Patients with tetralogy of Fallot (TOF) following surgical repair represent a growing population with congenital heart disease as they now survive into adulthood.1–4 Residual pulmonary regurgitation (PR) is an important determinant of outcome as it may contribute to right ventricular (RV) enlargement and dysfunction and result in exercise intolerance, a propensity for arrhythmias, and an increased risk for sudden cardiac death.3,5 Most studies suggest that restoration of pulmonary valve competency decreases RV volumes and improves exercise capacity, although a recent meta-analysis found that pulmonary valve replacement neither confers significant changes in RV ejection fraction (EF) nor changes the duration of the QRS complex.6–8 The long-term results of pulmonary valve replacement are also not well defined. Although the long-term consequences of and optimal timing for such intervention remain incompletely defined, the longitudinal assessment of PR and RV function remains critical in the medical care of the patient with TOF.6,9–12

Background—Patients with repaired tetralogy of Fallot are monitored for pulmonary regurgitation (PR) and right ventricular (RV) function. We sought to compare measures of PR and RV function on echocardiogram to those on cardiac magnetic resonance (CMR) and to develop a new tool for assessing PR by echocardiogram.

Methods and Results—Patients with repaired tetralogy of Fallot (n=143; 12.5±3.2 years) had an echocardiogram and CMR within 3 months of each other. On echocardiogram, RV function was assessed by (1) Doppler tissue imaging of the RV free wall and (2) myocardial performance index. The ratio of diastolic and systolic time-velocity integrals measured by Doppler of the main pulmonary artery was calculated. CMR variables included RV ejection fraction, RV volumes, and pulmonary regurgitant fraction (RF). Pulmonary regurgitation was graded as mild (RF<20%), moderate (RF=20–40%), and severe (RF>40%). On CMR, RF was 34±17% and RV ejection fraction was 61±8%. Echocardiography had good sensitivity identifying cases with RF>20% (sensitivity 97%; 95% CI: 92–99%) but overestimated the amount of PR when RF<20% (false-positive rate 36%; 95% CI: 18–57%). The diastolic and systolic time-velocity integrals on echocardiogram showed moderate correlation with RF on CMR (R=0.60; P<0.0001). On CMR, RF of 20% and 40% corresponded with a diastolic and systolic time-velocity integral of 0.49 (95% CI: 0.44–0.56) and 0.72 (95% CI: 0.68–0.76), respectively. RV myocardial performance index correlated modestly with RV ejection fraction (r=-0.33; P<0.001).

Conclusions—This study suggests that the diastolic and systolic time-velocity integrals ratio may make a modest contribution to the overall assessment of PR in patients with repaired tetralogy of Fallot and warrants further investigation. However, echocardiography continues to have a limited ability to quantify PR and RV function as compared with CMR. (Circ Cardiovasc Imaging. 2012;5:637-643.)

Key Words: echocardiography  regurgitation  tetralogy of Fallot
challenges, techniques such as tissue Doppler–derived tricuspid annular velocities, the RV myocardial performance index (MPI), and 3-dimensional calculation of volumes and function have emerged to aid in the echocardiographic assessment of RV systolic function but each method presents new challenges. Likewise, attempts at classifying the severity of PR by echocardiogram have been made. However, the inability of other studies to replicate these measures raises questions about their validity.

We, therefore, sought to compare qualitative and quantitative measures of PR and RV function on echocardiogram to those on CMR in a large cohort of postsurgical TOF patients, and to test new measurements of PR on echocardiogram. Such measurements may simplify the longitudinal clinical assessment of operated TOF patients and may provide end points for long-term research studies.

Methods
This study was approved by The Children’s Hospital of Philadelphia Institutional Review Board for human research, with written informed consent and assent obtained according to the institution’s guidelines.

Patients
Patients from 8 to 18 years of age with surgically repaired TOF were prospectively enrolled in a cross-sectional study (Table 1). An echocardiogram and CMR were performed within 3 months of each other in each patient according to a study protocol.

Echocardiography
Echocardiograms were performed using standard pediatric views in a Philips IE33 machine (Philips, Andover, MA). Images were acquired with 3 to 8 MHz transducers, suited for patient’s size, and acoustic windows. Color, pulse wave, and continuous-wave Doppler flow data across the pulmonary valve were acquired. Myocardial velocities using tissue Doppler were acquired from the lateral annulus of the tricuspid valve. Images were digitally stored and measurements were performed offline using Syngo Dynamics software (Siemens, Ann Arbor, MI) by a single echocardiographer (J.R.), who was blinded to subject information and CMR results.

Qualitative assessment of RV function was classified as normal, mildly, moderately, or severely decreased.

Quantitative RV function was assessed by (1) Doppler tissue imaging of the RV free wall just beneath the tricuspid valve annulus from which the systolic s’ wave, diastolic e’ and a’ waves were measured, corresponding to systolic, early, and late RV filling, respectively; and (2) MPI calculated from pulsed-wave Doppler interrogation of the tricuspid inflow (apical 4-chamber view) and main pulmonary artery flow (parasternal short-axis view). The sum of both isovolumetric intervals by the RV ejection time was obtained by subtracting the RV ejection time in the main pulmonary artery from the interval between cessation and onset of the RV isovolumetric contraction time and isovolumetric relaxation time.

The pulsed-wave Doppler tracing was used to obtain the time-velocity integrals of diastolic and systolic flows (Figure 1). The calculated ratio between the regurgitant (diastolic) time-velocity integral to the antegrade (systolic) time-velocity integral was called diastolic to systolic time-velocity integral ratio or DSTVI.

Cardiac Magnetic Resonance
CMR studies were performed on a 1.5-T Avanto Whole Body Magnetic Resonance System (Siemens Medical Solutions, Erlangen, Germany) with a 6-channel, body-array coil scanner using a standard imaging protocol, which included steady-state, free-precession cine CMR acquisitions in 4-chamber and long-axis planes and contiguous short-axis cine imaging from the atrioventricular junction through the cardiac apex. Sedation was used, when appropriate, according to the patient’s age and ability to lie still for the scan. To assess end-systolic and end-diastolic volumes (EDV) of the ventricles, a cine MR sequence in a short-axis view was used (TE/TR 2.0/45 ms; flip angle 75°–90°; matrix size 196 × 196). The RV infundibulum was included in the RV volume up to the pulmonary annulus. All volumes were indexed to body surface area and corresponding z-scores were calculated using published normative data. RVEF was calculated as (SV—EDV)/EDV, where SV is the stroke volume. Phase contrast velocity mapping with a flow-sensitive, gradient-echo sequence was performed in the main pulmonary artery to assess the regurgitant fraction (RF).

CMR variables included RVEF, RV EDV and RV end-systolic volume, and pulmonary artery RF. PR was graded as mild if the RF on CMR was <20%, moderate if it was between 20% and 40%, and severe if it was >40%.

Table 1. General Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>12.5 (±3.2)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>47 (33%)</td>
</tr>
<tr>
<td>Male</td>
<td>96 (67%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>114 (80%)</td>
</tr>
<tr>
<td>Black</td>
<td>16 (11%)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (9%)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>42.9 (±15.3)</td>
</tr>
<tr>
<td>Age at surgical repair, y</td>
<td>0.30 (0.10–0.57)</td>
</tr>
<tr>
<td>Time elapsed since surgical repair, y</td>
<td>11.5 (9.1–14.5)</td>
</tr>
<tr>
<td>Original pulmonary valve</td>
<td></td>
</tr>
<tr>
<td>Stenosis</td>
<td>112 (78%)</td>
</tr>
<tr>
<td>Atresia</td>
<td>22 (15%)</td>
</tr>
<tr>
<td>Absent</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Surgical repair</td>
<td></td>
</tr>
<tr>
<td>VSD closure only†</td>
<td>19 (13%)</td>
</tr>
<tr>
<td>Nontransannular patch‡</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Transannular patch</td>
<td>103 (72%)</td>
</tr>
<tr>
<td>RV-PA conduit</td>
<td>13 (9%)</td>
</tr>
</tbody>
</table>

RV PA indicates right ventricle to pulmonary artery; VSD, ventricular septal defect.

*Data are expressed as mean (±SD), median (interquartile range), or as number (%).

†Ventricular septal defect closure indicating that relief of outflow tract obstruction was not necessary.

‡Nontransannular patch refers to relief of right ventricular outflow tract obstruction without crossing the pulmonary valve annulus.

Statistical Analysis
Continuous variables were described using mean and SD or median with interquartile ranges when appropriate. Categorical variables were described using count and percentages. We calculated sensitivity and false-positive rate (1–specificity) of echocardiogram (defined
as mild PR or not) to grade PR using the RF found on CMR (dichotomized at 20%) as the gold standard. Pearson correlation was calculated between DSTVI on echocardiogram and RF on CMR. A linear regression of RF from CMR was fit on DSTVI from echocardiogram to identify clinically meaningful cut points of DSTVI. Measures of RV function from echocardiogram and CMR were correlated using Pearson correlation, and RV MPI was compared in patients with diminished RV systolic function and normal function. Statistical significance was reached if \( P \) values were <0.05 (2-sided tests). All analyses were performed using SAS statistical software version 9.2 (Cary, NC).

### Results

#### Patient Characteristics
The study cohort consisted of 143 patients with TOF following surgical repair who underwent an echocardiogram and CMR within 3 months of each other for study purposes. Patient characteristics are detailed in Table 1. Surgical repair consisted of 4 approaches: (1) simple closure of ventricular septal defect (VSD) when no significant RV outflow tract obstruction was present; (2) closure of the VSD with relief of RV outflow tract obstruction with a transannular patch; (3) closure of the VSD with relief of RV outflow tract obstruction with a nontransannular patch (transannular or nontransannular); and (4) closure of the VSD with placement of an RV to pulmonary artery conduit. Most of the patients did not have a residual VSD, and few (20/135) had RV outflow tract obstruction graded as greater than mild on CMR.

#### Assessment of PR and RV Function
Most patients (85%) had greater than mild PR assessed qualitatively both by echocardiogram and CMR. In addition, most patients had qualitatively normal RV systolic shortening by echocardiogram and CMR (75% and 90%, respectively). Quantitative measures of PR and RV function are detailed in Table 2 for each imaging modality. Of note, the mean RF by CMR in the cohort was 34.2% (±16.6%), and the mean RVEF was 60.6% (±8.2%), suggesting that the majority had at least moderate PR with preserved RV shortening.

#### Correlations Between Echocardiographic and CMR Measurements

##### Pulmonary Regurgitation

We tested the ability of echocardiography to identify patients with greater than mild PR as measured on CMR (RF>20%). Echocardiography was 97% sensitive to identify cases with RF>20% (107 in 110 patients; 95% CI: 92%–99%) qualitatively, but overestimated PR when it was mild on CMR (RF<20%), resulting in a false-positive rate of 36% (9 out of 25 patients; 95% CI: 18%–58%; Table 3)

As an alternative measure of PR by echocardiogram, the DSTVI correlated moderately with RF on CMR (\( r=0.60; P<0.001 \)). A CMR RF of 20% and 40% (representing the boundaries between mild/moderate and moderate/severe PR) corresponded with a DSTVI of 0.49 (95% CI: 0.44–0.56) and 0.72 (95% CI: 0.68–0.76), respectively (Figure 2). DSTVI >1 was present in 12 patients, all of which had RF>40% by CMR (Figure 2).

##### RV Function

Quantitative comparison of RV function by echocardiography and CMR showed a modest negative correlation between RV MPI and RV EF (\( r=-0.33; P<0.001 \)) (Figure 3). RV MPI was appropriately higher (0.34±0.16 compared with 0.20±0.13; \( P<0.001 \)) in those with diminished as compared to normal RV systolic function (EF≤50% versus 50%). The systolic annular velocity of the tricuspid valve (S') demonstrated no significant correlation with RVEF (\( r=0.006; P=0.94 \)).

### Discussion

Echocardiography plays an essential role in the longitudinal follow-up of patients with congenital heart disease.
Comparing PR by Echocardiography and CMR

The assessment of PR by echocardiography has been largely qualitative, although multiple attempts to better quantify PR have been undertaken.24–26,31,32 A number of measurements have been attempted including the Pulmonary Regurgitant Index, and in adults, the width of the vena contracta.18,24 However, such measurements have not proven reproducible and are not relevant to the repaired patient with TOF and a disrupted pulmonary valve.32 As a result, echocardiographers use a number of imprecise observations to assess PR, including Doppler patterns, the size of pulmonary arteries and right ventricle, the width of the PR regurgitant jet, and the extent of the diastolic retrograde flow.33 Because of these limitations, we explored whether the DSTVI could better quantify PR. Our data suggest that the DSTVI correlated with RF on CMR, with higher DSTVI ratios corresponding to worse PR, as expected. Although TVI has been used for the calculation of cardiac outputs and left-sided regurgitant lesions, we are not aware of its application in the quantification of pulmonary valve regurgitation. Therefore, although further validation and longitudinal studies are required to confirm its utility, it appears that the DSTVI may prove to be a helpful measure of PR. DSTVI>1 was found in some patients with severe PR as measured by CMR; we propose that this phenomenon results from higher diastolic regurgitant velocity and dynamic changes in the pulmonary cross-sectional area during the cardiac cycle in cases with severe PR. This finding merits further exploration in future studies.

Assessing RV Function by Echocardiogram and CMR

Analysis of RV function by echocardiography is likewise challenging. We found that the MPI correlated poorly with RV EF even though the MPI was largely normal as compared with children without congenital heart disease.15 This finding likely stems from the fact that isovolumic relaxation is not present or is shortened in a patient with severe PR whose RV is never entirely isovolumic during relaxation. In addition, the increased RV EDV secondary to PR may increase the ejection time across the pulmonary valve, thereby lowering the MPI, a phenomenon previously called pseudonormalization.35 When segregated by normal versus abnormal RV function on CMR, the MPI was appropriately lower in those with normal function, indicating that at least it followed the trend of EF, similar to previous studies.16 Thus, it appears that the RV MPI may be difficult to interpret in the face of significant PR when there is essentially no isovolumic relaxation of the RV.

Our data demonstrate that the tricuspid annular systolic velocity was decreased as compared with normal values in adults without congenital heart disease in the absence of adequate normative data for children.15,36 Similar findings have been reported in patients with TOF.37 Moreover, we were unable to confirm the previously reported association between the tissue Doppler–derived tricuspid valve lateral annulus systolic velocity and RV EF, even
though it is intuitive to compare 2 methods that evaluate systolic function.\textsuperscript{15,38} It is possible that in patients with TOF and considerable ventricular dilation secondary to PR, this comparison is limited by the greater load dependency of RVEF as compared with myocardial velocities.

Other methods with which to assess RV function have been proposed.\textsuperscript{39} We chose not to measure the RV fractional area change particularly because it was shown recently to correlate poorly with RV EF on CMR in a population with congenital heart disease.\textsuperscript{40} In addition, it is technically difficult to delineate the endocardial border in the repaired TOF RV, and this measurement does not incorporate the contribution from the RV outflow tract. The tricuspid annular plane systolic excursion is another modality to assess RV function that may prove useful in TOF but may be likewise limited by the exclusion of the RV outflow tract from the calculation.\textsuperscript{41}

In summary, our data suggest a modest correlation of DSTVI with pulmonary RF on CMR. Thus, the DSTVI may provide a quantitative tool to follow PR by echocardiography, although further validation and longitudinal studies are required to confirm its utility.

Limitations
Patients with severely decreased RV function were not represented in our cross-sectional study population, most likely given the relative youth of this cohort as compared with other studies that include adults.

Although sedation may result in differences in hemodynamics when comparing a sedated CMR to a nonsedated echocardiogram, we ensured that the interval between the tests did not exceed 3 months to minimize the possibility of hemodynamic changes over time.

Finally, the cross-sectional nature of this study does not allow for longitudinal inferences where these assessments would be most helpful.

Conclusions
Even with the techniques studied, echocardiography has a limited ability to quantify PR and RV function in the TOF population. We propose that the DSTVI ratio may be a helpful quantitative tool for the assessment of PR by echocardiography in conjunction with other measures. However, further validation and longitudinal studies are required to confirm its utility.
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Disclosures
None.

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**CLINICAL PERSPECTIVE**

Patients with tetralogy of Fallot represent a growing population of congenital heart disease. Clinicians seek to quantify pulmonary regurgitation and right ventricular function over successive appointments in patients with TOF to identify those in need of intervention or pulmonary valve replacement. To date, though echocardiography is the most valuable tool, it has fallen short in consistent quantification of pulmonary regurgitation and right ventricular function. In this study, we describe an echocardiographic tool with which to assess pulmonary regurgitation in tetralogy of Fallot that only modestly correlates with measurements made by cardiac magnetic resonance. In addition, echocardiographic measures of right ventricular function showed limited performance when compared with those derived from cardiac magnetic resonance. Although these echo measures still fall short of the reliability set by CMR for decision making, these results help motivate ongoing investigative efforts to improve echocardiographic assessment of the postoperative patient with tetralogy of Fallot.
Quantifying Pulmonary Regurgitation and Right Ventricular Function in Surgically Repaired Tetralogy of Fallot: A Comparative Analysis of Echocardiography and Magnetic Resonance Imaging

Laura Mercer-Rosa, Wei Yang, Shelby Kutty, Jack Rychik, Mark Fogel and Elizabeth Goldmuntz

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