

Clinical Applications of Cardiac Magnetic Resonance Imaging After Repair of Tetralogy of Fallot

W.A. Helbing,¹ **A. de Roos**²

¹Department of Pediatrics, Division of Pediatric Cardiology, Leiden University Medical Center, J-6-S, P.O. Box 9600, 2300 RC Leiden, The Netherlands

2 Department of Radiology, Leiden University Medical Center, J-6-S, P.O. Box 9600, 2300 RC Leiden, The Netherlands

Abstract. In the past 15 years, cardiovascular magnetic resonance (MR) has evolved into an imaging technique that provides adequate, and in part unique, information on residual problems in the follow-up of patients operated for tetralogy of Fallot. Spin-echo or gradient-echo cine magnetic resonance imaging allow detailed assessment of intracardiac and large vessel anatomy, which is particularly helpful in Fallot patients with residual abnormalities of right ventricular outflow and/or pulmonary artery. Multisection gradient-echo cine MRI can be used to obtain accurate measurements of biventricular size, ejection fraction, and wall mass. This allows serial follow-up of biventricular function. MR velocity mapping is the only imaging technique available that provides practical quantification of pulmonary regurgitation volume. MR velocity mapping can also be used to quantify right ventricular diastolic function in the presence of pulmonary regurgitation.

Key words: Magnetic resonance imaging — Pulmonary regurgitation — Restrictive diastolic physiology — Tetralogy of Fallot — Ventricular function — Ventricular hypertrophy

Tetralogy of Fallot (TOF) is the most common type of cyanotic congenital heart disease. Its incidence is approximately 5% or 6% of all patients with congenital heart disease [31]. Since the introduction of total surgical repair in 1955 [44], the long-term prognosis for these patients has become good but less than that of the normal age-matched population [57, 63]. Total repair within the first months of life is currently feasible [73], with low mortality. However, complications, residua, and sequelae may result in problems after total repair of TOF.

In the follow-up of patients who have undergone

repair of TOF an imaging technique is required that provides adequate information on (1) residual anatomical problems [ventricular septal defect (VSD), pulmonary stenosis, and right ventricular (RV) outflow aneurysm], (2) the extent of pulmonary stenosis (residual or recurrent), (3) the amount of pulmonary regurgitation, and (4) systolic and diastolic biventricular size and function. Echocardiography remains the principal diagnostic tool in these patients [22]. However, because of well-known limitations, transthoracic echocardiography often fails to provide necessary hemodynamic or anatomic information, particularly in operated patients [30, 48]. Magnetic resonance imaging (MRI) gives noninvasive images of the cardiovascular system with excellent image quality, unlimited choice of imaging planes, and accurate flow quantification, without the use of ionizing radiation. In the past 15 years, the role of MRI in cardiovascular imaging has gradually evolved. The purpose of this article is to review current clinical applications of MRI in patients operated for TOF.

MRI of Postoperative Anatomy

Six to 10% of patients after repair of TOF will require reoperation because of residual or recurrent VSD, RV outflow obstruction or aneurysm formation, and pulmonary artery stenosis [57, 63]. From the initial reports on the successful use of MRI for cardiovascular imaging, this technique has been recognized as well suited to image cardiac anatomy in postoperative patients with congenital heart disease, including those with TOF [10, 14, 15, 23, 27, 29, 36]. Both intracardiac and large vessel anatomy may be depicted clearly with electrocardiogram (ECG) gated spin-echo images [12, 38]. Transaxial, coronal, and sagittal views are generally applied. Angulated views tailored to the anatomical region of interest may provide additional information. Thus, RV hypertro-*Correspondence to:* W.A. Helbing phy, RV outflow tract stenosis, and pulmonary artery

Fig. 1. (A) Spin-echo image (coronal plane) of pulmonary artery of patient after correction of tetralogy of Fallot. Narrowing of the proximal left pulmonary artery is indicated (*). *1,* aorta; *2,* right ventricle; *3,* left ventricle. **(B)** MIP projection of gadolinium-enhanced 3-D MR angiogram of pulmonary artery of same patient (Fig. 1A). Narrowing of the proximal left pulmonary artery is indicated (*arrow*). Note detailed imaging of pulmonary artery branches.

anatomy and size may be assessed in postoperative TOF patients [1, 12, 14, 28, 29, 52]. For evaluation of RV outflow, main pulmonary artery (PA), and (PA) branches, angiography has long been considered the "gold standard." Of the noninvasive techniques, spinecho MRI and transthoracic echocardiography are equivalent for assessment of RV outflow and main PA in most patients, provided the acoustic window is adequate for echocardiography [12]. The sensitivity and specificity of these techniques are adequate for clinical purposes if compared with angiography [38, 87]. For identification of abnormalities of the left and right pulmonary artery, spin-echo MRI is clearly better than transthoracic echocardiography [12, 52, 91] (Fig. 1A). However, with noncontrast spin-echo MRI (2- and 3-dimensional), visualization of the peripheral pulmonary arteries is problematic, as is evaluation of the number and distribution of collateral vessels [28, 89, 90, 91]. Gradient-echo cine MR provides high contrast between lumens of blood vessels and adjacent tissues, rendering it an attractive technique for assessment of PA and aortopulmonary collateral vessel size and anatomy [91]. Contrast enhanced 3-D MR angiography is a relatively new technique that has allowed adequate visualization of thoracic large vessels [35, 42, 86]. The technique has successfully been applied in patients with congenital heart disease [42], but detailed evaluation in patients with TOF has not been performed (Fig. 1B).

Gradient-echo MRI allows the identification of a residual or recurrent VSD. Turbulent flow caused by the shunt through the VSD will result in proton dephasing within the jet. This will result in a local loss of signal intensity, observed as a signal void on gradient-echo images (Fig. 2). However, systematic evaluation of the use of MRI in the detection of residual VSDs has, to our knowledge, not been performed.

Many of the limitations of transthoracic echocardiography may be overcome by transesophageal echocardiography (TEE). In comparison to TEE, MRI provides better information on large vessel anatomy, including pulmonary artery branches [30]. For intracardiac anatomy and atrioventricular (AV) valve function TEE is probably better suited [30]. This allows a choice of imaging technique, tailored to the clinical problem.

Postoperative Functional Evaluation

Pulmonary Regurgitation

The current surgical policy in TOF, aimed at early complete surgical correction, results in considerable transannular patch rates, which induces residual pulmonary regurgitation [39]. Residual pulmonary regurgitation has been associated with RV dilatation, impaired biventricular function, limited exercise tolerance, and increased risk for ventricular arrhythmias [3, 70, 74, 77]. Therefore, assessment of the amount of pulmonary regurgitation is of direct clinical importance. Until recently, no practical, clinically useful technique for quantification of

Fig. 2. Gradient-echo MR image (transverse plane) at ventricular level of patient after Fallot repair. Note the VSD patch (*black arrowhead*). Signal void (*white arrowhead*) indicates turbulent flow into the RV caused by shunt flow through a residual VSD.

pulmonary regurgitation was available despite attempts using many different methods, including Doppler echocardiography, contrast ventriculography, and videodensitometry [40, 49, 74].

Velocity mapping MR is an accurate technique to assess velocity and volume of flow [13, 51, 84]. MR velocity mapping allows noninvasive, accurate quantification of valvular regurgitation, including pulmonary regurgitation in TOF [70, 72]. Rebergen et al. [70] studied 18 patients after repair of TOF. Age at repair of these patients was 3.9 ± 2.4 years, and age at the MR study was 16.5 ± 6.5 years. A transannular patch was used at repair in 8 patients [70]. MR velocity mapping was performed in a double-oblique plane, perpendicular to the main PA just below the bifurcation. The cardiac cycle was sampled with a time frame of 30 msec; resulting in 16 to 28 time frames, depending on heart rate. Instantaneous flow volumes in the PA were calculated by multiplying PA contour area (traced manually) with the spatial average flow within this contour [70]. Total forward and regurgitant flow per heart cycle were calculated by summation of instantaneous flow volumes (Fig. 3). Pulmonary forward flow showed good correlation with RV stroke volume as derived from multisection, multiphase gradient-echo MRI in patients without tricuspid regurgitation. The agreement between velocity mapping measurements of pulmonary regurgitant volume and the difference between right versus left ventricular stroke volume as obtained with multisection cine MRI was excellent [70]. Pulmonary regurgitant volume index ranged from 0.21 to 4.23 L/min/m² (mean 1.47 ± 1.17) L/min/m²; 30 \pm 18% of RV stroke volume). Significant differences in the amount of pulmonary regurgitation could be observed between patients with and those without a transannular patch [70]. This study clearly demonstrated the feasibility of assessment of quantification of pulmonary regurgitation in TOF and has provided the basis for several other clinical studies in TOF patients [9, 25, 60]. Earlier studies, in which the amount of pulmonary regurgitation could not be quantified in a practical way, suggested a negative influence of the amount of pulmonary regurgitation on exercise performance [8, 49, 74, 76, 94]. In a study of 19 children (age 12 ± 3 years) we confirmed with MRI that the actual amount of pulmonary regurgitation correlates directly with exercise performance [59]. Singh et al. [85] had similar observations in a recent MRI study.

The main disadvantage of MRI measurements of pulmonary regurgitation is that beat to beat information cannot be obtained with current MRI techniques [9]. This has hampered evaluation of respiratory influences on the amount of pulmonary regurgitation [9].

Pulmonary Stenosis

Right ventricular outflow and PA stenosis are among the most common hemodynamic problems after repair of TOF [9, 57, 63]. Adequate evaluation of these problems requires proper identification of the location and extent of the stenosis. As previously discussed, MRI is an adequate technique to study the morphology of the RV outflow and pulmonary arteries. MR velocity mapping enables measurement of velocities across a stenotic area. Using the modified Bernoulli equation the stenotic gradient can be calculated. This technique does not differ from Doppler echocardiography in its practical applications. The main advantage of MR velocity mapping compared to Doppler echocardiography is the unlimited choice of imaging planes with MRI. This allows for alignment with the velocity jet in any direction, which is often difficult with Doppler echocardiography, particularly in branch pulmonary stenosis. Separate assessment of left and right PA flow has been performed with MR velocity mapping in healthy volunteers and patients after a Fontan operation [7, 71]. This technique could be used to assess lung perfusion in TOF patients with branch pulmonary stenosis, possibly predicting the need for relief of local stenoses with a stent or surgical procedure. To our knowledge, MR has not been used for this purpose in patients with TOF.

Function of the Right and Left Ventricle

The importance of RV function as a determinant of outcome after repair of TOF has been underlined by many studies [21, 33, 39, 74, 94]. The combined effects of preoperative hypertrophy and hypoxemia, operative factors, and residual postoperative problems as pulmonary regurgitation and/or stenosis may result in impaired RV

Fig. 3. (A) Double oblique magnitude image obtained with the flow-adjusted gradient across the main pulmonary artery (*PA*) in early systole. *AO*, aorta. **(B)** Velocity map corresponding to Fig. 3A. Bright signal indicates (systolic) flow out of the right ventricle. Spatial peak and spatial average velocities are obtained from the brightest and average signal intensities across the pulmonary artery lumen, which is manually outlined. *PA,* pulmonary artery. **(C)** Velocity map of the same patient as in Figs. 3A and 3B. Dark signal indicates (diastolic) flow back into the right ventricle. Spatial peak and spatial average velocities are obtained from the darkest and average signal intensities across the pulmonary artery lumen, which is manually outlined (*PA*). Note mid-gray signal intensity in ascending aorta, indicating stationary or zero flow velocity in this diastolic time frame. **(D)** Time–volume flow velocity curve of pulmonary artery. Flow velocity–time frame was calculated by multiplying pulmonary artery contour area (Figs. 3B and 3C; traced manually) with the spatial average flow within this contour. Negative values indicate flow out of the right ventricle. Note diastolic backward flow during most of diastole, indicating pulmonary regurgitation, and late diastolic forward flow at end diastole.

function [3, 32, 37, 47, 67, 74, 75, 93, 95]. Serial noninvasive assessment of RV function is therefore required during follow-up of these patients. In patients with adequate acoustic windows, qualitative or simple quantitative transthoracic 2-D echocardiographic methods to assess RV size and ejection fraction may be used to select those patients in whom further evaluation is required [24]. As a result of problems in obtaining maximal RV dimensions, difficulties in obtaining standardized views, and intrinsic inadequacies in geometrical assumptions of the complex RV shape, transthoracic echocardiography has limited value for accurate assessment of RV size and ejection fraction [24, 34, 41, 43, 61, 66, 83], particularly in the operated older child, adolescent, and adult. Threedimensional echocardiography is a promising technique for measurement of RV size, but it has not been used for clinical studies in TOF [68, 92]. Multisection cine MRI

provides dimensionally accurate RV volume measurements [4, 26, 45, 62], even with abnormal RV shape. This is particularly important in the follow-up of patients with abnormal RV loading conditions.

The advantages of MRI compared to other noninvasive imaging techniques are less clear for the left ventricle (LV). However, the shape of the LV is altered in RV volume overload states, as with pulmonary regurgitation after TOF repair [78]. In these situations, calculations that rely on the assumption of a normal LV shape may not be accurate. LV volumes may be assessed without assumptions of ventricular geometry with MRI. MRI also allows detailed analysis of changes in LV wall thickness during the cardiac cycle [6].

Potential limitations of the technique include the time-consuming nature of analysis of a multisection, multiphase data set. The coarse trabeculation of the RV

Particularly for RV measurements, consensus with regard to the most optimal image plane is lacking. Both transverse views as well as images aligned with the LV short axis may be used [44, 54, 81]. In our experience, transverse sections improve speed of setup of the study. In this orientation, partial volume effects may cause difficulties in contour detection, particularly at the diaphragmatic level. However, it appears that ventricular volume measurements are less influenced by partial volume effects at the diaphragmatic level than by difficulties in AV valve border detection, which often occur in short-axis images [11]. Partial volume effects occur regardless of the image orientation, and accuracy of ventricular volume measurements has been shown not to be influenced by imaging plane strategy [11]. Therefore, for studies primarily aimed at the RV we tend to use transverse sections.

The importance of LV function in patients who have undergone repair of TOF has become increasingly clear [2, 3, 37, 75, 93]. For studies aimed at biventricular function or the interaction between RV and LV, images aligned with the LV short axis are probably best suited (Fig. 4). The number of studies on ventricular function in TOF in which MRI was used is limited [25, 59, 60, 85]. MRI was used to assess the influence of pulmonary regurgitation on RV size and function in a group of 18 patients aged 16.5 ± 6.5 years (range 8.6 to 30.2) previously discussed [70]. MR-derived RV end diastolic volume index was 138 ± 38 ml/m² in those patients with a transannular patch ($n = 8$) and 90 \pm 18 ml/m² in those without a transannular patch $(n = 10)$ $(p < 0.005)$ [70]. RV ejection fraction was generally normal in this group of 18 patients (59 \pm 8%, range 34–67%), who had a pulmonary regurgitant fraction (regurgitant pulmonary flow volume/forward pulmonary flow volume) of $30 \pm$ 18% [70]. A significant correlation could be established between the amount of pulmonary regurgitation and RV ejection fraction ($r = -0.59$), RV end diastolic volume $(r = 0.72)$, and RV end systolic volume $(r = 0.74)$ [70]. In a younger group of 19 TOF patients $(12 \pm 3 \text{ years})$, with larger amounts of pulmonary regurgitation (39 \pm 16%), we found RV ejection fraction (54 \pm 8%) to be significantly lower than that of an age- and sex-matched control group (66 \pm 7%, $p < 0.01$) [59]. This finding confirmed the correlation between the actual amount of pulmonary regurgitation and RV ejection fraction.

With regard to LV function, some studies in patients with residual pulmonary regurgitation after repair of TOF have indicated impaired LV function, whereas others have reported normal LV function in similar patient groups [2, 3, 37, 47, 67, 75]. This discrepancy has not

Fig. 4. Gradient-echo image of the heart of a patient operated for tetralogy of Fallot, at midventricular level at end diastole (*top*) and end systole (*bottom*). The endocardial and epicardial borders of the LV and RV are outlined. Ventricular volumes and wall mass are calculated by summation of ventricular cavity and wall areas outlined on a multisection, multiphase image set of a specific time frame multiplied by section thickness (and a specific gravity of 1.05 g/ml for wall mass). Note hypertrophy of RV wall. *, left ventricle

been fully explained. A possible explanation may be that the patient groups under study differed with regard to the amount of pulmonary regurgitation. This could not be assessed without MRI [95]. In two groups of patients in whom pulmonary regurgitation had been quantified with MRI, we noted significant differences in LV function. In a group of children with $39 \pm 16\%$ pulmonary regurgitation, LV ejection fraction was $52 \pm 10\%$ compared with 68 \pm 7% in controls (p < 0.001) [59]. In adults with 25 \pm 18% pulmonary regurgitation, LV ejection fraction did not differ from normal controls [60]. From these observations, it is suggested that LV function may be preserved with mild pulmonary regurgitation, but it will deteriorate with larger amounts of regurgitation. MRI is an excellent tool for further studies in this field since it is particularly suited for longitudinal studies of patient

groups. Currently, MRI has to our knowledge not been used for this purpose.

Right Ventricular Diastolic Function

In recent years, diastolic function of the RV has been recognized as an additional important factor in the longterm outcome of TOF [19, 25, 56, 64, 65, 85]. In adults, restriction of RV filling was associated with superior exercise performance [19]. Restrictive RV physiology has also been related to decreased QRS duration, indicating a decreased change of malignant ventricular arrhythmias [20]. An inverse relationship between age at repair and restrictive RV physiology has been documented [56]. Available data are inconclusive on the role of transannular patching in the development of restrictive RV physiology [56, 65]. From the studies on restrictive RV physiology, it may be hypothesized that a myocardial restrictive process, induced by factors related to age at repair, may limit the amount of pulmonary regurgitation and RV dilatation [19, 25]. The inability to quantify the amount of pulmonary regurgitation and RV size has been a major limitation of all echocardiographic studies on RV diastolic function [19, 56, 64, 65]. Other limitations of echocardiography in this setting are that it does not provide reliable measurements of RV wall mass and that diastolic RV function cannot be quantified with echo-Doppler techniques in the presence of inflow from two sources, as occurs with pulmonary regurgitation. These limitations of echocardiography have prevented adequate comparison of the studies on RV diastolic function in TOF [19, 25, 56, 64, 65, 85]. The opportunities to study RV diastolic function with MRI include quantification of tricuspid flow patterns with velocity mapping techniques and reconstruction of RV time–volume curves from tomographic (either spin-echo or gradient-echo) multislice cine MRI [55, 88]. By plotting RV volume of the various time phases of diastole against time, a RV time volume curve may be obtained. From this curve the usual indices of diastolic function may be derived [85, 88]. This is a very time-consuming process. Furthermore, with conventional MR gating techniques, information on the last part of diastole is not provided.

We have reconstructed RV time–volume flow curves that include the last part of diastole by combining tricuspid (Fig. 5) and pulmonary flow (see Fig. 3) volume curves, obtained with velocity mapping MRI with retrograde ECG gating [25] (Figs. 3 and 5). Time– volume curves were obtained by integration of the time– volume change curves (Fig. 6). From these curves indexes of diastolic function were derived (Fig. 6).

This method provides adequate temporal resolution (30 time frames/cardiac cycle) and requires drawing of less complicated contours (which may be performed semiautomatically). This technique may be associated with less inter- and intraobserver variability than tomographic cine MR techniques. Combined with a singlephase, multisection volume measurement, this technique provides most clinically important data on RV function in these patient groups, including RV mass. In a study of 19 children operated for TOF [age (mean \pm SD) 12 \pm 3 years, operated at 1.5 ± 1 years] and 12 healthy children, we found late diastolic forward pulmonary artery flow to be absent in 6 patients (group I) [25]. In 13 patients (group II) late diastolic forward pulmonary artery flow contributed 1% to 14% to RV stroke volume [25]. Significant differences with controls in group I were increased deceleration time $(315 \pm 91$ msec vs 168 ± 28 msec, $p < 0.001$) and decreased filling fraction (44 \pm 11% vs 55 ± 16 %, $p = 0.02$) [25]. These data indicate impaired RV relaxation. Significant differences between group II and controls for RV parameters were increased peak early filling rate (378 ± 124 vs 286 ± 112 ml/sec, *p* $= 0.018$) and increased deceleration time (230 \pm 40 msec, $p = 0.03$), which is less marked than in group I), indicating restriction to RV filling [25]. Pulmonary regurgitation, ventricular size, RV wall mass, and ejection fraction did not differ significantly between groups I and II [25]. Exercise function was diminished with restrictive RV physiology (group II; $p < 0.001$ vs controls) [25]. From this study it was concluded that both impaired relaxation and restriction to filling affect diastolic RV function in children with operated TOF and pulmonary regurgitation [25]. Contrary to the findings in adults [19], restrictive RV physiology was associated with decreased exercise function in these children [25]. The relation between abnormal RV diastolic function and decreased exercise performance in children operated for TOF has recently been confirmed in another MRI study [85]. Prospective MRI studies in properly matched groups of TOF patients should allow clarification of some of the discrepancies in the results of various studies on RV diastolic function in TOF.

Ventricular Mass

Left ventricular mass can be assessed accurately with echocardiography. For measurements of RV mass, echocardiography, angiography, and radionuclide techniques have various limitations [46]. Biventricular mass can be assessed in a reproducible and accurate way with MRI [46, 69, 79] (Fig. 4). Lorenz et al. [46] reported results of biventricular wall mass in 75 healthy subjects, age 8 to 55 years. The normal range for RV free wall mass in their study was 26 ± 5 g/m², for LV free wall mass $57 \pm$ 8 g/m², and for the interventricular septum 30 \pm 4 g/m².

In TOF intrinsic abnormalities of overall myoarchitecture are present [80]. Several studies have shown that myocardial hypertrophy and fibrosis may persist after surgical repair [53, 79, 82]. Ventricular hypertrophy has

time (ms) В **Fig. 5. (A)** Velocity map of double-oblique image obtained with the flow-adjusted gradient across the tricuspid valve (*T*) and mitral valve (*M*) of a patient operated for tetralogy of Fallot. Dark signal indicates (early diastolic) flow into the ventricle. Spatial peak and spatial average velocities are obtained from the darkest and average signal intensities across the tricuspid valve orifice, which is manually outlined. Note aliasing in pulmonary artery (*) as a result of high flow velocity with residual pulmonary stenosis. **(B)** Time–volume flow velocity curve of tricuspid valve. Flow velocity–time frame was calculated by multiplying tricuspid orifice area (Fig. 5A; traced manually) with the spatial average flow within this contour.

tricuspid flow (ml/s)

300

200

100

 -100

 -200

 -300

 θ

 θ

been associated with the risk of sudden death after repair of TOF [5]. These observations indicate the need for assessment of ventricular mass in the follow-up of operated TOF. As has been discussed, we have used MRI to assess RV mass in children with tetralogy and healthy age- and sex-matched controls [25]. In children operated for TOF, RV wall mass was significantly higher (26 ± 7) $g/m²$) than that of healthy children (17 \pm 2 g/m²). These findings could not directly be related to the measurements of ventricular function [25]. Again, MRI is the technique of choice with regard to follow-up studies, which will help to further understand the importance of increased RV mass in these patient groups.

300

200

Motion Tracking Techniques

150

300

450

600

750

Assessment of 3-D myocardial motion is another application of MRI techniques [50]. Available techniques are MR tagging and velocity-encoding techniques. By inducing magnetization changes in localized tissue areas, MR imaging allows superimposition of tagging grids on conventional MR images. The tagging grid then serves as a reference point in the myocardium, enabling tracking of these reference points during contraction [50]. Velocityencoding methods using phase encoding of the velocity of transverse magnetization to quantify the dynamics of the tissue [50]. These techniques allow analysis of re-

PAFR

PFR

20

10

Fig. 6. Right ventricular time–volume change curve (*A*) and right ventricular time–volume curve (*B*) of a Fallot patient. Negative values indicate flow out of the right ventricle (*A*) or decrease in right ventricular volume (*B*). The curve in A was obtained by summation of curves in Figs. 3B and 5B and the curve in B by integration of the curve in A. *AFF,* atrial filling fraction; *dt,* deceleration time; *FF,* filling fraction in first one third of diastole; *PFR,* peak filling rate; *PAFR,* atrial filling fraction; *RV,* right ventricle.

gional strain and wall motion. Currently, MRI tagging techniques have been applied in only a limited number of studies in patients with congenital heart disease, not including TOF [16–18]. These techniques will certainly help increase knowledge of ventricular dynamics in patients with abnormal loading conditions [58].

Conclusions

In clinical practice, both anatomical and functional information may be obtained with MRI in patients who have undergone surgical repair of TOF. This is particularly true for patients in whom transthoracic echocardiography fails to provide the required information. With MRI, the pulmonary artery may be imaged with great detail, often preventing the need for (invasive) x-ray angiography. Quantification of biventricular systolic and diastolic function and wall mass probably allows identification of those patients requiring more detailed (invasive) hemodynamic measurements. In many patients operated for TOF, MRI will allow clinical problem solving in an entirely noninvasive way.

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