Abnormal left ventricular flow organization following repair of tetralogy of Fallot

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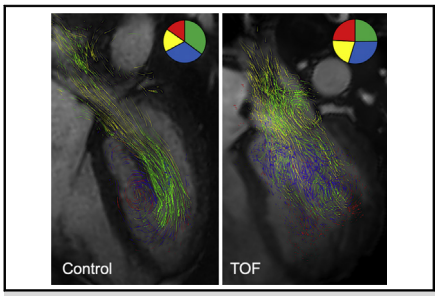
ABSTRACT

Background: Left ventricular intracavitary flow (LVICF) characteristics reflect diastolic function. Right ventricular (RV) volume overload due to pulmonary regurgitation (PR) adversely impacts interventricular interactions and left ventricular (LV) function. This aimed to determine whether patients with PR and mild to moderate RV dilation after repair of tetralogy of Fallot (TOF) repair have abnormal LVICF, and to determine whether RV dilation and biventricular function correlate with LVICF abnormalities.

Methods: Patients with repaired TOF with PR (n = 11) and controls (n = 11) underwent LVICF analysis. LV end-diastolic volume was partitioned into 4 flow components: direct flow, retained inflow, delayed ejection flow, and residual volume. Flow components were correlated with indexed biventricular size, function, and LV strain.

Results: The TOF patients had reduced direct flow (35% vs 25%; $P = .004$) and increased residual volume (15% vs 24%; $P = .026$) compared with controls. Retained inflow and delayed ejection flow did not differ. Reduced direct flow correlated with increased RV end-diastolic volume index ($R = 0.44$; $P = .042$), RV end-systolic volume index ($R = -0.46$; $P = .032$), reduced RV ejection fraction ($R = 0.45$; $P = .036$), and reduced LV circumferential strain ($R = 0.52$; $P = .014$). Increased residual volume correlated with increased RV end-systolic volume index ($R = 0.52$; $P = .013$), reduced LV ejection fraction ($R = -0.54$; $P = .010$), and reduced LV circumferential strain ($R = -0.44$; $P = .040$).

Conclusions: Patients with repaired TOF with mild to moderate RV dilation have abnormal LV diastolic direct flow and increased recirculating residual volume. These changes correlate with the degree of RV dilation and impaired LV function. (J Thorac Cardiovasc Surg 2020;160:1008-15)



Differences in left ventricular filling hemodynamics between a patient with tetralogy of Fallot and a control subject.

CENTRAL MESSAGE

Patients with repaired tetralogy of Fallot with mild-to-moderate right ventricular (RV) dilation and significant pulmonary regurgitation have abnormal left ventricular (LV) inflow filling correlated with the degree of RV dilation and impaired LV function.

PERSPECTIVE

Patients with tetralogy of Fallot and pulmonary regurgitation with mild to moderate right ventricular (RV) dilation have abnormal left ventricular (LV) intracavitary flow that is associated with impaired LV mechanics and the degree of RV dilation. Monitoring of LV flow hemodynamics may augment long-term clinical management of these patients and guide decision making regarding pulmonary valve replacement.

See Commentaries on pages 1016, 1017, and 1019.

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Abbreviations and Acronyms

4D-flow MRI = four-dimensional flow magnetic resonance imaging
bSSFP = balanced steady-state free precession
LV = left ventricular
LVICF = left ventricular intracavitary flow
PR = pulmonary regurgitation
PVR = pulmonary valve replacement
RV = right ventricular
TOF = tetralogy of Fallot

Repair of tetralogy of Fallot (TOF) commonly requires disruption of the pulmonary valve annulus, resulting in significant pulmonary regurgitation (PR). The accompanying chronic volume overload leads to right ventricular (RV) dilation, structural myocardial changes, electrophysiological abnormalities, and mechanical dysfunction.[1,2] If unaddressed, these changes adversely impact both RV and left ventricular (LV) function and long-term outcomes.[3-6]

Numerous studies have described biventricular systolic and diastolic dysfunction in patients with TOF.[4,7,8] The optimal timing of pulmonary valve replacement (PVR) remains controversial and is typically guided by patient symptoms or by volumetric and functional biventricular hemodynamic parameters in asymptomatic patients.[1,9,10] In general, these parameters are intended to trigger PVR in time to permit normalization of RV volume and preserve RV function. Although pulmonary valve replacement (PVR) mitigates RV volume overload, eliminates PR, and reduces RV volume, biventricular function remains impaired.[9,11,12] Previous investigations using 3-dimensional blood flow imaging in patients with repaired TOF identified significant reductions in systolic kinetic energy and altered distribution of hemodynamic forces inside the left ventricle that do not normalize after PVR.[13,14] Several investigators have attempted to determine whether LV mechanical indices can serve as prognostic indicators of biventricular function and overall clinical outcomes following repair of TOF.[4,7]

LV myocardial deformation indices are predictive of sudden cardiac death and life-threatening arrhythmias in these patients.[2,10,15] However, sensitive markers that can be used to inform the timing of PVR and avoid irreversible biventricular dysfunction remain unidentified.

Recently, 4-dimensional flow magnetic resonance imaging (4D-flow MRI) techniques have emerged that permit accurate assessment of LV intracavitary blood flow. Eriksson and colleagues[16,17] used 4D-flow MRI to characterize LV diastolic filling. These investigators determined that LV end-diastolic blood volume can be partitioned into 4 unique components based on the location of blood at the beginning and end of a single cardiac cycle: (1) direct flow, blood that crosses the mitral valve to enter the left ventricle and is ejected during the same cardiac cycle; (2) retained inflow, blood that crosses the mitral valve to enter the left ventricle but does not leave the left ventricle during the same cardiac cycle; (3) delayed ejection flow, blood present inside the left ventricle as part of the end-systolic volume that exits the left ventricle during the subsequent systole; and (4) residual volume, blood that recirculates inside the left ventricle for at least 2 cardiac cycles. The sum of these 4 blood flow components represents LV end-diastolic volume, and each component can be defined as a percentage.

The clinical relevance of diastolic LV intracavitary flow (LVICF) lies in the detection of early ventricular remodeling.[18,19] Even minor regional or global structural myocardial remodeling compromises ventricular function and is reflected by changes in LVICF patterns. Flow imaging studies characterizing diastolic filling in patients with cardiomyopathy, ischemic heart disease, and chronic obstructive pulmonary disease demonstrate that presystolic blood flow organization is abnormal and that energy-preserving ventricular filling is compromised.[17,20,21] Therefore, both systolic and diastolic flow conditions are important for the complete characterization of LV dysfunction and are likely relevant to patients with congenital heart disease, including repaired TOF with PR. To date, diastolic LVICF has not been described in patients with congenital heart disease, including repaired TOF with PR. Perturbations in diastolic LVICF could prove useful in the long-term clinical management of these patients and help guide the optimal timing of PVR.

The purpose of this study was to compare diastolic LVICF patterns in patients with repaired TOF with PR and moderate or less RV dilation with those in normal healthy controls using 4D-flow MRI. We hypothesized that the TOF patients would have abnormal diastolic LVICF, that diastolic flow hemodynamics through the left ventricle would be associated with biventricular size and function, and that intracardiac flow-based indices would correlate with myocardial tissue deformation as analyzed by circumferential and longitudinal strain.

METHODS

As part of a larger retrospective study investigating patients with repaired TOF (median age, 22 years; range, 12-55 years), we identified patients with mild to moderate RV dilation (RV end-diastolic volume index <150 mL/m^2) and significant PR (>20%) who underwent comprehensive clinically indicated cardiac MRI for the evaluation of RV outflow tract pathology and received 4D-flow MRI evaluation with full ventricular coverage. Patients with incomplete LV coverage, residual ventricular septal defect, and aortic or mitral insufficiency were excluded. Eleven TOF patients were compared with 11 healthy controls of similar age

(median age, 28 years; range, 9-53 years) and size distribution. This study was approved by the Colorado Multiple Institutional Review Board as part of larger retrospective study investigating TOF flow hemodynamic changes with waived informed consent.

Cardiac Magnetic Resonance Protocol

All subjects underwent cardiac magnetic resonance evaluation using a previously described TOF follow-up protocol with a 3-T magnet system (Ingenia; Philips Medical Systems, Best, The Netherlands).[22] Standard 2D cine balanced steady-state free precession (bSSFP) long-axis, short-axis, and 4 chamber-axis images were obtained during end-expiratory breath-holding for volumetric and functional analysis. 4D-flow MRI was acquired in a sagittal plane covering the mid-thorax with retrospective electrocardiographic gating and a diaphragmatic navigator for assessing blood flow hemodynamics. Typical sequence parameters were as follows: echo time, 2.4 to 2.6 ms; repetition time, 4.2 to 5.0 ms; flip angle, 10°; temporal resolution, 38 to 48 ms; field of view, 250 × 320 or 200 × 250 mm^2, 14 to 18 cardiac phases; voxel size, 2.0 × 2.0 × 2.0 to 2.8 mm^3; velocity encoding, 150 cm/s; acquisition time, 10 to 15 minutes depending on respiratory gating efficiency. In addition to standard volumetric and functional analysis, LV global myocardial circumferential and longitudinal strains were analyzed as shown previously.[23] Peak systolic values were sampled from both circumferential and longitudinal strain curves.

Intracardiac Flow Analysis

The 4D-flow MRI visualization and analysis was performed using the Circle CVI42 platform (version 5.9.3; Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Blood flow organization analysis was performed using an approach developed by Eriksson and colleagues[16,24] using a pathline-based particle tracking algorithm within a previously defined anatomic region of interest, in this case represented by the LV cavity. The schematic of the 4D-flow postprocessing and particle tracking analysis is depicted in Figure 1. Step 1 consisted of careful segmentation of the LV cavity defined by time-resolved magnetic resonance angiography reconstructed from the 4D-flow MRI datasets. The LV cavity was basally delineated by the aortic and mitral valve annuli and apically by the endocardial extent of the LV. In addition, superimposed bSSFP images served as navigation aids for definition of the LV borders. Step 2 consisted of manual segmentation of the inflow and outflow boundaries defined by the mitral valve orifice and aortic valve annulus, respectively. Generated net inflow and outflow waveforms were compared with respect to the overall net flow for internal consistency. Step 3 required definition of the temporal boundary conditions dictating the initiation and termination of particle tracking

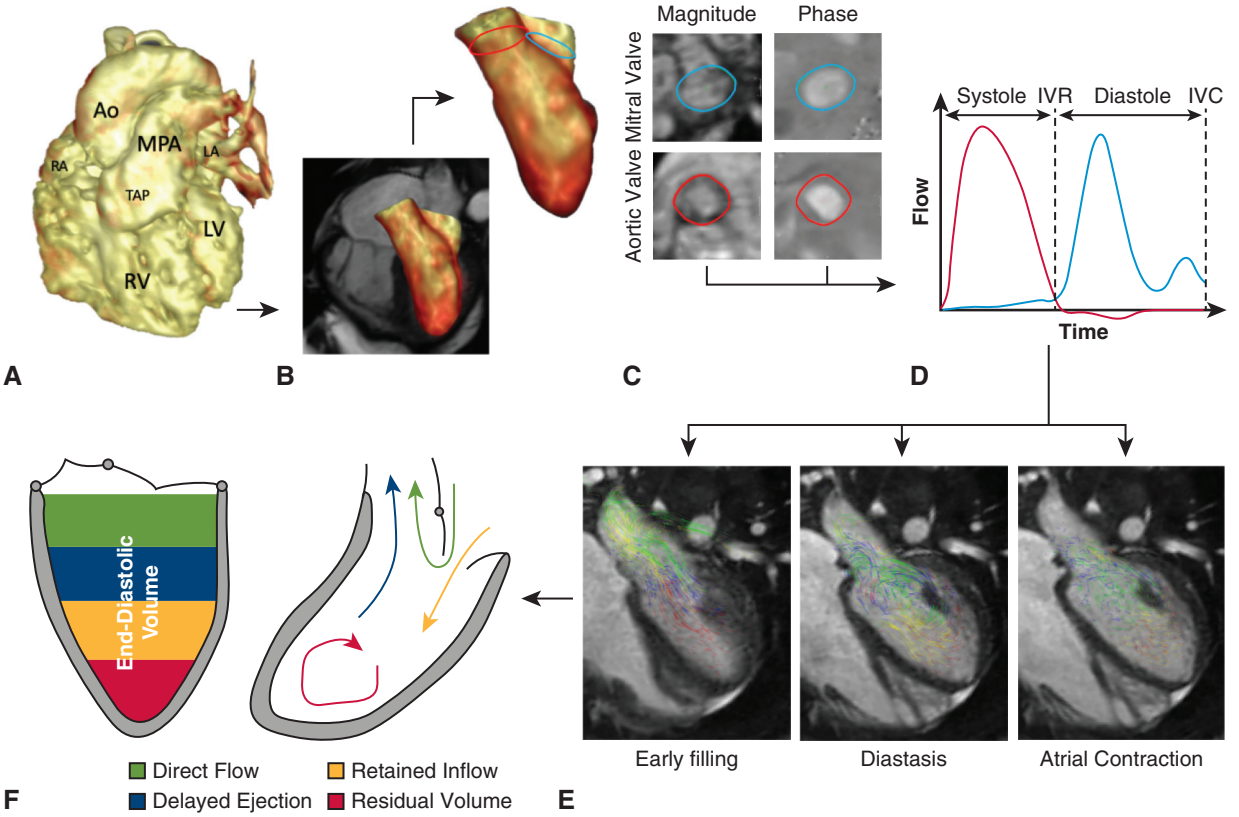

FIGURE 1. The postprocessing pipeline for the flow component analysis. A, Time-resolved magnetic resonance angiography reconstructed from the 4D-flow magnetic resonance imaging (MRI) datasets required for the manual (B) segmentation of the LV cavity. C and D, Segmentation of the inflow and outflow boundaries defined by mitral valve orifice and aortic valve annulus (C) with subsequent generation of inflow and outflow waveforms and the definition of the isovolumetric contraction (*IVC*) to the time of isovolumetric relaxation (*IVR*) (D). E, Resulting visualization of the particle tracking superimposed on the balanced steady-state free precession (bSSFP) image throughout diastole. F, The resulting combination of pathline trajectories and temporal-geometrical conditions recognizes the 4 blood flow components—direct flow, delayed ejection, retained inflow, and residual volume—and the summation of all blood flow components represents the end-diastolic volume. *AO*, Aorta; *MPA*, main pulmonary artery; *LA*, left atrium; *RA*, right atrium; *TAP*, transannular patch; *LV*, left ventricular; *RV*, right ventricular.

throughout the cardiac cycle. Particles are emitted and temporally tracked in the forward and backward direction from the time of isovolumetric contraction to the time of isovolumetric relaxation. The resulting combination of pathline trajectories and temporal-geometric conditions define 4 LV diastolic blood flow components based on the location of blood at the beginning and end of a single cardiac cycle, as previously described by Eriksson and colleagues: direct flow, retained inflow, delayed ejection flow, and residual volume. The sum of these blood flow components represents LV end-diastolic volume; therefore, each component is reported as a percentage of LV end-diastolic volume.[16,17]

Statistical Analysis

Analyses were performed in Prism version 7.0 or higher (GraphPad Software, La Jolla, Calif). Variables were checked for the distributional assumption of normality using normal plots, in addition to Kolmogorov–Smirnov and Shapiro–Wilk tests. Demographic and clinical characteristics between groups were compared using the Student *t* test for normally distributed continuous variables or Mann–Whitney rank-sum test for non-normally distributed variables and the χ^2 test or Fisher's exact test for categorical variables. The relationship between the blood inflow indices and standard hemodynamics was analyzed using Pearson's method.

RESULTS

Group demographics and MRI hemodynamics are summarized in Table 1. There were no significant between-group differences in age, sex, or body size distributions. All patients had undergone complete TOF repair with a transannular patch. At the time of MRI evaluation, no TOF patients or controls were receiving afterload-reducing medications. LV size and ejection fraction did not differ between the groups. As expected, the TOF group had a higher RV end-diastolic volume index (119 mL/m^2 vs 90 mL/m^2; $P = .007$), a higher RV end-systolic volume index (59 mL/m^2 vs 36 mL/m^2; $P < .001$), and a lower RV ejection fraction (51% vs 60%; $P = .002$). The TOF patients also had lower LV global longitudinal strain (15.1% vs 17.3%; $P = .046$) and LV global circumferential strain (17.2% vs 19.8%; $P = .027$).

Figure 2 depicts the end-diastolic LVICF partitioning analysis. Compared with controls, the TOF patients had reduced direct flow (25% vs 35%; $P = .004$) and increased residual volume (24% vs 15%; $P = .026$). Delayed ejection flow (30% vs 32%; $P = .759$) and retained inflow (21% vs 18%; $P = .302$) did not differ significantly between the groups. The particle tracking analyses of representative TOF and control subjects are compared in Figure 3.

To determine whether changes in diastolic LVICF components were associated with biventricular function and size, we performed a linear regression analysis of each specific flow component and each considered MRI hemodynamic marker. Direct flow inversely correlated to RV end-systolic volume index ($R = -0.46$, $P = .032$), RV stroke volume ($R = -0.57$; $P = .005$), and RV ejection fraction ($R = 0.45$; $P = .036$). In addition, direct flow directly correlated with LV global circumferential strain ($R = 0.52$; $P = .014$). Residual volume directly correlated with RV end-diastolic ($R = 0.44$; $P = .042$) and end-systolic ($R = 0.52$; $P = .013$) volume indices, and inversely correlated with LV ejection fraction ($R = -0.54$; $P = .010$). All significant correlations are depicted in Figure 4.

DISCUSSION

Disruption of pulmonary valve integrity is commonly required during the repair of TOF and leads to PR, RV volume overload and adverse RV remodeling. Consequently, the long-term follow-up and management of TOF patients is largely directed at surveillance of RV size and functional parameters. Adverse RV-mediated interventricular interactions in TOF negatively impact LV function

TABLE 1. Demographic and hemodynamic data

Parameter	TOF group (N = 11)	Control group (N = 11)	*P* value
Age, y, mean ± SD	25.7 ± 15.9	26.7 ± 17.3	.137
Female sex, n (%)	6 (55)	5 (45)	.669
BSA, m^2, mean ± SD	1.64 ± 0.30	1.40 ± 0.37	.143
LV EDVi, mL/m^2, mean ± SD	83 ± 11	80 ± 15	.753
LV ESVi, mL/m^2, mean ± SD	37 ± 7	33 ± 8	.379
LV SVi, mL/m^2, mean ± SD	46 ± 8	47 ± 9	.884
LV EF, %, mean ± SD	55 ± 6	60 ± 5	.104
LV CI, L/min/m^2, mean ± SD	4.0 ± 1.1	3.4 ± 0.6	.208
LV GLS, -%, mean ± SD	15.1 ± 2.1	17.3 ± 0.9	.046*
LV GCS, -%, mean ± SD	17.2 ± 1.9	19.8 ± 1.3	.027*
RV EDVi, mL/m^2, mean ± SD	119 ± 22	90 ± 17	.007*
RV ESVi, mL/m^2, mean ± SD	59 ± 13	36 ± 6	<.001*
RV EF, %, mean ± SD	51 ± 5	60 ± 5	.002*

TOF, Tetralogy of Fallot; *SD*, standard deviation; *BSA*, body surface area; *LV*, left ventricular; *EDVi*, end-diastolic volume index; *ESVi*, end-systolic volume index; *SVi*, stroke volume index; *EF*, ejection fraction, *CI*, cardiac index, *GLS*, global longitudinal strain; *GCS*, global circumferential strain; *RV*, right ventricular. *$P < .05$.

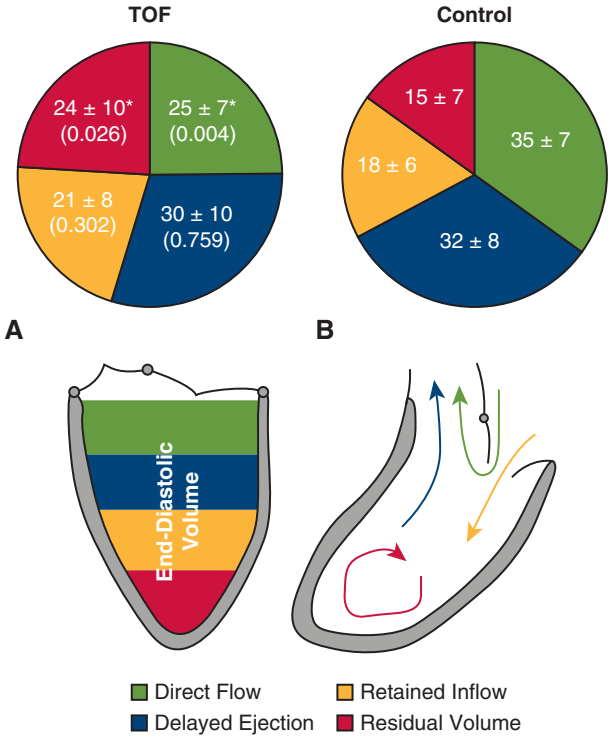

FIGURE 2. Proportions of different flow components in patients with tetralogy of Fallot (*TOF*) (A) and controls (B). The patients with TOF had decreased direct flow and increased residual volume (24% vs 15%). The proportions of patients with delayed ejection and retained inflow were similar in the TOF and control groups. *$P < .05$ compared with control.

and have been demonstrated by impaired systolic and diastolic LV tissue mechanics,[4,7,8] LV structural myocardial characteristics,[3] and even abnormal LV flow hemodynamics.[13,14] The treatment of pulmonary insufficiency requires PVR. Numerous studies have demonstrated that PVR effectively eliminates pulmonary insufficiency and reverses RV volume overload. Symptomatic patients typically improve; however, neither RV or LV function is improved by PVR.[9,11] Despite the increasing prevalence of PVR operations in patients with repaired TOF, data guiding the optimal timing for intervention are incomplete.[9,11] In this study, relatively young patients with repaired TOF with PR and only mild-to-moderate RV dilation had abnormal diastolic LVICF hemodynamics that have previously been associated with diastolic dysfunction.[21,25,26] The changes we observed in LVICF components correlated with standard MRI-derived ventricular size and functional indices, as well as with global measures of LV myocardial deformation. Given the relatively low risk of PVR in the current era, intervention to correct pulmonary insufficiency before irreversible LV functional impairment ensues seems reasonable, but reliable markers of early LV functional impairment are not widely available. Our results support the premise that early markers of irreversible ventricular dysfunction might exist in the intracardiac flow domain.[27,28]

Previous studies have demonstrated impaired intracardiac flow hemodynamics in both the RV and LV in patients with TOF.[13,14,29] Sjoberg and colleagues[14] calculated the kinetic energy of blood flow in the RV and LV and reported that peak systolic LV kinetic energy was decreased in patients with TOF, whereas LV diastolic inflow kinetic energy was normal. Importantly, in a smaller subset of patients who underwent PVR, systolic kinetic energy did not normalize. Similarly, Jeong and coworkers[29] reported similar reductions in LV systolic kinetic energy. Neither of these studies reported any associations between flow hemodynamic markers and standard clinical markers of LV size or function. In contrast, we observed that altered LVICF components correlated with reduced LV circumferential strain and LV ejection fraction. Unlike systolic kinetic energy, flow partitioning is more reflective of diastolic function. In a remarkable work, Eriksson and colleagues[17] showed that presystolic blood flow organization inside the LV can be partitioned into different flow components, and that the fate of these components during the subsequent systolic ejection is dependent on 3 factors: position within the ventricle, flow orientation with respect to the LV outflow tract, and diastolic momentum of the individual components. Presystolic momentum is a major determinant of the blood flow ejecting components direct flow and delayed ejection flow, which together make up the total forward LV stroke volume during a given cardiac cycle. Our results demonstrate that reduced direct flow in patients with repaired TOF and only mild to moderate RV dilation is accompanied by a commensurate increase in recirculating residual volume. Similar studies in patients with dilated cardiomyopathy and ischemic cardiomyopathy have reported similar findings, with reduced direct flow and increased residual volume components but normal delayed ejection flow and retained inflow.[16,20] The reduced diastolic LV direct flow component in patients with TOF is best explained by a loss of diastolic inflow momentum related to global LV myocardial dysfunction and tissue changes (ie, fibrosis), which have been previously described in patients with repaired TOF and significant pulmonary insufficiency.[3,8]

To summarize, a compliant and nondilated left ventricle appears to be critical for the generation of an optimal pressure gradient and intracavitary blood flow arrangement necessary for energetically efficient blood transfer, which can be well studied using 4D-flow MRI–derived hemodynamic derivatives.

Studies analyzing quantitative flow indices, such as kinetic energy and flow-derived pressure gradients, have demonstrated LV abnormalities in patients with TOF who fail to normalize after PVR.[13,14] These studies are consistent with other reports demonstrating a lack of

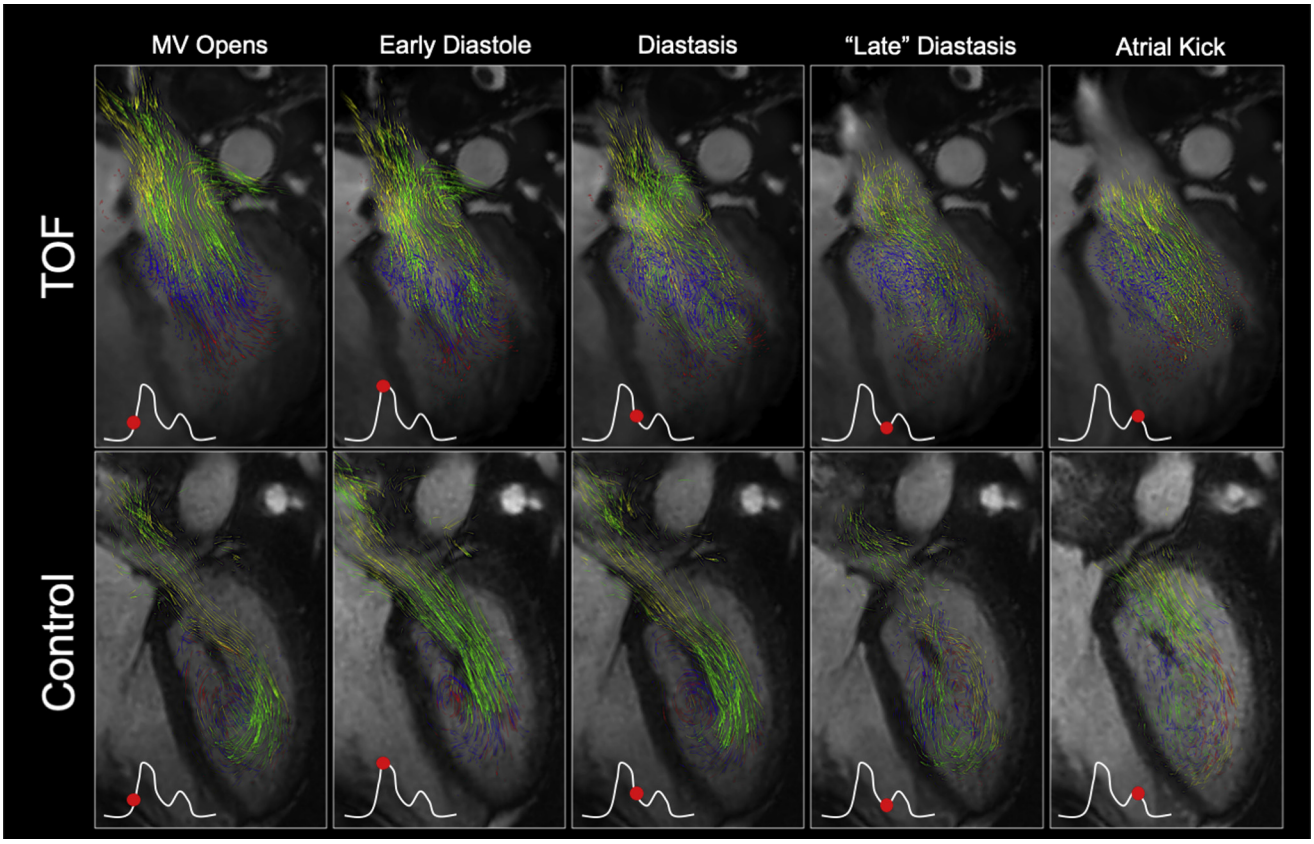

FIGURE 3. Left ventricular (LV) inflow comparison between a representative patient with tetralogy of Fallot (*TOF*) and a control subject. Direct flow (*green*) represented significantly larger proportion of the LV end-diastolic volume in control subjects (25%) compared with TOF patients (35%). In contrast, the proportion of residual volume (*red*) was increased in patients with TOF (24%) compared with controls (15%).

improvement in RV and LV ejection fraction following PVR.[9,11] In this study, we observed that TOF patients with PR and less significant RV dilation (<150 mL/m^2) already demonstrated abnormal distributions of LVICF components that directly correlate with reduced LV circumferential strain, a sensitive marker of LV function. LV functional parameters are well correlated with clinical outcomes in TOF and are predictive of sudden cardiac death and life-threatening arrhythmias.[10,15] The effect of PVR on diastolic LVICF components has not yet been determined. Our patient cohort did not meet the criteria that we currently favor for PVR (eg, RV end-diastolic volume index >150 mL/m^2) or those advocated by many authorities,[1,9,11] Because LV diastolic direct flow is decreased even in patients with mild RV dilation, with the magnitude of reduction correlated with the degree of RV dilation, this parameter could prove useful as an index to guide the timing of PVR. However, longitudinal mapping of the biventricular function and 4D-flow MRI–based analyses will need to be performed simultaneously before and after PVR to evaluate the sensitivity of intracardiac flow hemodynamics. Further prospective research is warranted to determine the effect of PVR on LV diastolic flow components and to determine whether a threshold value of direct flow at which PVR can be expected to improve or normalize LV diastolic function can be identified.

The primary limitations of this study are its retrospective nature and relatively small sample size. Full ventricular coverage for the 4D-flow MRI evaluation results in significant scanning time and presently limits intracardiac flow hemodynamic evaluation. Consequently, we included both pediatric and adult patients, which may have variably impacted the ventricular function. This type of flow component analysis has not been previously applied in patients with structural heart disease or in pediatric patients. Theoretically, the ejection fraction calculated by bSSFP should be equal to the sum of direct flow and delayed ejection flow. In this study, the discrepancy between the average ejection fraction derived by bSSFP and average sum of direct flow and delayed ejection was 0% in the TOF group and 7% in the healthy control group, comparable to previous studies.[16,20] Furthermore, this technique has been shown to have good test–retest repeatable results,[30] and we mitigated additional sources

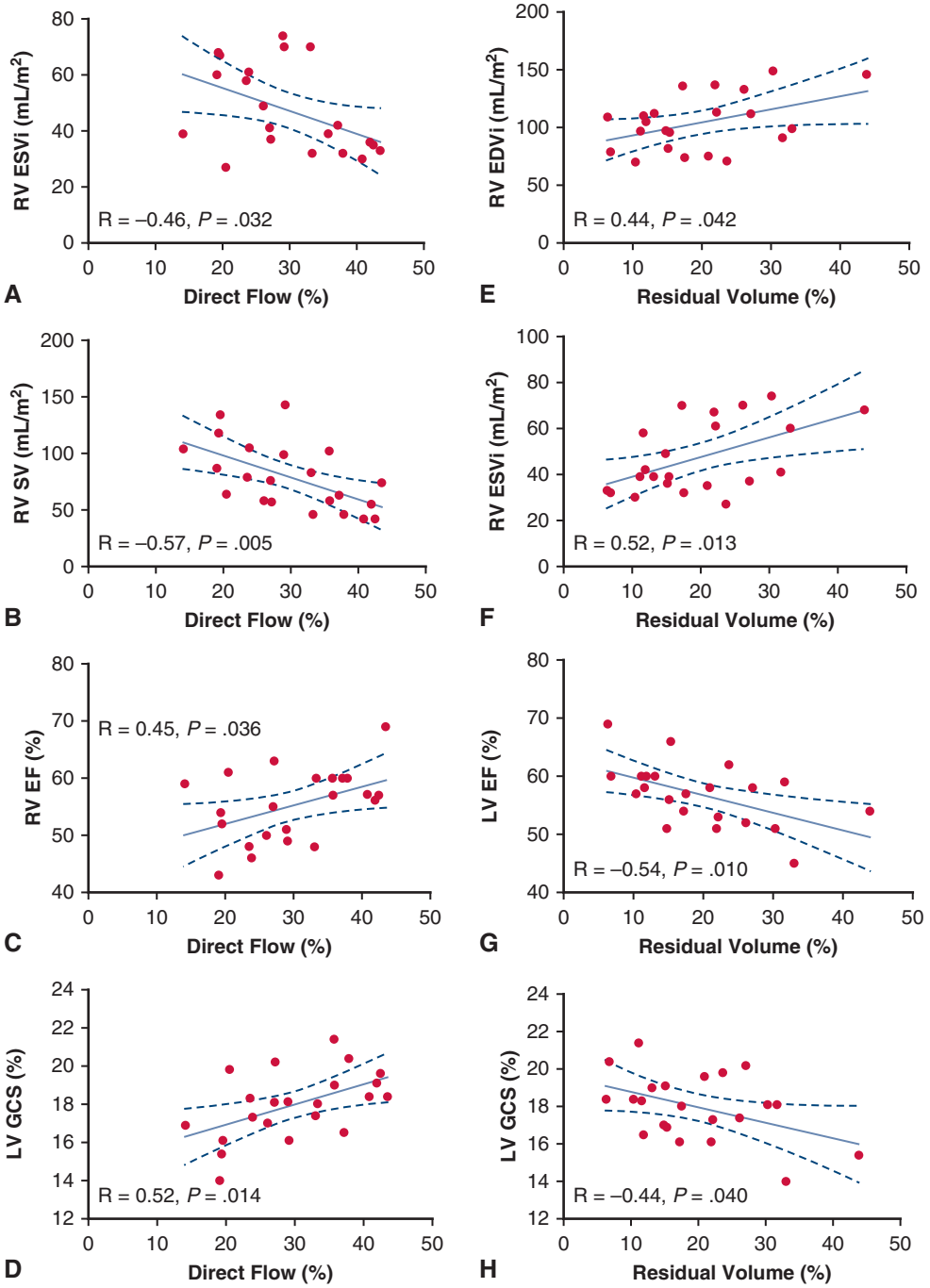

FIGURE 4. Summary of observed significant correlations between 4D-flow magnetic resonance imaging (MRI)-derived flow components and MRI hemodynamic markers of biventricular size and function. Direct flow inversely correlated with right ventricular (*RV*) end-systolic volume index (A), RV stroke volume (B), and RV ejection fraction (C). Direct flow directly correlated with left ventricular (*LV*) global circumferential strain (D). Residual volume directly correlated with RV end-diastolic (E) and end-systolic (F) volume indices. Residual volume negatively correlated with LV ejection fraction (G) and LV global circumferential strain (H). *ESVI*, End-systolic volume index; *SV*, stroke volume; *EF*, ejection fraction; *GCS*, global circumferential strain; *EDVI*, end-diastolic volume index.

of error associated with the analysis by applying a uniform 4D-flow MRI postprocessing algorithm. Our results match previously reported trends reporting alterations in LV flow components in other forms of heart disease.[20] Therefore, we believe that measurement error would be mostly associated with the 4D-flow MRI technique itself, which is notorious for its suboptimal spatiotemporal resolution. Unfortunately, we did not have patients with pre- and

post-PVR 4D-flow MRI data, which would permit determination of the impact of PRV on these parameters. Our future goal is to perform simultaneous LVICF and tissue deformation analyses to gain further insight into flow hemodynamics with respect to regional LV function. We also plan future studies focusing on patient-specific changes in biventricular flow hemodynamics and tissue mechanics following PVR. Finally, the ideal control group would comprise patients who underwent ventricular septal defect closure or similar corrective surgery, which would allow us to control for the potential effect of surgery on LV function.

In conclusion, patients with TOF and PR with mild-to-moderate RV dilation have abnormal diastolic LV intracavitary flow components characterized by a reduction in the direct flow component and an increase in recirculating residual volume. These changes in diastolic LV flow hemodynamics are associated with impaired LV mechanics and the degree of RV dilation. Monitoring of LV flow hemodynamics may augment long-term clinical management of these patients. Future studies assessing biventricular flow hemodynamics are needed to determine whether an abnormal flow component distribution can serve as an indicator for earlier PVR.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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