

ORIGINAL RESEARCH

# Modified Ventricular Global Function Index Correlates With Exercise Capacity in Repaired Tetralogy of Fallot

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**BACKGROUND:** Cardiac MRI (CMR) derived ventricular global function index (GFI), a ratio of stroke volume to the sum of mean ventricular cavity and myocardial volumes, has demonstrated improved prediction of clinical outcomes in adults with atherosclerotic disease over ejection fraction. We sought to assess CMR derived GFI and a novel modification that accounts for unique loading conditions in patients with repaired tetralogy of Fallot (rTOF) and determine its correlation with exercise performance.

**METHODS AND RESULTS:** Seventy-five patients with rTOF who underwent CMR were identified. Clinical variables were recorded and biventricular GFI calculated. A right ventricular (RV) effective GFI (eGFI) was derived by incorporating effective stroke volume. Thirty-five pediatric patients were matched with 29 age-matched healthy controls. Twenty-five patients completed cardiopulmonary exercise tests within 6 months of CMR. Stepwise regression models were used to determine univariate and multivariable predictors of indexed and percent predicted peak  $\text{VO}_2$ . Median age at CMR was 20 years (interquartile range, 13–28). Pediatric rTOF patients had lower RV eGFI ( $P < 0.001$ ), RV ejection fraction ( $P=0.002$ ), but higher indexed RV end-diastolic and end-systolic volumes ( $P < 0.001$ ,  $P < 0.001$ ) compared with controls. Univariate analysis demonstrated a correlation between indexed peak  $\text{VO}_2$  with RV eGFI ( $R^2=0.32$ ,  $P=0.004$ ), but with neither RVGFI, RV ejection fraction, indexed RV volumes nor RV mass. RV eGFI remained significantly associated with indexed peak  $\text{VO}_2$  during multivariable modeling.

**CONCLUSIONS:** Reduced RV eGFI was associated with reduced exercise capacity in rTOF patients, while RV GFI, RV ejection fraction, indexed RV volumes and mass were not. Our modification of the GFI, RV eGFI, may be a valuable non-invasive marker of cardiac function in rTOF.

**Key Words:** congenital heart disease ■ exercise ■ imaging and diagnostic testing ■ magnetic resonance imaging

**W**ith improvement in surgical techniques and patient management, there is a growing population of patients with tetralogy of Fallot (TOF) who have undergone repair. Despite improvements in early survival, there continues to be a high incidence of impaired functional status, heart failure, arrhythmias, and death, which often occur in the setting of right ventricle (RV) dysfunction with either volume- and/or pressure-loading of the RV.<sup>1,2</sup> In an attempt to ameliorate these outcomes, pulmonary valve replacement (PVR) is often performed in symptomatic patients or

asymptomatic patients who have significant RV dilation or RV systolic dysfunction. However, using current guidelines, PVR does not lead to survival benefit or reduce other major adverse postoperative events.<sup>3</sup> Recent investigations identifying risk factors and biomarkers for these adverse outcomes after PVR have shown that preoperative RV hypertrophy and dysfunction, not ventricular volumes, particularly in patients approaching their third decade of life, are associated with worse outcomes—highlighting the importance of maintaining myocardial health.<sup>4,5</sup> Moreover, left

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For Sources of Funding and Disclosures, see page 8.

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## CLINICAL PERSPECTIVE

### What Is New?

- Right ventricular effective global function index may be a more comprehensive marker of poor myocardial health and exercise intolerance than currently used indices.

### What Are the Clinical Implications?

- The association between reduced right ventricular effective global function index with impaired exercise performance establishes biologic plausibility which may form the basis of larger scale studies assessing the value of preoperative effective global function index in defining potential thresholds for timing of pulmonary valve replacement and predicting outcomes.

## Nonstandard Abbreviations and Acronyms

<b>BSA</b>	body surface area
<b>CMR</b>	cardiac MRI
<b>CPET</b>	cardiopulmonary exercise testing
<b>EF</b>	ejection fraction
<b>GFI</b>	global function index
<b>LV</b>	left ventricle
<b>LVEDVi</b>	indexed left ventricular end-diastolic volume
<b>LVESVi</b>	indexed left ventricular end-systolic volume
<b>PRF</b>	pulmonary regurgitant fraction
<b>PVR</b>	pulmonary valve replacement
<b>rTOF</b>	repaired tetralogy of Fallot
<b>RV</b>	right ventricle
<b>RVEDVi</b>	indexed right ventricular end-diastolic volume
<b>RVESVi</b>	indexed right ventricular end-systolic volume
<b>TOF</b>	tetralogy of Fallot

ventricular (LV) systolic and diastolic dysfunction are emerging as important, albeit often neglected, components in risk stratification for poor outcomes after PVR.<sup>5,6</sup>

Systolic function is most often inferred from the calculated ejection fraction (EF).<sup>7,8</sup> However, EF is not a direct measure of myocardial contractility but instead a reflection of ventricular remodeling, and should always be interpreted in the context of ventricular preload and afterload.<sup>9-13</sup> Moreover, EF alone can be an insensitive marker to assess either systolic<sup>14</sup> or

diastolic dysfunction.<sup>15</sup> While associations between EF and outcomes are measurable in postoperative tetralogy patients, such associations are weak, and the overlap with those not experiencing adverse events is large,<sup>4</sup> making EF a poor marker in individual patients. The cardiac MRI (CMR) derived ventricular global function index (GFI), defined as a ratio of the stroke volume to the sum of mean ventricular cavity and myocardial volume, has been proposed as a better marker of ventricular function because it incorporates structural, mechanical, and preload indices.<sup>14</sup> Indeed, GFI was shown to be a better predictor of clinical outcomes in adult patients with atherosclerosis compared with EF.<sup>14,16</sup> Establishing GFI, or the lesion-specific modification we describe in the current study, as a novel and more robust predictor of hard clinical end points in patients with repaired TOF (rTOF) will require prospective testing in a large, likely multi-center, study after biologic plausibility has been established. To do the latter, this "proof-of-principle" study leverages the known association between impaired exercise capacity as assessed by cardiopulmonary exercise testing (CPET) and poorer outcomes in patients with rTOF,<sup>17-19</sup> and so describes CMR derived RV and LV GFI in patients with rTOF and explores its relationship with exercise performance.

## METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. The current study was approved by Cincinnati Children's Hospital Medical Center's Institutional Review Board. Informed consent was deferred given the retrospective nature of the study.

### Patient Population

Seventy-five patients with rTOF who underwent CMR with technically adequate images to allow for assessment of ventricular volumes and systolic function from January 2015 to November 2018 at a single institution were identified. Patients aged <10 years at the time of CMR, those with pulmonary atresia and major aortopulmonary collaterals, those with absent pulmonary valve syndrome, or those who had undergone PVR before the CMR were excluded from the study. Clinical variables were obtained from retrospective chart review.

### CMR Assessment

CMR studies were performed on 1.5 Tesla Phillips Ingenia scanners. Cardiac functional imaging was performed using a standard retrospective ECG-gated, segmented steady state free precession technique and included a short axis stack of cine steady

state free precession images from cardiac base to apex as previously described.<sup>20</sup> Scan parameters included 6 mm slice thickness with no gap; 1.5 mm<sup>2</sup> acquired in-plane resolution; field of view manipulated to maintain constant resolution for body size; 30 phase/RR interval; minimum TE; TR ≈2.8 ms.<sup>21</sup> Contours were drawn manually at the endocardial and epicardial borders from short axis cine stack images spanning the ventricular base to apex using cvi42, Circle Cardiovascular Imaging Inc., Calgary, Canada.

### Global Function Index Calculation

Biventricular GFI was calculated for each patient using the following formula as previously described<sup>14</sup>:

$$\text{GFI} = \left[ \frac{\text{Stroke volume (SV)}}{\frac{\text{End diastolic volume(EDV)+End systolic volume(ESV)}{2} + \frac{\text{Ventricular mass}}{1.05}} \right] \times 100$$

$$\text{GFI} = \left[ \frac{\text{EDV} - \text{ESV}}{\frac{\text{EDV} + \text{ESV}}{2} + \frac{\text{Ventricular mass}}{1.05}} \right] \times 100$$

For assessment of the RV, the GFI was calculated twice, first using the total RV stroke volume, RV GFI, and a separate index, RV eGFI, using an effective stroke volume that corrected for pulmonary regurgitation. Accounting for an effective RV stroke volume has been suggested in prior studies assessing patients with rTOF.<sup>22,23</sup> Tricuspid regurgitation was not accounted for in this effective stroke volume as all patients had mild or less tricuspid regurgitation. This yielded the following formula below:

$$\text{RV eGFI} = \left[ \frac{\text{RV SV}_{\text{effective}}}{\frac{\text{RV EDV} + \text{RV ESV}}{2} + \frac{\text{RV ventricular mass}}{1.05}} \right] \times 100$$

$$\text{RV eGFI} = \left[ \frac{\text{RV SV} \times (1 - \text{pulmonary regurgitant fraction})}{\frac{\text{RV EDV} + \text{RV ESV}}{2} + \frac{\text{RV ventricular mass}}{1.05}} \right] \times 100$$

$$\text{RV eGFI} = \left[ \frac{(\text{RV EDV} - \text{RV ESV}) \times (1 - \text{pulmonary regurgitant fraction})}{\frac{\text{RV EDV} + \text{RV ESV}}{2} + \frac{\text{RV ventricular mass}}{1.05}} \right] \times 100$$

### Pediatric Age-Matched Controls

Thirty-five pediatric (46%) patients were matched with 29 age-matched controls. Controls were patients who

had undergone CMR for assessment of pectus deformity and had normal ventricular chamber volumes, LV EF ≥55%, RV EF ≥50%, and no cardiovascular anomalies.

### Cardiopulmonary Exercise Tests

Twenty-five (33%) patients had undergone maximum CPET within 6 months of the CMR. All patients underwent exercise testing on a stationary cycle ergometer (Lode Corival) using an incremental ramp protocol. The incremental rate was chosen based on the patient's body surface area (BSA) with a goal to reach intolerance in ≈10 minutes. Cardiopulmonary responses to exercise were assessed breath-by-breath (Ultima Cardio2, MGC Diagnostics). Peak predicted VO<sub>2</sub> was calculated per Wasserman et al and Cooper et al.<sup>24,25</sup> A maximum exercise test was defined by a respiratory exchange ratio ≥1.1. Only patients with maximum exercise testing were included in the analysis. An abnormal CPET was defined as a percent predicted VO<sub>2</sub> of <80%.

### Pulmonary Valve Replacement

Our institution follows previously published guidelines about timing of PVR in asymptomatic or symptomatic patients with rTOF. These recommended functional and volumetric cutoffs were considered in the statistical analysis.<sup>26</sup>

### Statistical Analysis

Two-sided T tests were used to test for differences between groups, and *P*<0.05 were considered statistically significant. Linear regression models for both RV GFI and eGFI were created to determine univariate predictors of peak VO<sub>2</sub> indexed to body weight, percent predicted peak VO<sub>2</sub>, and minute ventilation/carbon dioxide production slope. A stepwise multivariable linear regression model with *P*<0.1 on univariate analysis as the significance level for entry and *P*<0.05 as the significance level to remain in the multivariable model was constructed to determine significantly associated predictors of outcome variables. No multiplicity adjustment was applied. Statistical analysis was performed using JMP (Version 14.1.0, Cary, NC).

## RESULTS

### Demographics and Exercise Testing

The study cohort consisted of 75 rTOF patients. The median age at TOF repair was 8 months (interquartile range, 4–18); median age at CMR was 19 years (interquartile range, 13–28). Fifty-six (75%) patients had a history of repair with a transannular patch. Fifteen (20%) patients underwent pulmonary valve replacement (PVR) following the CMR, with asymptomatic RV

dilation being the indication in 4 of these patients. The indication for the remaining nine were: RV outflow tract aneurysm, conduit and branch pulmonary artery stenosis, dilation with diminished function or symptomatic with severe regurgitation. The mean age for the 25 patients who underwent CPET was 24 years (range 10–40). Of the 25 patients who had maximal effort CPET, 12 (48%) patients had an abnormal percent predicted peak  $\text{VO}_2$  (Table 1).

### Volumetric Assessment

Eleven (15%) patients had indexed RV end-diastolic volumes (RVEDVi) to BSA  $>150 \text{ mL/m}^2$  with a mean RVEDVi of  $118.6 \pm 30.6 \text{ mL/m}^2$  for the entire cohort. Nine (12%) patients had indexed RV end-systolic volumes (RVESVi) to BSA  $>80 \text{ mL/m}^2$  with a mean RVESVi of  $58.4 \pm 18.7 \text{ mL/m}^2$  for the entire cohort. The mean LV end-diastolic volume indexed to BSA (LVEDVi) was  $79.6 \pm 13.8 \text{ mL/m}^2$ , and the mean LV end-systolic volume indexed to BSA (LVESVi) was  $34.9 \pm 8.6 \text{ mL/m}^2$ .

### Functional Assessment

Eighteen (24%) patients had diminished RV systolic function (RV EF  $<48\%$ ). The mean RV EF was  $51.3 \pm 6.0\%$ , while the mean RV GFI and eGFI were  $56.7 \pm 8.0\%$  and  $38.5 \pm 11.1\%$ , respectively, for the entire cohort. Twenty-seven (36%) patients had severe pulmonary regurgitation (pulmonary regurgitant fraction  $>40\%$ ). For the entire cohort, the mean pulmonary regurgitant fraction (PRF) was  $32.1 \pm 15.9\%$ ; the indexed pulmonary regurgitant volume was  $20.6 \pm 13.5 \text{ mL/beat per m}^2$ ; and the peak pulmonary valve flow velocity was  $2.0 \pm 0.5 \text{ m/s}$  (Table 1). Thirty (40%) patients had diminished LV systolic function (LV EF  $<55\%$ ). For the entire cohort, the mean LV EF was  $56.3 \pm 5.4\%$ , while the mean LV GFI was  $46.7 \pm 6.8\%$ .

### Pediatric rTOF Compared With Controls

Compared with controls, pediatric rTOF patients had statistically significant higher RVEDVi ( $P < 0.001$ ) and RVESVi ( $P < 0.001$ ) (Table 2). There was no difference in RV mass indexed ( $P = 0.06$ ) or RV GFI ( $P = 0.2$ ) between the 2 groups. Both RV EF ( $P = 0.002$ ) and RV eGFI ( $P < 0.001$ ) were lower compared with controls. LVEDVi ( $P < 0.001$ ), LVESVi ( $P = 0.025$ ), and LV GFI ( $P = 0.033$ ) were significantly lower than age-matched controls. There was no difference in LV mass ( $P > 0.99$ ) or LV EF ( $P = 0.4$ ).

### PVR Compared With No PVR

During a median follow up period of  $\approx 19$  months (interquartile range, 12–25) following CMR, 15 patients

**Table 1. Demographics and CMR Parameters**

	Total (n=75)
Female, n (%)	41 (55)
Median age at repair, mo	8 (4–18.25)
Median age at CMR, y	19 (13–28)
Number with history of repair via transannular patch, n (%)	56 (75)
Median time from repair to CMR, y	19 (12–25)
CMR	
RV	
RVEDVi, mL/m <sup>2</sup>	118.6 $\pm$ 30.6
RVESVi, mL/m <sup>2</sup>	58.4 $\pm$ 18.7
RV mass indexed, g/m <sup>2</sup>	22.0 $\pm$ 7.0
Pulmonary regurgitant fraction, %	32.1 $\pm$ 15.9
PRVi, mL/beat per m <sup>2</sup>	20.6 $\pm$ 13.5
Pulmonary valve peak velocity, m/s	2.0 $\pm$ 0.5
RV EF, %	51.3 $\pm$ 6.0
RV GFI, %	56.6 $\pm$ 7.9
RV eGFI, %	38.5 $\pm$ 11.1
LV	
LVEDVi, mL/m <sup>2</sup>	79.6 $\pm$ 13.8
LVESVi, mL/m <sup>2</sup>	34.9 $\pm$ 8.6
LV mass indexed, g/m <sup>2</sup>	41.4 $\pm$ 11.8
LV EF, %	56.3 $\pm$ 5.4
LV GFI, %	46.7 $\pm$ 6.8
CPET	
RER	1.2 $\pm$ 0.1
Peak $\text{VO}_2$ /kg, mL/min per kg	25.8 $\pm$ 7.5
% predicted max $\text{VO}_2$ , %	78.5 $\pm$ 7.5
VE/ $\text{VCO}_2$	31.2 $\pm$ 5.8

Demographic data are medians with interquartile ranges in parenthesis. Cardiac magnetic resonance and exercise data are mean $\pm$ SD. CMR indicates cardiac magnetic resonance; LV EF, left ventricular ejection fraction; LV GFI, left ventricular global function index; LVEDVi, left ventricular end-diastolic volume indexed to body surface area; LVESVi, left ventricular end-systolic volume indexed to body surface area; PRVi, pulmonary regurgitant volume indexed to body surface; RER, respiratory exchange ratio; RV EF, right ventricular ejection fraction; RV eGFI, right ventricular effective global function index; RV GFI, right ventricular global function index; RVEDVi, right ventricular end-diastolic volume indexed to body surface area; RVESVi, right ventricular end-systolic volume indexed to body surface area; and VE/ $\text{VCO}_2$ , minute ventilation/carbon dioxide production.

underwent PVR. The median age at PVR was 22 years (interquartile range, 17.5–31). There was no difference in RV EF ( $P = 0.3$ ) or RV GFI ( $P = 0.6$ ), however RV eGFI was lower in patients who underwent PVR ( $P < 0.001$ ) (Table 3). Patients who underwent PVR also had higher RVEDVi ( $P < 0.001$ ), RVESVi ( $P = 0.001$ ), RV mass index ( $P = 0.017$ ), and indexed pulmonary regurgitant volume ( $P < 0.001$ ), (Table 3). There were no differences in LVEDVi ( $P = 0.7$ ), LVESVi ( $P > 0.99$ ), LV mass indexed ( $P = 0.9$ ), or peak pulmonary valve velocity ( $P = 0.2$ ) between the 2 groups. LV EF ( $P = 0.46$ ) and LV GFI ( $P = 0.6$ ) were similar between

**Table 2. Pediatric rTOF Patients versus Age-Matched Controls**

	Pediatric rTOF (n=35)	Controls (n=29)	P Value
Female, n (%)	22 (63)	10 (34)	0.024
Age at CMR, y	14 (13–16)	13 (12–15)	0.21
CMR			
LVEDVi, mL/m <sup>2</sup>	80.0±9.9	91.1±13.7	<0.001
LVESVi, mL/m <sup>2</sup>	33.4±5.5	37.7±8.7	0.025
LV mass indexed, g/m <sup>2</sup>	39.85±9.4	39.7±10.35	>0.99
LV EF, %	58.2±4.844	59.1±4.8	0.4
LV GFI, %	49.5±5.8	53.1±7.3	0.033
RVEDVi, mL/m <sup>2</sup>	121.9±31.4	96.8±16.5	>0.001
RVESVi, mL/m <sup>2</sup>	57.5±18.3	43.9±11.8	>0.001
RV mass indexed, g/m <sup>2</sup>	23.2±7.2	19.7±7.2	0.06
RV EF, %	53.9±6.0	58.1±4.7	0.003
RV GFI, %	58.1±7.2	60.7±9.3	0.2
RV eGFI, %	40.3±12.4	60.7±9.3	<0.001

Agers are medians and interquartile ranges. Data are mean±SD. CMR indicates cardiac magnetic resonance; LV EF, left ventricular ejection fraction; LV GFI, left ventricular global function index; LVEDVi, left ventricular end-diastolic volume indexed to body surface area; LVESVi, left ventricular end-systolic volume indexed to body surface area; rTOF, repaired tetralogy of Fallot; RV EF, right ventricular ejection fraction; RV eGFI, right ventricular effective global function index; RV GFI, right ventricular global function index; RVEDVi, right ventricular end-diastolic volume indexed to body surface area; and RVESVi, right ventricular end-systolic volume indexed to body surface area.

the 2 groups. When RV eGFI was categorized into quartiles, an RV eGFI <29.5% (25th percentile of the entire cohort) was associated with increased relative risk of undergoing PVR (risk ratio, 5.7; CI, 2.6–12.7,  $P<0.001$ ).

### eGFI Pre- and Post-PVR

Four patients in the cohort had CMR assessment pre- and post-PVR. There was a reduction in RV volumes that approached statistical significance (Table 4). There was no change in RV EF or RV GFI. RV eGFI had a mean improvement of 22% ( $P=0.011$ ). There was a significant improvement in PRF ( $P=0.015$ ). LVEDVi was increased by 11.6 mL/m<sup>2</sup> ( $P=0.02$ ). There was no change in LVESVi, LV EF, or LV GFI.

### CMR Associations With CPET

For indexed peak VO<sub>2</sub>, univariate analysis demonstrated an association with LVEDVi, LVESVi, RV eGFI, and PRF (Table 5). With multivariate modeling, LVEDVi and RV eGFI remained significantly associated. When analyzing percent of predicted peak VO<sub>2</sub>, LVEDVi, RV eGFI, and PRF were associated by univariate analysis. With multivariate modeling, only LVEDVi remained significantly associated. For minute ventilation/carbon dioxide production slope, univariate analyses demonstrated an association with LV mass, RV mass, and

**Table 3. CMR Characteristics of Those Who Underwent PVR Compared With Those Who Did Not**

	No PVR (n=60)	PVR (n=15)	P Value
Age, y	21.2±11.4	25.1±10.0	0.2
LVEDVi, mL/m <sup>2</sup>	79.2±12.7	81.0±18.0	0.7
LVESVi, mL/m <sup>2</sup>	35.0±8.8	34.8±8.2	>0.99
LV mass indexed, g/m <sup>2</sup>	41.4±12.1	41.6±11.3	0.9
LV EF, %	56.2±5.7	56.9±4.3	0.6
LV GFI, %	46.5±6.9	47.5±6.6	0.6
RVEDVi, mL/m <sup>2</sup>	110.1±22.2	152.6±36.3	<0.001
RVESVi, mL/m <sup>2</sup>	53.6±13.8	77.8±23.5	0.001
RV mass indexed, g/m <sup>2</sup>	20.7±5.9	26.9±8.7	0.017
RV EF, %	52.1±6.5	50.0±7.3	0.3
RV GFI, %	57.0±7.6	55.6±9.5	0.6
RV eGFI, %	40.6±10.8	29.7±7.5	<0.001
PRF, %	28.8±14.9	45.0±13.2	<0.001
PRVi, mL/beat per m <sup>2</sup>	17.4±11.0	33.7±14.8	<0.001
PV peak velocity, m/s	1.9±0.4	2.2±0.7	0.1

Data are mean±SD. CMR indicates cardiac magnetic resonance; LVEDVi, left ventricular end-diastolic volume indexed to body surface area; LVESVi, left ventricular end-systolic volume indexed to body surface area; LV EF, left ventricular ejection fraction; LV GFI, left ventricular global function index; PRF, pulmonary regurgitant fraction; PRVi, pulmonary regurgitant volume indexed to body surface area; PV, pulmonary valve; PVR, pulmonary valve replacement; RV EF, right ventricular ejection fraction; RVEDVi, right ventricular end-diastolic volume indexed to body surface area; RVESVi, right ventricular end-systolic volume indexed to body surface area; and RVGFI, right ventricular global function index.

RVESVi. With multivariate modeling, only RV mass remained significantly associated.

## DISCUSSION

This study demonstrates that our novel modification of the GFI, incorporating effective stroke volume rather than total stroke volume (eGFI), may be a useful non-invasive method to assess myocardial health in patients after tetralogy of Fallot. Reduced RV eGFI was associated with impaired exercise capacity in patients with rTOF, while RV EF, RV GFI using the total RV stroke volume, indexed RV volumes and mass were not. While preoperative RV volumes and EF are the most commonly used indices to determine the need for PVR in asymptomatic patients, their optimal thresholds continue to be debated, and they do not appear to be related to hard clinical end points such as death, heart failure or ventricular tachycardia after PVR.<sup>4</sup> Instead, other markers of myocardial health such as RV mass/volume ratio and LVESVi, particularly in older patients, are emerging as important predictors of these adverse outcomes.<sup>4</sup> It remains to be seen, however, whether these markers are simply associations or predictive biomarkers that are beneficially modifiable by PVR.<sup>5</sup> What is clear from these data is that risk

**Table 4. CMR Comparison Pre- and Post-PVR**

	Patient A		Patient B		Patient C		Patient D		Cohort	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Mean Difference	P Value
LVEDVi, mL/m <sup>2</sup>	61.8	67.3	64.5	78.3	107.1	116.5	96.9	115.8	11.6	0.02
LVESVi, mL/m <sup>2</sup>	39.6	27.7	27.9	33.1	46.0	52.4	50.5	52.1	0.3	0.9
LV mass indexed, g/m <sup>2</sup>	28.6	29.7	26.1	38.7	54.3	48.5	69.5	72.1	2.6	0.5
LV EF, %	61.4	58.8	56.8	57.7	57.0	55.0	47.9	54.6	0.7	0.7
LV GFI, %	54.1	52.2	51.5	48.8	47.6	49.0	33.2	41.2	1.2	0.7
RVEDVi, mL/m <sup>2</sup>	94.7	75.7	150.5	95.2	236.5	140.5	174.5	143.4	-50.3	0.06
RVESVi, mL/m <sup>2</sup>	46.7	34.8	73.5	50.4	122.6	71.3	94.5	81.0	-25.0	0.07
RV mass indexed, g/m <sup>2</sup>	16.4	13.5	23.4	10.6	46.1	14.2	34.1	47.7	-8.3	0.4
RV EF, %	50.6	54.0	51.2	47.1	48.1	49.3	45.8	43.5	-0.5	0.8
RV GFI, %	91.1	78.0	80.3	76.0	64.1	71.0	64.5	53.2	-5.4	0.3
RV eGFI, %	39.5	60.1	22.9	54.1	31.9	57.0	27.8	40.4	22.4	0.011
PRF, %	29	0	60	N/A	46	1	42	1	-38.3	0.015
PRVi, mL/beat per m <sup>2</sup>	14.2	0	46.2	N/A	58.2	0.6	34.6	0.4	-35.4	0.1

CMR indicates cardiac magnetic resonance; LV EF, left ventricular ejection fraction; LV GFI, left ventricular global function index; LVEDVi, left ventricular end-diastolic volume indexed to body surface area; LVESVi, left ventricular end-systolic volume indexed to body surface area; N/A, not available; PRF, pulmonary regurgitant fraction; PRVi, pulmonary regurgitant volume indexed to body surface area; PVR, pulmonary valve replacement; RV EF, right ventricular ejection fraction; RV eGFI, right ventricular effective global function index; RV GFI, right ventricular global function index; RVEDVi, right ventricular end-diastolic volume indexed to body surface area; and RVESVi, right ventricular end-systolic volume indexed to body surface area.

stratification of patients before PVR needs to be improved, and markers that incorporate functional indices that go beyond simple volumetric calculations will be potentially more informative. CMR-derived GFI has been proposed as a more sensitive marker of ventricular function compared with traditional metrics, such as EF, as it integrates both structural and mechanical behavior.<sup>14</sup> EF has been recognized as an imperfect marker of myocardial function, being influenced by both preload and afterload.<sup>9</sup> Consequently, myocardial GFI may better reflect ventricular function, considering not only the ventricular stroke volume, but also accounting for the influences from ventricular preload and hypertrophy. Indeed, this index was shown to be a better predictor of clinical outcomes in adult patients with atherosclerosis compared with EF.<sup>14,16</sup>

In the current study, we describe for the first time, to our knowledge, a modification of the GFI which we define as the effective GFI by using an effective stroke volume in these rTOF patients characterized by substantial pulmonary regurgitation. Our patients had significantly lower RV function as measured by both RV EF and RV eGFI values compared with controls. Importantly, in multivariate analysis, RV eGFI but neither RV GFI, RV EF, nor RV volume indices was correlated with exercise performance. Our finding of an association between reduced RV eGFI with impaired exercise performance is important for 2 reasons—first, impaired exercise performance correlates with poor outcomes<sup>17–19</sup>; and second, we believe this establishes biologic plausibility that may form the basis of larger

scale studies of the value of preoperative GFI in defining potential thresholds for PVR and predicting outcomes thereafter.

The lack of correlation between RV EF, RVEDVi, RVESVi, or RV mass with poor exercise performance is consistent with prior studies, and further underscores their potential lack of utility as singular predictive indexes either for preoperative performance or postoperative outcomes. However, when incorporated, with ventricular mass, as components of the GFI, they perhaps better describe global myocardial health and functional performance. It is important to recognize that to account for pulmonary regurgitation we calculated effective stroke volume for the RV eGFI. Interestingly there was no association between RV GFI and exercise performance, while there was an association between RV eGFI and exercise performance. Furthermore, in univariate analysis, PRF correlated with both indexed and percent predicted peak VO<sub>2</sub>, which questions the influence of pulmonary regurgitation on the correlation of RV eGFI to exercise performance. However, the association of PRF did not hold upon multivariate analysis while RV GFI remained associated to indexed peak VO<sub>2</sub> and percent predicted VO<sub>2</sub>. This suggests that it is the cumulative input of effective RV stroke volume, volumes and mass which relays the most relevant clinical information. Overall, these data support RV eGFI as a non-invasive and easy-to-measure marker of myocardial health in the rTOF population.

**Table 5. Univariate and Multivariate Associations of CMR Parameters to Exercise Parameters**

	R <sup>2</sup>	Parameter Estimate±SD	P Value
Univariate analysis of VO <sub>2</sub> /kg			
LVEDVi, mL/m <sup>2</sup>	0.50	0.29±0.06	<0.001
LVESVi, mL/m <sup>2</sup>	0.33	0.48±0.14	0.003
LV mass indexed, g/m <sup>2</sup>	0.15	0.24±0.12	0.05
LVEF, %	0.00	0.10±0.31	0.7
LV GFI, %	0.02	0.13±0.23	0.6
RVEDVi, mL/m <sup>2</sup>	0.04	-0.06±0.06	0.3
RVESVi, mL/m <sup>2</sup>	0.16	-0.06±0.03	0.051
RV mass indexed, g/m <sup>2</sup>	0.00	0.05±0.30	0.9
RV EF, %	0.09	0.40±0.27	0.2
RV GFI, %	0.07	0.29±0.23	0.2
RV eGFI, %	0.36	0.49±0.12	0.002
PRF, %	0.29	-0.24±0.08	0.006
PRVi, mL/beat per m <sup>2</sup>	0.18	-0.24±0.11	0.035
PV peak velocity, m/s	0.02	2.04±3.32	0.5
Multivariate analysis, R <sup>2</sup> =0.67			
LVEDVi, mL/m <sup>2</sup>		0.24±0.05	<0.001
RV eGFI, %		0.32±0.10	0.003
Univariate analysis of % predicted peak VO <sub>2</sub>			
LVEDVi, mL/m <sup>2</sup>	0.19	0.35±0.15	0.03
LVESVi, mL/m <sup>2</sup>	0.14	0.60±0.31	0.07
LV mass indexed, g/m <sup>2</sup>	0.03	0.19±0.24	0.4
LVEF, %	0.03	0.52±0.60	0.4
LV GFI, %	0.09	0.64±0.42	0.1
RVEDVi, mL/m <sup>2</sup>	0.00	-0.03±0.12	0.8
RVESVi, mL/m <sup>2</sup>	0.01	-0.03±0.06	0.6
RV mass indexed, g/m <sup>2</sup>	0.03	-0.19±0.22	0.7
RV EF, %	0.00	0.24±0.55	0.7
RV GFI, %	0.00	0.11±0.45	0.8
RV eGFI, %	0.16	0.58±0.27	0.047
PRF, %	0.16	-0.36±0.17	0.046
PRVi, mL/beat per m <sup>2</sup>	0.07	-0.29±0.22	0.2
PV peak velocity, m/s	0.07	8.44±6.27	0.2
Multivariate analysis, R <sup>2</sup> =0.19			
LVEDVi, mL/m <sup>2</sup>		0.35±0.15	0.031
Univariate analysis of VE/VCO <sub>2</sub> slope			
LVEDVi, mL/m <sup>2</sup>	0.00	-0.03±0.07	0.7
LVESVi, mL/m <sup>2</sup>	0.01	-0.06±0.14	0.6
LV mass indexed, g/m <sup>2</sup>	0.31	-0.10±0.03	0.004
LVEF, %	0.00	-0.08±0.25	0.8
LV GFI, %	0.04	0.17±0.18	0.4
RVEDVi, mL/m <sup>2</sup>	0.03	-0.04±0.05	0.4
RVESVi, mL/m <sup>2</sup>	0.20	-0.06±0.02	0.025
RV mass indexed, g/m <sup>2</sup>	0.45	-0.29±0.07	<0.001
RV EF, %	0.04	0.22±0.22	0.3
RV GFI, %	0.07	0.24±0.18	0.2

(Continued)

**Table 5. Continued**

	R <sup>2</sup>	Parameter Estimate±SD	P Value
RV eGFI, %	0.03	0.11±0.12	0.4
PRF, %	0.00	-0.01±0.08	0.9
PRVi, mL/beat per m <sup>2</sup>	0.00	0.00±0.10	0.9
PV peak velocity, m/s	0.03	-2.21±2.66	0.4
Multivariate analysis, R <sup>2</sup> =0.45			
RV mass indexed, g/m <sup>2</sup>		-0.29±0.07	<0.001

CMR indicates cardiac magnetic resonance; LV EF, left ventricular ejection fraction; LV GFI, left ventricular global function index; LVEDVi, left ventricular end-diastolic volume indexed to body surface area; LVESVi, left ventricular end-systolic volume indexed to body surface area; PRF, pulmonary regurgitant fraction; PRVi, pulmonary regurgitant volume indexed to body surface area; PV, pulmonary valve; RV EF, right ventricular ejection fraction; RV eGFI, right ventricular effective global function index; RV GFI, right ventricular global function index; RVEDVi, right ventricular end-diastolic volume indexed to body surface area; RVESVi, right ventricular end-systolic volume indexed to body surface area; and VE/VCO<sub>2</sub>, minute ventilation/carbon dioxide production.

Our data disagree somewhat with the findings of Rashid and colleagues who evaluated a larger cohort of similarly aged patients with rTOF who underwent CPET and CMR. Similar to our findings, RV size did not correlate with peak VO<sub>2</sub> in their study, but indices of RV systolic function including RV EF and stroke volume index did correlate significantly.<sup>27</sup> Of note, our patients had lower indexed RV volumes and higher RV EF when compared with the study by Rashid and are consistent with a study in younger patients with rTOF that demonstrated only a weak association between RV EF and exercise performance. The most highly correlated index in that study was echocardiographically-derived RV longitudinal strain, which is perhaps a more sensitive marker of myocardial performance.<sup>28</sup> Moreover, in our study, there was no change in RV EF or RV GFI in the few patients who underwent PVR, while RV eGFI showed a statistically significant improvement. Taken together this suggests that while RV EF may become associated with worsening exercise performance in the aging patient with depressed RV systolic function, RV eGFI may be a more sensitive marker of poor myocardial health and exercise intolerance before the onset of frank RV systolic dysfunction.

**Limitations**

There were several limitations to our study including its retrospective nature from a single center. While our study cohort benefits from being a relatively homogeneous group with primarily RV dilation, as discussed, it will be important to assess GFI in a larger, more heterogeneous TOF cohort with residual pulmonary stenosis or mixed pressure- and volume-overloading to assess its clinical utility in the broad clinical phenotype more typical of the entire population of patients in long-term follow-up. In addition, given our relatively small cohort

and short follow-up duration, there were no primary clinical end points such as death or sustained ventricular tachyarrhythmia which occurred to assess correlation with eGFI. Few patients underwent PVR to draw any definitive conclusions. Moreover, it would be worthwhile to see if calculating RV GFI using an “effective” stroke volume continues to have a better association with exercise performance compared with calculating the GFI using the total stroke volume. Furthermore, the use of patients with pectus excavatum as a control group may not be truly reflective of a normal control group, although we only included those with normal biventricular chamber sizes and systolic function. From a technical standpoint, calculation of RV mass can have a higher degree of variability with respect to reproducibility of measurements in both the thin, dilated RV and that with hypertrophy and increased trabeculations.<sup>29</sup> Finally, we did not have a normal adult control group for comparison in this study, and there are no published normative data on RV GFI.

## CONCLUSIONS

Patients with rTOF had lower RV eGFI compared with age-matched controls. Reduced RV eGFI was associated with reduced exercise capacity, while RV EF, indexed RV volumes, and mass were not. This supports RV eGFI as a potentially valuable non-invasive marker of cardiac function in the rTOF population.

## ARTICLE INFORMATION

Received February 20, 2020; accepted May 29, 2020.

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### Sources of Funding

None.

### Disclosures

None.

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