Pulmonary Regurgitation in the Late Postoperative Follow-up of Tetralogy of Fallot

Volumetric Quantitation by Nuclear Magnetic Resonance Velocity Mapping

Sidney A. Rebergen, MD; Jan G.J. Chin, MD; Jaap Ottenkamp, MD; Ernst E. van der Wall, MD; Albert de Roos, MD

Background. Pulmonary regurgitation frequently occurs after surgical correction of tetralogy of Fallot. To date, reliable quantification of pulmonary regurgitation has not been possible, and therefore the clinical significance of pulmonary regurgitation is controversial. Nuclear magnetic resonance (NMR) velocity mapping allows accurate measurement of volumetric flow. The feasibility and accuracy of NMR velocity mapping to quantify pulmonary regurgitation volumes are studied in patients after Fallot repair.

Methods and Results. In 18 patients (mean age, 16.5±6.5 years; late 12.6±5.2 years) after Fallot surgery, forward and regurgitant volume flow was measured in the main pulmonary artery with NMR velocity mapping. To validate the measurements of pulmonary forward flow, right ventricular stroke volume was used as an internal reference standard. Pulmonary regurgitation volumes were compared with the differences between the corresponding right and left ventricular stroke volumes. Ventricular volumes were measured with a multiseciton gradient echo NMR method. In addition, the relation between pulmonary regurgitation and right ventricular volumes was studied. Measurements of pulmonary regurgitation volume with NMR velocity mapping closely corresponded with the tomographically determined volumes (r=.93). Forward pulmonary volume flow was nearly identical to right ventricular stroke volume (r=.98). Pulmonary regurgitation volume was significantly correlated with end-diastolic volume (r=.82, P<.0005), end-systolic volume (r=.63, P<.01), and stroke volume (r=.89, P<.0005) of the right ventricle but not with right ventricular ejection fraction (r=−.41, P=NS).

Conclusions. NMR velocity mapping is an accurate method for the noninvasive, volumetric quantification of pulmonary regurgitation after surgical correction of tetralogy of Fallot. (Circulation. 1993;88[part 1]:2257-2266.)

KEY WORDS • nuclear magnetic resonance • regurgitation • lungs • flow • magnetic resonance imaging • defects

Surgical approaches for correction of tetralogy of Fallot, the most common form of cyanotic congenital heart disease, have been considerably refined since the first report of intracardiac repair in 1955.1 Complete repair is now often performed in infancy without a prior palliative shunt procedure.2 Despite improved surgical techniques, residual pulmonary stenosis and pulmonary regurgitation are common postoperative sequelae in patients with tetralogy of Fallot. Pulmonary regurgitation will occur especially when a transannular patch is used for relief of the outflow obstruction of the right ventricle.3 Considerable controversy exists regarding the significance of residual pulmonary regurgitation. According to early case reports and experimental studies,4 pulmonary regurgitation was considered a benign lesion, at least when present as an isolated abnormality. In addition, many authors reported pulmonary regurgitation to be well tolerated clinically, up to several decades after repair.5–8 Others9,10 emphasize that pulmonary regurgitation-induced right ventricular volume overload may predispose to the development of ventricular arrhythmia, a risk factor for sudden death. Furthermore, several studies11–19 suggest that postoperative pulmonary regurgitation may be partly responsible for abnormal right ventricular hemodynamics or limited exercise capacity in otherwise asymptomatic tetralogy of Fallot patients. Even left ventricular dysfunction has been attributed to pulmonary regurgitation.13

Until now, the evaluation of the clinical significance of pulmonary regurgitation in postoperative tetralogy of Fallot has been troublesome since there was no technique that could accurately quantitate pulmonary volume flow. Attempts have been made to estimate the severity of pulmonary regurgitation using Doppler echocardiography,9,15,18 contrast ventriculography,7,14 pressure-volume loops,16,19 videodensitometry,12 or auscultation.8,13 Nuclear magnetic resonance (NMR) velocity mapping pro-
Patient Data and Nuclear Magnetic Resonance Measurement Results

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<th>Patient</th>
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<td>65  27  38</td>
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a indicates infundibulectomy; b, infundibulectomy with valvulotomy; c, transannular patch; cycle, cardiac cycle; EDV, end-diastolic volume; ESV, end-systolic volume; F, female; FPF, forward pulmonary flow; LV, left ventricle; M, male; NA, not available; NPF, net pulmonary flow; RPF, regurgitant pulmonary flow; RF, regurgitant fraction (RPF/FPF); RV, right ventricle, and SV, stroke volume.

*Previous palliative shunt procedure.

Methods

Patient Group

Eighteen (12 male and 6 female) patients were studied following total surgical correction of tetralogy of Fallot. At the surgery procedure, a transannular outflow patch was used in 8 patients. In the remaining 10 patients, infundibulectomy of the right ventricle was performed with additional pulmonary valvulotomy in 6 patients without, however, dissection of the pulmonary annulus (Table). Age at correction of the entire patient group was 3.9±2.4 years (range, 0.4 to 7.8 years). The patients with a transannular patch (2.77±2.0 years) were younger at the repair procedure than the patients in whom a transannular patch had not been used (4.72±2.48 years, P<.05). Age at NMR study was 16.5±6.5 years (range, 8.6 to 30.2 years), corresponding to 12.6±5.2 years (range, 6.6 to 24.0 years) after Fallot repair (Table). Body surface area was 1.48±0.36 m² (range, 0.87 to 1.98 m²). A prior palliative shunt procedure had been used in 4 patients (Table).

In 9 patients, residual pulmonary stenosis was present (defined as a right ventricle–to–main pulmonary artery pressure gradient >15 mm Hg) as reported from postoperative (within 8 to 24 days after repair) catheterization data that were available in 17 of 18 patients. Five of those 9 patients (patients 4, 7, 14, 15, and 16; Table) had a gradient >25 mm Hg but <35 mm Hg. In 1 patient (patient 14; Table), severe residual pulmonary stenosis was confirmed by a gradient of 80 mm Hg found at catheterization shortly after the NMR study, and this patient was reoperated recently. Patients with residual ventricular septal defects or valvular lesions other than pulmonary incompetence were excluded from the study. All patients were asymptomatic, and 2 patients (patients...
NMR Imaging

Using a Gyroscan S15 machine (Philips Medical Systems, Best, The Netherlands) operating at 1.5 T, the NMR studies were initiated with conventional spin echo series in the coronal and sagittal plane, enabling selection of the oblique imaging plane for NMR velocity mapping of the main pulmonary artery (Fig 1A and B). Transverse multisection multiphase gradient echo NMR imaging of the ventricles was performed with an echotime of 12 ms, a time frame interval of 30 ms, a slice thickness of 10 mm with an interslice gap of 1 mm, a field of view of 30x30 cm, and two measurements of a 100x128 acquisition matrix. Approximately 10 contiguous slices were sufficient to cover the entire ventricular compartment from the caudal margin of the right ventricle to the main pulmonary artery. Both spin echo and gradient echo NMR data acquisition was triggered by the R-wave of the ECG.

NMR velocity mapping was performed with the flow-adjusted gradient sequence that uses a velocity-encoding magnetic field gradient in the direction of flow and velocity-compensating gradients in the other directions. Magnetic spins of intravascular protons that flow along the velocity-encoding gradient accumulate a phase-shift that is proportional to velocity, and a velocity-encoded phase image can be reconstructed in addition to a conventional magnitude image (Fig 1C).

Unfortunately, phase errors, caused by, for example, inhomogeneity of the magnetic field, are superimposed on the velocity-induced phase shifts. To reconstruct an accurate two-dimensional display of flow velocity, the flow-adjusted gradient sequence acquires velocity-encoded data and fully velocity-compensated data interleaved in consecutive cardiac cycles. The phase errors are eliminated by subtracting a velocity-compensated phase image from the corresponding velocity-encoded phase image, yielding a velocity map that will show mid-gray signal intensity in areas of stationary tissue or when velocity is zero. Intravascular signal intensity increases with velocity toward white or black for opposite directions of flow with respect to the imaging plane (Fig 1D and E). If volume flow is to be measured, the imaging section must be orientated perpendicular to the vessel of interest, with encoding of the velocity in the direction of true flow. To ensure that the plane for velocity mapping is exactly perpendicular to the vessel of interest, angulations for such a plane are determined from orthogonal scout views. Measurements of volume flow in the great arteries with the flow-adjusted gradient sequence have been validated previously at our institution.

NMR velocity mapping was performed in a double oblique plane perpendicular to the main pulmonary artery at ±2 cm proximal from the pulmonary bifurcation. Velocity maps were acquired with an echo time of 8 to 10 milliseconds, a time frame interval of 30 milliseconds, a slice thickness of 10 mm, a field of view of 30x30 cm, and two measurements of a 100x128 matrix. The maximum phase shift was set to occur with 250 cm/s, and aliasing was not encountered. In both multislice gradient echo NMR and velocity mapping, the cardiac cycle was sampled with a number of time frames that varied from 16 to 28 (depending on the heart rate) to preserve the desired time frame interval of 30 milliseconds.

NMR Image Analysis

Forward and regurgitant pulmonary volume flow was measured from the velocity maps by manually tracing the main pulmonary artery contour. Instantaneous flow volumes were calculated by multiplying contour area and spatial average flow velocity within the contour. Instantaneous flow volumes were summed to give total forward flow and total regurgitant flow per cardiac cycle (Fig 2).

Ventricular stroke volumes were calculated from end-diastolic and end-systolic volumes, measured from endocardial contours manually traced on the multisecton gradient echo NMR image set (Fig 3). Ventricular stroke volumes and pulmonary flow volumes were multiplied by heart rate and corrected for body surface area to give both left-sided and right-sided cardiac indexes, pulmonary forward flow index, and pulmonary regurgitation index (L·min⁻¹·m⁻²). The total duration of an NMR study was 60 to 75 minutes, of which 50% was required for multislice gradient echo imaging of the ventricles.

Validation of Pulmonary Regurgitation Volume Measurement

Earlier studies have used NMR measured stroke volume differences to calculate aortic and mitral regurgitation. A similar approach was used in the current study by comparing pulmonary regurgitation measured by NMR velocity mapping with the difference between right-sided and left-sided cardiac output. In absence of shunt lesions or regurgitation through the other valves as in tricuspid incompetence, pulmonary regurgitation should equal this difference. Additional validation was achieved by comparing forward pulmonary flow with right-sided cardiac output. The results of the endocardial contour tracings were disclosed to the observers only after the velocity mapping studies had been analyzed.

Doppler Echocardiography

Using echocardiographic examinations that had been performed within 1 year prior to the NMR study (n=15), the severity of pulmonary regurgitation was judged from the amplitude and the duration of the Doppler signal of retrograde pulmonary flow and graded semiquantitatively as mild (group 1, n=5), moderate (group 2, n=4), or severe (group 3, n=4). Echocardiographic results were equivocal in two patients in whom there was doubt if regurgitation was moderate or severe. The NMR measurements of pulmonary regurgitation volumes obtained from each category were compared.

Statistical Analysis

Values are expressed as mean±SD when appropriate. Linear regression analysis together with calculation of the standard error of the estimate (SEE) was performed for comparison of measurement results. For comparison between patient subgroups, unpaired Student's t tests and one-way ANOVA with Scheffé F test were used. A value of P<.05 was considered significant.
Fig 1. This page and facing page. A, Coronal spin echo image showing the great arteries. The solid line perpendicular to the main pulmonary artery indicates the plane for velocity mapping. B, Sagittal spin echo image showing the right ventricle and the main pulmonary artery. The plane for velocity mapping perpendicular to the pulmonary artery is indicated by the solid line. C, Double oblique axial gradient echo nuclear magnetic resonance image perpendicular to the pulmonary trunk. The angles of obliquity were determined as shown in Fig 1A and B. This magnitude image, showing high signal intensity in all areas of flow, is obtained with the flow-adjusted gradient sequence. Note the right-sided descending aorta. D, Velocity map in systole, corresponding to Fig 1C, with high signal intensity in the pulmonary artery, reflecting flow into the imaging section or toward the head. Very low signal intensity in the descending aorta represents flow out in the opposite direction. E, Velocity map in diastole corresponding to Fig 1C and D. Low signal intensity in the pulmonary artery and the left ventricular cavity reflecting flow in caudal direction, indicating pulmonary regurgitation and ventricular filling, respectively.
**Results**

**Validation of NMR Velocity Mapping**

In all patients (n=18), pulmonary regurgitation volume index as measured from NMR velocity mapping (1.47±1.17 L·min⁻¹·m⁻²; range, 0.21 to 4.23) corresponded closely with pulmonary regurgitation volume index calculated from the difference between right-sided and left-sided cardiac indexes (1.33±1.09 L·min⁻¹·m⁻²; range, 0.04 to 4.34): y=0.995x+0.147, r=.93, SEE=.45 (Fig 4a).

In three patients (4, 14, and 15; Table), turbulent flow in mid systole caused NMR signal amplitude to be insufficient for reconstruction of the corresponding phase images. This precluded the measurement of antegrade pulmonary flow in these patients. In the remaining (n=15) patients, adequate signal was preserved with peak flow velocities that ranged from 70 to 230 cm/s in systole and from 50 to 190 cm/s in diastole. In these 15 patients, forward pulmonary flow volume index (4.62±1.48 L·min⁻¹·m⁻²; range, 2.58 to 7.58) showed close agreement with right-sided cardiac index (4.50±1.43 L·min⁻¹·m⁻²; range, 2.61 to 7.87): y=0.97x+0.11, r=.98, SEE=.28 (Fig 4b). The results of these comparisons indicate that both forward and regurgitant pulmonary volume flow can be accurately measured by NMR velocity mapping.

**Additional NMR Findings**

Regurgitant pulmonary stroke flow (mL per cardiac cycle per m²) was linearly correlated with right ventricular end-diastolic volume (r=.82, P<.0005) (Fig 5a). Pulmonary regurgitation volume also correlated with right ventricular stroke volume (r=.89, P<.0005, Fig 5b) and showed a weak but significant correlation with right ventricular end-systolic volume (r=.63, P<.01).

However, significant correlation of pulmonary regurgitation with right ventricular ejection fraction (0.59±0.08; range, 0.34 to 0.67) could not be demonstrated (r=−.41, P=NS, Fig 5c). Ventricular ejection fraction was calculated in the usual way: stroke volume divided by end-diastolic volume. A virtually normal range of right ventricular ejection fractions was measured in the majority of the patients, with the exception of patient 13 (Table), in whom a right ventricular ejection fraction of 0.34 was calculated.

Pulmonary regurgitant fraction (regurgitant pulmonary flow volume divided by forward pulmonary flow volume) was 0.30±0.18 (range, 0.06 to 0.60; n=15) and was associated with right ventricular end-diastolic volume (r=.84, P<.0005), with right ventricular end-systolic volume (r=.72, P<.001), and with right ventricular stroke volume (r=.74, P<.005) and inversely correlated with right ventricular ejection fraction (r=−.59, P<.05).

No significant correlations between pulmonary regurgitation, expressed as either absolute volume flow or as a fraction of forward flow, and left ventricular volumes could be demonstrated.

Pulmonary regurgitation volumes were greater in the patients in whom a transannular patch had been used for reconstruction of the right ventricular outflow tract (n=8) compared with patients with an intact pulmonary annulus (n=10 with right ventricular infundibuleucotomy including n=6 with additional pulmonary valvulotomy): 2.17±1.25 versus 0.92±0.78 L·min⁻¹·m⁻² (P<.01, Fig 6). Right ventricular end-diastolic volume index was also higher in the transannular patch group: 137.5±37.8 versus 89.9±31.1 mL/m² in the intact pulmonary annulus group (P<.005), obviously reflecting more severe pulmonary regurgitation and greater right ventricular volume load.

The differentiation by Doppler echocardiography of mild pulmonary regurgitation (group 1) from both moderate (group 2) and severe (group 3) pulmonary regurgitation was only partially confirmed by a significant difference in regurgitation volumes measured by NMR: 5.78±2.58 mL/m² in group 1 versus 34.93±11.30 mL/m² and 27.40±14.60 mL/m² in groups 2 (P<.05) and
3 (P<.05), respectively. However, the NMR-measured volumes of groups 2 and 3 were not significantly different (Fig 7).

Discussion

Results of the Present Study

Our study demonstrates that pulmonary regurgitation measurements by NMR velocity mapping corresponded closely with the results of a tomographic NMR method that is totally different from the velocity mapping approach. These results imply that NMR velocity mapping is an accurate and noninvasive method for volumetric quantitation of pulmonary regurgitation in patients after surgical correction of tetralogy of Fallot. In addition, the ability of NMR to measure right ventricular volumes tomographically, without the use of geometric assumptions, allowed a more comprehensive study of pulmonary regurgitation in postoperative tetralogy of Fallot.

NMR velocity mapping results were compared with the estimated severity of pulmonary regurgitation as judged from Doppler echocardiographic examination prior to the NMR study. Because Doppler echocardiography provides only semiquantitative estimates of pulmonary regurgitation, a solid comparison between NMR and echocardiography for this purpose is not possible. Therefore, the current study merely intended to demonstrate the feasibility and accuracy of NMR for measuring pulmonary regurgitation. The NMR results were viewed against echocardiographic estimates because the latter are routinely used in the follow-up of postoperative tetralogy of Fallot. In this study, NMR and Doppler echocardiography did agree in those patients in whom Doppler indicated mild pulmonary regurgitation. However, it appears that when Doppler shows moderate or severe regurgitation or when echocardiography results are equivocal, reliable assessment of the severity of pulmonary regurgitation requires further analysis. NMR velocity mapping has already been demonstrated to be a reliable tool for measuring volume flow in the pulmonary arteries.20-24,26 The current study has provided validation of this technique for the volumetric measurement of pulmonary regurgitation. Quantitation of volume flow data that can be corrected for body surface area may be valuable in the evaluation of the true significance of pulmonary regurgitation in patients following repair of tetralogy of Fallot.

No left ventricular volume abnormalities in relation to pulmonary regurgitation were found in our study. Although abnormal left ventricular volumes have been reported at rest in patients after tetralogy of Fallot repair,12,13 this is not a widely acknowledged finding, and the effects of pulmonary regurgitation on left ventricular function remain to be revealed.

Fig 3. Axial mid-ventricular gradient echo nuclear magnetic resonance (NMR) images of end diastole (left upper panel) and end systole (right upper panel). The lower panels show the same images with tracings of the left and right ventricular endocardial contours superimposed. Ventricular cavity areas, obtained from a contiguous set of axial gradient echo NMR images, are summed to yield ventricular volumes.
Comparison With Previous Studies

Several alternative angiographic methods to assess pulmonary regurgitation have been described, either qualitative\textsuperscript{11} or semiquantitative.\textsuperscript{5,7} Regurgitant fractions have been calculated from angiographically determined ventricular volumes\textsuperscript{14} and with a dye-dilution technique.\textsuperscript{12} Some studies\textsuperscript{8,13} have used only clinical auscultatory criteria.

The findings of the current study confirm those of Redington et al.\textsuperscript{16} who showed that the right ventricle copes with increasing volume load and subsequent increased right ventricular end-diastolic volume by increasing right ventricular stroke volume and thereby preserving ejection fraction. In this particular study, absolute pulmonary regurgitation volume was measured from an increase in right ventricular volume during "isovolumetric" relaxation as revealed from pressure-volume loops.\textsuperscript{16} Although this invasive approach provides unique hemodynamic information, it may not be ideally suited for the assessment of pulmonary regurgitation because with this method pulmonary regurgitation cannot be differentiated from the normal increase in right ventricular volume due to tricuspid filling. Our results show that pulmonary regurgitation often continues in mid diastole (Fig 3). In addition, postoperative follow-up of tetralogy of Fallot clearly requires a non-invasive technique that is suitable for repetitive studies. Echocardiography is a widely available technique that provides real-time information and will answer most of the clinical questions regarding patients after Fallot repair. But especially in the adult patient, bony deformations, sternal sutures, and interposed lung tissue may complicate echocardiographic studies. Although transesophageal echocardiography will provide additional information, its semi-invasive character often is not appreciated by the patient. Furthermore, results of echocardiography are rather operator dependent, and most important, Doppler velocities cannot be transformed easily into volumetric flow data. Theoretically, under the assumptions of a flat velocity profile within a constant vessel diameter and with the use of a correction factor for the angle between ultrasound beam and vessel, Doppler echocardiography can measure regurgitant pulmonary volume flow but only when pulmonary stenosis is absent.\textsuperscript{34} Although Marx et al.\textsuperscript{15} calculated regurgitant fractions from forward and regurgitant flow velocities in the pulmonary artery, it must be realized that the pulmonary flow velocities measured by Doppler are merely a reflection of the pressure difference between pulmonary artery and right ventricle and not necessarily an accurate representation of the severity of pulmonary regurgitation.\textsuperscript{26}
Limitations of the Current Approach

Some limitations of NMR imaging were encountered in the current study. Although it did not interfere with the measurements of regurgitant flow, pulmonary volume flow in mid systole could not be quantitated in three cases (patients 4, 14, and 15; Table) due to loss of NMR signal amplitude. This signal void was very likely caused by turbulent flow that occurred as a result of the residual gradients across the right ventricular outflow tract, measured at postoperative catheterization in these patients (patient 14 was reoperated recently for severe residual right ventricular outflow tract obstruction). The availability of shorter echo times on newer NMR imaging systems may reduce the occurrence of signal loss in turbulent flow, but there are many other factors that determine the extent of signal void.23,35

The fact that NMR data acquisition is triggered by the R-wave of the ECG imposes a few additional shortcomings. First, data collection is rather time consuming since images are built up over several hundred cardiac cycles. For the same reason, NMR does not yet routinely provide real-time images, the image quality is reduced in patients with arrhythmias, and the performance of exercise studies is troublesome. Finally, in the current study, data were acquired with prospective triggering, and images could be obtained from the final 100 to 150 milliseconds of diastole. Fortunately, pulmonary regurgitation never continued into this interval, and the flow measurements were not affected. Retrospective
Extensive regurgitant use of NMR velocity mapping in clinical routine.

With regard to the current study, the actual duration of one NMR velocity mapping experiment was only 4 to 7 minutes, but the total examination time was relatively long because the imaging protocol included the collection of gradient echo images of the ventricles required for validation purposes. Altered hemodynamics during the time interval between NMR imaging of the ventricles and velocity mapping may explain why in 2 patients (patients 2 and 13, Table) regurgitant pulmonary flow measured by NMR velocity mapping only moderately agreed with the difference between left and right ventricular output. On the other hand, overestimation of regurgitant flow by NMR velocity mapping, demonstrated occasionally for the aorta, may have occurred in these particular patients.

Finally, postprocessing of the data includes time-consuming manual tracing of endocardial and vascular contours, and automated contour detection programs are being developed to improve this aspect of cardiovascular NMR imaging.

Clinical Implications

As the population of patients after Fallot repair increasingly survives into adulthood with a relatively unknown outcome, the need for frequent hemodynamic follow-up becomes apparent. Because tetralogy of Fallot repair has been increasingly performed in infants with extensive use of transannular patches, residual pulmonary regurgitation and signs of right ventricular volume overload will be frequently encountered in postoperative tetralogy of Fallot patients.

Regarding the hemodynamic consequences of pulmonary regurgitation under resting conditions, the present study shows that right ventricular volumes increase with the severity of pulmonary regurgitation. Right ventricular ejection fraction was substantially reduced in only one patient (patient 13, Table), who also showed the largest pulmonary regurgitation volume and the largest right ventricular end-diastolic volume. The capability of the right ventricle to adapt to pulmonary regurgitation depends to a great extent on right ventricular afterload determined by pulmonary artery pressure and pulmonary stenosis. Right ventricular dilatation may also induce tricuspid regurgitation with further deterioration of right ventricular performance, and in such patients, timely pulmonary valve replacement may preserve right ventricular function. NMR velocity mapping appears to be ideally suited for monitoring pulmonary regurgitation, and this technique may provide the optimal timing for surgical treatment of residual pulmonary regurgitation following repair of tetralogy of Fallot.

The patients in the current study were asymptomatic, and the slight exercise restrictions that were exhibited by a few patients may be attributed to coexisting pulmonary stenosis. To assess the clinical importance of pulmonary regurgitation in postoperative tetralogy of Fallot, subsequent NMR studies with simulation of exercise conditions by pharmacologic stress agents should provide additional insights into the deleterious effects of pulmonary regurgitation that have been reported previously.

It is concluded that NMR velocity mapping can accurately quantitate pulmonary regurgitation volumes and that the severity of pulmonary regurgitation is directly related to changes in right ventricular volume. This method may be of considerable value for the assessment of the long-term detrimental effects of pulmonary regurgitation on right ventricular function in patients after tetralogy of Fallot repair.

References

Pulmonary regurgitation in the late postoperative follow-up of tetralogy of Fallot. Volumetric quantitation by nuclear magnetic resonance velocity mapping.
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