Differential Regurgitation in Branch Pulmonary Arteries After Repair of Tetralogy of Fallot
A Phase-Contrast Cine Magnetic Resonance Study

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Background—The importance of pulmonary regurgitation (PR) after repair of tetralogy of Fallot (TOF) is increasingly recognized, but little is known regarding its underlying mechanisms. This phase-contrast cine magnetic resonance (PC MR) study was performed to evaluate the relative contribution of each lung to total regurgitant volume.

Methods and Results—Twenty-two patients with significant PR underwent a PC MR 3 to 16 years after repair of TOF. Regurgitant fraction of the main pulmonary artery was 39±10%. Regurgitant fraction of the left pulmonary artery (LPA: 46±18%) was greater than that of the right pulmonary artery (34±16%; P=0.002). The average contribution of the LPA to the total regurgitant flow volume was 54±19%, whereas its average contribution to the total forward flow volume was 44±13% (P=0.002). In 4 patients, regurgitant flow in the LPA accounted for 75% to 100% of the total regurgitant flow. There was a linear relationship between regurgitant fraction and fraction of the regurgitant flow duration in the main pulmonary artery (P<0.001) and right pulmonary artery (P=0.001) but not in the LPA (P=0.129).

Conclusions—PR after repair of TOF is commonly associated with differential regurgitation in the branch pulmonary arteries, which is usually greater in the LPA. Although the cause of this disparity requires further investigation, those patients with a significant unilateral contribution to total PR may be amenable to localized techniques to reduce regurgitation. (Circulation. 2003;107:2938-2943.)

Key Words: regurgitation ▪ arteries ▪ tetralogy of Fallot ▪ magnetic resonance imaging ▪ heart defects, congenital

Despite a low surgical mortality for repair of tetralogy of Fallot (TOF), postoperative residual morbidity is not uncommon. Chronic pulmonary regurgitation, an inevitable consequence of a transannular patch repair or pulmonary valvotomy, has become a significant determinant of late consequence of a transannular patch repair or pulmonary valvotomy, and ventricular dysfunction, arrhythmia, and the risk of sudden death.2–5 In this regard, pulmonary valve replacement has increasingly been recommended.6 The characteristics of pulmonary regurgitation after repair of TOF have been studied extensively by a variety of methods.2–4,7–10 However, the contribution of each branch pulmonary artery to total pulmonary regurgitation has not been investigated. It has been reported that TOF is associated with a different geometric orientation of the branch pulmonary arteries, unequal pulmonary vascularity, and pulmonary perfusion abnormalities, each of which may independently modify the amount of pulmonary regurgitation.11–13

Phase-contrast cine magnetic resonance (PC MR) has been proven as an accurate method of evaluation of the velocity, volume, and pattern of blood flow.14–16 PC MR has 2 important advantages. First, it provides velocity data from the entire cross-sectional area of the vessel, enabling accurate calculation of flow volume. Second, imaging is not compromised by the presence of air, bone, or surgical scar. Therefore, any vessel, in any anatomic location and orientation, can be imaged in any desired plane. Previous studies have validated the utility and accuracy of PC MR in evaluation of pulmonary regurgitation at the main pulmonary artery level, and it is now used as a routine clinical tool in such patients.8,9

We recently recognized, during clinical PC MR studies, that pulmonary valve regurgitation may be associated with markedly different patterns of regurgitation in the branch pulmonary arteries. This experience prompted us to formally assess these flow patterns in the branch pulmonary arteries in all patients undergoing magnetic resonance (MR) for evaluation of the pulmonary arterial anatomy and flow distribution in the lungs after surgical repair of TOF.
TABLE 1. Patient Characteristics and Details of Previous Surgery

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Male:female, n</td>
<td>12:10</td>
</tr>
<tr>
<td>Age at total repair, mo</td>
<td>20.3 ±13.5 (2 wk–48 mo)</td>
</tr>
<tr>
<td>Diagnosis, n</td>
<td>TOF 19 (with APVS in 1), PA/VSD 3</td>
</tr>
<tr>
<td>Previous palliation, n</td>
<td>BTS 7 (right in 5, left in 1, both in 1), RVOT patch 1</td>
</tr>
<tr>
<td>Type of total repair, n</td>
<td>TOF 19: TAP 16, infundibular patch 2, no patch 1, PA/VSD 3: RVOT patch 1, RV-PA homograft conduit 2</td>
</tr>
<tr>
<td>Age at MR study, mo</td>
<td>147.3 ±51.8 (42–206)</td>
</tr>
<tr>
<td>Interval between last surgery and MR, mo</td>
<td>116.9 ±48.0 (40–195)</td>
</tr>
</tbody>
</table>

Age and interval data are presented as mean ±SD with ranges. APVS indicates absent pulmonary valve syndrome; PA/VSD, pulmonary atresia with ventricular septal defect; BTS, Blalock-Taussig shunt; RVOT, right ventricular outflow tract; TAP, transannular RVOT patch; and RV-PA, right ventricle to pulmonary artery.

Methods

Patients

The study population consisted of 22 patients with TOF who underwent complete repair and showed significant pulmonary regurgitation, defined as a regurgitant fraction of >10% measured by PC MR. Patient characteristics and details of previous surgery are summarized in Table 1. No patient showed more than a trivial degree of tricuspid regurgitation. The Research Ethics Board of our institution approved the study.

MR Imaging

The MR studies were performed on a 1.5-T system (Signa CV/i; GE Medical Systems). The MR protocol included anatomic imaging of the thorax in the axial plane with a cine plane-refocused echo or a FIESTA (fast imaging employing steady-state acquisition) sequence; contrast-enhanced angiography with a fast SPGR (spoiled gradient-refocused) echo sequence; a ventricular function study in the short-axis plane with a cine gradient-refocused echo or FIESTA sequence; and PC imaging of the main (MPA), right (RPA), and left (LPA) pulmonary arteries and atrioventricular valves with a fast PC sequence in a through plane. The total scan time ranged from 38 to 95 minutes (mean 59.5 minutes). Fast PC imaging was performed with retrospective ECG gating. The imaging parameters included repetition time of 10.0 to 14.6 ms, echo time of 4.5 to 5.6 ms, and 4 to 8 views per segment, giving a true temporal resolution of 80 to 226 ms (mean 128 ms) at a heart rate of 52 to 119 bpm. The effective temporal resolution was improved by reconstructing 20 phases per cardiac cycle by a standard interpolation technique. Other parameters were matrix 256×128 to 160, field of view 18 to 40 cm, in-plane spatial resolution 0.7 to 1.5×1.1 to 3.1 mm, slice thickness 4 mm, flip angle 15° or 20°, and number of excitations 1 (for breath-hold study) or 2 (for non–breath-hold study). The upper velocity limit was set initially at 150 cm/s and increased by 50 to 100 cm/s if there was an aliasing artifact. The MPA was targeted at its midpoint between the pulmonary valve and the bifurcation, the RPA behind the ascending aorta, and the LPA below the distal aortic arch and/or above the left main bronchus (Figure 1). To minimize measurement errors, the imaging plane was prescribed strictly perpendicular to the vessel by the double-oblique technique.

Data Analysis and Measurement

Acquired MR image data were postprocessed in a commercially available workstation (Advantage Windows 3.0; GE Medical Systems). Built-in flow-analysis software was used to generate time-averaged flow-volume curves of the MPA, RPA, and LPA (Figure 1), and the following parameters were measured or calculated: forward flow volume; regurgitant flow volume; net forward flow volume (forward flow volume–regurgitant flow volume); total forward flow volume (sum of forward flow volumes in RPA and LPA); total regurgitant flow volume (sum of regurgitant flow volumes in RPA and LPA); regurgitant fraction (regurgitant flow volume×100/forward flow volume, in %); fraction of forward flow duration (number of phases showing forward flow in time–flow-volume curve×100/20, in %); fraction of regurgitant flow duration (number of phases showing reversed flow in time–flow-volume curve×100/20, in %); and blood flow ratio to the right and left lungs (net forward flow to right lung [%]/net forward flow to left lung [%]). A blood flow ratio (R/L) between 61/39 and 43/57 was considered normal.

To correlate pulmonary artery size and the blood flow volume to the lungs, the diameters of the RPA and LPA at the hilum were compared. To evaluate correlation between the size of the branch pulmonary arteries and the volumes of forward flow, regurgitant flow, and net forward flow, cross-sectional areas of the proximal RPA and LPA shown at PC MR were measured. To evaluate the effect of pulmonary arterial geometry on regurgitation in the RPA and LPA, the pulmonary arterial anatomy seen at MR was classified into 3 types: (1) symmetrical branching; (2) asymmetric branching with the angle between the MPA and LPA greater than the angle between the MPA and RPA; and (3) asymmetric branching with the angle between the MPA and RPA greater than the angle between the MPA and LPA.
TABLE 2. Size Versus Blood Flow Volume in the Branch Pulmonary Arteries

<table>
<thead>
<tr>
<th>Size Difference</th>
<th>Net Blood Flow Distribution</th>
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<tbody>
<tr>
<td>RPA&gt; LPA (n=7)</td>
<td>6  1  0</td>
</tr>
<tr>
<td>RPA= LPA (n=11)</td>
<td>3  8  1</td>
</tr>
<tr>
<td>RPA&lt; LPA (n=3)</td>
<td>0  2  1</td>
</tr>
</tbody>
</table>

Statistical Analysis

Descriptive data are presented as mean±SD and range. For comparison of flow parameters in branch pulmonary arteries, a paired t test was performed. Linear regression analysis was performed to evaluate the association between the measured data and calculated parameters. We used an SPSS-PC software package for statistical analyses. A probability value <0.05 was considered to be statistically significant.

Results

Blood Flow and Branch Pulmonary Artery Size

The diameters of the RPA and LPA at the hilum were similar (discrepancy <10%) in 12 patients (Table 2). The RPA was larger than the LPA in 7 patients, and the LPA was larger than the RPA in 3 patients. The blood flow ratio to the right and left lungs was normal (range 61/39 to 43/57) in 11 patients (Table 2). Among these 11, the RPA and LPA were equally sized in 8, the RPA was larger than the LPA in 2, and the RPA was smaller than the LPA in 1 patient. Blood flow to the left lung was significantly decreased (blood flow to the left lung <39%) in 9 patients. Among these 9, the LPA was smaller than the RPA in 6, and the RPA and LPA were equally sized in 3. Blood flow to the right lung was significantly reduced (blood flow to the right lung <43%) in 2 patients. One of these 2 patients had diffuse hypoplasia of the RPA with a focal narrowing, and the other had equally sized branches. Altogether, only 2 patients had LPA flow greater than RPA flow.

There were weak correlations between the cross-sectional area of the proximal branch pulmonary artery and the forward ($R^2=0.218$, $P=0.029$) and regurgitant ($R^2=0.221$, $P=0.027$) flow volumes. However, there was no significant correlation between the cross-sectional area of the proximal branch pulmonary artery and the net forward flow volume ($R^2=0.120$, $P=0.114$).

Regurgitant Fraction and Fractions of Forward and Regurgitant Flow Durations

Values for MPA, RPA, and LPA are listed in Table 3. There was a linear relationship between the regurgitant fraction and the fraction of regurgitant flow duration in the MPA ($R^2=0.560$, $P<0.001$) and RPA ($R^2=0.455$, $P=0.001$) but not in the LPA ($R^2=0.111$, $P=0.129$; Figure 2). There was no significant correlation between the regurgitant fraction in the MPA and the maximum pulmonary regurgitant flow velocities ($R^2=0.140$, $P=0.105$).

Regurgitant Fraction in Branch Pulmonary Arteries

Regurgitant fraction was greater in the LPA (46±18%; range 26% to 91%) than in the RPA (34±16%; range 0% to 62%; $P=0.002$; Figure 3). Only 3 patients had greater regurgitant fraction in the RPA than in the LPA. The average contribution of the LPA to the total regurgitant flow volume was 54±19% (range 19% to 100%), whereas its average contribution to the total forward flow volume was 44±13% (range 21% to 76%). In 4 patients, regurgitant flow from the LPA was >75% of total regurgitant flow (Figure 1), and in 1 patient, regurgitation from the LPA accounted for 100% of the regurgitation flow in the MPA. In all 3 types of pulmonary arterial geometry, more cases had greater regurgitation from the LPA than from the RPA.

Discussion

Pulmonary regurgitation is an important determinant of late morbidity after repair of TOF. Although it is well tolerated in the short term, it is associated with progressive exercise intolerance, ventricular dysfunction, arrhythmia, and late sudden death. Although pulmonary regurgitation at the level of the pulmonary valve and MPA has been studied extensively, pulmonary blood flow in the branch pulmonary arteries has not been investigated previously. The average regurgitant fraction in the present study population was greater in the LPA than in the RPA. The contribution of the LPA to the total regurgitant flow volume was 54±19%, whereas its average contribution to the total forward flow volume was 44±13%. These data suggest that decreased net blood flow to the left lung in these patients is primarily due to increased regurgitation rather than to decreased forward flow.

A small amount of regurgitant flow is also seen in the normal branch pulmonary arteries for a short period of time in the late systolic and early diastolic phase. This normal regurgitant flow that is not associated with regurgitation into the right ventricle is reported to be greater in the RPA than in the LPA. This is in contrast to the regurgitant flow in the branch pulmonary arteries in the present study population, which showed a larger amount of retrograde flow in the LPA than in the RPA for a more prolonged period of time.

The reasons for these unusual but important differential patterns of flow are not immediately apparent and appear unrelated to absolute size of the proximal branch vessels. The present study showed that the size of the branch

TABLE 3. Parameters of Pulmonary Regurgitation in the MPA, RPA, and LPA

<table>
<thead>
<tr>
<th></th>
<th>MPA (n=20)</th>
<th>RPA (n=22)</th>
<th>LPA (n=22)</th>
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<tbody>
<tr>
<td>Regurgitant fraction</td>
<td>38.6±10.2 (24–63)</td>
<td>33.8±16.2 (0–62)</td>
<td>46.4±18.1 (26–91)</td>
</tr>
<tr>
<td>Fraction of forward flow duration</td>
<td>55.8±6.9 (41.3–67.5)</td>
<td>58.4±12.2 (42.5–100)</td>
<td>53.1±7.4 (36.3–67.5)</td>
</tr>
<tr>
<td>Fraction of regurgitant flow duration</td>
<td>43.9±6.8 (32.5–56.3)</td>
<td>40.4±11.4 (0–57.5)</td>
<td>44.8±7.4 (32.5–63.8)</td>
</tr>
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</table>

All values are percentages, with ranges in parentheses.
arteries at the hilum was not predictive of the net forward flow volume in 32% of cases. In addition, there was no significant correlation between the size of the proximal branch pulmonary arteries and net forward flow volume. There was only a weak correlation between the cross-sectional area of the proximal branch pulmonary artery and the regurgitant flow volume ($R^2=0.221$, $P=0.027$). The present data also showed no relationship between the regurgitant fraction and regurgitation duration in the LPA, in contrast to RPA flow, which showed a significant linear relationship between the 2. It is clear that more subtle hemodynamic differences must account for our observations. Some years ago, Wilson and Amplatz\textsuperscript{11} reported that long-axis rotation of the heart resulted in a tendency to left-upper-lobe hypovascularity in patients with severe TOF. Experimental flow dynamic studies in pulmonary blood flow have demonstrated a marked influence of pulmonary artery geometry on absolute blood flow volume.\textsuperscript{19–21} It can also be speculated that differential regurgitation in the present study population would be due, at least in part, to different branching patterns of the RPA and LPA. However, we could not find any correlation between the 2 variables. The state of the pulmonary arteriolar beds and pulmonary vascular resistance, including compliance of the vessel wall, airway pressure, venous resistance, and left arterial pressure, may also significantly influence pulmonary blood flow patterns. For example, Chaturvedi et al\textsuperscript{10} showed that a small increase in airway pressure led to increased total pulmonary regurgitation, presumably because of subtle changes in pulmonary vascular resistance during positive-pressure lung inflation. When there is levocardia, as in a normal individual, the left lung may have a higher impedance than the right lung because of its

Figure 2. Scatterplots showing relationship between fraction of regurgitant flow duration and regurgitant fraction. There was a linear relationship between regurgitant fraction and fraction of regurgitant flow duration in MPA and RPA but not in LPA.

Figure 3. Vertical scatterplots of regurgitant fraction in branch pulmonary arteries. Regurgitant fraction was greater in LPA than in RPA. Only 3 patients had greater regurgitant fraction in RPA. Bars represent mean±SD.
relatively smaller volume. The left lung volume can be further reduced with cardiomegaly, leading to vulnerability to atelectasis and collapse and thereby a rise in vascular resistance. Furthermore, it has been reported that the intra-acinar arteries in TOF are smaller than normal, and the number of alveoli are reduced. These findings are considered secondary to decreased pulmonary blood flow before repair, which is often more marked in the left lung. Although speculative, any or all of these mechanisms may conspire to influence the degree of pulmonary regurgitation from an individual lung, and all warrant further investigation.

Clinical Implications
Although it is likely that the mechanisms of differential regurgitation are multifactorial, the clinical implications in the individual patient are similar. Enlargement of a stenosed or hypoplastic pulmonary artery, avoidance of atelectasis, and restoration of pulmonary valve competence all have a role in management. An intriguing additional therapeutic option may exist in those patients in whom pulmonary regurgitation is predominantly from 1 pulmonary artery. Insertion of a valved stent in the LPA might be expected to reduce total regurgitation by up to 100% in some patients and may be a particularly attractive option in those patients with a grossly dilated right ventricular outflow tract, who would otherwise be unsuitable for implantation of an existing valved stent in the MPA.

Study Limitations and Direction of Future Studies
Segmented k-space filling in fast PC sequences results in reduced true temporal resolution. Although the temporal resolution is improved by linear interpolation or view sharing in fast PC imaging, some inaccuracy in measurement of absolute values of flow velocity and volume is unavoidable. However, the inaccuracy is considered to be minimal when the regurgitant fractions in the branch pulmonary arteries are compared within a single patient.

Another cause for inaccurate flow measurement in PC imaging is turbulent flow. In the present study, we observed signal loss during end systole in 1 of 3 stenotic pulmonary arteries in which the imaging plane was distal to the stenosis. In the remaining 2, the imaging plane was through the stenotic segment, and no signal loss was observed.

Although we defined preferential regurgitation from the LPA in patients with TOF and postoperative pulmonary regurgitation, we could not evaluate the contribution of the factors that can influence pulmonary blood flow, such as lung volume, peripheral pulmonary arterial pathology and resistance, cross-sectional area of the vascular bed, and lung parenchymal pathology. Also not assessed was whether differential regurgitation was a universal phenomenon present in most cases with pulmonary regurgitation of other origins. It would be important to understand the mechanics of regurgitant flow by using 3D computer modeling, which could provide insights into future modifications or new developments of surgical and interventional procedures. It is also important to develop methods to investigate the flow pattern and vascular compliance of the peripheral lung fields.

Conclusions
This PC MR study showed that differential regurgitation in the branch pulmonary arteries is common in patients after TOF repair. The average contribution of the LPA to the total regurgitant flow volume was greater than its average contribution to the total forward flow volume. In some cases, the difference was so significant that regurgitation from the LPA contributed to the majority of pulmonary regurgitation. These data may have important implications for the surgical and nonsurgical management of chronic pulmonary regurgitation.

References


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