Influence of Pulmonary Regurgitation Inequality on Differential Perfusion of the Lungs in Tetralogy of Fallot After Repair

A Phase-Contrast Magnetic Resonance Imaging and Perfusion Scintigraphy Study

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Objectives
The purpose of this study was to evaluate the influence of pulmonary regurgitation inequality on differential perfusion of the lungs in tetralogy of Fallot (TOF) after repair.

Background
Asymmetry of lung perfusion is one of the best predictors of outcome in TOF after repair. A recent phase-contrast magnetic resonance imaging (PC-MRI) study found prominent regurgitation inequality between the bilateral pulmonary arteries in TOF after repair.

Methods
Forty-three TOF post-repair patients (median age 51 months, 31 men) received PC-MRI and 99mTc-labeled macroaggregates of albumin perfusion scintigraphy (PS) in the same day. We took PC-MRI measurements of forward flow volume (FFV), backward flow volume (BFV), and net flow volume (NFV) (NFV = FFV - BFV) and regurgitation fraction (RF) (RF = BFV/FFV) at the left and right pulmonary arteries (LPA and RPA). The differential perfusion of the left lung (L%) (L% = left lung/left + right lung) as calculated by NFV ratio, by FFV ratio of PC-MRI, and by PS were compared.

Results
The discrepancy between L% by NFV versus L% by PS was affected by the severity of RF of LPA (r = 0.51, p = 0.001); agreement between L% by NFV versus L% by PS was good (intraclass correlation coefficient [RI] = 0.87) if RF of LPA < 0.4 (n = 23) but downgraded (RI = 0.51) and underestimated the L% (median of error = -14%, range = -25.3% to 5.5%) if RF of LPA > 0.4 (n = 20). In contrast, agreement between L% by FFV versus L% by PS was high and unaffected by RF of LPA (RI = 0.94, 0.92, respectively).

Conclusions
While integrating PC-MRI of pulmonary artery as a comprehensive MRI evaluation of TOF after repair, conventional NFV ratio method tended to underestimate the left lung perfusion and may lead to unnecessary intervention. The FFV ratio method should be used for precise assessment of differential lung perfusion. (J Am Coll Cardiol 2007;49:1880–6) © 2007 by the American College of Cardiology Foundation

Residual pulmonary regurgitation occurs inevitably in tetralogy of Fallot (TOF) after complete surgical correction. Pulmonary regurgitation has been associated with right ventricular dilatation, impaired biventricular function, limited exercise tolerance, and increased risk for ventricular arrhythmia and has become a significant determinant of late symptoms and long-term outcome (1–3).

Phase-contrast magnetic resonance imaging (PC-MRI) has been validated as a simple and accurate method to evaluate the severity of regurgitation in the main pulmonary artery in TOF after repair (4–6). This technique can be also applied at right pulmonary artery (RPA) and left pulmonary artery (LPA) to represent the hilar entrance flow of respective lung as an index of differential lung perfusion in most congenital heart diseases (7,8), even in those with suspected peripheral pulmonary stenosis (9). Phase-contrast flow measurement has been integrated in comprehensive cardiopulmonary MRI in evaluation of TOF (6,10).
In TOF after repair, it is important to know the differential lung perfusion, because asymmetry of lung perfusion is one of the predictors of outcome and exercise capacity (11–14). Although the impact of pulmonary regurgitation on right ventricular dysfunction has been extensively investigated, its impact on lung perfusion has not been explored yet. Recently, Kang et al. (15) found that in repaired TOF, the branch pulmonary arteries often have unequal regurgitation fraction (RF) and contribute unequally to total regurgitation. The impact of RF inequality on differential lung perfusion is an important yet not investigated issue. In the present study, we used PC-MRI, as compared with 99mTc-labeled macroaggregates of albumin perfusion scintigraphy (PS), to investigate the influence of RF inequality on differential lung perfusion in TOF after repair.

**Methods**

**Subjects.** Forty-three patients of TOF after total repair were prospectively enrolled. The MRI and PS were performed on the same day. Table 1 lists the patient characteristics. The Research Ethics Board of Kaohsiung Veterans General Hospital approved this study, and the patients’ parents all gave written informed consent.

**MRI protocol. MRI.** The magnetic resonance (MR) studies were performed on a 1.5-T system (Signa CV/I, GE Healthcare, Milwaukee, Wisconsin). The MR protocol included: 1) anatomic imaging of the thorax in the axial plane with electrocardiography (ECG)-gated spin-echo T1-weighted image with respiratory compensation for patients unable to hold their breath or ECG-gated fast spin-echo T1-weighted images for those who could hold their breath; 2) PC-MRI at the main pulmonary artery, RPA, and LPA with a PC sequence in a cross-sectional plane; and 3) 3-dimensional contrast-enhanced MR angiography with a fast spoiled gradient-refocused echo sequence. The PC-MRI was performed with retrospective ECG gating and the following imaging parameters: repetition time of 7.3 to 8.0 ms, echo time of 3.4 to 3.7 ms, and 4 views per segment, flip angle of 20° or 30°, and number of excitation of 1 (for breath hold study) or 4 to 6 (for non-breath hold study). The acquisition matrix was 256 × 128 and interpolated into 256 × 256 in raw data with field of view of 12 to 18 cm, slice thickness of 4 to 6 mm to obtain at least 100 pixels encompassed in the target vessel. The true temporal resolution was 58.4 to 64 ms, the effective temporal resolution was improved by re-constructing 20 phases per cardiac cycle by a standard interpolation technique (15,16). The upper velocity limit was set initially at 150 cm/s and increased by 100 cm/s if there was an aliasing artifact. The main pulmonary artery was targeted at its midpoint between the pulmonary valve and the bifurcation, the RPA behind the ascending aorta at the midpoint between the orifice and the first branch of RPA, and the LPA below the distal aortic arch and/or above the left main bronchus (Fig. 1A). To decrease errors, the imaging planes were prescribed strictly perpendicular to the vessels by the double-oblique technique (15,16).

To investigate whether RF changes from central pulmonary artery to lobar pulmonary arteries, in the last 16 cases of this study, we performed an additional PC-MRI scan at 1 to 2 cm below the LPA and RPA to encompass the left descending pulmonary artery and right descending pulmonary artery in the lower lobes. The location was determined by the reformed 3-dimensional MR angiography (17).

**LUNG PERFUSION SCINTIGRAPHY.** All lung perfusion scans were performed with a double-head rotating large field of view camera (Siemens ECAM, Siemens Corp., Hoffman Estates, Illinois), equipped with a low-energy, parallel-hole, all-purpose collimator and interfaced to a computer (Siemens E.SOFT) with the patients in the supine position with 99mTc-labeled macroaggregates of albumin injected via a peripheral vein. A dose of 18.5 MBq to a maximum of 74 MBq was used and data were acquired over 2 min. As particles are homogeneously distributed in the lungs, relative pulmonary blood flow is thereby reflected by radioactivity distribution and the percentage relative perfusion was calculated for each lung.

**Data analysis and measurement.** Acquired PC-MRI data were processed in an independent workstation (Advantage Windows 4.1, GE Healthcare). Dedicated flow-analysis software (CV Flow, GE Healthcare) was used to generate flow volume-time curves of the ascending aorta, main pulmonary artery, RPA, and LPA (Fig. 1B). The regions of interest were generated semiautomatically for each of the 20

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient Characteristics and Details of Previous Surgery</th>
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<tbody>
<tr>
<td>Male:female, n</td>
<td>31:12</td>
</tr>
<tr>
<td>Age of total repair, months</td>
<td>14 [2–92]*</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Tetralogy of Fallot with pulmonary stenosis: 28 with pulmonary atresia: 15</td>
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<tr>
<td>Palliation before total repair, n</td>
<td>mBTS: 13</td>
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<tr>
<td>Type of total repair, n</td>
<td>TAP: 27, infundibular: 14, no patch: 2</td>
</tr>
<tr>
<td>Peripheral pulmonary stenosis</td>
<td>9</td>
</tr>
<tr>
<td>Pulmonary valve replacement</td>
<td>0</td>
</tr>
<tr>
<td>Age at MR study, months</td>
<td>51 [14–186]*</td>
</tr>
<tr>
<td>Interval between surgery and MR, months</td>
<td>30 [6–150]*</td>
</tr>
</tbody>
</table>

*Median [range].

mBTS = modified Blalock-Taussig shunt; MR = magnetic resonance; TAP = transannular right ventricular out tract patch.
phases with the consensus of 2 observers, and the following parameters were calculated: forward flow volume (FFV), backward flow volume (BFV), net flow volume (NFV), and RF (Fig. 1D). Net flow volume (NFV) was defined as FFV minus BFV. Regurgitation fraction was defined as BFV divided by FFV.

Differential perfusion of the left lung (L%), according to NFV ratio, is defined as

\[
L\% \text{ by NFV} = \frac{\text{NFV of LPA}}{(\text{NFV of LPA} + \text{NFV of RPA})} \times 100\%
\]

We used the same method to calculate the L% by FFV and L% by PS, which represented the differential perfusion of the left lung according to FFV ratio and perfusion scintigraphy ratio, respectively.

**Statistical analysis.** The parameters were expressed as median (minimum to maximum) and analyzed by Wilcoxon signed rank test. Correlation between the parameters was evaluated by Spearman correlation coefficient (Rs). The agreement of L%PS versus L%FFV and L%PS versus L%NFV was done by intraclass correlation (Ri) and Bland-Altman plot (18).
All p < 0.05, 2-sided, were considered statistically significant. All analyses were done with SPSS 13.0 for Windows (SPSS, Chicago, Illinois).

**Results**

**PS-MR flow measurement.** The details of PC-MRI measurements of LPA and RPA are listed in Table 2. We found the FFV of LPA was significantly smaller than that of RPA (p < 0.001), whereas the BFV of the 2 had no difference (p = 0.14). As a result, the NFV of the LPA was significantly smaller than that of RPA (p < 0.001).

The RF of LPA was 0.40 (0.01 to 0.77), which was significantly higher than that of RPA (0.30 [0.01 to 0.52]) (p = 0.002). There was no significant correlation between the 2 (Rs = 0.30, p = 0.085). The ratio of RF in LPA over RF in RPA of the 43 patients was 1.33 (0.31 to 14.37). In 34 of the 43 patients (79%), the ratio was >1.0.

The cross-sectional area of LPA was 99 (27 to 382) mm², which was not significantly different from that of the RPA (117 [23 to 522] mm²) (p = 0.73).

The duration of backward flow in LPA was 32.0 ± 6.3% of cardiac cycle, which was not different from that in RPA (39.9 ± 7.7%) (p = 0.14).

The RF of RPA had significant correlation with its area (Rs = 0.44, p = 0.008), whereas RF of LPA did not.

**Differential perfusion of left lung assessed by PS and by PC–MRI.** Table 3 and Figure 2 show the results of the differential perfusion of left lung (L%) assessed by perfusion scintigraphy, by NFV ratio, and by FFV ratio of PC-MRI. The intra-class correlation (Ri) between L% by NFV and L% by PS was 0.70 (95% confidence interval [CI] 0.51 to 0.82), which was lower than that between L% by FFV and L% by PS (Ri = 0.94, 95% CI 0.88 to 0.96).

**EFFECT OF RF ON DIFFERENTIAL PERFUSION OF LEFT LUNG.** Because the RF of LPA was larger than RF of RPA in most patients (34 of 43), we used RF of LPA as a predictor to investigate the effect of RF severity on the discrepancy between L% by NFV or by FFV versus L% by PS. Figure 3 shows that RF of LPA was a significant predictor of discrepancy of L% by NFV versus L% by PS (R = −0.51, p = 0.001), whereas RF of LPA had no correlation with the discrepancy between L% by FFV versus L% by PS (R = 0.01, p = 0.94).

Based on the findings from Figure 3—which show that the larger the RF of LPA, the greater the underestimation of L% by NFV—we used the median of RF of LPA (0.4) as a threshold to divide the 43 cases into 2 subgroups. We found that, in the subgroup with RF of LPA ≥ 0.4 (n = 20), the agreement between L% by NFV versus L% by PS was the lowest (Ri = 0.51, 95% CI = 0.12 to 0.77), as shown in Table 3. As a result, the L% by NFV tended to underest-i-
mate the left lung perfusion (median of difference −14%, range −25.3% to 5.5%); in comparison, agreement between L% by FFV versus L% by PS remained high (Ri = 0.92, 95% CI = 0.82 to 0.97) (median of difference −0.2%, range −10.8% to 6.3%) (Table 3).

COMPARISON OF RF AT PROXIMAL SEGMENT VERSUS DISTAL SEGMENT OF PULMONARY ARTERY. Additional scans of PC-MRI were performed over the bilateral descending pulmonary arteries in the latest 16 cases of the 43 cases. The RF of left descending pulmonary artery was 0.23 (0.01 to 0.46), which was significantly smaller than that of respective LPA (0.35 [0.01 to 0.77]) (p = 0.001). The RF of right descending pulmonary artery was 0.14 (0 to 0.34), which was significantly smaller than that of respective RPA (0.23 [0.01 to 0.52]) (p = 0.006) (Fig. 4). Our finding indicated that pulmonary regurgitation was significantly more severe in the proximal (hilar) segment than in the distal (lobar) segment of pulmonary arteries.

Discussion

Phase-contrast MRI at LPA and RPA provides the absolute volume of bulk flow input into the lungs (16). Conventionally, NFV (i.e., FFV minus BFV if any) is used to represent the total flow volume passing through the interrogated vessel. In contrast, PS employs 99mTc-labeled macroaggregates of albumin embolized at capillary level to represent the relative tissue perfusion ratio of the lung. To predict the differential lung perfusion with PC-MRI, previous reports calculated the NFV ratio of LPA and RPA and found good agreement with that by PS ratio in the scenario of most congenital heart diseases (7–9). Our result showed that in TOF after repair in which severe RF often occurs, FFV ratio instead of conventional NFV ratio of LPA and RPA should be used to predict the differential lung perfusion.

The underlying mechanism of this phenomenon is unclear; however, it might be partly supported by 2 observations in the present study: 1) there was significant difference in FFV between LPA and RPA but no difference in BFV (Table 2), which indicated FFV was the major cause of the differential perfusion of the bilateral lungs; and 2) RF in the right and left descending pulmonary arteries was smaller than that in RPA and LPA, respectively (Fig. 4), suggesting that RF decreased as flow propagating from central to peripheral segments. We postulated that the RF might gradually decrease to minimal or 0 at the point of peripheral arterioles where macroaggregates of albumin are deposited in PS. This postulation was further supported by the observation of flow pulsatility in the peripheral pulmonary arterioles (19). As a result, L% by FFV was closer to L% by PS.

Because peripheral pulmonary stenosis, especially over LPA, might occur in approximately 20% of patients with TOF after repair (14), the effect of peripheral pulmonary stenosis on accuracy of PC-MRI requires investigation. Recent study has confirmed that PC-MRI is feasible for differential lung perfusion in patients with suspected unilateral pulmonary stenosis (9). In the present series of 43 cases,
the cross-sectional area of LPA was not statistically smaller than that of RPA (Table 2). However, there were 9 cases of clinically suspected peripheral pulmonary stenosis. We found there was no effect of peripheral pulmonary stenosis on the agreement between L% by PS versus L% by NFV (Ri = 0.69 for the 9 cases with peripheral pulmonary stenosis, Ri = 0.71 for the remaining 34 cases) and L% by PS versus L% by FFV (Ri = 0.96 and Ri = 0.93, respectively).

**Clinical impact.** Precise estimation of pulmonary perfusion has gained an increasingly important role in comprehensive evaluation of cardiopulmonary function in TOF after repair (11–14). Because peripheral pulmonary stenosis occurs not uncommonly over the LPA in repaired TOF, underestimation of differential perfusion of the left lung by conventional PC-MRI method with NFV ratio, as illustrated in Figure 1, would lead to an overestimation of LPA stenosis; as a result, unnecessary invasive procedures such as catheterization and balloon vascular dilatation might be conducted.

Our study showed a method to improve the accuracy of PC-MRI in assessment of the differential lung perfusion and therefore could substitute PS in postoperative evaluation of TOF. The clinical impacts include: 1) avoiding isotope radiation of PS; 2) increasing cost-effectiveness of MRI; and 3) providing absolute quantitation of flow volume that is useful in serial comparison of each artery, not only relative ratio as does PS. All 3 impacts are further enhanced in long-term follow-up of TOF after repair.

In addition, the ability of absolute quantitation of flow velocity, flow volume, and cross-sectional area simultaneously enhances PC-MRI to derive some sophisticated indexes such as systolic flow volume and pulse wave velocity (20), which might carry clinical impacts other than FFV in certain instances. Whereas the NFV (= FFV − BFV) represents the actual flow volume entering the lung in the presence of regurgitation, the sum of FFV and BFV (= FFV + BFV) might be proportional to total flow volume after valvular replacement and might be useful to predict the pulmonary perfusion improvement after valvular replacement.

**Study limitations.** As reported by Kang et al. (15), we could not find an explanation for RF in LPA that was larger than that in RPA. For PC flow measurement of the peripheral pulmonary artery, we had performed only in 16 of our cases at limited arteries (single slice of the lower lobes). However, flow measurement at lobar pulmonary artery has been proven feasible (17), and the significant results from our 16 cases support our hypothesis. In the present study, we used the static distribution of 99mTc-labeled macroaggregates of albumin as standard reference of lung tissue perfusion. Future study with positron emission tomography with ECG-gating technique might provide more accurate and detailed information of pulmonary blood flow to serve as a gold standard (19,21).

**Conclusions**

In patients with TOF after repair, PC-MRI showed that regurgitation in the LPA was usually larger than that in the RPA. The regurgitation inequality had a substantial impact on the differential lung perfusion; especially in those cases with severe regurgitation of LPA. Assessment of differential lung perfusion by PC-MRI with conventional NFV ratio tended toward substantial underestimation of the left lung perfusion, which might lead to unnecessary intervention. Assessment should be calculated by FFV ratio of PC-MRI to improve the accuracy of differential lung perfusion that is critical to integrate PC-MRI as an important predictor of cardiopulmonary function in TOF after repair.

**Acknowledgments**

The authors thank MR technologists Chia-Chi Hsiau and Hung-Chieh Huang for image acquisition and research assistants Hui-Chu Chang, Chin-Ying Tsai, and Yu-Ying Lin for data management.

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