (<34)	48 ± 10	42 ± 9	0.02	0.483
LA reservoir strain, % (>25)	22 ± 4	23 ± 5	0.40	0.172
RV global longitudinal strain, % (<−18)	−16 ± 4	−18 ± 3	0.03	0.449
dP/dtic, mm Hg/s (>800 mm Hg/s)	495 ± 216	531 ± 243	0.07	0.374
RV end-diastolic area, cm^2 (≤25)	42 ± 9	35 ± 11	0.02	0.483
RV end-systolic area, cm^2 (≤14)	29 ± 5	20 ± 6	0.003	0.622
RV fractional area change, % (>35)	40 ± 8	43 ± 9	0.40	0.172
RV cardiac index, mL/m^2 (2.5-4.0)	2.7 ± 0.6	2.9 ± 0.4	0.07	0.374
Tricuspid regurgitation severity				
Moderate	4 (8%)	16 (33%)	0.003	0.636
Moderate/severe	18 (38%)	22 (46%)	0.40	0.172
Severe	26 (54%)	10 (21%)	0.001	0.713
Nonsystemic indices				
RA volume index, mL/m^2 (<27[a]/<32[b])	24 ± 7	22 ± 6	0.30	0.213
RA reservoir strain, % (>31)	30 ± 6	33 ± 8	0.40	0.172
RA pressure, mm Hg (<8)	9 ± 3	8 ± 3	0.60	0.213
LV longitudinal strain, % (<−18)	−25 ± 6	−23 ± 4	0.30	0.213
LV systolic pressure, mm Hg (<40)	37 ± 8	39 ± 7	0.60	0.107
≥Mod mitral regurgitation	3 (6%)	2 (4%)	0.70	0.079
≥Mod pulmonary regurgitation	1 (2%)	–	–	
Pulmonary valve mean gradient, mm Hg	12 ± 6	10 ± 5	0.10	0.341

Values are mean ± SD, n (%), or median (IQR). [a,b]Female/male patients.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-II receptor blocker; CIED = cardiac implantable electronic device; dP/dtic = mean rate of pressure rise during isovolumetric contraction; LA = left atrium; LV = left ventricle; NT-proBNP = N-terminal prohormone brain natriuretic peptide; NYHA = New York Heart Association; PVR = pulmonary valve replacement; RA = right atrium; RV = right ventricle; RV-PA = right ventricular to pulmonary artery; sTVR = systemic tricuspid valve replacement.

identified 48 consecutive patients that underwent exercise test pre- and post-sTVR and 48 propensity-matched controls (**Figure 1**). Supplemental Table 1 shows between-group comparisons of the baseline clinical, echocardiographic, and exercise indices before propensity matching, while **Tables 1 and 2** show between-group comparisons of the baseline clinical, echocardiographic, and exercise indices after

TABLE 2 Baseline Cardiopulmonary Exercise Test

	sTVR (n = 48)	Control (n = 48)	*P* Value	Standardized Diff
Indices at rest				
VO_2 at rest, mL/kg/min	3.4 ± 1.2	3.6 ± 0.9	0.20	0.264
Heart rate at rest, beats/min	74 ± 12	71 ± 15	0.40	0.172
Systolic BP at rest, mm Hg	114 ± 15	119 ± 11	0.40	0.172
O_2 saturation at rest, %	99 ± 1	99 ± 1	0.90	0.206
Indices at peak exercise				
Peak VO_2, mL/kg/min	20.4 ± 7.2	22.4 ± 6.1	0.20	0.264
Peak VO_2, %-predicted	59 ± 21	61 ± 18	0.30	0.213
Heart rate at peak exercise, beats/min	134 ± 22	136 ± 18	0.40	0.172
Heart rate at peak exercise, % predicted	77 ± 11	78 ± 9	0.70	0.079
SV (O_2 pulse) at peak exercise, mL/beat	10.6 ± 3.3	11.2 ± 3.2	0.20	0.264
SV (O_2 pulse) at peak exercise, %-predicted	54 ± 16	57 ± 19	0.60	0.107
Systolic BP at peak exercise, mm Hg	139 ± 26	143 ± 21	0.40	0.172
VE/VCO_2 slope	29 ± 4	31 ± 5	0.30	0.213
O_2 saturation at peak, %	98 ± 1	97 ± 1	0.70	0.079

Values are mean ± SD.

BP = blood pressure; sTVR = systemic tricuspid valve replacement; SV = stroke volume; VE/VCO_2 = ventilatory equivalent for carbon dioxide; VO_2 = oxygen consumption.

propensity matching. Compared to controls, the sTVR group had more sRV dilation and systolic dysfunction, more left atrial dilation, and higher proportion of patients with severe systemic tricuspid regurgitation, but no other significant differences between the 2 groups (Table 1). Similarly, both groups had comparable exercise indices and New York Heart Association (NYHA) functional class (Tables 1 and 2). There was a poor correlation between NYHA functional class and peak VO_2 in the sTVR group (r = 0.34, P = 0.07) and in the control group (r = 0.31, P = 0.09) (P interaction = 0.20).

FOLLOW-UP ECHOCARDIOGRAM AND EXERCISE TEST. All 48 patients in the sTVR group underwent sTVR with mechanical prosthesis, and concomitant procedures performed during sTVR were mitral valve repair (n = 6) and pulmonary valve replacement (n = 1). There was no surgical mortality. Additionally, 2 patients underwent implantation of a dual chamber pacemaker prior to hospital discharge, and another 2 patients underwent implantation of a dual chamber pacemaker within 1 year after sTVR because of high-grade heart block. In the control group, 1 patient underwent implantation of a dual chamber pacemaker between the first and second exercise tests.

All patients underwent a follow-up exercise test and echocardiograms (inclusion criteria), and the interval between the baseline tests and the follow-up tests was similar between the sTVR group and the control group (28 ± 9 vs 24 ± 11 months, respectively, P = 0.10). The sTVR group had a higher postoperative peak VO_2 (65% ± 19% vs 53% ± 21%-predicted, P = 0.008) and higher peak stroke volume (O_2 pulse) (11.1 ± 2.9 vs 9.9 ± 3.4 mL/beat, P = 0.01), but there was no significant between-group difference in peak heart rate postoperatively (79% ± 10% vs 78% ± 9%-predicted, P = 0.70) (Table 3). Compared to the baseline exercise test, the sTVR group had more improvement in peak VO_2 (6% ± 4% vs −8% ± 3%-predicted, P = 0.001) (Central Illustration).

There was a significant increase in the number of asymptomatic patients (NYHA I) from 28 (58%)

TABLE 3 Temporal Change in Echocardiographic and Exercise Test Indices

	sTVR (n = 48)	Control (n = 48)	*P* Value
Δ Echocardiographic indices			
LA volume index, mL/m^2	−2 ± 4	3 ± 2[a]	0.5
LA reservoir strain, %	3 ± 1[a]	−2 ± 1[a]	0.002
RV global longitudinal strain, %	2 ± 1[a]	−2 ± 2[a]	0.007
dP/dtic, mm Hg/s	79 ± 41[a]	−8 ± 56	0.01
RV end-diastolic area, cm^2	−6 ± 3[a]	2 ± 3	<0.001
RV end-systolic area, cm^2	−2 ± 2	0 ± 2	0.10
RV fractional area change, %	−5 ± 3[a]	−1 ± 3	0.005
RV cardiac index, l/min/m^2	0.3 ± 0.1[a]	−0.2 ± 0.1[a]	0.003
Δ Exercise indices			
Peak VO_2, mL/kg/min	1.8 ± 0.2[a]	−2.1 ± 0.3[a]	0.02
Peak VO_2, % predicted	6 ± 4[a]	−8 ± 3[a]	0.001
Heart rate at peak exercise, bmp	2 ± 8	−1 ± 9	0.30
SV (O_2 pulse) at peak exercise, mL/beat	1.4 ± 0.3[a]	−1.2 ± 0.93[a]	0.04
SV (O_2 pulse) at peak exercise, %-predicted	7 ± 4[a]	−5 ± 3[a]	0.001
Systolic BP at peak exercise, mm Hg	9 ± 5	1 ± 6	0.08
VE/VCO_2 slope	−2.2 ± 0.5[a]	0.7 ± 0.6	0.02
O_2 saturation at peak, %	0 ± 1	−1 ± 2	0.40

Values are mean ± SD. Note that indices were calculated as postoperative indices minus preoperative indices.

[a]A statistically significant change between the baseline and follow-up tests.

BP = blood pressure; dP/dtic = mean rate of pressure rise during isovolumetric contraction; LA = left atrium; RV = right ventricle; sTVR = systemic tricuspid valve replacement; SV = stroke volume; VE/VCO_2 = ventilatory equivalent for carbon dioxide; VO_2 = oxygen consumption.

pre-sTVR to 39 (81%) post-sTVR ($P = 0.02$) and a postoperative reduction in N-terminal prohormone brain natriuretic peptide (log transformed N-terminal prohormone brain natriuretic peptide 7.3 ± 1.4 (preop) vs 5.7 ± 1.2 (postop), $P < 0.001$), which is a marker of neurohormonal activation. The sTVR group also had an improvement in left atrial reservoir strain, sRV global longitudinal strain, and sRV cardiac index and a reduction in sRV end-diastolic area and RV fractional area change after sTVR (Table 3). There was modest correlation between baseline RV global longitudinal strain and dP/dtic (r = 0.63, $P < 0.001$) and between postoperative improvement in RV global longitudinal strain and dP/dtic (r = 0.69, $P < 0.001$). In contrast to the improvement in sRV global longitudinal strain and dP/dtic, we observed a decrease in sRV fractional area change after sTVR suggesting that the preoperative sRV fractional area change might have underestimated the severity of sRV systolic dysfunction in the setting of severe tricuspid regurgitation. All patients had normal prosthetic tricuspid valve function at the time of follow-up echocardiogram.

The control group had a temporal reduction in peak VO_2, and this was mostly due to a reduction in stroke volume at peak exercise without any significant change in peak heart rate (Table 3). Although the control group had an overall reduction in peak VO_2, there was no significant temporal decrease in the number of asymptomatic patients from baseline (33 [69%] at baseline vs 30 [53%] at follow-up assessment, $P = 0.30$). The control group also had a temporal reduction in left atrial reservoir strain, sRV cardiac index, and sRV global longitudinal strain and an increase in left atrial volume and sRV end-diastolic area (Table 3).

In contrast to the temporal decrease in N-terminal prohormone brain natriuretic peptide observed in the sTVR group, the control group had a temporal increase in N-terminal prohormone brain natriuretic peptide (log transformed N-terminal prohormone brain natriuretic peptide 6.1 ± 1.2 [baseline] vs 6.9 ± 1.0 [follow-up], $P = 0.008$).

DETERMINANTS OF POSTOPERATIVE IMPROVEMENT IN PEAK VO_2. Of the preoperative demographic, echocardiographic, and exercise indices analyses, systolic blood pressure at rest, sRV global longitudinal strain, and preoperative peak VO_2 were independently associated with postoperative improvement in peak VO_2 (Table 4).

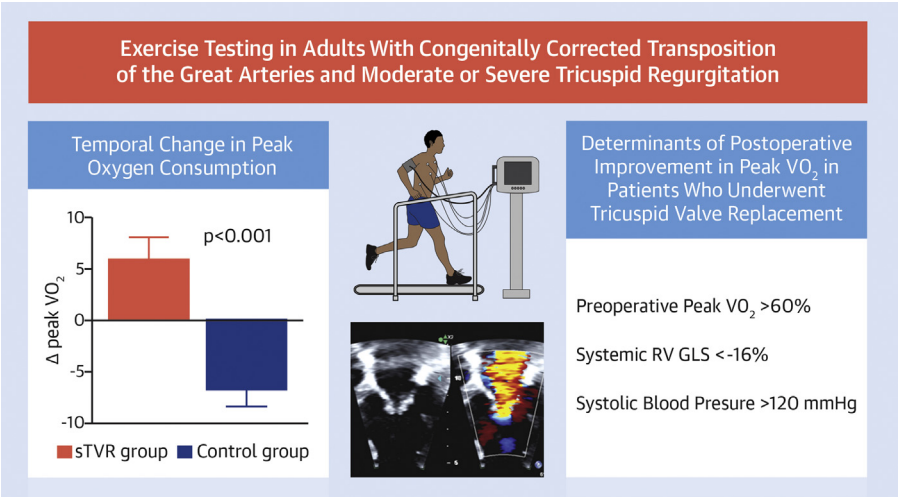
Of the 48 patients, 31 (65%) had postoperative improvement in peak VO_2 (postoperative peak VO_2 > preoperative peak VO_2). Receiver operating characteristic curve showed that preoperative peak VO_2 >60% (OR 2.11, 95% CI 1.93 to −2.31, area under the curve [AUC] 0.783), sRV global longitudinal strain <−16% (OR 1.32, 95% CI 1.19-1.54, AUC 0.694), and systolic blood pressure <120 mm Hg (OR 1.98, 95% CI 1.83-2.14, AUC 0.756) provided the optimal cutoff points to detect postoperative improvement in peak VO_2 (Central Illustration). In an exploratory analysis, we substituted RV global longitudinal strain with dP/dtic in the logistic regression model, and a preoperative dP/dtic >537 mm Hg/s (OR 1.42, 95% CI 1.27-1.64, AUC 0.706) provided the optimal cutoff points to detect postoperative improvement in peak VO_2.

DISCUSSION

In this retrospective cohort study of adults with cc-TGA and significant systemic tricuspid regurgitation, we demonstrated that sTVR was associated with improvement in peak VO_2 and that the mechanism of improvement in peak VO_2 was due to improved stroke volume at peak exercise, without any significant change in heart rate reserve. Systolic blood pressure, sRV systolic function as measured by global longitudinal strain or dP/dtic, and preoperative peak VO_2 were independently associated with postoperative improvement in peak VO_2.

Several studies have assessed aerobic capacity in adults with cc-TGA, and collectively these studies showed a reduced aerobic capacity in this population (peak VO_2 of 18-27 mL/kg/min corresponding to 60% to 69%-predicted),[8,12,14-16] and this is similar to the results observed in the current study. Additionally, these prior studies showed that reduced peak VO_2 in adults with cc-TGA was due to chronotropic incompetence and impaired stroke volume at peak exercise.[13] Chronotropic incompetence is usually due to high-grade heart block, which is very common in this population, and pacemaker implantation is an effective therapy for this complication.[28] Impaired stroke volume at peak exercise has been attributed to sRV systolic dysfunction and tricuspid regurgitation although this association has been inconsistent across studies.[8,12,14-16] A limitation of these previous studies was that most of them were based on cross-sectional analysis and hence were unable to assess the temporal relationship between sRV hemodynamics (sRV systolic function and tricuspid regurgitation) and change in aerobic capacity. In contrast, the current study showed that patients with cc-TGA and tricuspid regurgitation had a temporal deterioration in sRV systolic function and aerobic capacity (control group)

CENTRAL ILLUSTRATION **Temporal Change in Aerobic Capacity in Adults With Congenital Corrected Transposition of Great Arteries**



Egbe AC, et al. JACC Adv. 2022;1(2):100027.

(Left) Comparison of temporal change in peak oxygen consumption (Δ peak VO_2) between patients that underwent systemic tricuspid regurgitation (sTVR) in **red** and the control group in **blue**. The temporal change in peak VO_2 was higher in the sTVR group than that in the control group. **(Middle-top)** Schematic of patient performing exercise test. **(Middle-bottom)** Transthoracic echocardiogram showing systemic tricuspid regurgitation. **(Right)** Determinants of postoperative improvement in peak VO_2 among patients that underwent systemic tricuspid regurgitation. Postoperative improvement in peak VO_2 (defined as postoperative peak VO_2 minus postoperative peak VO_2). RV GLS = right ventricular global longitudinal strain.

and that sTVR (which eliminated tricuspid regurgitation) was associated with improvement in aerobic capacity and sRV systolic function (sTVR group). Concordant with improvement in aerobic capacity, we also observed an improvement in ventilatory efficiency (reduction in VE/VCO_2) in the sTVR group but not in the control group. Although the current study did not assess the effect of sTVR on clinical outcomes, the observed improvement in aerobic capacity and ventilatory efficiency suggests that sTVR may improve clinical outcomes since improvement in these indices have been shown to improve prognosis in patients with heart failure.[29,30] We postulate that 1 of the mechanisms for improvement in aerobic capacity and ventilatory efficiency may be related to a reduction in sRV filling pressure (after sTVR) and increase in sRV effective (physiologic) stroke volume, which, in turn, improved stroke volume at peak exercise. Another potential mechanism for postoperative improvement in aerobic capacity was that elimination of sRV volume overload after sTVR led to a reduction in wall stress because of reduction in sRV volumes. A reduction in sRV volumes led to sRV reverse modeling and improvement in sRV systolic function, which, in turn, led to improved stroke volume at peak exercise and aerobic capacity. This is similar to the hemodynamic improvement after mitral valve surgery in patients with normal cardiac anatomy and chronic mitral regurgitation.[10,31]

Another important finding was the decrease in sRV fractional area change after sTVR. sRV Fractional area change, which is analogous to ejection fraction, can "*mask*" sRV systolic dysfunction because of reduced sRV afterload in the setting of tricuspid regurgitation. Restoring tricuspid valve competence resulted in an increase in sRV afterload, which then "*unmasks*" a preexisting sRV systolic dysfunction, and in turn, a reduction in sRV fractional area change, analogous to the drop in left ventricular ejection fraction after mitral valve surgery in patients with normal cardiac anatomy.[32,33] In contrast, global longitudinal strain and dP/dtic are less load-dependent and hence is a more accurate approximation of systolic function.[32,33]

In addition to the increased afterload imposed on the sRV after sTVR, the sRV in patients with cc-TGA is coupled to the systemic arterial circulation and hence has to overcome systemic arterial afterload in order to eject systemic cardiac output. However, unlike the left ventricle, the RV is not structurally and

TABLE 4 Determinants of Peak VO_2 Improvement After sTVR

	Univariable		Multivariable	
	β ± SE	*P* Value	β ± SE	*P* Value
Preop demographic indices				
Age, per 5 y	−0.25 ± 0.08	0.001	–	–
Male	1.31 ± 1.69	0.40		
Body mass index, per kg/m^2	−0.32 ± 0.18	0.02	–	–
CIED	−0.14 ± 0.08	0.006	–	–
Systolic blood pressure, per 5 mm Hg	−1.01 ± 0.74	0.005	−0.72 ± 0.49	0.02
Diastolic blood pressure, per 5 mm Hg	−0.66 ± 0.35	0.01	–	–
NYHA functional class II/III (vs I)	−0.26 ± 0.53	0.30		
Concomitant mitral valve surgery	0.09 ± 0.23	0.60		
Preop echocardiographic indices				
LA reservoir strain, per %	0.08 ± 0.02	0.008	–	–
RV global longitudinal strain, per %[a]	0.13 ± 0.04	<0.001	0.11 ± 0.05	0.02
RV fractional area change, per %	0.19 ± 0.43	0.40		
RV cardiac index, L/min/m^2	0.16 ± 0.27	0.40		
RA reservoir strain, per %	0.18 ± 0.08	0.03	–	–
LV global longitudinal strain, per %[a]	−0.23 ± 0.39	0.30		
Preop exercise indices				
Predicted peak VO_2, per %	0.15 ± 0.04	<0.001	0.16 ± 0.06	0.009
Peak heart rate, per beats/min	0.03 ± 0.16	0.40		
Forced expiratory volume, per %	0.23 ± 0.26	0.09		
Forced vital capacity, per %	0.21 ± 0.41	0.20		
VE/VCO_2 slope, per unit	−0.09 ± 0.13	0.10		

Values are mean ± SD. [a]Note that RV and LV global longitudinal strain were modeled as absolute values (ie, without the negative sign).

CIED = cardiac implantable electronic device; LA = left atrium; LV = left ventricle; NYHA = New York Heart Association; RA = right atrium; RV = right ventricle; sTVR = systemic tricuspid valve replacement; SV = stroke volume; VE/VCO_2 = ventilatory equivalent for carbon dioxide; VO_2 = oxygen consumption.

functionally adapted for the systemic circulation because of its thin walls and single coronary artery blood supply.[1,2] We postulate that this is likely responsible for the negative correlation between systolic blood pressure (a close approximation of pulsatile systemic arterial afterload) and sRV systolic function and aerobic capacity in this study.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS. An important negative finding from the current study was the lack of correlation among aerobic capacity, NYHA functional status, and RV fractional area change (analogous to ejection fraction). The patients in the control group had a temporal deterioration of aerobic capacity, Doppler-derived cardiac index, sRV global longitudinal strain, and neurohormonal activation, even though their NYHA function class and RV fractional area change remained stable. Perhaps, these indices should not be used for risk stratification.

Another important clinical implication of the current data is the need for optimal blood pressure control. Although more than 70% of the patients were receiving a renin-angiotensin-aldosterone system (RAAS) antagonist, more than 50% of the patients still had resting systolic blood pressure >120 mm Hg, suggesting suboptimal blood pressure control. Although previous studies have not shown that RAAS antagonists improved RV systolic function in patients with cc-TGA,[34] we speculate that RAAS should be used for afterload reduction and titrated to maintain normal blood pressure because of the deleterious effect of hypertension on sRV systolic function and aerobic capacity in this population. Further studies are required to determine whether strict blood pressure control will result in improved clinical outcomes in this population, similar to the beneficial effects of strict blood pressure control (target systolic blood pressure <120 mm Hg) observed in the SPRINT (A Randomized Trial of Intensive versus Standard Blood-Pressure Control) trial and other observational studies.[35,36]

STUDY LIMITATIONS. This is a retrospective study conducted in a single adult congenital heart disease referral center, and hence, it is prone to selection and ascertainment bias. Furthermore, the current study could not determine whether postoperative improvement in aerobic capacity was associated with improved clinical outcomes because of a small sample size and limited follow-up. VO_2 is dependent on central factors (heart rate and stroke volume) and peripheral factors (tissue oxygen uptake and consumptions).[21] Hence, using O_2 pulse (VO_2/heart rate) as surrogate for stroke volume did not account for the effect of tissue oxygen

uptake and consumption. The improvement in peak VO_2 in the sTVR group could have been influenced by other factors apart from the changes in loading conditions from a competent tricuspid valve. The temporal decline in aerobic capacity could have been influenced by other factors apart from chronic volume load to systemic tricuspid regurgitation. Although we controlled for the differences in baseline characteristics using propensity matching, there were still some residual between-group differences in baseline characteristics (such as a higher prevalence of patients with severe tricuspid regurgitation and more advanced cardiac remodeling in the sTVR group), and these differences could have influenced the results of the study.

We did not correct sRV global longitudinal strain for sRV end-diastolic volume; hence, sRV global longitudinal strain may not provide a true approximation of RV contractility in the setting of severe systemic tricuspid regurgitation because it is sensitive to preload. However, the correlation observed between sRV global longitudinal and dP/dtic suggested that the observed change in sRV systolic function indices after sTVR was more likely due to an improvement in contractility rather than just changes in loading conditions.

CONCLUSIONS

There was an improvement in aerobic capacity after sTVR in patients with cc-TGA and severe tricuspid regurgitation. Postoperative improvement in aerobic capacity was associated with systolic blood pressure, sRV systolic function (sRV global longitudinal strain and dP/dtic), and preoperative peak VO_2, and these indices should be integrated into the clinical decision process. Additionally, NYHA functional status and sRV fractional area change did not correlate with temporal changes in aerobic capacity and hemodynamic characteristics and hence should not be used for risk stratification. Further studies are required to determine whether strict blood pressure control and optimal timing of sTVR based on the indices proposed in this study would result in improved clinical outcomes in this population.

ACKNOWLEDGMENT James Welper performed offline image analysis for this study.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The Mayo Adult Congenital Heart Disease Registry is supported by the Al-Bahar Research grant. Dr Egbe is supported by National Heart, Lung, and Blood Institute (NHLBI) grants (K23 HL141448, R01 HL158517 and R01 160761). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: There was an improvement in aerobic capacity after sTVR in patients with cc-TGA and severe tricuspid regurgitation. Postoperative improvement in aerobic capacity was associated with systolic blood pressure, sRV systolic function (sRV global longitudinal strain and dP/dtic), and preoperative peak VO_2, and these indices should be integrated into the clinical decision process.

TRANSLATIONAL OUTLOOK: Further studies are required to determine whether strict blood pressure control and optimal timing of sTVR based on the indices proposed in this study would result in improved clinical outcomes in this population.

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KEY WORDS exercise capacity, transposition of great arteries, tricuspid regurgitation, tricuspid valve replacement

APPENDIX For a supplemental table, please see the online version of this paper.