Right and left ventricular function and flow quantification in pediatric patients with repaired tetralogy of Fallot using four-dimensional flow magnetic resonance imaging

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Abstract

Background: To assess the accuracy and reproducibility of right ventricular (RV) and left ventricular (LV) function and flow measurements in children with repaired tetralogy of Fallot (rTOF) using four-dimensional (4D) flow, compared with conventional two-dimensional (2D) magnetic resonance imaging (MRI) sequences.

Methods: Thirty pediatric patients with rTOF were retrospectively enrolled to undergo 2D balanced steady-state free precession cine (2D b-SSFP cine), 2D phase contrast (PC), and 4D flow cardiac MRI. LV and RV volumes and flow in the ascending aorta (AAO) and main pulmonary artery (MPA) were quantified. Pearson's or Spearman's correlation tests, paired t-tests, the Wilcoxon signed-rank test, Bland–Altman analysis, and intraclass correlation coefficients (ICC) were performed.

Results: The 4D flow scan time was shorter compared with 2D sequences (P < 0.001). The biventricular volumes between 4D flow and 2D b-SSFP cine had no significant differences (P > 0.05), and showed strong correlations (r > 0.90, P < 0.001) and good consistency. The flow measurements of the AAO and MPA between 4D flow and 2D PC showed moderate to good correlations (r > 0.60, P < 0.001). There was good internal consistency in cardiac output. There was good intraobserver and interobserver biventricular function agreement (ICC > 0.85).

Conclusions: RV and LV function and flow quantification in pediatric patients with rTOF using 4D flow MRI can be measured accurately and reproducibly compared to those with conventional 2D sequences.

Keywords: 4D flow, Cardiac magnetic resonance, Repaired tetralogy of Fallot

Background

Congenital heart disease (CHD) is the most common birth defect in China [1]. Tetralogy of Fallot (TOF) is the most common cyanotic CHD [2, 3]. Patients with repaired TOF (rTOF) develop pulmonary valve regurgitation, which leads to right ventricular (RV) enlargement and dysfunction. Therefore, ventricular function and flow information, especially RV function and pulmonary regurgitation (PR), must be provided by magnetic resonance imaging (MRI) during follow up of rTOF [4].

Cardiac function and flow measurements by cardiac magnetic resonance (CMR) are usually analyzed using conventional two-dimensional (2D) balanced steady-state free precession (b-SSFP) cine and 2D phase contrast...
(PC) sequences. The accuracy of 2D b-SSFP cine has been validated and the technique is widely used in post-operative functional assessment with CHD [5–10]. 2D PC is the primary method used to measure blood flow volume and velocity in CMR [11]. However, the conventional 2D b-SSFP cine and 2D PC sequences are relatively time-consuming. Each sequence highly depends on the technologist to determine appropriate scan planes and parameters, which limits its availability [12, 13]. Since long acquisition time and extended sedation make CMR difficult for young children, four-dimensional (4D) flow can assess both ventricular function and flow information with only one sequence, the imaging time can be significantly saved [14, 15].

In this study, we aimed to assess the RV and left ventricular (LV) function and flow measurements in children patients with rTOF using 4D flow, compared with conventional 2D MRI sequences.

Methods

Patient population
We retrospectively identified pediatric patients with rTOF who were referred for CMR at our hospital and informed consent was waived. We included patients with rTOF who underwent 2D CMR (2D cine b-SSFP, 2D PC) and 4D flow MRI for ventricular function and flow assessment from September 2018 to September 2019.

Image acquisition
All images were performed on a 3.0-T MRI scanner with an eight-channel phased-array cardiac coil (Discovery 750, GE Healthcare, Waukesha, WI, USA) with electrocardiography (ECG) gating. Deep sedation was used in patients aged under 6 years.

Conventional 2D b-SSFP cine planes were acquired in a four-chamber view, two- and three-chamber views, and a short axis view. Then, 2D PC and whole-heart 4D flow sequences were performed after administration of gadolinium contrast agent (0.05–0.10 mmol/kg injected intravenously at 1.0–1.5 ml/s, Magnevist, Bayer). Velocity encoding (VENC) for 2D PC was 150–200 cm/s for the ascending aorta (AAO) and 150–380 cm/s for the main pulmonary artery (MPA) according to the results of the recent echo.

4D flow acquisition was performed in coronal or axial plane full volumetric coverage of the great arteries with ECG gating (30 interpolated phases per cardiac cycle) and without respiratory triggering. With the acceleration technique of kt-ARC and the parallel imaging with reduction factor R of 2, the resulting scan time was on the order of 5–10 min. We selected thinner slice thickness in order to achieve isotropic voxels [16, 17]. The range of VENC for 4D flow was 120–380 cm/s in all three directions according to the results of echo as 2D PC. The acquisition parameters expressed as a range of these three sequences were detailed in Table 1.

Image postprocessing
Automated corrections were preprocessed on 2D PC or 4D flow to avoid aliasing artefacts. To acquire cardiac volume results using 4D flow using dedicated software (Arterys Inc., San Francisco, CA, USA), short-axis and axial imaging planes were automatically generated. After manual segmentation of the LV and RV (Fig. 1), end-diastolic volume indexed (EDVi), end-systolic volume indexed (ESVi), stroke volume indexed (SVi), ejection fraction (EF), and cardiac output indexed (COi) were computed at end-diastole and end-systole. All ventricular volume and function measurements were normalized to body surface area (BSA) using the Mosteller method.

To quantify AAO and MPA flow with 4D flow using the Artery platform, AAO and MPA cross-sectional

| Table 1 | The acquisition parameters in 2D b-SSFP cine, 2D PC and 4D flow sequences |
|---------|----------------------------------------------------------|
| Repetition time (TR, ms) | 3.46 (3.22–3.73) | 5.56 (4.97–6.03) | 4.58 (4.31–5.04) |
| Echo time (TE, ms) | 1.54 (1.43–1.66) | 2.95 (2.38–3.16) | 2.22 (2.09–2.40) |
| Flip angle (°) | 45/50 | 20 | 8–15 |
| Views per Segment | 12–14 | 2–4 | / |
| Temporal resolution (ms) | 55.36 (51.52–59.68) | 44.48 (39.76–48.24) | 36.63 (34.48–40.32) |
| Acquired spatial resolution (mm) | 1.5–2.5 × 1.5–2.5 | 1.5–2.5 × 1.5–2.5 | 1.02–2.00 |
| Slice thickness(mm) | 5.0–8.0 | 4.0–5.0 | 1.00–2.00 |
| Interpolated Cardiac phases/cycle | 30 | 30 | 30 |
| VENC (cm/s) | N/A | 150–380 | 120–380 |
| Navigator gating | No | Yes | Yes |
| ECG triggering | Yes | Yes | Yes |
planes were reconstructed perpendicular to the direction of flow in early systole. AAO flow was measured at the midpoint of the AAO. Because there were no clearly defined pulmonary valves in patients with rTOF, MPA flow was measured at the midpoint of the pulmonary trunk. The AAO and MPA contours were adjusted at different time points, and then the net flow, forward flow, peak velocity, and regurgitation fraction (RF) of both AAO and MPA were calculated automatically (Fig. 1). The AAO and MPA flow volumes were multiplied by the related forward flow and heart rate values.

2D b-SSFP cine and 2D PC analyses were performed using Circle Cardiovascular Imaging software (CVI42 v.5.9.3, Circle Cardiovascular Imaging Inc., Calgary, Canada). Each sequence was manually processed by the board-certified radiologist with specialty training in pediatric cardiac imaging, which was the same person who postprocessed the 4D flow sequence (Fig. 1). Trabeculations and papillary muscles of the LV and RV were included as part of the ventricular cavity and a smooth endocardial border was drawn to improve reproducibility [18]. After segmenting 2D PC sequences, net flow, forward flow, peak velocity, and RF in both the AAO and MPA were obtained.

Statistical analysis
Statistical analyses were performed using SPSS 25.0 software (Chicago, IL, USA) and GraphPad Prism 7 (San Diego, CA, USA), and a significance level of 0.05 was applied for all statistical tests. Continuous variables were checked for a normal distribution using the Shapiro–Wilk test, and expressed as mean ± standard deviation (SD). Categorical variables are presented as number (%). Either Pearson’s or Spearman’s correlation test was used to test the correlation in the results between 4D flow and 2D MR sequences according to the variable distribution. Correlation (r) was considered poor for values between 0.30 and 0.50, moderate for values between 0.50 and 0.70, and good for values between 0.70 and 1.00. A paired t-test or the Wilcoxon signed-rank test was used to test the difference between 4D flow and 2D MR sequences according to the variable distribution. Correlation (r) was considered poor for values between 0.30 and 0.50, moderate for values between 0.50 and 0.70, and good for values between 0.70 and 1.00. A paired t-test or the Wilcoxon signed-rank test was used to test the difference between 4D flow and 2D MR sequences. The agreement in measurements between 4D flow and 2D MR sequences was assessed by Bland–Altman analysis, which calculated the mean difference or mean percentage difference between measurements and 95% limits of agreement (LOA, mean ± 1.96 SD). The intraclass correlation coefficients (ICC) with 95% confidence interval (CI) were applied to test intraobserver and interobserver reproducibility between 4D flow and 2D b-SSFP cine. Interobserver reproducibility in ventricular function was
assessed by two radiologists both with >3 years’ experience in reading CMR in a double-blinded manner.

Results

Demographics

Demographic information of all 30 patients with rTOF underwent CMR were summarized in Table 2. There was no significant difference ($P = 0.724$) in heart rate between 4D flow (77.03 ± 13.30 bpm) and 2D acquisition (76.60 ± 12.38 bpm). The scan times of 4D flow and 2D sequences were 8.10 ± 2.25 min and 34.66 ± 7.41 min, respectively ($P < 0.001$). The postprocessing times of 4D flow and 2D sequences were about 40 min and 45 min respectively. The echocardiography performed at the same time as CMR did reported that 21 patients had mild tricuspid regurgitation, one patient had the residual interventricular shunt and eight patients had interatrial shunt. Three cases were experienced minor aliasing on 4D flow and were corrected automatically by Arterys.

Comparison of ventricular function

The ventricular function of both ventricles was shown in Table 3 for 2D cine b-SSFP and 4D flow short axis view. The correlations in biventricular function between CMR 4D flow and 2D b-SSFP cine sequences were strong ($r > 0.90$, $P < 0.001$; Table 3). There were no significant differences ($P > 0.050$) in biventricular function between 4D flow and 2D b-SSFP cine sequences. As Figs. 2 and 3 showed, the mean percentage differences in biventricular function between 4D flow and b-SSFP were near zero, and the biventricular LOA were narrow and the RV volume LOA between 4D flow and b-SSFP were slightly wider when compared with the LV volume LOA.

The right ventricular function using the 4D flow axial plane and the results were shown in Tables 4 and 5. There were no significant differences ($P > 0.050$) when comparing the right ventricular volume measurements in 4D flow axial plane to those of 2D b-SSFP cine or those of 4D short axis view. Besides, the correlations of right ventricular function were strong ($r > 0.85$, $P < 0.001$). And the mean differences in right ventricular volumes were near zero and the LOA were narrow whether comparing the right ventricular volume measurements in 4D flow axial plane to those of 2D b-SSFP cine or those of 4D short axis view.

Comparison of AAO and MPA flow quantification

We compared the consistency of net flow, forward flow, peak velocity, and RF of the AAO and MPA between 4D flow and 2D PC, which showed moderate to good correlation and agreement (Table 6). The AAO and MPA correlations of net flow, forward flow, peak velocity, and RF were moderate to good ($r = 0.643–0.923$, $P < 0.001$), and the peak velocity showed the weakest correlation among the three flow measurements for the AAO and the MPA. There was a wider LOA for MPA flow quantification compared with AAO between 4D flow and 2D PC, and the mean differences in MPA flow measurements were larger when compared with AAO between 4D flow and 2D PC.

Table 2: Summary of patient demographics

|                          | All patients ($n = 30$) |
|--------------------------|-------------------------|
| Male (%)                 | 80                      |
| Height (cm)              | 119.97 ± 28.52          |
| Weight (kg)              | 23.83 ± 14.57           |
| BSA (m²)                 | 0.89 ± 0.37             |
| Age at CMR (years)       | 6.30 ± 4.19             |
| Age at TOF repair (months)| 10.88 ± 7.01            |
| Duration between surgery and CMR (years) | 5.62 ± 4.06 |

Table 3: Comparison of Ventricular Function Data between 2D b-SSFP cine and 4D Flow

| Measurements            | 4D flow short axis view (mean ± SD) | 2D b-SSFP cine (mean ± SD) | Paired t-test/ Wilcoxon | Correlation |
|-------------------------|-------------------------------------|----------------------------|-------------------------|-------------|
| LVEDV (ml/m²)           | 74.23 ± 10.66                       | 74.54 ± 10.60              | 0.509                   | 0.971       | < 0.001 |
| LVESV (ml/m²)           | 32.75 ± 7.06                        | 32.66 ± 7.47               | 0.888                   | 0.983       | < 0.001 |
| LVSV (ml/m²)            | 41.48 ± 7.98                        | 41.74 ± 7.86               | 0.347                   | 0.979       | < 0.001 |
| LVEF (%)                | 55.81 ± 6.70                        | 56.11 ± 6.87               | 0.238                   | 0.958       | < 0.001 |
| LVCOI (L/min/m²)        | 3.10 ± 0.67                         | 3.14 ± 0.63                | 0.455                   | 0.958       | < 0.001 |
| RVEDV (ml/m²)           | 132.77 ± 36.68                      | 132.40 ± 36.85             | 0.691                   | 0.991       | < 0.001 |
| RVESV (ml/m²)           | 62.87 ± 21.95                       | 62.11 ± 21.67              | 0.124                   | 0.993       | < 0.001 |
| RVSV (ml/m²)            | 69.90 ± 15.78                       | 70.31 ± 16.26              | 0.471                   | 0.982       | < 0.001 |
| RVEF (%)                | 53.43 ± 4.31                        | 53.83 ± 4.25               | 0.067                   | 0.964       | < 0.001 |
| RVCOI (L/min/m²)        | 5.25 ± 1.25                         | 5.32 ± 1.22                | 0.371                   | 0.946       | < 0.001 |
Comparison of internal consistency with 4D flow and 2D sequences

We also applied internal consistency for systemic and pulmonary flow volumes between 4D flow and 2D sequences by comparing CO estimated from LVSV or RVSV and CO estimated from AAO or MPA forward volumes (Table 7, Fig. 4). The correlations in LVCO or RVCO and AAO or MPA forward volumes measured by 4D flow and 2D sequences were good ($r > 0.80$, $P < 0.001$). There was a narrow LOA between LVCO or RVCO and AAO or MPA forward flow volume with both 4D flow and 2D PC, and the mean differences were near zero for both 4D flow and 2D sequences. With a minor mean aortic RF ($< 10\%$) (Table 6) in patients with rTOF, the red closed symbols in the scatter plot (Fig. 4) were near the line of identity ($y = x$), which validated that LVCO was well matched to AAO forward flow volume with 2D PC and 4D flow. Despite the mean pulmonary RF was moderate to severe ($> 20\%$) (Table 6), the blue open symbols in the scatter plot (Fig. 4) were near the line of identity ($y = x$), which validated that RVCO was well matched to MPA forward flow volume with 2D PC and 4D flow.

Intraobserver and interobserver reproducibility for ventricular function

The intraobserver and interobserver ICCs of biventricular function for both 4D flow and 2D b-SSFP cine were
Fig. 3  Bland–Altman and correlation plots in RVEDVi, RVESVi, RVSVi, RVEF, and RVCOi between 4D flow and 2D b-SSFP cine. The mean percentage differences and LOA are represented with red and gray dashed lines, respectively.

Table 4  Comparison of right ventricular function data between 2D b-SSFP cine and 4D flow axial plane

| Measurements | Paired t-test/Wilcoxon | Correlation | Bland–Altman | Mean difference |
|--------------|------------------------|-------------|--------------|----------------|
| RVEDVi (ml/m²) | 0.671 | 0.999 | < 0.001 | (−2.16, 2.24) | 0.04 ± 1.12 |
| RVESVi (ml/m²) | 0.652 | 0.997 | < 0.001 | (−5.78, 5.17) | −0.30 ± 2.80 |
| RVSVi (ml/m²) | 0.467 | 0.993 | < 0.001 | (−4.88, 5.70) | 0.41 ± 2.70 |
| RVEF (%) | 0.388 | 0.958 | < 0.001 | (−4.08, 4.85) | 0.39 ± 2.28 |
| RVCOi (L/min/m²) | 0.634 | 0.891 | < 0.001 | (−19.94, 18.64) | −0.65 ± 9.84 |
summarized in Table 8. Intraobserver and interobserver reproducibility demonstrated very well (ICC > 0.85) with both 4D flow and 2D b-SSFP cine when quantifying LV and RV function.

**Discussion**

CMR is the reference method used to assess ventricular volume, function, and flow as well as longitudinal follow up of patients over time [8, 19, 20]. 2D b-SSFP cine is widely preferred for the evaluation of cardiac function with lower interobserver variability and good blood myocardium contrast [21, 22]. 2D PC is the primary method used to quantify blood flow with the magnitude image used to provide anatomical information and the phase image used to provide velocity information [11, 23]. All 2D multiplanar sequences require a relatively long scan time, which is challenging for pediatric patients who cannot do MRI or who require deep sedation [24]. Previous studies have demonstrated that 4D flow MRI can provide flow information and assess cardiac function precisely and reliably [14, 25, 26]. Our study confirmed these findings in pediatric patients with rTOF.

The 4D flow results of biventricular function compared with 2D b-SSFP cine sequences demonstrated a more accurate ventricular volume assessment compared with prior published research [14, 25, 26]. A previous study showed that contrast agent has been validated to improve the signal-to-noise ratio and suppress background noise [27]. Our ventricular results indicated that 4D flow with contrast agent could provide an adequate image quality to acquire precise ventricular function measurements comparable to 2D b-SSFP cine. However, RV LOA of volumes between 4D flow and b-SSFP were relatively wider when compared with LV LOA of volumes in this study, which was attributable to the irregular and enlarged RV geometry in patients with rTOF especially in basal slices’ segmentation, or because the relatively thinner RV

| Measurements | Paired t-test/Wilcoxon | Correlation | Bland–Altman |
|--------------|------------------------|-------------|--------------|
|              | P-value | r-value | P-value | LOA | Mean difference |
| RVEDVi (ml/m²) | 0.470 | 0.998 | <0.001 | (−4.11, 3.51) | −0.30 ± 1.94 |
| RVESVi (ml/m²) | 0.764 | 0.997 | <0.001 | (−6.93, 7.01) | −0.04 ± 3.56 |
| RVSVi (ml/m²)  | 0.326 | 0.992 | <0.001 | (−6.30, 5.26) | −0.52 ± 2.95 |
| RVEF (%)      | 0.568 | 0.957 | <0.001 | (−4.81, 4.37) | −0.22 ± 2.34 |
| RVCOi (L/min/m²) | 0.158 | 0.979 | <0.001 | (−13.07, 9.34) | −1.87 ± 5.72 |

| Measurements | Correlation | LOA | Mean difference |
|--------------|-------------|-----|-----------------|
|              | P-value | r-value | P-value | LOA | Mean Difference |
| 4D LVCO vs. 4D AAO forward flow volume | 0.924 | (−1.52, 0.47) | −0.52 ± 0.51 |
| 2D LVCO vs. 2D AAO forward flow volume | 0.944 | (−1.21, 0.54) | −0.34 ± 0.45 |
| 4D RVCO vs. 4D MPA forward flow volume | 0.834 | (−2.20, 3.33) | 0.57 ± 1.41 |
| 2D RVCO vs. 2D MPA forward flow volume | 0.967 | (−1.01, 1.56) | 0.27 ± 0.66 |

| Measurements | Correlation | LOA | Mean difference |
|--------------|-------------|-----|-----------------|
|              | P-value | r-value | P-value | LOA | Mean Difference |
| AAO net flow (ml/beat) | 29.14 ± 12.10 | 32.06 ± 12.26 | 0.816 | (−6.81, 12.64) | 2.92 ± 4.96 |
| AAO forward flow (ml/beat) | 29.67 ± 12.41 | 33.12 ± 12.99 | 0.923 | (−6.40, 13.31) | 3.45 ± 5.03 |
| AAO peak velocity (cm/s) | 83.57 ± 14.32 | 77.59 ± 11.27 | 0.643 | (−25.58, 13.63) | −5.98 ± 10.00 |
| AAO RF (%) | 1.70 ± 1.42 | 2.91 ± 2.19 | 0.752 | (−1.63, 4.05) | 1.21 ± 1.45 |
| MPA net flow (ml/beat) | 36.60 ± 18.00 | 33.21 ± 14.93 | 0.831 | (−21.50, 14.13) | −3.69 ± 9.09 |
| MPA forward flow (ml/beat) | 55.48 ± 30.12 | 60.12 ± 29.09 | 0.891 | (−22.51, 31.78) | 4.64 ± 13.85 |
| MPA peak velocity (cm/s) | 159.13 ± 50.34 | 151.92 ± 53.53 | 0.779 | (−75.12, 60.70) | −7.21 ± 34.65 |
| MPA RF (%) | 29.93 ± 13.85 | 41.75 ± 13.62 | 0.790 | (−3.91, 27.54) | 11.82 ± 8.02 |
myocardial wall made it harder to delineate than the LV. With the advantage of 4D flow 3D dataset, different from previous studies [14, 25, 26], both the short axis plane and axial plane could be obtained during the post-processing of 4D flow, and could provide reliable measurements for follow-up of the right ventricular function in patients with rTOF.

The net flow, forward flow and RF of the AAO and MPA measured by 4D flow and 2D PC demonstrated a moderate to good correlation ($r > 0.60$, $P < 0.001$) and agreement. Nevertheless, peak velocity and RF measurements showed relatively poorer correlation and agreement compared with net flow and forward flow for both AAO and MPA by 4D flow or 2D PC, which was significantly affected by the orientation of the AAO and MPA.

### Table 8 Intraobserver and interobserver reproducibility for quantifying ventricular volumes

|                      | Intraobserver reproducibility (n = 10) | Interobserver reproducibility (n = 10) |
|----------------------|---------------------------------------|---------------------------------------|
|                      | 4D flow ICC (95%CI)                   | 2D b-SSFP cine ICC (95%CI)            | 4D flow ICC (95%CI) | 2D b-SSFP cine ICC (95%CI) |
| LVEDVi               | 0.992 (0.971, 0.998)                  | 0.996 (0.985, 0.999)                  | 0.991 (0.965, 0.997) | 0.995 (0.982, 0.999)      |
| LVESEvi              | 0.997 (0.940, 0.999)                  | 0.999 (0.989, 0.999)                  | 0.995 (0.981, 0.991) | 0.997 (0.990, 0.999)      |
| LVESVi              | 0.989 (0.960, 0.997)                  | 0.998 (0.991, 0.999)                  | 0.977 (0.915, 0.994) | 0.988 (0.956, 0.997)      |
| LVEF                 | 0.979 (0.925, 0.994)                  | 0.990 (0.961, 0.997)                  | 0.951 (0.828, 0.986) | 0.975 (0.906, 0.993)      |
| LVOEi                | 0.947 (0.817, 0.985)                  | 0.973 (0.899, 0.993)                  | 0.906 (0.690, 0.974) | 0.939 (0.789, 0.983)      |
| RVESVi               | 0.949 (0.809, 0.986)                  | 0.977 (0.914, 0.994)                  | 0.902 (0.679, 0.973) | 0.955 (0.842, 0.988)      |
| RVESVi               | 0.953 (0.826, 0.987)                  | 0.986 (0.948, 0.996)                  | 0.911 (0.704, 0.975) | 0.973 (0.902, 0.993)      |
| RVEF                 | 0.978 (0.917, 0.994)                  | 0.971 (0.893, 0.992)                  | 0.956 (0.847, 0.988) | 0.944 (0.806, 0.985)      |
| RVCOi                | 0.972 (0.895, 0.992)                  | 0.973 (0.898, 0.993)                  | 0.945 (0.809, 0.985) | 0.947 (0.815, 0.985)      |
| RVCOi                | 0.951 (0.816, 0.987)                  | 0.968 (0.882, 0.991)                  | 0.861 (0.565, 0.961) | 0.925 (0.722, 0.980)      |
image plane by 4D flow or 2D PC with no use of valve-tracking, and was also influenced by the turbulent flow in 2D PC and 4D flow [18]. Though the mean difference of RF between 4D flow and 2D PC was around 10%, which is considered clinically acceptable [28]. As the prior study showed, patients with rTOF may have a combination of pulmonary stenosis and regurgitation, which can lead to turbulent flow, dephasing within a volume, and resultant signal loss with PC MRI [4]. Our pulmonary regurgitation was measured at the MPA both by 2D PC and 4D flow, while the prior studies showed that PR measured at the pulmonary valve and valve tracking method can further improve reliability and accuracy of flow measurements [4, 26]. Our study indicated that 4D flow showed a higher peak velocity estimation in both the AAO and MPA compared with 2D PC, which is consistent with a previous study [28]. This study [28] demonstrated that 4D flow could analyze peak velocity with better accuracy than 2D PC compared with the echo standard. The greater mean difference and wider LOA for MPA flow were detected compared with AAO flow measurements between 2D PC and 4D flow. This was due to the complicated hemodynamics in patients with rTOF, which may be caused by pulmonary valve insufficiency and RV enlargement after RV outlet tract correcting surgery [4].

To further test the accuracy of 4D flow measurements, we used internal consistency validation by comparing AAO and MPA forward flow volume obtained by 4D flow or 2D PC with LVCO and RVCO obtained by 4D flow or 2D cine b-SSFP [16]. According to the internal consistency of systemic forward flow volumes between 4D flow and 2D sequences, LVCO was matched to AAO forward flow volumes in all 30 cases with minor aortic RF (<10%) in both 4D flow and 2D sequences. Besides, RVCO was also matched to the forward volume in the MPA while 29 out of the 30 patients with rTOF had significant (>10%) MPA regurgitation by 2D PC. The whole exact inlet and outlet match of the RVCO and LVCO showed good internal consistency in ventricular function and flow assessment in both the LV and RV between 4D flow and 2D CMR sequences, which showed that the 4D method had a similar accuracy and addressed the occasional discrepancy to evaluate ventricular function and AAO and MPA flow in postoperative patients with TOF compared with the reference 2D method.

The ICC results demonstrated high intraobserver and interobserver reproducibility (ICC > 0.85) of biventricular function between 4D flow and 2D b-SSFP cine. For both 2D and 4D flow sequences, intraobserver and interobserver ICC of LV measurements having greater agreement than RV measurements, while our results had better RV ICC than previously published values [24]. Due to the abnormal RV geometry in patients with rTOF, it is challenging to quantify RV volume accurately and reliably. Importantly, the intraobserver and interobserver ICCs of 4D flow volume measurements for both the LV and RV were similar to 2D b-SSFP cine. In addition, greater interobserver variability was noted for EF and COi measurements (ICC = 0.861–0.975), which may be explained by the fact that the error in two independent volume measurements may be increased by dividing them. Compared to prior reports [25], volume measurements in 4D flow and 2D b-SSFP cine had equally well intraobserver and interobserver reproducibility.

4D flow with a short scanning time is an ideal technology that provides comprehensive assessment of cardiac function and flow quantification simultaneously for patients with rTOF [4, 29]. Furthermore, 4D flow data are obtained for all parameters in a single identical heart rate and hemodynamic status, while the 2D data are obtained during different time points when the heart rate and hemodynamics change continuously, which can sometimes be significant. What’s more, 4D flow allows more precise prescription of the planes for flow measurement during postprocessing. The measurement plane can be adjusted for each cardiac phase according to the changing direction of flow or the motion of the object structure. Although valve tracking was not employed in this study, prior studies demonstrated that valve tracking method can further improve reliability and accuracy of flow measurements [26, 30]. Lastly, as any vessel included in the imaging volume can be assessed after imaging, 4D flow provides unlimited opportunity for internal validation.

This study had several limitations as below. First, this was a single-center study without inter-institution and inter-software assessment. Second, this study was limited by the small sample involved, which only included patients with post-operative TOF and was not heterogeneous with other types of CHD. Lastly, even quicker 4D flow imaging and compressed sense 2D imaging may be available soon for further studies [31, 32].

**Conclusions**

RV and LV function and flow quantification in pediatric patients with rTOF using 4D flow MRI can be measured accurately and reproducibly compared to those with conventional 2D sequences. 4D flow MRI has good potential for clinical application, especially in pediatric patients.

**Abbreviations**

RV: Right ventricular; LV: Left ventricular; rTOF: Repaired tetralogy of Fallot; 4D: Four-dimensional; 2D: Two-dimensional; MRI: Magnetic resonance imaging; b-SSFP: Balanced steady-state free precession; PC: Phase contrast; AAO: Ascending aorta; MPA: Main pulmonary artery; ICC: Intraclass correlation coefficients; CHD: Congenital heart disease; PR: Pulmonary regurgitation; CMR: Cardiac magnetic resonance; ECG: Electrocardiography; VENC: Velocity encoding.
TR: Repetition time; TE: Echo time; EDVi: End-diastolic volume indexed; ESVi: End-systolic volume indexed; S1V: Stroke volume indexed; EF: Ejection fraction; COi: Cardiac output indexed; BSA: Body surface area; RF: Regurgitation fraction; SD: Standard deviation; LOA: Limits of agreement; CI: Confidence interval.

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Authors’ contributions
Study concepts and design: YZ and YX. Literature research: YX, LH, and RO. Clinical studies: YX and RO. Experimental studies/data analysis: YX, AS, QW, XY, YP, FF, and LH. Statistical analysis: XY, WY, and LH. Manuscript preparation: XY. Manuscript editing: XY and YZ. All authors have read and approved the manuscript.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
In accordance with the ethical principles of the Declaration of Helsinki and International Ethical Guidelines for Biomedical Research Involving Human Subjects promulgated by the Council for International Organizations of Medical Sciences, this study was approved by the ethical committee of Shanghai Children’s Medical Center (SCMCIRB-W2021034) and informed consent was waived.

Consent for publication
Not applicable.

Competing interests
The author Ms. Fei Feng from GE Healthcare is a consultant to Arterys Inc. Other authors declare that they have no competing interests.

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References
1. Zhao QM, Liu F, Wu L, et al. Prevalence of congenital heart disease at live birth in China. J Pediatr. 2019;204:53–8. https://doi.org/10.1016/j.jpeds.2018.08.040.
2. Lee S, Kim YJ, Jung JW, et al. Evaluation of flow pattern in the ascending aorta in patients with repaired Tetralogy of Fallot using four-dimensional flow magnetic resonance imaging. Korean J Radiol. 2019;20:1334. https://doi.org/10.3348/kjr.2019.00086.
3. van der Hulst AE, Westenberg JJ, Kroft LJ, et al. Tetralogy of Fallot: 3D velocity-encoded MRI for evaluation of right ventricular valve flow and diastolic function in patients after correction. Radiology. 2010;256:724–34. https://doi.org/10.1148/radiol.10092269.
4. Isorni MA, Martins D, Ben Moussa N, et al. 4D flow MRI versus conventional 2D for measuring pulmonary flow after Tetralogy of Fallot repair. Int J Cardiol. 2020;300:132–6. https://doi.org/10.1016/j.ijcard.2019.10.030.
5. Le TT, Tan RS, De Deyn M, et al. Cardiovascular magnetic resonance reference ranges for the heart and aorta in Chinese at ST. J Cardiovasc Magn Reson. 2016;18:21. https://doi.org/10.1186/s12968-016-0236-3.
6. D’Errico L, Lamacce JM, Jimenez Juan L, et al. Effects of slice orientation on reproducibility of sequential assessment of right ventricular volumes and ejection fraction: short-axis vs transverse SSFP cine cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2016;18(1):60. https://doi.org/10.1186/s12968-016-0282-x.
7. van der Ven JPG, Sadighy Z, Valangiagiacomo Buechel ER, et al. Multicentre reference values for cardiac magnetic resonance imaging derived ventricular size and function for children aged 0–18 years. Eur Heart J Cardiovasc Imaging. 2020;21:102–13. https://doi.org/10.1093/ehjci/jez164.
8. Buechel EV, Kaiser T, Jackson C, et al. Normal right- and left ventricular volumes and myocardial mass in children measured by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2009;11(1):19. https://doi.org/10.1186/1532-429X-11-19.
9. Petersen SE, Aung N, Sanghvi MM, et al. Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort. J Cardiovasc Magn Reson. 2017;19:18. https://doi.org/10.1186/s12968-017-0327-9.
10. Pednekar AS, Wang H, Flamm S, et al. Two-center clinical validation and quantitative assessment of respiratory triggered retrospectively cardiac gated balanced-SSFP cine cardiovascular magnetic resonance imaging in adults. J Cardiovasc Magn Reson. 2018;20:44. https://doi.org/10.1186/s12968-018-0467-6.
11. Franz S, Chung T, Greil GF, et al. Guidelines and protocols for cardiovascular magnetic resonance in children and adults with congenital heart disease: SCMR expert consensus group on congenital heart disease. J Cardiovasc Magn Reson. 2013;15(1):51. https://doi.org/10.1186/1532-429X-15-51.
12. Cheng JY, Hanneman K, Zhang T, et al. Comprehensive motion-compensated highly accelerated 4D flow MRI with ferumoxytol enhancement for pediatric congenital heart disease: motion-compensated accelerated 4D flow. J Magn Reson Imaging. 2016;43:1353–68. https://doi.org/10.1002/jmri.25106.
13. Feneis JF, Kyubwa E, Atianzar K, et al. 4D flow MRI quantification of mitral and tricuspid regurgitation: reproducibility and consistency relative to conventional MRI. J Magn Reson Imaging. 2018;48:1147–58. https://doi.org/10.1002/jmri.26040.
14. Hsiao A, Lustig M, Alley MT, et al. Rapid pediatric cardiac assessment of flow and ventricular volume with compressed sensing parallel imaging volumetric cine phase-contrast MRI. AJR Am J Roentgenol. 2012;198W:W50–9. https://doi.org/10.2214/AJR.11.6969.
15. Lawley CM, Broadhouse KM, Callaghan FM, et al. 4D flow magnetic resonance imaging: role in pediatric congenital heart disease. Asian Cardiovasc Thorac Ann. 2018;26:28–37. https://doi.org/10.1111/1747-4930.13177.
16. Dyerfeldt P, Bissell M, Barker AJ, et al. 4D flow cardiovascular magnetic resonance consensus statement. J Cardiovasc Magn Reson. 2015;17:72. https://doi.org/10.1186/s12968-015-0174-5.
17. Zhong L, Schrauben EM, Garcia J, et al. Intracardiac 4D flow MRI in congenital heart disease: recommendations on behalf of the ISMRM Flow & Motion Study Group. J Magn Reson Imaging. 2019;50:677–81. https://doi.org/10.1002/jmri.26858.
18. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post-processing in cardiovascular magnetic resonance - 2020 update: Society for Cardiovascular Magnetic Resonance (SCMR). Board of Trustees Task Force on Standardized Post-Processing. J Cardiovasc Magn Reson. 2020;22:19. https://doi.org/10.1186/s12968-020-00610-6.
19. Pennell DJ, Sechtem UP, Higgins CB, et al. Clinical indications for cardiovascular magnetic resonance - 2020 update: Society for Cardiovascular Magnetic Resonance (SCMR). Board of Trustees Task Force on Standardized Post-Processing. J Cardiovasc Magn Reson. 2020;22:19. https://doi.org/10.1186/s12968-020-00610-6.
21. Vermersch M, Longère B, Coisne A, et al. Compressed sensing real-time cine imaging for assessment of ventricular function, volumes and mass in clinical practice. Eur Radiol. 2020;30:609–19. https://doi.org/10.1007/s00330-019-06341-2.

22. Lancellotti P, Nikono VT, Badano LP, et al. Expert consensus for multimodality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr. 2015;26:1013–32. https://doi.org/10.1093/ehjci/jet238.

23. Muscogiuri G, Suranyi P, Eid M, et al. Pediatric cardiac MR imaging: practical preoperative assessment. Magn Reson Imaging Clin N Am. 2019;27:243–62. https://doi.org/10.1016/j.mric.2019.01.004.

24. Hisao A, Yousaf U, Alley MT, et al. Improved quantification and mapping of anomalous pulmonary venous flow with four-dimensional phase-contrast MRI and interactive streamline rendering. J Magn Reson Imaging. 2015;42:1765–76. https://doi.org/10.1002/jmri.24928.

25. Hanneman K, Kino A, Cheng JY, et al. Assessment of the precision and reproducibility of ventricular volume, function, and mass measurements with ferumoxytol-enhanced 4D flow MRI. J Magn Reson Imaging. 2016;44:383–92. https://doi.org/10.1002/jmri.25180.

26. Jacobs KG, Chan FP, Cheng JY, et al. 4D flow vs. 2D cardiac MRI for the evaluation of pulmonary regurgitation and ventricular volume in repaired tetralogy of Fallot: a retrospective case control study. Int J Cardiovasc Imaging. 2020;36:657–69. https://doi.org/10.1007/s10554-019-01751-1.

27. Bock J, Frydrychovicz A, Stalder AF, et al. 4D phase contrast MRI at 3 T: effect of standard and blood-pool contrast agents on SNR, PC-MRA, and blood flow visualization. Magn Reson Med. 2010;63:330–8. https://doi.org/10.1002/mrm.22199.

28. Gabbour M, Schnell S, Jarvis K, et al. 4-D flow magnetic resonance imaging: blood flow quantification compared to 2-D phase-contrast magnetic resonance imaging and Doppler echocardiography. Pediatr Radiol. 2015;45:804–13. https://doi.org/10.1007/s00247-014-3246-z.

29. Kramer CM, Barkhausen J, Bucciarelli-Ducci C, et al. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. J Cardiovasc Magn Reson. 2020;22:17. https://doi.org/10.1186/s12968-020-00607-1.

30. Kamphuis VP, Roest AAW, Ajmone MN, et al. Automated cardiac valve tracking for flow quantification with four-dimensional flow MRI. Radiol. 2019;290:70–8. https://doi.org/10.1148/radiol.2018180807.

31. Pruitt A, Rich A, Liu YM, et al. Fully self-gated whole-heart 4D flow imaging from a 5-minute scan. Magn Reson Med. 2021;85:1222–36. https://doi.org/10.1002/mrm.28491.

32. Vial J, Bouzener R, Pichois R, et al. MRI assessment of right ventricular volumes and function in patients with repaired Tetralogy of Fallot using kat-ARC accelerated sequences. AJR Am J Roentgenol. 2020;215:807–17. https://doi.org/10.2214/AJR.19.22726.

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