Assessment of early diastolic intraventricular pressure gradient in the left ventricle among patients with repaired tetralogy of Fallot

Running head: Early diastolic IVPG in repaired TOF

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Abstract

Assessment of left ventricular (LV) dysfunction is vital in patients with repaired tetralogy of Fallot (rTOF). The early diastolic intraventricular pressure gradient (IVPG) in the LV plays an important role in diastolic function. IVPG is calculated as the intraventricular pressure difference divided by the LV length, which allows to account for differences in LV size and therefore calculate IVPG in children. We aimed to investigate the mechanisms of LV diastolic dysfunction by measuring mid-to-apical IVPG as an indicator of the active suction force sucking blood from the left atrium into the LV. We included 38 rTOF patients and 101 healthy controls. The study population was stratified based on age group into children (4–9 years), adolescents (10–15 years) and adults (16–40 years). IVPGs were calculated based on mitral inflow measurements obtained using color M-mode Doppler echocardiography. Although total IVPGs did not differ between rTOF patients and controls, mid-to-apical IVPGs in adolescents and adults were smaller among rTOF patients than among controls (0.15 + 0.05 vs. 0.21 + 0.06 mmHg/cm, $p < 0.05$; 0.09 + 0.07 vs. 0.17 + 0.05 mmHg/cm, $p < 0.001$; respectively). Additionally, only mid-to-apical IVPG correlated linearly with peak circumferential strain ($\rho = 0.217$, $p = 0.011$), longitudinal strain ($\rho = -0.231$, $p = 0.006$), torsion ($\rho = -0.200$, $p = 0.018$), and untwisting rate in early diastole ($\rho = -0.233$, $p = 0.006$). In rTOF, the mechanisms underlying diastolic dysfunction involve reduced active suction force, which correlates with reduced LV deformation in all directions.

Keywords: Tetralogy of Fallot; Intraventricular pressure gradient; Diastolic dysfunction; Echocardiography

Introduction

In patients with repaired tetralogy of Fallot (rTOF), it is vital to detect left ventricular (LV) systolic dysfunction as early as possible, because LV dysfunction is one of the strongest determinants of poor clinical outcomes in these patients [1]. LV dysfunction is usually observed late after surgical correction of tetralogy of Fallot (TOF) [2], and its precise mechanisms remain unclear. Because ventricular diastolic dysfunction may predate systolic dysfunction and clinical symptoms [3], it is important to detect diastolic dysfunction both accurately and early. However, it is difficult to assess diastolic dysfunction in patients with rTOF by using conventional echocardiographic methods because such methods cannot distinguish the contribution of factors such as impaired myocardial relaxation, decreased recoil attributable to a stiffer ventricle, and dyssynchronous ventricular relaxation [4]; moreover, conventional echocardiographic measurements do not account for key features noted in patients with rTOF, including abnormal muscle structure, presence of an artificial patch, and abnormal pre- and after-load of ventricles [1, 3, 4].

The suction force that sucks blood from the left atrium (LA) into the LV during early diastole correlates with the tau index and represents the gold-standard indicator of diastolic function [5], where it plays a fundamental role [6-9]. This force is based on the intraventricular pressure difference (IVPD). While cardiac catheterization was previously necessary for measuring the IVPD, Greenberg et al. described a non-invasive method based on echocardiography [10]. Furthermore, assessment of IVPD in LV

segments (e.g., basal or mid-to-apical IVPD) has provided new and deep insight into the mechanisms underlying diastolic function [6,9]. Specifically, mid-to-apical IVPD was found to be an indicator of active suction force [6,9], which is more important when assessing diastolic function in a clinical setting, while basal IVPD was mainly affected by LA pressure.[9] Despite the usefulness of segmental IVPDs for the analysis of diastolic dysfunction [6,9,11], to the best of our knowledge, no previous study has employed this approach for the assessment of diastolic function in patients with rTOF.

When cardiac function is assessed in the pediatric population, the size of the heart represents an important issue to be considered, as the LV in adolescents and adults is almost twice as long as the LV in infants. Popovic et al. demonstrated the effect of LV size on the magnitude of IVPD and recommended the use of the intraventricular pressure gradient (IVPG) instead [12]. Since the IVPG is calculated as the IVPD divided by the LV length, LV size can be accounted for, and cardiac function can be accurately assessed in pediatric patients.

In the present study, we aimed to investigate the mechanistic details of LV diastolic dysfunction in patients with rTOF. As our study included also pediatric patients, we used IVPG, rather than IVPD, to assess diastolic dysfunction. Furthermore, we obtained and analyzed segmental IVPGs, with special focus on mid-to-apical IVPG.

Materials and methods

We performed a prospective echocardiographic study of consecutive patients who visited the Department of Pediatrics at Juntendo University Hospital between May 2013 and September 2015. The inclusion criteria were as follows: (1) rTOF, (2) age between 4 and 40 years, (3) normal sinus rhythm, (4) absence of chromosomal defects, and (5) absence of other systemic diseases. Data regarding the rTOF patients were compared with those regarding controls of within the same age and sex group. The controls were recruited from among non-cardiac patients (evaluated for non-cardiac chest pain or presenting with innocent cardiac murmurs) or local community volunteers examined at Juntendo University or Shizuoka Children's Hospital. The inclusion criteria for the controls were: no history of cardiovascular disease, normal sinus rhythm on electrocardiography, and normal echocardiographic findings. The study was approved by our local institutional review board. Written, informed consent for participation was obtained from all participants or their legal guardians.

Echocardiography

All subjects underwent full echocardiography performed using a GE Vivid E9 device (GE Healthcare, Milwaukee, WI, USA) equipped with an S6 or M5S probe. For each plane, three consecutive cardiac cycles were acquired while the participant held their breath at end-expiration. In younger children, we selected three cardiac cycles from the end-expiration phase. LV end-diastolic volume, end-systolic

volume, and ejection fraction were calculated with the modified Simpson method using the measurements obtained in the apical two- and four-chamber views. The mitral inflow E-wave, A-wave, E/A ratio, duration from the onset of the Q-wave to aortic valve closure, and mitral valve opening were measured using pulse-wave Doppler. The peak myocardial velocities during early diastole (e') were measured at the mitral lateral annulus by using tissue Doppler imaging. The pressure gradient at the right ventricular outflow tract was estimated based on the peak continuous-wave Doppler velocity. The right ventricular end-diastolic area, end-systolic area, and fractional area change were measured as described in the relevant guidelines [13]. In addition, color M-mode measurements were obtained using the apical four-chamber view [7,10]. Three LV short-axis planes at the basal, mid, and apical levels were acquired at frame rates of 75–115 frames/s. For each plane, 3 consecutive cardiac cycles were acquired and stored digitally for offline analysis using the EchoPAC system version 108.1.4 (GE Healthcare, Milwaukee, WI, USA).

Measurements of LV deformation

The following parameters characterizing myocardial deformation were measured according to a protocol described in detail elsewhere [14]: peak torsion, untwisting rate during early diastole, peak circumferential strain, peak circumferential strain rate during early diastole, peak longitudinal strain, and peak longitudinal strain rate during early diastole.

Measurements of IVPGs

For the measurement of IVPG, color M-mode images were analyzed with an in-house code written in MATLAB (The MathWorks, Natick, MA, USA) using the following image-processing algorithm (Figure 1):

$$(\partial P)/(\partial s) = -\rho \cdot ((\partial v)/(\partial t) + v \cdot (\partial v)/(\partial s)) \quad (1)$$

The images were reconstructed using a de-aliasing technique. In Equation (1), P is the pressure, ρ is a constant representing the density of blood (1060 kg/m3), v is the transmitral flow velocity, s is the position along the scan line (i.e., a line along the transmitral flow where the color Doppler M-mode measurements were taken), and t is the time. The relative pressures within the region of interest can be calculated from the reconstructed velocity field [6]. At each point along the scan line, the relative pressure was expressed as the difference between the pressure at that position and the pressure at the position of the mitral annulus at aortic valve closure. By calculating the line integral along the scan line, the temporal profile of the LV apex pressure relative to the LA pressure was obtained. Subsequentlty, the peak IVPD from the mitral valvular annulus to the LV apex was calculated as described in detail elsewhere [6,7,10], via a protocol previously validated against direct measurements using micromanometers [7,10]. All data were measured from at least three beats, and the mean values were used for the final analysis. Because our study population included participants from three age groups and the LV length was almost twice as high in adults than in children, we calculated the IVPG

as IVPD divided by LV length [12].

The total IVPG was divided into the basal and mid-to-apical IVPG (Figure 2). The basal segment was defined as the first third of the LV length from the mitral valve to the LV apex; the remaining segment, which measured two-thirds of the LV length, was defined as the mid-to-apical segment. We applied this approach because some of our patients were children, and therefore the ventricular space could only be divided using relative distances. For comparison, previous studies that included only adults defined the basal segment as the first 2 cm from the mitral valve [6,9], which would have been inappropriate in our pediatric participants. To quantify the characteristics of segmental IVPGs, the values were expressed as percentages of segmental IVPG from the total IVPG (i.e., as basal IVPG/total IVPG · 100 and mid-to-apical IVPG/total IVPG · 100).

Grouping

The study population was stratified according to age: the groups of children with (TOF1) or without rTOF (Control1) included participants aged 4–9 years; the groups of adolescents with (TOF2) or without rTOF (Control2) included participants aged 10–15 years; and the groups of adults with (TOF3) or without rTOF (Control3) included participants aged 16–40 years.

Statistical analysis

All data are expressed as means ± standard deviations. After evaluating data for normality, between-group differences were assessed using one-factor analysis of variance with a post hoc Tukey-Kramer comparison test for data with normal distributions or with the Steel-Dwass test for data with non-normal distributions. The correlation between IVPGs and each variable was evaluated using the Spearman correlation coefficient, which was expressed as ρ, as some values showed non-normal distributions. To estimate intra-observer reliability for IVPG measurements, randomly selected 5 patients and 5 controls were examined in the same manner. Two independent observers analyzed the same images, and one blinded observer repeated the analysis on a separate day. Bland-Altman limits of agreement analysis was used for assessing intra-observer and inter-observer reliability. Statistical significance was set at $p < 0.05$. Analyses were performed using JMP® version 8.1 (SAS Institute Inc., Cary, NC, USA).

Results

The baseline characteristics and results of the conventional echocardiographic measurements of the 38 patients with rTOF and 101 controls included in the study are listed in Table 1. The detailed characteristics of the patients who underwent rTOF are listed in Table 2. In terms of cardiac dysfunction, all patients were classified as having New York Heart Association functional class 1

without any clinical symptoms.

IVPG measurements

Representative data collected in normal controls and in patients with rTOF are shown in Figure 2. An overview of the total and segmental IVPG measurements is provided in Figure 3 (see also supplementary Table 1). Regarding the relationship between IVPG and age, the total IVPG did not differ significantly between rTOF patients and controls. Although total IVPG was smaller in adults with rTOF than in children with rTOF (TOF3 vs. TOF1), no such difference was noted among controls. For each age group, basal IVPG was higher in patients with rTOF than in controls. However, there was no significant difference in basal IVPG between patients with rTOF and controls when the data for all age groups were pooled. The mid-to-apical IVPG in adolescents and adults were lower among patients with rTOF than among controls (TOF2 vs. Control2; TOF3 vs. Control3; respectively). Interestingly, mid-to-apical IVPG was lower in adults with rTOF than in children with rTOF (TOF3 vs. TOF1). The % of mid-to-apical IVPG was significantly smaller in patients with rTOF than in controls for all age groups. Furthermore, the % of mid-to-apical IVPG was significantly smaller in adults with rTOF than in children with rTOF (TOF3 vs. TOF1), although no such difference was noted among controls. The % of basal IVPG was significant larger in patients with rTOF than in controls for all age groups. Moreover, the % of basal IVPG was significantly larger in adults with rTOF than in

children with rTOF (TOF3 vs. TOF1), while no such difference was noted among controls.

LV deformation parameters

Myocardial deformation measurements are listed in table 3. Torsion and untwisting rate in absolute values were significant smaller in children and adolescents with rTOF than in controls (TOF1 vs. Control1; TOF2 vs. Control2, respectively). The absolute value of the circumferential strain in adolescents was smaller among patients with rTOF than among controls (TOF2 vs. Control2). The absolute value of longitudinal strain in both adolescents and adults was significant smaller in patients with rTOF than in controls (TOF2 vs. Control2; TOF3 vs. Control3; respectively). In each age group, neither the circumferential nor the longitudinal strain rate differed between patients with rTOF and controls.

Relationship between LV deformation and inflow parameters and IVPGs

Both torsion and untwisting rate correlated only with mid-to-apical IVPG, and not with basal IVPG. As the value of the untwisting rate was negative, the correlation coefficient between the untwisting rate and mid-to-apical IVPG was negative. Similarly, circumferential and longitudinal strain correlated only with mid-to-apical IVPG, and not with basal IVPG. As the values of these parameters were negative, their correlation coefficient describing the relationship with mid-to-apical IVPG was

negative. On the other hand, the circumferential and longitudinal strain rates correlated mainly with basal IVPG and total IVPG. The peak E and E/e' correlated with the total and basal IVPG, but not with mid-to-apical IVPG.

Intra- and inter-observer variabilities

Bland–Altman analyses indicated excellent intra- and inter-observer reliabilities for the measurement of total, basal, and mid-to-apical IVPG (Figure 4). Intra- and inter-observer reliabilities were excellent for total, basal and mi-to-apical IVPG.

Discussion

Mechanisms to create mid-to-apical IVPG

Although the total IVPG did not differ significantly between patients with rTOF and controls, segmental IVPG did. Therefore, it is worth to consider the role of each segment for diastolic function. The first concern is which segment creates the active suction force, as this is an important part of diastolic function [6,9] and it correlates with the tau index [8]. Previous reports have focused on segmental IVPD in an effort to analyze the mechanisms underlying this force. Steine et al. [5] showed that, in an experimental model of ischemia, the peak early diastolic IVPD was decreased only in the apical portion, with abnormal LV motion, suggesting that the force acted only in the apical segment.

Several reports also suggested a similar mechanism of reduced suction force in the apical segment in patients with diastolic dysfunction [5,6,15]. The second concern refers to the factors affecting the magnitude of the suction force. The major determinant of diastolic suction is the elastic energy stored during systole [16,17,18]. Nikolic et al. [16] showed that the suction volume from the LA to the LV during diastole was directly related to the magnitude of the LV elastic recoil as a potential energy stored during systole. As the circumferential and longitudinal strains represent the magnitude of LV deformation, these parameters relate to the elastic recoil in the circumferential and longitudinal directions, respectively. In our study, the values of the circumferential and longitudinal strains correlated only with mid-to-apical IVPG, and not with basal IVPG. Based on the theories descried above, these correlations are considered to be very reasonable.

Besides the strain, torsional deformation is also considered to play an important role in LV diastolic function to create active suction. Systolic torsional deformation is one of the mechanisms by which potential energy is stored during ejection, in the form of a global LV “spring” [8]; this energy is promptly released during the isovolumetric relaxation time and early diastole, and can be estimated as the peak untwisting rate, which is proportional to the tau index and IVPD [8]. We found that the torsion and untwisting rate were lower in rTOF patients than in controls, which is consistent with the findings of previous studies [14, 15], and moreover showed a significant correlation with mid-to-apical IVPG. Therefore, reduced torsional deformation is also considered an important causative factor of diastolic

dysfunction in rTOF.

Mechanisms of elevation of basal IVPG

Unlike mid-to-apical IVPG, basal IVPG was higher in rTOF patients than in controls for all age groups. Patients with rTOF are speculated to have abnormal LV diastolic function with abnormally high E/e' [4, 19], which is associated with elevated LA pressure [19]. Iwano et al. [9] concluded that, in patients with diastolic heart failure, basal IVPD was preserved because of an increase in LA pressure, and this basal IVPD maintained the peak E despite reduced LV suction. Our data showed that both E and E/e' correlated only with basal IVPG, and not with mid-to-apical IVPG, suggesting that elevation of basal IVPG in rTOF was indeed caused by elevated LA pressure. Although the LA pressure in patients with diastolic dysfunction increases at the stage of reduced LV compliance, we noted that the absolute value of IVPG was very small. Therefore, although our data may reflect elevated LA pressure, it is not clear whether basal IVPG is clinically useful or not.

Clinical implications

In patients with TOF, the extent of LV deformation may decrease for a variety of reasons such as pressure overload [14], volume overload of the right ventricle with unfavorable ventricular–ventricular interactions [20], abnormal muscle fiber structure [21], duration and severity of preoperative cyanosis,

cardiopulmonary bypass, patching of the ventricular septal defect, myocardial fibrosis, and ventricular dyssynchrony [2, 20-23]. Regarding LV deformation parameters and clinical outcomes in patients with rTOF, Diller et al. recently showed that conventional echocardiographic parameters such as EF and E/e' were not useful predictors, whereas longitudinal strain was one of the strongest predictors [1]. On the contrary, Orwat et al. reported that, in younger patients with TOF, the strongest prognostic marker was circumferential strain [24]. Therefore, it may be considered that the usefulness of circumferential and longitudinal strains as indicators of clinical outcome has been confirmed.

The magnitude of the differences between rTOF patients and controls was much higher for mid-to-apical IVPG than for longitudinal or circumferential strains. Specifically, relative to the values noted in controls, mid-to-apical IVPG was 34% lower in adolescents and 50% lower in adults with rTOF, whereas circumferential and longitudinal strains were only 17%–20% lower. This finding is likely related to the fact that a decrease in ventricular deformation in any direction (i.e., circumferential strain, longitudinal strain, and torsion) affects mid-to-apical IVPG, as suggested by the correlations we found shown between mid-to-apical IVPG and LV deformation parameters. Therefore, compared to LV deformation parameters, a reduced mid-to-apical IVPG may represent a be more sensitive indicator of LV dysfunction and clinical outcomes.

Limitations

Several potential limitations should be considered. First, although the accuracy of echocardiography-based measurement of IVPD has been validated by comparison to direct measurements using micromanometers [7,20], such validation was not performed in studies involving human children. However, the fundamental structure and motion of the LV are thought to be the same as those in the models used for validation. Specifically, Popović et al. [12] showed the utility of IVPG data in small animals, where the size of the heart is smaller than that in human infants. Therefore, the measurement approach used in the present study is considered to be accurate. Second, as this study included a small number of patients, the conclusions may be underpowered. Studies with a larger sample size are needed before a robust conclusion can be put forth regarding the usefulness of mid-to-apical IVPD as an early marker of LV dysfunction in patients with rTOF.

Conclusions

Regarding the mechanisms underlying LV diastolic dysfunction, our findings suggest that patients with rTOF have reduced mid-to-apical IVPG, which indicates reduced active suction force related with reduced LV deformation. The measurement of mid-to-apical IVPG may be useful for quantifying diastolic dysfunction in patients with rTOF. These represent new insights regarding diastolic dysfunction in patients with rTOF.

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Compliance with ethical standards

Conflict of interest: The authors declare that there is no conflict of interests.

Ethical approval: All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study, or from their legal representatives.

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Figure Legends

Figure 1. Calculation of the intraventricular pressure gradient (IVPG). From the four-chamber view showing mitral inflow (a), the corresponding color M-mode Doppler image is captured (b) with the cursor parallel to the mitral inflow in an apical four-chamber view. The zero line of the Nyquist limit for two-dimensional color Doppler imaging is placed on the lower edge of the scale, and the Nyquist limit was set at 30% above the peak E wave velocity to mitigate the aliasing phenomenon. Euler's equation, shown in Equation (1), was used to calculate the intraventricular pressure difference at each point. A three-dimensional temporal and spatial profile of the IVPG is generated (c). Subsequently, the total IVPG (d) and segmental IVPGs (e) in early diastole are identified.

Figure 2. Examples of intraventricular pressure gradients (IVPGs) in normal controls (a to d) and in patients with rTOF (e to h). In normal controls, the mid-to-apical IVPG is maintained (d). However, the IVPG decreased rapidly in the basal segments, and a reduced mid-to-apical IVPG was observed in rTOF patients with very small apical IVPG (h).

rTOF = repaired tetralogy of Fallot; AoV = Aortic valve

Figure 3. Box plots of the distribution of values for intraventricular pressure differences and gradients. The study population was composed of TOF patients and normal controls, and was stratified according

to age group as follows: TOF1 and Control1, 4–9 years; TOF2 and Control2, 10–15 years; and TOF3 and Control3, 16–40 years. *$p < 0.05$ and **$p < 0.001$ refer to comparisons between TOF and controls from the same age group; †$p < 0.05$ and refer to comparisons between TOF1 and TOF2 or TOF3, or between Control1 and Control2 or Control3.

IVPG = intraventricular pressure gradient

Figure 4. Bland-Altman plots depicting intraobserver and interobserver reliability for the measurement of = intraventricular pressure gradient (IVPG) values. Total IVPG (a, b), basal IVPG (c, d), and mid-to-apical IVPG (e, f) were measured in 10 subjects.

IVPG = intraventricular pressure gradient

Table

Table1

Baseline characteristics and basic measurements

	TOF 1 (n=12)	TOF 2 (n=13)	TOF 3 (n=13)	Control 1 (n=32)	Control 2 (n=33)	Control 3 (n=36)
Age (y)	7.0 ± 1.3	13.0± 1.2 †	24.2± 7.1 † † §§	7.7 ± 1.3	12.4 ± 1.3 ††	25.7 ± 5.4 †† §§
Male / Female	6/6	8/5	4/9	19/12	1716	18/18
Body Height (cm)	115 ± 9	153 ±8 ††	160 ±11 ††	122 ± 9	151 ± 8 ††	166 ± 9 †† §§
Body Weight (kg)	19.3 ± 4.0	46.8 ± 11.2 ††	56.3 ± 8.4 †† §	24.1 ± 4.5	43.8 ± 7.4 ††	59.8 ± 10.9 †† §§
Body surface area (m^2)	0.79 ± 0.11	1.41 ± 0.19 ††	1.58 ± 0.15 ††	0.90 ±0.11	1.36 ± 0.13 ††	1.66 ± 0.19 †† §§
Heart rate (bpm)	81.0 ± 15.9	69.0 ± 7.1 †	58.3 ± 8.0 †† §	76.1 ± 10.4	69.7 ± 10.8	61.2 ± 8.1 †† §
Systolic blood pressure (mmHg)	94.7 ± 7.0	99.2 ±12.6	113.8 ±11.6 ††§	99.9 ± 9.3	106.2 ± 9.9 ††	118.1±12.0 ††
Diastolic blood pressure (mmHg)	50.0 ± 6.9	55.8 ± 6.8 ††	66.1 ± 9.9 ††	54.0 ± 8.3	59.0 ± 9.2 ††	70.1 ± 9.6 †† §§
LV Length (cm)	5.71 ± 0.57	7.54 ± 0.51 ††	7.62 ± 0.63 ††	5.78 ± 0.51	7.10 ± 0.63 ††	7.90 ± 0.78 †† §§
LV EDV/BSA (ml/m^2)	46.4 ± 6.9	52.4 ± 17.2	45.8 ± 8.4	44.5 ± 9.7	46.6 ± 12.6	49.0 ± 14.6
LV ESV/BSA (ml/m^2)	15.6 ± 2.5	17.3 ± 6.6	16.3 ± 4.2	14.9 ± 4.4	15.5 ± 4.8	17.9 ±5.9
LV ejection fraction (%)	66.1 ± 3.3	67.6 ± 4.2	64.4 ± 5.7	66.7 ± 3.7	66.9 ± 4.0	63.3 ± 4.5 † §

E (m/sec)	1.20 ± 0.20 *	1.29 ± 0.10 **	1.01 ±0.23 † §§	1.02 ± 0.13	1.07 ± 0.17	0.91 ± 0.14 §
A (m/sec)	0.50 ± 0.18	0.44 ±0.08	0.44 ±0.08	0.45 ± 0.09	0.50 ± 0.13	0.48 ± 0.10
E/A ratio	2.71 ± 1.12 **	2.97 ± 0.72 *	2.42 ± 0.70	2.34 ± 0.57	2.24 ± 0.55	1.98 ± 0.55
e' lateral (cm/sec)	14.4 ± 3.9*	17.2 ± 4.8	15.1 ± 3.1	18.9 ± 2.4	18.8 ± 3.4	18.0 ± 2.8
E/e' ratio	9.20 ± 3.92 **	8.09 ± 2.37 *	6.93 ± 2.03 * †	5.48 ± 1.01	5.83 ± 1.22	5.13 ± 0.94
RV EDA/BSA (cm^2/m^2)	14.8 ± 4.0 **	14.1 ± 3.1 *	11.4 ± 1.7 *	10.5 ± 2.9	10.1 ± 3.6	7.9 ±2.6 † §
RV ESA/BSA (cm^2/m^2)	6.7 ± 3.1	6.6 ± 1.8	5.3 ± 1.3	5.0 ± 1.8	5.0 ± 2.2	3.8 ± 1.7
RV Fractional Area Change (%)	55.7 ± 11.3	53.2 ± 7.2	53.1 ± 8.9	53.1 ± 9.1	52.5 ± 8.1	52.7 ± 9.0
TAPSE (mm)	14.7 ± 3.4 **	16.3 ± 2.9 **	15.6 ± 3.0 **	19.2 ± 2.1	21.0 ± 3.9	21.5 ± 2.7 †
MAPSE (mm)	14.0 ± 3.0	15.8 ± 2.5	14.7 ± 2.7	13.0± 1.9	14.5 ± 2.0 †	14.7 ± 1.6

TOF = Tetralogy of Fallot; LV = left ventricle; EDV = end diastolic volume; ESV = end systolic volume; BSA = body surface area; RV = right ventricle; EDA = end diastolic area; ESA = end systolic area;

The study population was composed of TOF patients and normal controls, and was stratified according to age group as follows: TOF1 and Control1, 4–9 years; TOF2 and Control2, 10–15 years; and TOF3 and Control3, 16–40 years. *$p < 0.05$ and **$p < 0.001$ refer to comparisons between TOF and controls from the same age group; †$p < 0.05$ and ††$p < 0.001$ refer to comparisons between TOF1 and TOF2 or TOF3, or between Control1 and Control2 or Control3; §$p < 0.05$ and §§$p < 0.001$ refer to comparisons between TOF2 and TOF3, or between Control2 and Control3.

Table2 Patient Characteristics			
	TOF 1 (n=12) 4-9y	TOF 2 (n=13) 10−15 y	TOF 3 (n=12) ≧16 y
Age at repair （year）	1.5 ± 0.5	1.4 ± 0.5	2.6 ± 1.2
Duration from the repair (year)	5.5 ± 1.5	11.7 ± 1.2	21.6 ±6.3
Transannular patch (TAP), n (%)	8 ()	9 ()	8 (66.7)
Non transannular patch, n (%)	4 (33.3)	1 (7.7)	5(41.7)
Rastelli , n (%)	0 (0)	3 (23.1)	0 (0)
previous shunt palliation, n (%)	5 (41.7)	3 (23.1)	4 (33.3)
Pulmonary regurgitation ≧ moderate, n (%)	9 (75.0)	9 (69.2)	8 (66.7)
RVOT pressure gradient (mmHg)	17.8 ±13.9	28.7 ± 12.4	21.2 ± 9.7
QRS duration (msec)	124 ± 24	121 ± 27	134 ± 35
NYHA class ≧Ⅱ (%)	0	0	0

TOF = Tetralogy of Fallot; RVOT = right ventricular outflow tract; NYHA = New York Heart Association

Table 3

Myocardial deformation measurements

	TOF 1 (n=12)	TOF 2 (n=13)	TOF 3 (n=13)	Control 1 (n=32)	Control 2 (n=33)	Control 3 (n=36)
Torsion (degree)	8.0 ± 3.4 *	7.4 ± 4.0 **	8.6 ± 5.3	9.1 ± 4.5	13.6 ± 3.2 ††	11.8 ± 4.8
Untwisting rate (degree/sec)	-87.6 ± 36.7 *	-68.0 ± 32.1 *	-74.0 ± 32.8	-93.0 ± 36.5	-111.6 ± 27.8	-95.9 ± 33.3
CS (%)	-16.1 ± 3.8	-13.9 ± 3.5 *	-15.0 ± 3.0	-16.7 ± 2.9	-17.6 ± 2.7	-16.5 ± 3.0
CSR (1/sec)	1.68 ± 0.36	1.47 ± 0.28	1.31 ± 0.25 †	1.40 ± 0.34	1.36 ± 0.29	1.22 ± 0.21
LS (%)	-17.7 ± 2.4	-13.8 ± 2.8 * ††	-14.0 ± 3.0 *	-18.8 ± 1.6	-16.7 ± 2.1 †	-16.8 ± 2.1 †
LSR (1/sec)	2.15 ± 0.46	1.92 ± 0.36	1.76 ± 0.35	2.13 ± 0.41	1.95 ± 0.41	1.81 ± 0.27 †

TOF = Tetralogy of Fallot; LV = left ventricle; IVPD = intraventricular pressure difference; IVPG = intraventricular pressure gradient; CS = circumferential strain; CSR = circumferential strain rate; LS = longitudinal strain; LSR = longitudinal strain rate

The study population was composed of TOF patients and normal controls, and was stratified according to age group as follows: TOF1 and Control1, 4–9 years; TOF2 and Control2, 10–15 years; and TOF3 and Control3, 16–40 years. *$p < 0.05$ and **$p < 0.001$ refer to comparisons between TOF and controls from the same age group; †$p < 0.05$ and ††$p < 0.001$ refer to comparisons between TOF1 and TOF2 or TOF3, or between Control1 and Control2 or Control3; §$p < 0.05$ and §§$p < 0.001$ refer to comparisons between TOF2 and TOF3, or between Control2 and Control3.

Table 4 Relationship between IVPGs and other parameters						
	Total IVPG		Basal IVPG		Mid to apical IVPG	
	ρ	p	ρ	p	ρ	p
Torsion (degree)		0.918	-	0.069	0.217	0.011
Untwisting rate (degree/sec)		0.626		0.205	- 0.231	0.006
CS (%)		0.078		0.762	-0.200	0.018
CSR (1/s)	0.390	< 0.001	0.440	< 0.001		0.305
LS (%)	-0.184	0.030		0.271	-0.233	0.006
LSR (1/s)	0.260	0.002	0.257	0.002	-	0.276
E (cm/sec)	0.457	< 0.001	0.503	< 0.001		0.124
e'		0.163		0.847	0.254	0.003
E/e'	0.178	0.037	0.303	< 0.001		0.212

TOF = Tetralogy of Fallot; LV = left ventricle; IVPD = intraventricular pressure difference; IVPG = intraventricular pressure gradient; CS = circumferential strain; CSR = circumferential strain rate; LS = longitudinal strain; LSR = longitudinal strain rate

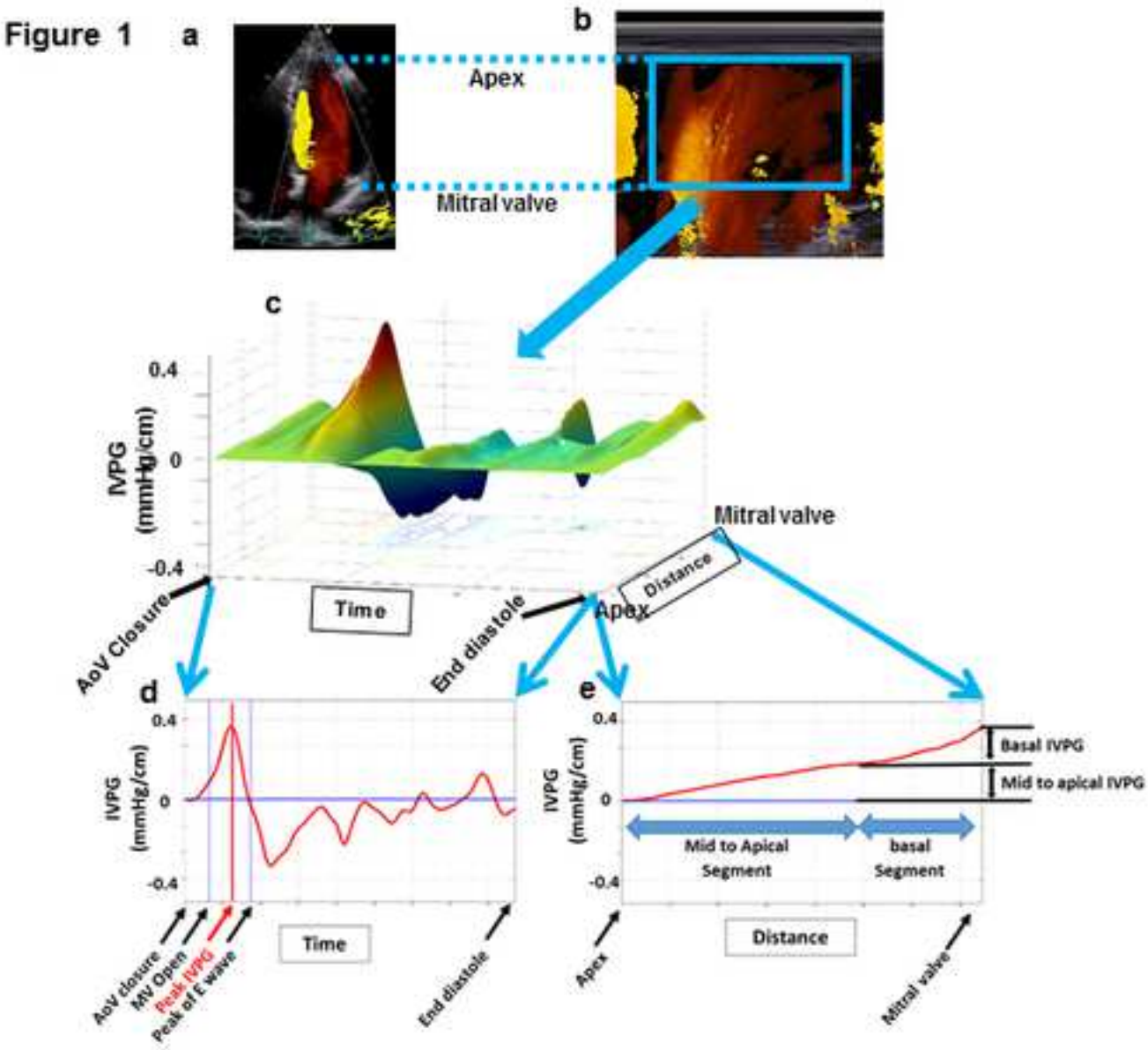

Figure 2

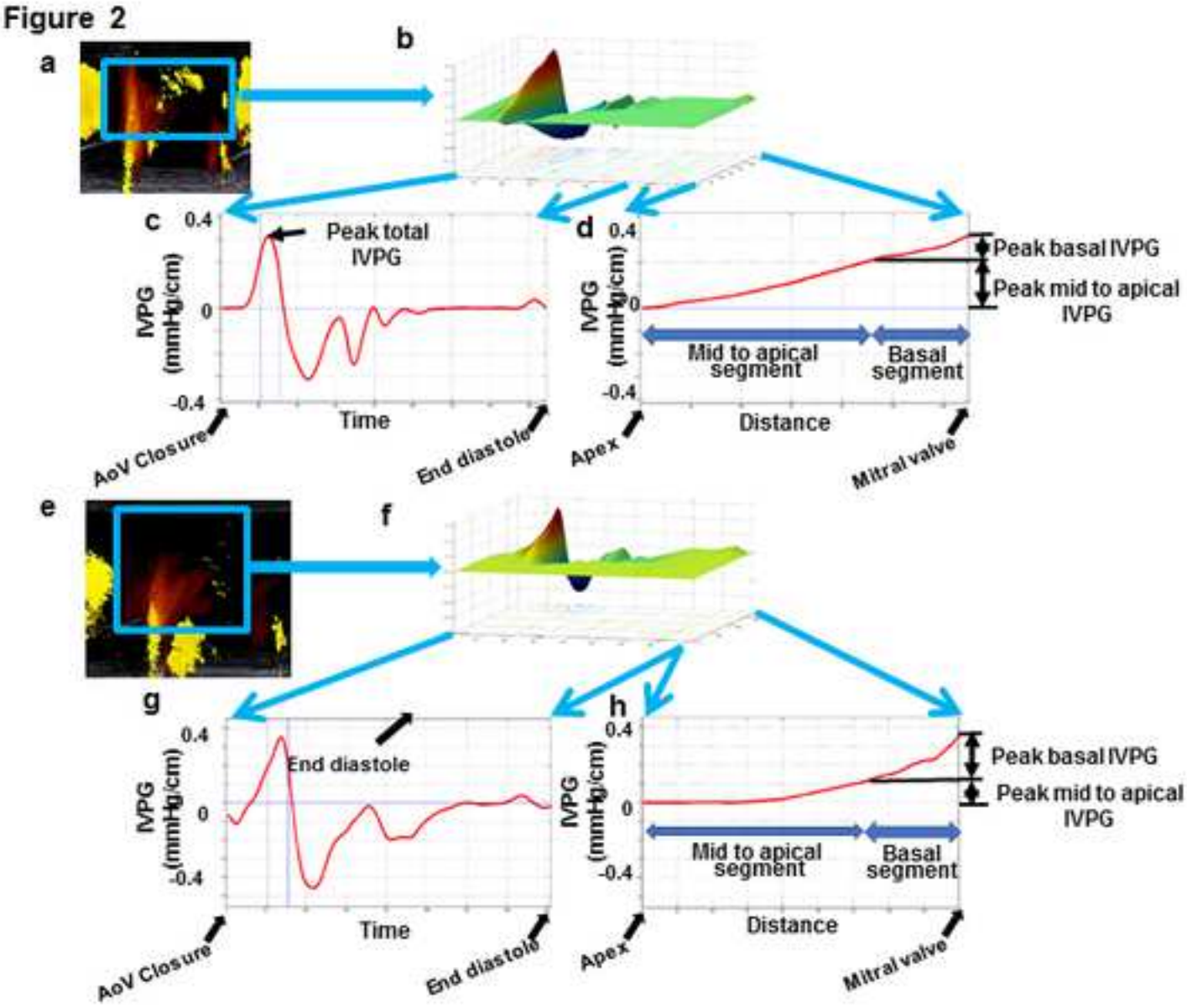

Figure3

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Figure 3

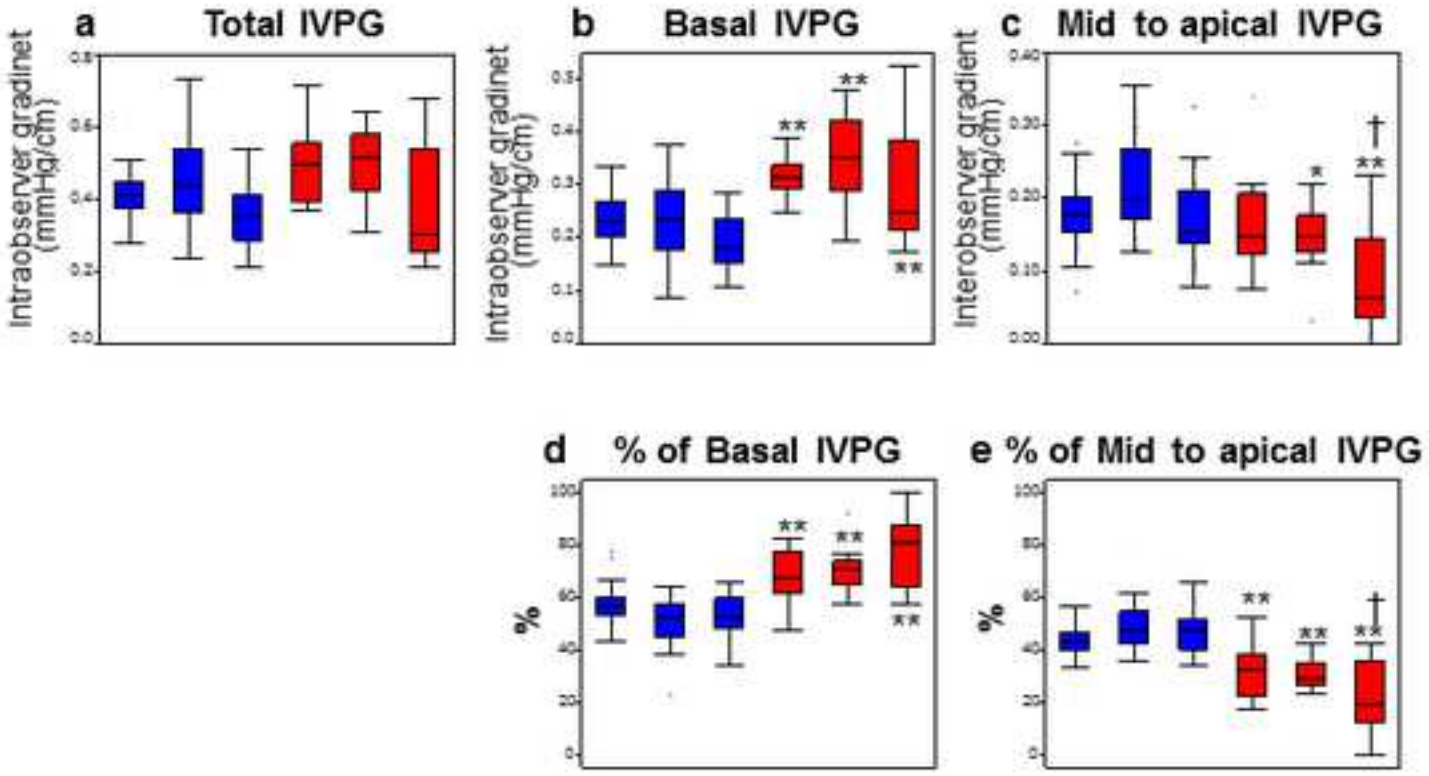
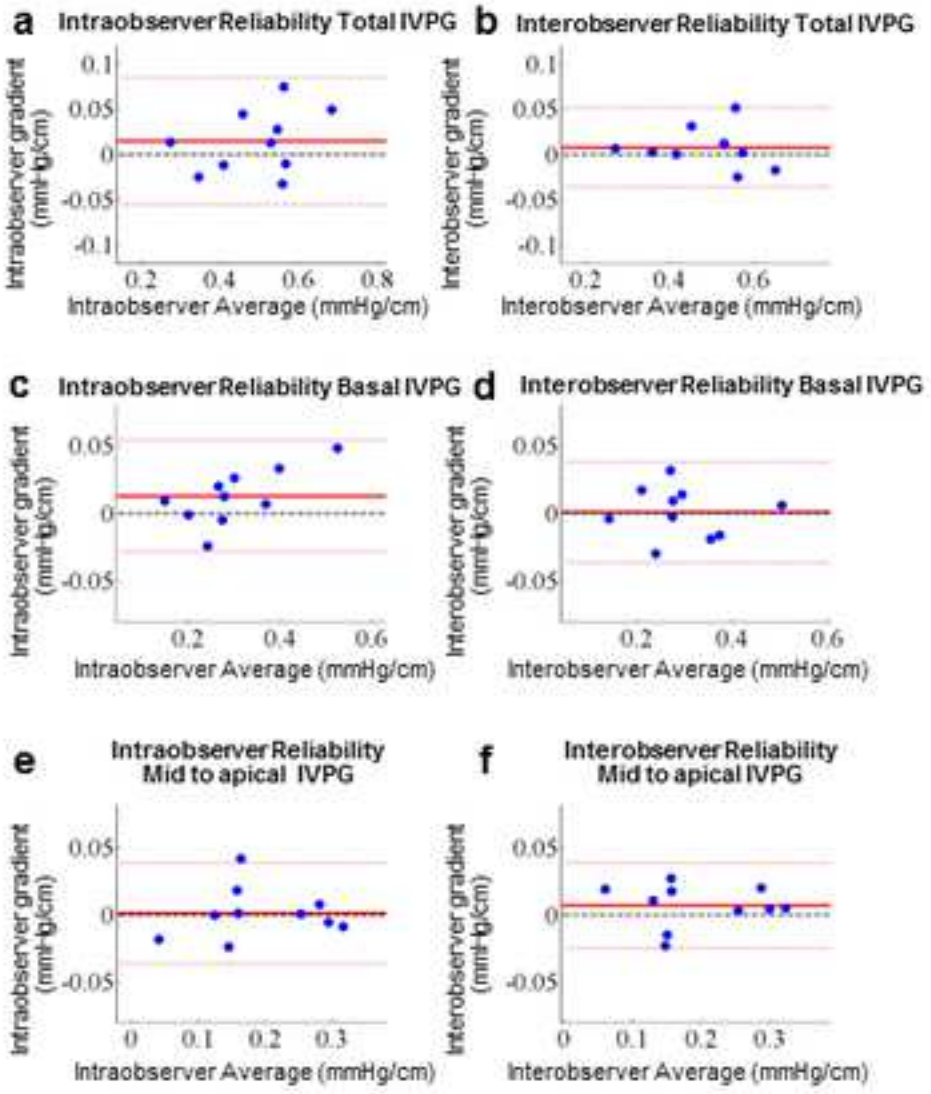


Figure 4



Supplemental table1 IVPGs and % IVPGs						
	TOF 1 (n=12)	TOF 2 (n=13)	TOF 3 (n=13)	Control 1 (n=32)	Control 2 (n=33)	Control 3 (n=36)
Total IVPG (mmHg/cm)	0.50 ± 0.11	0.50 ± 0.10	0.38 ± 0.16	0.41 ± 0.07	0.43 ± 0.11	0.36 ± 0.08
Basal IVPG (mmHg/cm)	0.33 ± 0.08 **	0.35 ± 0.11 **	0.29 ± 0.11**	0.23 ± 0.05	0.22 ± 0.07	0.19 ± 0.05
Mid to apical IVPG (mmHg/cm)	0.16 ± 0.07	0.15 ± 0.05*	0.09 ± 0.07** †	0.18± 0.4	0.21 ± 0.06	0.17 ± 0.05
% of Basal IVPG (%)	68.1 ± 9.9 **	70.4 ± 8.7 **	79.2 ± 13.4**†	57.2 ± 7.6	50.7 ± 9.5	52.5 ± 8.0
% of Mid to apical IVPG (%)	31.9 ± 9.9 **	29.6 ± 8.7 **	20.8 ± 13.4** †	42.8 ± 7.6	49.2 ± 9.5	47.6 ± 8.0

TOF = Tetralogy of Fallot; IVPG = intraventricular pressure gradient

The study population was composed of TOF patients and normal controls, and was stratified according to age group as follows: TOF1 and Control1, 4–9 years; TOF2 and Control2, 10–15 years; and TOF3 and Control3, 16–40 years. *$p < 0.05$ and **$p < 0.001$ refer to comparisons between TOF and controls from the same age group; †$p < 0.05$ refer to comparisons between TOF1 and TOF2 or TOF3.