Effects of Right Ventricular Hemodynamic Burden on Intraventricular Flow in Tetralogy of Fallot: An Echocardiographic Contrast Particle Imaging Velocimetry Study

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Background: The purpose of this investigation was to test the hypothesis that flow patterns in the right ventricle are abnormal in patients with repaired tetralogy of Fallot (TOF). High-resolution echocardiographic contrast particle imaging velocimetry was used to investigate rotation intensity and kinetic energy dissipation of right ventricular (RV) flow in patients with TOF compared with normal controls.

Methods: Forty-one subjects (16 with repaired TOF and varying degrees of RV dilation and 25 normal controls) underwent prospective contrast imaging using the lipid-encapsulated microbubble (Definity) on Sequoia systems. A mechanical index of 0.4, three-beat high-frame rate (>60 Hz) captures, and harmonic frequencies were used. Rotation intensity and kinetic energy dissipation of flow in the right and left ventricles were studied (Hyperflow). Ventricular volumes and ejection fractions in all subjects were derived from same-day cardiac magnetic resonance (CMR).

Results: Measurable planar maps were obtained for the left ventricle in 14 patients and the right ventricle in 10 patients among those with TOF and for the left ventricle in 23 controls and the right ventricle in 21 controls. Compared with controls, the TOF group had higher RV indexed end-diastolic volumes (117.8 ± 25.5 vs 88 ± 15.4 mL/m², P < .001) and lower RV ejection fractions (44.6 ± 3.6% vs 51.8 ± 3.6%, P < .001). Steady-streaming (heartbeat-averaged) flow rotation intensities were higher in patients with TOF for the left ventricle (0.4 ± 0.13 vs 0.29 ± 0.08, P = .012) and the right ventricle (0.53 ± 0.15 vs 0.26 ± 0.12, P < .001), whereas kinetic energy dissipation in TOF ventricles was lower (for the left ventricle, 0.51 ± 0.29 vs 1.52 ± 0.69, P < .001; for the right ventricle, 0.4 ± 0.24 vs 1.65 ± 0.91, P < .001).

Conclusions: It is feasible to characterize RV and left ventricular flow parameters and planar maps in adolescents and adults with repaired TOF using echocardiographic contrast particle imaging velocimetry. Intraventricular flow patterns in the abnormal and/or enlarged right ventricle in patients with TOF differ from those in normal young adults. The rotation intensity and energy dissipation trends in this investigation suggest that they may be quantitative markers of RV and left ventricular compliance abnormalities in patients with repaired TOF. This hypothesis merits further investigation. (J Am Soc Echocardiogr 2014;27:1311-8.)

Keywords: Two-dimensional echocardiography, Congenital heart surgery, Tetralogy of Fallot, Cardiac blood flow

Echocardiographic particle imaging velocimetry (PIV) is an ultrasound technique for the quantification of multidirectional blood flow within cardiac chambers by the application of speckle-tracking to contrast-enhanced two-dimensional echocardiographic images.1 Left ventricular (LV) and left atrial flows have been previously characterized using this technique.1-9 In the LV, vortical flow structures form below the mitral valve leaflets in early diastole and support redirection of blood from the LV inflow to the outflow. It has been shown in a number of investigations that intraventricular flow patterns in the left ventricle are altered with changes in the shape or contractility of the chamber.9,10,13 Flow in the right ventricle has not been previously characterized using echocardiographic PIV. Concepts developed from the left ventricle cannot be directly translated to
METHODS

Study Design
This was a single-center, prospective, clinical study. The institutional review board approved the study protocol. Inclusion criteria consisted of (1) repaired TOF, (2) age ≥ 13 years, (3) absence of any intracardiac shunt on previous imaging studies, and (4) sinus rhythm. Specific exclusion criteria were (1) greater than mild tricuspid valve regurgitation, (2) greater than mild pulmonary valve regurgitation, (3) contraindications to ultrasound contrast, and (4) lack of consent to participate in the study protocol. Young adult controls were recruited in response to an advertisement inviting participation, which was approved by the institutional review board and placed in the institutional employee newsletter. Informed, written consent was obtained from all patients or legal guardians, as well as the recruited controls.

Echocardiography
All examinations were performed using a Sequoia 512 system (Siemens Medical Solutions USA Inc, Mountain View, CA), equipped with low–mechanical index real-time pulse sequence schemes (1.7 MHz; contrast pulse sequencing). Before the administration of ultrasound contrast, all patients underwent complete diagnostic imaging, including spectral and color Doppler evaluation of the ventricular inflow, outflow, and valves according to the standard institutional practice for CHD evaluation. For echocardiographic PIV, the lipid-encapsulated microbubble Definity (Lantheus Medical Imaging, North Billerica, MA) was infused as a 3% dilution (4–6 mL/min). A mechanical index of 0.4 and settings to achieve the highest possible frame rate (consistently >60 Hz) were used. Two to three three-beat captures of two-dimensional images were obtained for the right ventricle (apical four-chamber view), and separate captures were obtained for the left ventricle (apical four-chamber view). The contrast images were exported to a dedicated echocardiographic PIV software program (Hyperflow; AMID srl, Sulmona, Italy) for analysis, as described previously. Figures 1 and 2 demonstrate echocardiographic PIV tracking and steady-streaming (heartbeat-averaged) color maps of flow fields in normal controls and in patients with TOF for the left and right ventricles, respectively. The software evaluated blood velocities and, from these, generated parameters of kinetic energy dissipation and vortex properties in the flow field. The kinetic energy dissipation is a measure of the amount of energy loss by friction within the right and left ventricles; it increases when the flow is more irregular (turbulent) and mechanical performance is reduced. The lower the energy dissipation in blood flow through the ventricular chamber, the higher the ventricular efficiency. The kinetic energy dissipation can be computed from the appropriate combination of spatial variation of the velocity vector field. It is normalized with the average amount of kinetic energy in the heartbeat to be a dimensionless parameter not directly influenced by chamber size, and it characterizes the amount of kinetic energy dissipated with respect to that available. The vortex is automatically delineated in the steady-streaming (heartbeat-averaged) field, including the rotation from inlet to outlet, and its area, as a percentage of chamber area, is evaluated. The flow rotation intensity is the amount of swirl calculated inside this vortex (its circulation) normalized with the total swirl in the whole chamber. The diastolic rotation is the unnormalized circulation (summing up the clockwise and counterclockwise values) in the whole chamber in the diastolic period. These rotation properties characterize the circulatory component of intraventricular flow.

Cardiac Magnetic Resonance (CMR)
Quantitative RV volumes were obtained from CMR performed within 2 hours of the echocardiographic PIV study. Contiguous echocardiographic PIV and CMR examinations were performed in controls in the same manner as in patients with TOF. A 1.5-T scanner (Intera R version 12.6.1.3; Philips Medical Imaging, Best, The Netherlands) with a five-channel cardiac coil (Philips Medical Imaging) was used. Cardiac synchronization was performed with vector electrocardiography. Ventricular dimensions and function were assessed using steady-state free precession cine (repetition time, 2.8–3.2 msec; echo time, 1.4–1.6 msec; field of view, 380 × 380 mm; matrix size, 160 × 130 to 228 × 216) during brief periods of breath holding in the following planes: ventricular two-chamber, four-chamber, LV and right ventricular (RV) outflow tract, and short axis with 12 to 14 equidistant slices (slice thickness, 6–8 mm; interstice spacing, 0–2 mm). Measurements of LV and RV end-diastolic and end-systolic volumes were obtained from short-axis cine stack by manual tracing of endocardial contours. A single observer (L.L.) performed all measurements using commercially available software packages (Medis Medical Imaging, Leiden, The Netherlands). Ventricular end-diastolic volumes and mass were adjusted to body surface area using the Haycock formula. Each normal control underwent quantitative CMR assessment from steady-state free precession cine images acquired at rest in the two-chamber, four-chamber, and short-axis planes as above.

Statistical Analysis
Data are presented as mean ± SD; categorical variables are reported as frequencies and percentages. A comparison of continuous variables was accomplished with linear regression analysis. Echocardiographic PIV data were compared between the TOF group and functional abnormalities are commonly seen. The adaptive responses of the right ventricle to long-term load stresses in this lesion are incompletely understood, so assessment of intraventricular flow fields may provide information about the circulatory performance of the right ventricle. The purpose of this investigation was to test the hypothesis that flow patterns in the right ventricle measured by echocardiographic PIV are abnormal in patients with repaired TOF. The specific aims were (1) to investigate intraventricular flow rotation intensity and energy dissipation in patients with TOF in comparison with normal controls using echocardiographic PIV and (2) to evaluate the differences and similarities in quantitative flow parameters between the right and left ventricles in patients with TOF.
and normal controls a two-tailed unpaired Student’s t test. To assess intraobserver and interobserver agreement, measurements of flow rotation intensity and energy dissipation in the left and right ventricles were repeated in 10 randomly chosen TOF studies by the primary observer and by a second blinded observer. Bland-Altman plots were derived to identify possible bias (mean divergence) and the limits of agreement (2 SDs of the divergence). Mean percentage error was calculated as the absolute difference between the two sets of measurements divided by the average of the two sets and multiplied by 100%.

**Figure 1** Echocardiographic PIV results of LV blood flow velocity field in a normal control (A) and in a patient with TOF (B). Each panel shows one image of the velocity vector field at one instant (left), one color map image of the rotation level (vorticity stream function) at another instant with superimposed velocities (middle), and the color map image of the rotation level for the steady-streaming (heart-beat-averaged) flow field. Red indicates counterclockwise rotation, and blue indicates clockwise rotation.

**Figure 2** Echocardiographic PIV results of RV blood flow velocity field in a normal control (A) and in a patient with TOF (B). Each panel shows one image of the velocity vector field at one instant (left), one color map image of the rotation level (vorticity stream function) at another instant with superimposed velocities (middle), and the color map image of the rotation level for the steady-streaming (heart-beat-averaged) flow field. Red indicates counterclockwise rotation, and blue indicates clockwise rotation.
observations, divided by the mean of the observations: \( \frac{\text{Absolute}(X_1 - X_2)}{\text{Mean}(X_1, X_2)} \times 100 \), where \( X_1 - X_2 \) is the absolute value of the difference between observer 1 and observer 2. In addition, intraclass correlation coefficients were calculated according to standard methodology. \( P \) values < .05 were considered significant. Statistical analyses were performed using SPSS version 17.0.2 (SPSS, Inc, Chicago, IL) and Minitab version 16.1 (Minitab Inc, State College, PA).

**RESULTS**

The study population consisted of 41 subjects: 16 patients with TOF (10 men, six women) and 25 normal adult controls (15 men, 10 women). In the TOF group, 11 patients (69%) had primary repair, and five (31%) were repaired by the use of transannular patches, and five (31%) had previous shunt palliation before definite repair. Nine patients (57%) were repaired without transannular patches, and five (31%) were excluded from analysis were excluded either for suboptimal planar maps suitable for intraventricular flow analysis were obtained for the left ventricle in 14 patients and the right ventricle in 10 patients. For controls, intraventricular flow analysis was feasible for the left ventricle in 23 and the right ventricle in 21. Those who were excluded from analysis were excluded either for suboptimal image quality in the apical four-chamber view (often from RV dilation) or because of bubble density that was too high (saturation), prohibiting analysis of bubble velocity. None of the patients with TOF had evidence of antegrade diastolic flow in the pulmonary artery, coincident with atrial systole (restrictive RV physiology).

Demographic and CMR measurements in patients with TOF and control subjects who had measurable planar maps are shown in Table 1. There was no significant difference between the TOF group and control subjects who had measurable planar maps. Compared with controls, the TOF group had higher RV indexed end-diastolic volume (177.8 ± 25.5 vs 88 ± 15.4 mL/m², \( P < .001 \)) and lower LV indexed end-diastolic volume, and LV ejection fraction. Compared with controls, the TOF group had higher RV indexed end-diastolic volume (177.8 ± 25.5 vs 88 ± 15.4 mL/m², \( P < .001 \)) and lower LV indexed end-diastolic volume (117.8 ± 25.5 vs 97.0 ± 177.0, \( P = .016 \)). The single subject with relatively higher RV end-diastolic volume (177 mL/m²) had only mild tricuspid regurgitation and pulmonary regurgitation by echocardiography and magnetic resonance imaging) and qualitatively mild RV dilatation on echocardiography. Measurements of pulsed Doppler of the tricuspid inflow and tissue Doppler of the lateral tricuspid annulus showed mild elevation of the E/e′ ratio in the TOF group (6.8 ± 2.4 vs 3.8 ± 1.4 in controls, \( P < .001 \)), indicating abnormal diastolic filling.

Table 2 shows intraventricular flow parameters compared between the groups. Flow rotation intensity in the left ventricle was higher in patients with TOF compared with controls (0.40 ± 0.13 in patients with TOF vs 0.29 ± 0.08 in controls, \( P = .012 \)). The diastolic rotation in the left ventricle was also lower in patients with TOF. Dissipation of kinetic energy within the left ventricle was lower in patients with TOF (0.40 ± 0.13 in patients with TOF vs 0.29 ± 0.08 in controls, \( P = .012 \)).
Table 3 Correlations of intraventricular flow parameters in patients with TOF with age, ventricular end-diastolic volume, and ejection fraction

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<td>Flow rotation intensity</td>
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\( EDV \), End-diastolic volume; \( EF \), ejection fraction.

\( P < .001 \). For the right ventricle in patients with TOF, flow rotation intensity was significantly higher (0.53 ± 0.15 vs 0.26 ± 0.12, \( P < .001 \)), while kinetic energy dissipation was lower (0.4 ± 0.24 vs 1.65 ± 0.91, \( P < .001 \)). When measures of flow rotation intensity and energy dissipation were compared with patient age, RV end-diastolic volume, RV ejection fraction, and RV \( E/e' \) ratio, no correlations were found (Table 3). Bland-Altman analysis showed good intraobserver and interobserver agreement for flow rotation intensity and energy dissipation measurements for the left and right ventricles in patients with TOF, as represented in Figures 3 and 4. The mean percentage error between observers for flow rotation intensity was 21% for the left ventricle and 23% for the right ventricle. For kinetic energy dissipation, the mean percentage error was 14% for the left ventricle and 16% for the right ventricle. The results of intraclass correlations are shown in Table 4. For both the left and right ventricles, intraclass correlations for kinetic energy dissipation were greater than those for flow rotation intensity.

**DISCUSSION**

Two-dimensional echocardiography remains the primary imaging modality for repaired CHD, with its excellent temporal and spatial resolution, portability, and low cost. Patients with repaired TOF undergo echocardiographic assessments as part of routine follow-up. There is limited experience with contrast echocardiography in children and adults with CHD; however, recent clinical trials have shown that ultrasonic contrast imaging is safe in this population.16

This is the first report of quantifying intraventricular flow for the right ventricle in patients with CHDs using echocardiographic PIV. Intraventricular flow properties of the right ventricle have been difficult to assess because of its complex shape. Previous studies have highlighted an unsteady flow distribution within the RV inlet.17

Interestingly, the right ventricle has a relatively streamlined geometry that allows easy transit (i.e., conduit) of blood, which differs markedly from the left ventricle, in which flow must make a U-turn from the inlet to the outlet.17

Thus, in contrast to the left ventricle, dominant vortices do not appear fundamental for the normal RV flow transit.17

Previous work on RV flow used either direct numeric simulation combined with geometry extracted from echocardiography17 or four-dimensional phase-contrast CMR.17 Using the latter, it was shown that asymmetric and transient diastolic flow patterns are formed below the tricuspid valve that rapidly dissipate in diastole, and the superior aspect of the rotating flow moves into the RV outflow tract.18,19

Presence of helical flow in the RV outflow tract and pulmonary arteries has been demonstrated by CMR.19,20 However, in the apical aspect of the right ventricle, there is very limited flow.18

The main findings of the present study are the following: (1) measurement of intraventricular flow parameters by PIV is feasible in both ventricles for normal individuals and most patients after surgical repair of TOF, and (2) in this group of patients with repaired TOF and relatively favorable hemodynamic outcomes with preserved systolic function, RV and LV flow parameters were different from those of normal controls. Although subjects with TOF had mild to moderate RV dilatation and normal or low normal RV ejection fractions, these were not severe changes and were not associated with statistically significant alterations in LV ejection fraction or end-diastolic volume compared with controls. The calculated flow rotation intensities in both the right and left ventricles were higher in patients with TOF, whereas the energy dissipation was low. We speculate that the ventricular dilatation combined with its noncompliance is responsible for the reduction of energy dissipation, which is due to the conservation of kinetic energy in a coherent nonturbulent intraventricular rotational motion. Ventricular noncompliance and change in geometry could be responsible for a failure to dissipate energy and, as a consequence, the maintenance of high intraventricular rotational energy. It must be noted that the TOF cohort had mild diastolic filling abnormality evident on Doppler, with a mean \( E/e' \) ratio > 6.

Finite element simulations in normal and volume loaded animal hearts using real-time three-dimensional geometric data have demonstrated alterations in RV flow fields with changes in RV geometry,21 and our observations would support that concept. Our work is also agreement with early studies of Bellhouse et al.,22 who showed altered strength of flow in dilated ventricles. The significance of flow rotation intensity (measured as diastolic rotation) has been studied in the left ventricle. The intracavitary kinetic energy contributes to vortex formation in the left ventricle and efficient energy transfer with low dissipation. Changes in diastolic rotation (referred to as “vortex strength” by Abe et al.,23 although it is not strictly a measure of a vortex property) correlated with LV mechanics and were associated with adverse clinical outcomes in adult patients with heart failure.23 In a similar way, our findings in patients with TOF would suggest a relation between RV flow properties and RV performance.

Diastolic filling is associated with a continuous energy transfer process between the blood and myocardium that affects performance of the ventricle.23 Chamber compliance, right atrial function, pulmonary vascular resistance, and intraventricular flow all affect diastolic filling and energy distribution of the right ventricle. On the basis of CMR studies in a small number of patients with hypoplastic left heart syndrome, de Vecchi et al.23 suggested that abnormal flow patterns with vortex formation occur in the systemic right ventricle, and this might cause changes in the intraventricular pressure gradient and the rate of energy transfer. The shape of the ventricle was also found to have a role, with a spherical (as opposed to an elliptical) RV shape facilitating better energy transfer.

Although the findings of this study demonstrate the feasibility of echocardiographic PIV for both ventricles, it must be noted that planar maps suitable for intraventricular flow analysis were not obtained in all subjects. Among 41 subjects, LV analyses were achieved in 37 (92% of controls and 88% of patients with TOF) and RV analyses in 31 (84% of controls and 63% of patients with TOF). Besides image quality, the factors...
influencing feasibility are the appropriate density of contrast microbubbles and a sufficient frame rate. Images in this series excluded from analyses were excluded because of either suboptimal image quality or unsuitable bubble density. For intraventricular blood motion analysis, bubble density must be sufficient to appreciate their motion and well below saturation, to ensure that bubbles are distinguishable. When these limiting factors were avoided, bubble density was demonstrated to have only a weak influence on the results of blood motion analysis. The general rule is that images for echocardiographic PIV analysis need to be acquired when bubble density is such that blood motion is visually well appreciable. Second, a sufficiently high frame rate is required. The high frame reduces the limitation of echocardiographic PIV with high velocities, whereby the
modulus is underestimated, although the direction remains correctly evaluated. This has been previously demonstrated experimentally and in an artificial phantom. On the basis of these validation studies and previous clinical applications, a frame rate > 60 Hz was assumed sufficient to appreciate intracavitary flow velocities and was used in our study.

**Study Limitations**

This investigation consisted of a small group of older patients with repaired TOF, with more or less homogenous residua and not more than mild tricuspid valve or mild pulmonary valve regurgitation. By design, we chose to minimize the effects of greater degrees of regurgitation flow on intracavitary RV flow. Therefore, the results of this study may not be generalizable to younger patients or those with less favorable hemodynamics after TOF repair. The absence of patients with TOF with severe RV dilation precluded meaningful subgroup analysis of flow parameters. Although controls and patients did not differ in body weight, heart rate, or LV size or function, they were significantly older compared with patients, so some of the differences in flow patterns may be secondary to maturational changes. Inability to include the RV infundibulum in the flow fields is another weakness of this investigation. Depending on the acquisition frame rate, echocardiographic PIV can underestimate high velocities, and the spatial resolution of current ultrasound limits accurate imaging of the small-scale features of ventricular flow. All measurements were limited to the information available on the two-dimensional scanned slice of the actual three-dimensional flow field. A complete time-resolved, three-dimensional, and three-directional flow field was not measured in this study. It is therefore implicitly assumed that the information on the scan plane is representative of the three-dimensional flow. Although the reliability of this assumption cannot be validated here, alterations of fluid dynamics cannot be strictly regional, and therefore presumptions that they influence the entire flow domain are likely sound. Four-dimensional cine phase-contrast CMR allows visualization of the changing multidirectional flow fields through the entire heart and great vessels with full three-dimensional coverage. However, CMR four-dimensional flow techniques are hampered by the requirement for long acquisition times and complex and time-consuming postacquisition data analysis. The present investigation was not designed to identify the precise causes most responsible for the RV compliance changes, which could include the septal patch, intrinsic myocardial abnormalities, intraventricular conduction delay, infundibular muscle resection and ventriculotomy. Similarly, this study does not provide insight into the mechanism for the LV changes that could, in addition to the foregoing, include ventriculoventricular interactions.

**CONCLUSIONS**

Characterization of RV and LV flow parameters in patients with TOF is feasible using echocardiographic contrast PIV. It demonstrated that flow patterns in patients with TOF present abnormal properties with higher circulation and reduced energy dissipation that are potentially related to ventricular compliance changes. These insights into RV and LV functional properties in TOF merit further investigation, including evaluation of intraventricular PIV characteristics of the hypertrophic, restrictive, or dysfunctional right ventricle in patients with TOF with poorer results from surgical repair.

**ACKNOWLEDGMENTS**

The authors are grateful to the patients who participated in this study. The authors thank Partho P. Sengupta, MD, for helpful suggestions on image acquisition. The authors also appreciate the assistance of the echocardiography laboratory staff at the University of Nebraska Medical Center.

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