Noninvasive Leg-Positive Pressure Stress Echocardiography Reveals Preload Reserve in Adult Patients after Complete Repair of Tetralogy of Fallot

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Non-invasive leg-positive pressure stress echocardiography reveals the preload reserve in adult patients after complete repair of tetralogy of Fallot

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Abstract

Introduction: Long-term sequelae such as right ventricular dysfunction and reduced hemodynamic reserve are the main determinants of cardiovascular outcomes after repair of tetralogy of Fallot (TOF). Echocardiographic parameters at rest offer only partial information on impaired hemodynamics in these patients, and data during stress testing are lacking. The leg-positive pressure (LPP) maneuver has recently been reported to be able to apply acute preload stress. We hypothesized that the preload reserve is impaired and ventricular interaction is exacerbated in TOF patients.

Methods: In this prospective cross-sectional study, we recruited 44 consecutive TOF patients and 30 normal controls. Echocardiography was performed both at rest and during LPP stress, and preload reserve was defined as the change between baseline stroke volume (SV) and that obtained during LPP stress. The eccentricity index was calculated as the ratio of the left ventricular antero-posterior to septal-lateral dimensions to quantify ventricular interaction.

Results: LPP stress significantly increased SV from 73±14 to 83±16 mL (P<0.01) in controls, while the increase in SV was significantly blunted (from 75±19 to 79±18 mL, P value <0.01 for interaction) in TOF patients. The eccentricity index significantly changed during LPP stress in TOF patients only from 1.07±0.13 to 1.13±0.14 (P value <0.01 for interaction). TOF patients were sub-divided into two subgroups based on the median value of increased response in SV (22 with sufficient and 22 with insufficient preload reserve). Multivariate analysis identified significant pulmonary regurgitation as the only independent determinant factor for insufficient preload reserve

(odds ratio 4.57; confidence interval 1.048-19.90, *P*=0.04).

Conclusions: In patients after repair of TOF, ventricular interaction was exacerbated and preload reserve was impaired especially in patients with significant pulmonary regurgitation. LPP stress test may direct tailored treatment approaches, risk stratification, and clinical decision making such as more aggressive pharmacologic therapy, meticulous outpatient follow-up, or earlier re-intervention.

Keywords: Leg-positive pressure stress, Preload reserve, Tetralogy of Fallot, Pulmonary regurgitation, Ventricular interaction

Abbreviations

TOF = tetralogy of Fallot

PR = pulmonary regurgitation

RV = right ventricle

LPP = leg-positive pressure

SV = stroke volume

LV = left ventricle

TAPSE = tricuspid annular plane systolic excursion

FAC = fractional area change

Tetralogy of Fallot (TOF) is the most common cyanotic congenital cardiac malformation, occurring in approximately 1 of 3,500 births and accounting for 7-10% of all congenital heart diseases.[1] Intracardiac repair of TOF has been performed for over six decades, and the survival after TOF repair continues to improve, mainly due to advances in open heart surgery. However, the majority of these patients have residual hemodynamic impairments despite early successful repair, including pulmonary regurgitation (PR), residual right ventricular (RV) outflow tract obstruction, and pulmonary stenosis, which ultimately leads to progressive RV remodeling and dysfunction.[2] Moreover, prominent RV enlargement leads to further hemodynamic disturbances through adverse ventricular interdependence.[3] As a consequence, patients after complete repair of TOF have a lower maximum cardiac output[4] and peak oxygen consumption[5] during exercise stress testing, which suggests that their hemodynamic reserve may be significantly impaired.[4, 5, 6] However, up to date, clinical data on the hemodynamic reserve in these patients are critically lacking.

A novel acute preload stress maneuver using leg-positive pressure (LPP) non-invasively redistributes the venous blood volume in the lower limbs back into the effective circulatory volume without an increase in total body fluid volume, thus revealing the preload reserve in patients with chronic heart failure.[7, 8] We hypothesized that the ability of TOF patients to utilize the Frank-Starling mechanism is impaired and ventricular interaction worsens during interventions that increase cardiac preload.

The purpose of this study was to investigate the RV preload reserve and its determinant

factors in TOF patients using acute preload stress echocardiography with LPP.

METHODS

Study Population

This prospective cross-sectional study included 44 adult patients with TOF at Kobe University hospital between April 2017 and March 2019. TOF patients, who presented to our adult congenital heart disease center and had undergone complete repair of TOF, were eligible for this study. Patients were excluded from the study if they met any of the following criteria: (1) meeting the volumetric criteria for pulmonary valve replacement due to severe PR (i.e. RV end-diastolic volume index ≥160 mL/m^2 or RV end-systolic volume index ≥80 mL/m^2),[9] (2) open-heart surgery within the last six months, (3) unstable heart failure, functional class IV according to New York Heart Association (NYHA), (4) tachyarrhythmias such as atrial fibrillation and pacemaker with non-sequential pacing mode, (5) orthopedic trauma or active skin lesions in the lower limbs, (6) history of venous thrombosis or pulmonary embolism. Based on these criteria, one patient was excluded, and 44 patients were entered in the study. The control group comprised 30 healthy volunteers with no history of cardiovascular disease and with normal electrocardiograms and two-dimensional and Doppler echocardiograms. For age- and sex-matching, variable ratio matching method was used in this study.

The study protocol was registered at the University Hospital Medical Information Network (UMIN) Clinical Trial Registry under UMIN 000038369 and conformed to the ethical principles outlined in the Declaration of Helsinki. This study was approved by the local ethics committee of our institution (No.180118), and written informed consent was obtained from all participants.

Standard Echocardiographic Examination

All echocardiographic studies were performed with a commercially available echocardiographic system (Aplio Artida; Toshiba Medical Systems, Tochigi, Japan). Digital routine cine loops were obtained from standard parasternal and apical views, and echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging.[10] The left ventricular (LV) ejection fraction and volumes were calculated using the modified biplane Simpson's method. Forward stroke volume (SV) was assessed by means of pulsed-wave Doppler method at the LV outflow tract because no patients with repaired TOF had residual intra-cardiac shunts. Cardiac output was calculated by multiplying stroke volume by heart rate.

The eccentricity index was calculated as the ratio between the LV antero-posterior (i.e. parallel to the septum) and the septal-lateral dimensions (i.e. perpendicular to the septum), which were measured in the parasternal short-axis view at end-diastole, to assess the degree of ventricular interaction. As pericardial constraint and ventricular interaction increase, the septum becomes less convex toward the RV. An eccentricity index that exceeds 1.0 indicates exacerbating ventricular

interdependence.[11] Restrictive physiology was evaluated with pulsed-wave Doppler of pulmonary artery flow with the sample volume 1 cm distal to the pulmonary valve. Restrictive physiology was present if antegrade pulmonary artery flow in late diastole could be detected throughout the respiratory cycle.[12]

The RV end-diastolic area, RV end-systolic area, and the fractional area change (RVFAC) were measured from the RV-focused apical four-chamber view.[11] Tricuspid annular plane systolic excursion (TAPSE) and peak systolic velocity (S′) of the tricuspid annulus were measured as indices of RV longitudinal systolic function.[11]

Assessment of Valvular Disease

PR was semi-quantified in the parasternal short-axis view. A PR color jet width that occupied more than 50% of the RV outflow tract width or the detection of a reversal Doppler signal in the pulmonary arteries were defined as significant PR.[13] If the severity of PR was undefined, cardiac magnetic resonance imaging (MRI) was used and a quantitative regurgitant fraction of more than 25% was defined as significant PR.[13] A peak jet velocity at the stenotic pulmonary valve or an RV outflow of more than 3 m/sec was defined as significant pulmonary stenosis.[14] A vena contracta width of more than 3 mm was considered as significant tricuspid regurgitation.[13]

Speckle-Tracking Strain Analysis

Digital 2-dimensional gray-scale data were obtained at baseline and during LPP stress. Speckle-tracking analyses of both LV and RV were performed with dedicated software (Ultra

Extend; Toshiba Medical Systems), as described previously.[15] Briefly, LV global longitudinal strain (GLS) was assessed from standard apical views, and the average values of the longitudinal strain from 3 apical views were calculated to obtain the LV-GLS. Similarly, GLS from the RV (RV-GLS) was calculated by taking an averaging of the 3 regional systolic strains from the RV free wall.[15]

Preload Stress Echocardiography

For preload stress echocardiography, we used a commercially available LPP machine (Dr. Medomer DM-5000EX, Medo Industries Co., Ltd., Tokyo, Japan). The procedure of the LPP stress maneuver was previously described.[7, 8] Briefly, the device is designed to apply continuous external pressure around both lower limbs of 100 mmHg (Figure 1, right-upper panel). This pressure has been shown to provide an effective but safe increase in cardiac preload based on evidence from invasive hemodynamic study.[8] All echocardiographic analyses were performed 20 seconds after the inflation of the air-bags. If the data acquisition time elapsed more than 3 minutes, air-bags were temporarily deflated and then re-inflated for the continued analysis so as to make sure that LPP stress could provide adequate acute preload stress. Echocardiographic measurements were obtained both at rest and during LPP stress, and the preload reserve was defined as the absolute change between baseline forward SV and forward SV obtained during LPP stress. All echocardiographic measurements were averaged from three cardiac cycles.

Statistical Analysis

Continuous variables were presented as mean values with the standard deviation for normally distributed data and as the median with interquartile range for non-normally distributed data. Categorical variables were expressed as absolute values and percentages. The parameters between the TOF patient and control group were compared by the Student *t*-test or Mann-Whitney U test, as appropriate. Proportional differences were evaluated by means of Fisher's exact test or χ^2 test, as appropriate. Differences in hemodynamic responses between the groups were tested by two-way repeated measures analysis of variance, with the case status as the grouping factor and the time point (i.e. baseline and during LPP stress) as the repeated factor. The initial univariate logistic regression analysis to identify univariate predictors of the preload reserve was followed by a multivariate logistic regression model using stepwise selection, with the *P*-values for entry into the model set at <0.10. The intraclass correlation coefficient was used to determine inter- and intra-observer reproducibility from 10 randomly selected subjects. Statistical significance for each step was defined as a *P* value <0.05. All analyses were performed with MedCalc version 18.11.6 (MedCalc Software; Ostend, Belgium).

RESULTS

Baseline Characteristics

The baseline characteristics of the 44 patients with repaired TOF and the 30 age- and sex-matched controls are summarized in Table 1. As expected, TOF patients showed significantly

more global RV remodeling along with impaired contractile function compared with normal controls. However, there was no significant difference in the baseline forward SV between the groups. Although restrictive physiology was not observed in controls, almost half of the patients with TOF showed restrictive physiology. Although the eccentricity index was found to be significantly higher in TOF patients at baseline, it was not associated with the degree of RV remodeling.

Preload Stress Test

The acute preload stress test was well tolerated by all participants without any complications associated with positive-leg pressure, and all of the standard echocardiographic data at rest and during LPP stress test could be measured in all participants. Of note, about 5 minutes were needed to determine all LPP stress data per patient using this protocol.

Table 2 shows the comparison of response to LPP stress between the TOF patients and controls. During LPP stress, most LV and RV parameters significantly increased in response to the acute preload stress in both groups, but the responses in left ventricular end-diastolic volume and RVFAC were significantly blunted in TOF patients (P=0.03, P <0.01 for interaction, respectively). As a result, the response in forward SV and cardiac output was significantly reduced in TOF patients (P value <0.01 for interaction) compared with the response in the controls (Figure 1). In 11 TOF patients, the forward SV decreased during LPP stress. The eccentricity index significantly worsened during the acute preload stress (P value <0.01 for interaction) in TOF patients only (Figure 2).

TOF Patients with and without Preload Reserve

Patients with TOF were subdivided into two subgroups based on the results of median value of increased response in SV (cut-off value of 4 mL) during LPP stress, 22 TOF patients with and 22 without preload reserve. No significant differences in terms of clinical characteristics, mode of initial surgical repair, age at initial intracardiac repair, and history of previous Blalock-Taussig shunt existed between these two subgroups (Table 3). The prevalence of restrictive physiology was quite similar between TOF subgroups. However, TOF patients without a preload reserve were more likely to have significant PR compared to those with a preload reserve (59% vs. 27%, P=0.03).

Table 4 shows a comparison of the changes in echocardiographic parameters during LPP stress testing between the two TOF patient subgroups with and without preload reserve. Although baseline RVEDA and RV-GLS were comparable between the two subgroups, both TAPSE and S' at baseline were significantly higher in TOF patients without a preload reserve. As a whole, TOF patients exhibited an increased response with regard to LV end-diastolic volume, RV end-diastolic area, and RVFAC to the preload increasing intervention. However, no significant differences were observed in the extent of the changes in these parameters between the two TOF subgroups. As regard to myocardial deformation indices, baseline LV-GLS and RV-GLS were significantly impaired at the same level in both subgroups, while both LV-GLS and RV-GLS did not increase during LPP stress only in patients without preload reserve. Although the baseline cardiac output was comparable, the response in cardiac output was significantly lower in patients without a preload reserve (P value for interaction <0.01).

Predictors of insufficient Preload Reserve

Table 5 shows the odds ratios and 95% confidence intervals of each variable determined with univariate and multivariate logistic regression analysis for the prediction of insufficient preload reserve. Although an increase in TAPSE, S', and the presence of significant PR were associated with insufficient preload reserve in the univariate analysis, in the multivariate analysis only significant PR (odds ratio: 4.57; 95% confidence interval: 1.048-19.90, *P*=0.04) was independently associated with insufficient preload reserve. Neither the presence of restrictive physiology nor the change in ventricular interaction during LPP stress predicted the hemodynamic response to acute preload stress.

Figure 3 shows the two representative cases, one of a patient with and one of a patient without preload reserve.

Reproducibility of the measurements

Agreement for speckle-tracking strain values and that of eccentricity index was generally acceptable. The intra-observer variability assessed in terms of intraclass correlation coefficient was 0.978 (95% CI: 0.915-0.995) for baseline LV-GLS, 0.990 (95% CI: 0.959-0.997) for LPP stress LV-GLS, 0.992 (95% CI: 0.967-0.998) for baseline RV-GLS, 0.992 (95% CI: 0.968-0.998) for LPP stress RV-GLS, 0.996 (95% CI: 0.985-0.999) for baseline eccentricity index, and 0.990 (95% CI: 0.959-0.997) for LPP stress eccentricity index. The inter-observer variability for these measurements was 0.936 (95% CI: 0.765-0.984), 0.946 (95% CI: 0.781-0.985), 0.923 (95% CI: 0.722-0.980), 0.942

(95% CI: 0.786-0.985), 0.959 (95% CI: 0.843-0.990), and 0.974 (95% CI: 0.899-0.994), respectively.

DISCUSSION

The major findings of this study were as follows: First, the RV functional parameters were significantly impaired in adult patients after intracardiac repair of TOF compared to controls, along with marked structural remodeling and exacerbated ventricular interaction at baseline. Second, although baseline forward SV was comparable between TOF patients and controls, preload reserve was significantly reduced, and ventricular interaction was significantly enhanced during LPP stress in TOF patients, confirming our hypothesis. Finally, significant PR was more prevalent in TOF patients without preload reserve and only independent determinant for the lack of preload reserve.

Preload Reserve in Patients after Complete TOF Repair

Even after complete intracardiac repair of TOF in their childhood, adult patients generally have sequelae, that include clinical or subclinical RV dysfunction as a consequence of initial surgical trauma, residual RV outflow tract obstruction, pulmonary stenosis, and chronic volume overload due to significant PR.[2] In chronic RV dysfunction, the reduction in cardiac output is usually compensated by ventricular dilatation. In other words, TOF patients cope with these hemodynamic impairments by recruiting the preload reserve at the expense of increased cardiac work. One can speculate that these compensatory mechanisms would easily fail in situations of hemodynamic stress or during exertion. Festa et al.[5] investigated 70 mostly asymptomatic TOF patients who underwent cardiopulmonary

exercise test.[5] They found that these patients had a 38% lower exercise capacity and 39% reduced peak oxygen consumption compared to normal subjects. More recently, Marcussio et al.[4] have expanded these results to study 21 asymptomatic TOF patients by investigating non-invasively assessed cardiac output during an exercise stress test.[4] They demonstrated that there was no significant difference in cardiac output at rest compared to normal subjects. However, these patients showed a 16% lower peak cardiac output because of their limited ability to increase forward SV during exercise. These results clearly indicate that hemodynamic reserve is latently impaired in patients after complete repair of TOF. The lack of hemodynamic reserve in patients with TOF may actually be multifactorial. These factors might include impaired RV[6] and LV[16] contractile function, bi-ventricular diastolic dysfunction,[17] presence of significant PR,[18] and adverse ventricular interdependence.[19]

In our study, the increase in cardiac output in response to LPP stress was significantly impaired in TOF patients, especially in cases with significant PR. This can be rephrased as an "exhaustion of the preload reserve". One might speculate that this exhaustion of the preload reserve may become critical under certain conditions because the true nature of RV is that of "flow generator" that pumps out a large amount of venous return into the pulmonary vasculature. Therefore, it is conceivable that the lack of preload reserve may lead to impaired exercise capacity and hemodynamic fragility in circumstances such as systemic infections, other organ diseases, pregnancy, or delivery.

Ventricular Interaction during Preload Stress

Another possible mechanism leading to exhaustion of preload reserve in TOF patients is adverse ventricular-ventricular interaction. Thus far, TOF was thought to be merely a disease of the right heart. However, there is increasing awareness of the impact of adverse ventricular interactions on the long-term outcomes after TOF repair.[19] Because both ventricles are inseparably linked at multiple levels that include the shared ventricular septum, cardiac myofibers, coronary vasculature, and pericardial sac. It is plausible that problems on one side of the heart can adversely affect the other. Previous studies demonstrated possible mechanisms of LV dysfunction associated with RV volume overload and dysfunction, e.g., a shift of the ventricular septum to the left caused by RV dilatation,[20, 21] and an association between RV and LV myocardial fibrosis as well as between RV volume overload and LV myocardial fibrosis.[22] Among these mechanisms, the leftward shift of the septum in a limited pericardial space might be the main factor in the resulting adverse ventricular interaction.

In TOF patients, the eccentricity index was significantly higher than in the controls and further increased during the LPP stress test. However, changes in the eccentricity index during LPP stress test were not independent determinants of the lack of preload reserve. This observation might explain that, while adverse ventricular interaction may be associated with the hemodynamic disturbances observed in these patients, its contribution to the lack of hemodynamic reserve may be relatively small compared to that of significant PR.

Clinical Implications

Current guidelines regarding re-intervention in patients after complete TOF repair are mainly based on the subjective symptoms, as well as the size and function of the RV.[9] However, most of these patients rarely complain of heart failure-related symptoms even in case of significant sequelae. Consequently, a practical implication of our results is that preload stress echocardiography using LPP could identify patients at potentially high-risk who are still asymptomatic but may have preclinical hemodynamic impairment before they manifest hemodynamic decompensation. Moreover, although the present study was not designed to determine the optimal timing for pulmonary valve replacement, the observations in this study are worth noting when considering pulmonary valve replacement in an asymptomatic patient after complete TOF repair.

From the practical point of view, we believe that hemodynamic analysis using LPP stress is a valuable assessment tool because it is not time consuming, highly feasible, not technically demanding, and quite easy to perform in the daily clinical settings. Therefore, we believe this novel technique may potentially be complementary to cardiopulmonary exercise test or useful when exercise stress is submaximal.

Limitations

There are certain limitations to this study. First, as with most studies on congenital heart diseases, this pilot study included a small number of patients from a single center. Thus concerns

regarding insufficient statistical power should be considered. Moreover, not all parameters that could potentially affect the preload reserve were entered into the multivariate model because of the problem of overfitting. Therefore, we could not be able to draw a definitive conclusion regarding the clinical importance of the significant PR for the lack of preload reserve in patients with TOF. Second, the relationships between the lack of preload reserve and long-term clinical outcome or exercise tolerance were not part of this study. Thus, future studies in larger patient populations should address the impact of limited preload reserves on cardiovascular outcomes and exercise capacity. Third, the cross-sectional design of this study precluded an analysis of development of ventricular dysfunction over time and the optimal timing of pulmonary valve replacement. Moreover, the data regarding serial changes in RV response to LPP stress are lacking. Fourth, because cardiac MRI could not be performed in all patients of this study, the quantitative assessment of PR, volumetric assessment of ventricular interaction,[23] and evaluation of myocardial fibrosis were not part of this study. From a practical point of view, however, hemodynamic analysis using a conventional Doppler during LPP stress could be a valuable assessment tool because it was not time-consuming, expensive, or requiring specialized equipment. It can be safely performed without the limitation of cardiac devices and easily integrated into daily clinical practice. Finally, multivariate analysis revealed the presence of significant PR was a significant determinant factor for insufficient preload reserve, while the confidence interval for odds ratio was relatively wide. Although our results may be due to the

statistical characteristics for analyzing dichotomous parameters, we should be cautious about the clinical application of these results until further research confirms their applicability.

CONCLUSIONS

In adult patients after complete TOF repair, LPP stress echocardiography demonstrated significantly impaired preload reserve and exacerbated ventricular interaction, especially in patients with significant PR. Based on the quantitative assessment of preload reserve, tailored treatment approaches could serve to prevent acute hemodynamic exacerbation, enhance the quality of life, and enable better risk stratification in these patients.

Availability of Data and Material

The data, analytic methods, and study materials will be made available by the corresponding author on request for purposes of reproducing the results or replicating the procedure.

Conflict of Interest: The authors declare no conflict of interest.

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Figure Legends

Figure 1: **Changes in forward stroke volume during leg-positive pressure stress for normal controls and patients after complete repair of tetralogy of Fallot**

Each plot and bars represent mean values and standard deviations, respectively. The arrows indicate the changes in forward stroke volume during LPP stress.

LPP, leg-positive pressure; SV, stroke volume; TOF, tetralogy of Fallot.

Figure 2: Changes in eccentricity index during leg-positive pressure stress for normal controls and patients after complete repair of tetralogy of Fallot

Each plot and bars represent mean values and standard deviations, respectively. The arrow indicates the change in the eccentricity index during LPP stress.

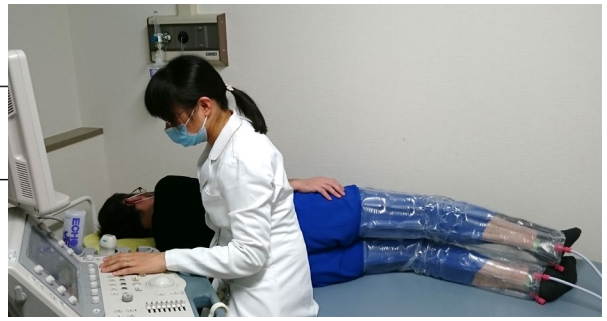
LPP, leg-positive pressure; EI, eccentricity index; TOF, tetralogy of Fallot.

Figure 3: Representative cases of tetralogy of Fallot patients with and without preload reserve

In a patient with preload reserve (left panel), the forward stroke volume (SV) increased in response to acute preload stress. In a patient without preload reserve (right panel), the forward SV decreased in response to acute preload stress. Severe pulmonary regurgitation and significant right ventricular remodeling are visible.

TOF, tetralogy of Fallot; PR, pulmonary regurgitation; LPP, leg-positive pressure.

Figure 1



(ml)
Forward stroke volume (SV)
130
120
110
100
90
80
70
60
50
40
P < 0.01
Increased
10 ± 4 ml
Increased
3 ± 5 ml
73 ± 14 ml
83 ± 16 ml
75 ± 19 ml
79 ± 18 ml
P < 0.01
P < 0.01
Baseline
During LPP
Baseline
During LPP
Normal controls
TOF patients

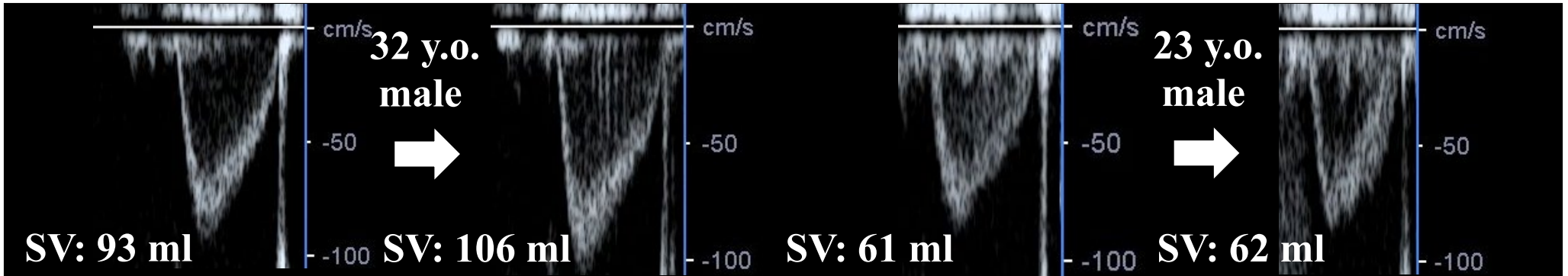

32 y.o.
male
23 y.o.
male
cm/s
-50
-100
SV: 93 ml
SV: 106 ml
SV: 61 ml
SV: 62 ml

Figure 2

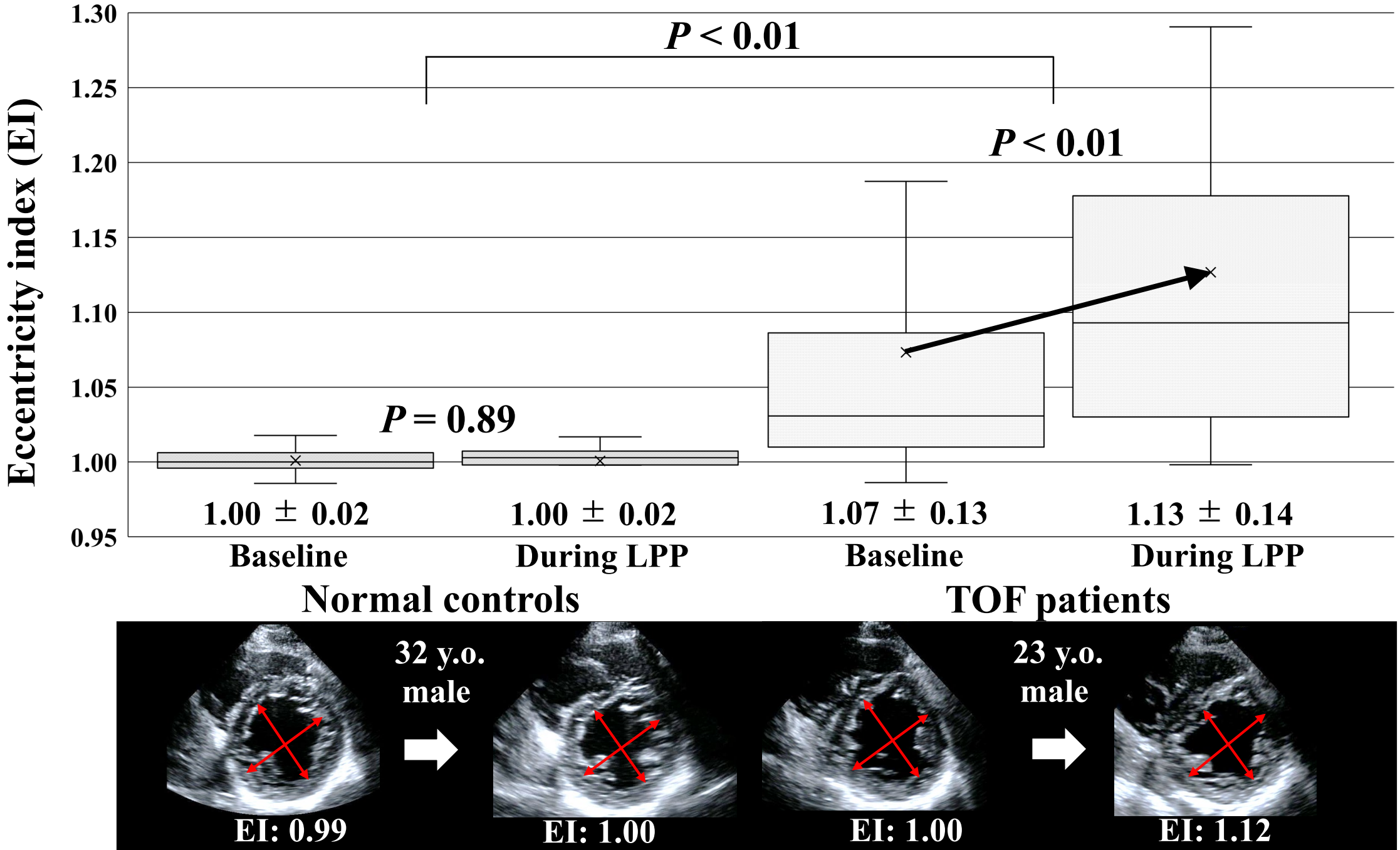

Eccentricity index (EI)
1.30
1.25
1.20
1.15
1.10
1.05
1.00
0.95
P < 0.01
P < 0.01
P = 0.89
1.00 ± 0.02
1.00 ± 0.02
1.07 ± 0.13
1.13 ± 0.14
Baseline
During LPP
Baseline
During LPP
Normal controls
TOF patients
32 y.o. male
23 y.o. male
EI: 0.99
EI: 1.00
EI: 1.00
EI: 1.12

Figure 3

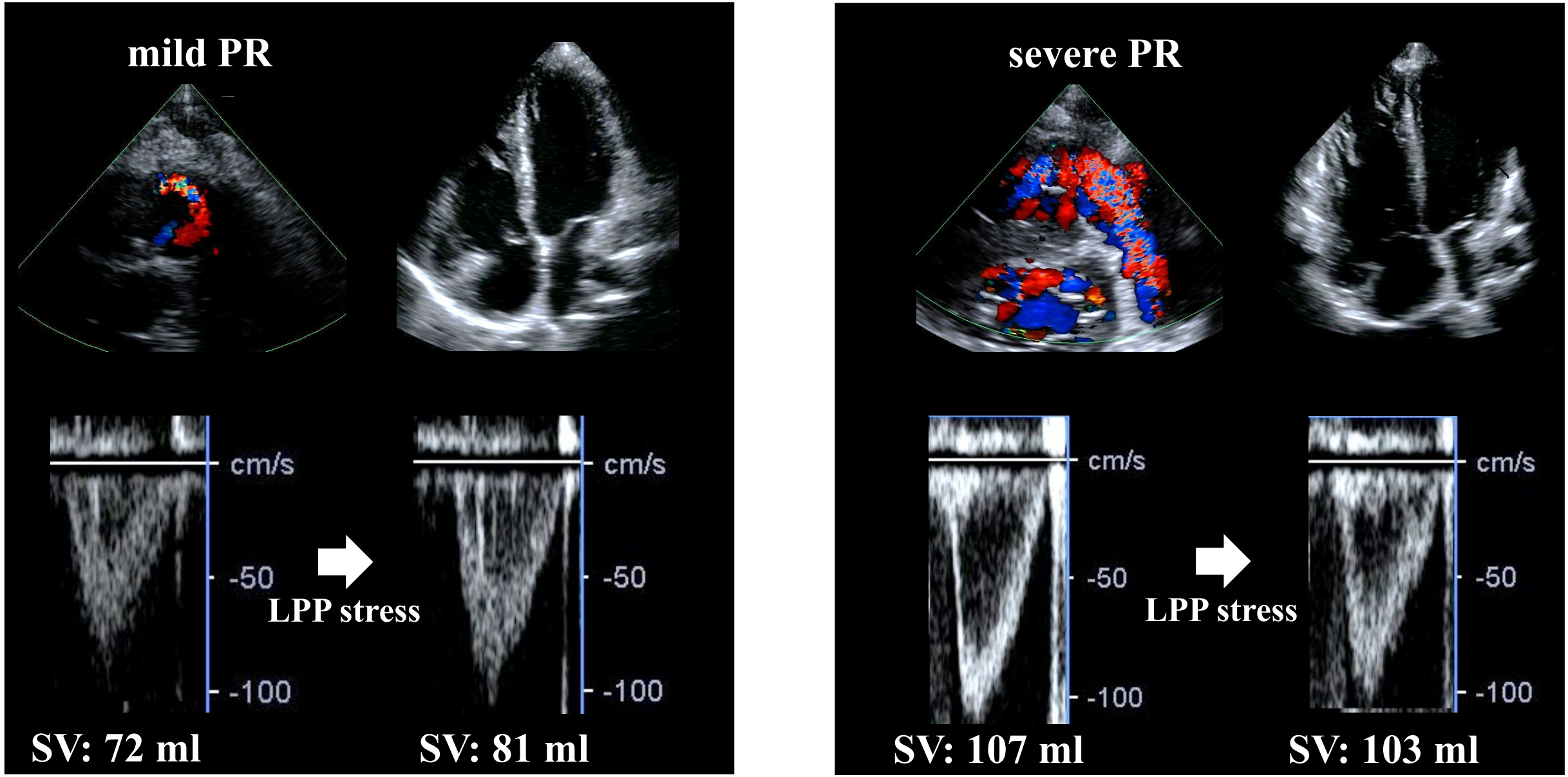

TOF patients with preload reserve
25 y.o. male
mild PR
cm/s
-50
-100
LPP stress
cm/s
-50
-100
SV: 72 ml
SV: 81 ml
TOF patients without preload reserve
23 y.o. male
severe PR
cm/s
-50
-100
LPP stress
cm/s
-50
-100
SV: 107 ml
SV: 103 ml

Table 1: Baseline characteristics for patients with repaired tetralogy of Fallot and normal controls

	Normal controls (n = 30)	TOF patients (n = 44)	*P* value
Age, years	36 ± 10	34 ± 15	0.70
Female, n (%)	15 (50)	26 (59)	0.44
BSA, m^2	1.6 ± 0.2	1.6 ± 0.2	0.45
NYHA functional class I/II, n (%)	30 (100) / 0 (0)	39 (89) / 5(11)	<0.01
Systolic BP, mmHg	115 ± 12	115 ± 15	0.97
Diastolic BP, mmHg	65 ± 10	65 ± 8	0.90
Stroke volume, mL	73 ± 14	75 ± 19	0.56
HR, bpm	60 ± 10	66 ± 11	0.01
Cardiac output, L/min	4.3 ± 0.9	5.0 ± 1.4	0.04
Parameters of LV			
LVEDV, mL	97 ± 19	85 ± 24	0.02
LVESV, mL	35 ± 7	35 ± 14	0.92
LVEF, %	64 ± 3	59 ± 6	<0.01
E/A ratio	1.8 ± 0.5	2.1 ± 1.0	0.46
E/e' ratio	6.5 ± 1.6	9.5 ± 5.1	<0.01
LV-GLS, %	-17.3 ± 1.4	-13.6 ± 1.4	<0.01
Parameters of RV			
RVEDA, cm^2	18 ± 3	28 ± 7	<0.01
RVESA, cm^2	10 ± 2	17 ± 5	<0.01
RVFAC, %	47 ± 3	40 ± 9	<0.01
TAPSE, mm	25 ± 3	16 ± 4	<0.01
S', cm/sec	14 ± 2	9 ± 2	<0.01
TR-PG, mmHg	16 ± 3	32 ± 15	<0.01
IVC, mm	14 ± 4	16 ± 3	<0.01
RV-GLS, %	-21.2 ± 2.8	-12.4 ± 2.8	<0.01
Restrictive physiology, n (%)	0 (0)	21 (48)	<0.01
Prevalence of valvular disease			
Significant TR, n (%)	0 (0)	5 (11)	<0.01
Presence of PS, n (%)	0 (0)	9 (20)	<0.01

Significant PR, n (%)	0 (0)	19 (43)	<0.01
Ventricular interaction			
Eccentricity index	1.00 ± 0.02	1.07 ± 0.13	<0.01

Data are presented as n, mean ± SD, n (%), or median (interquartile range).
TOF, tetralogy of Fallot; BSA, body surface area; BP, blood pressure; HR, heart rate; NYHA, New York Heart Association; LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; RV, right ventricle; EDA, end-diastolic area; ESA, end-systolic area; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; PG, pressure gradient; IVC, inferior vena cava; GLS, global longitudinal strain.

Table 2: Changes in hemodynamic and echocardiographic parameters with leg-positive pressure stress for patients with repaired tetralogy of Fallot and normal controls

	Normal controls (n = 30)		TOF patients (n = 44)		*P* values for two-way repeated measures ANOVA		
	Baseline	During LPP	Baseline	During LPP	Between two groups	Effects of LPP	Group × LPP interaction
Stroke volume, mL	73 ± 14	83 ± 16	75 ± 19	79 ± 18	0.76	<0.01	<0.01
HR, bpm	60 ± 10	62 ± 10	66 ± 11	68 ± 10	0.01	0.02	0.94
Cardiac output, L/min	4.3 ± 0.9	5.1 ± 1.1	5.0 ± 1.4	5.3 ± 1.6	0.17	<0.01	0.03
Parameters of LV							
LVEDV, mL	97 ± 20	105 ± 18	84 ± 24	90 ± 24	<0.01	<0.01	0.03
LVESV, mL	35 ± 7	35 ± 7	35 ± 14	36 ± 14	0.98	0.04	0.25
LVEF, %	64 ± 3	66 ± 3	59 ± 6	61 ± 6	<0.01	<0.01	<0.01
E wave velocity, cm/sec	86 ± 14	86 ± 12	101 ± 25	99 ± 24	<0.01	0.44	0.39
A wave velocity, cm/sec	52 ± 13	53 ± 13	55 ± 26	56 ± 24	0.47	0.35	0.81
E/A ratio	1.8 ± 0.5	1.8 ± 0.7	2.1 ± 1.0	2.0 ± 1.0	0.12	0.60	0.70
e' velocity, cm/sec	14 ± 3	14 ± 2	12 ± 4	12 ± 3	<0.01	0.12	0.38
E/e' ratio	6.5 ± 1.6	6.5 ± 1.3	9.5 ± 5.1	9.8 ± 5.5	<0.01	0.50	0.66
LV-GLS, %	-17.3 ± 1.4	-17.9 ± 1.5	-13.6 ± 1.4	-14.2 ± 1.5	<0.01	<0.01	0.63
Parameters of RV							
RVEDA, cm^2	18 ± 3	18 ± 4	28 ± 7	29 ± 7	<0.01	0.29	0.43

RVESA, cm^2	10 ± 2	9 ± 2	17 ± 5	17 ± 5	<0.01	0.03	0.05
RVFAC, %	47 ± 3	51 ± 3	40 ± 9	41 ± 9	<0.01	<0.01	<0.01
TAPSE, mm	25 ± 3	26 ± 4	17 ± 4	18 ± 4	<0.01	0.01	0.99
S', cm/sec	14 ± 2	14 ± 2	9 ± 2	9 ± 2	<0.01	0.82	0.22
E wave velocity, cm/sec	56 ± 9	58 ± 8	72 ± 16	71 ± 17	<0.01	0.11	0.98
A wave velocity, cm/sec	28 ± 6	28 ± 7	44 ± 20	44 ± 15	<0.01	0.51	0.91
E/A	2.1 ± 0.5	2.2 ± 0.5	2.0 ± 1.0	1.8 ± 0.7	0.13	0.03	0.40
TR-PG, mmHg	17 ± 3	15 ± 3	32 ± 15	33 ± 16	<0.01	0.75	0.11
IVC, mm	14 ± 4	16 ± 4	16 ± 3	15 ± 4	0.67	0.06	0.01
RV-GLS, %	-21.2 ± 2.8	-22.3 ± 2.9	-12.4 ± 2.8	-12.8 ± 2.9	<0.01	<0.01	0.20

ANOVA, analysis of variance; LPP, leg-positive pressure. All other abbreviations as in Table 1.

Table 3: Baseline comparisons of patients with repaired tetralogy of Fallot with and without preload reserve

	TOF with Preload reserve (n=22)	TOF without Preload reserve (n=22)	*P* value
Age, years	36 ± 16	36 ± 15	0.37
Female, n (%)	14 (64)	12 (55)	0.54
Systolic BP, mmHg	114 ± 17	116 ± 13	0.78
Diastolic BP, mmHg	63 ± 8	67 ± 8	0.12
HR, bpm	65 ± 12	67 ± 9	0.51
Stroke volume, mL	75 ± 20	76 ± 19	0.60
Cardiac output, L/min	4.8 ± 1.5	5.1 ± 1.4	0.04
Restrictive physiology, n (%)	11 (50)	10 (45)	0.77
NYHA functional class I/II, n (%)	19 (86) / 3 (14)	20 (91) / 2 (9)	0.64
QRS duration, msec	135 ± 30	130 ± 26	0.51
BNP, pg/mL	6 - 370 (53)	4 - 129 (35)	0.87
Mode of initial repair Pulmonary commissurotomy, n (%)	11 (50)	8 (36)	0.37
Transannular patch, n (%)	7 (32)	8 (36)	0.75
Pulmonary valve replacement, n (%)	0 (0)	1 (5)	0.32
Unknown, n (%)	4 (18)	5 (23)	0.71
Age at initial intracardiac repair, years	2 - 46 (5)	0 - 35 (5)	0.51
Previous Blalock-Taussig shunt, n (%)	7 (32)	4 (18)	0.30
Prevalence of valvular disease			
Significant TR, n (%)	2 (9)	3 (14)	0.64
Presence of PS, n (%)	3 (14)	6 (28)	0.27
Significant PR, n (%)	6 (27)	13 (59)	0.03

BNP, brain natriuretic peptide; PS, pulmonary stenosis; PR, pulmonary regurgitation. All other abbreviations as in Table 1.

Table 4: Subgroup comparisons of changes in hemodynamic and echocardiographic parameters during leg-positive pressure stress for repaired tetralogy of Fallot patients with and without preload reserve

	TOF with Preload reserve (n=22)		TOF without Preload reserve (n=22)		*P* values for two-way repeated measures ANOVA		
	Baseline	LPP	Baseline	LPP	Between two groups	Effects of LPP	Group × LPP interaction
Parameters of LV							
LVEDV, mL	84 ± 22	91 ± 22	85 ± 25	89 ± 26	0.95	<0.01	0.05
LVESV, mL	36 ± 14	37 ± 14	34 ± 14	35 ± 15	0.72	0.02	0.66
LVEF, %	58 ± 6	60 ± 6	60 ± 6	61 ± 6	0.42	<0.01	0.13
LV-GLS, %	-13.8 ± 2.0	-14.7 ± 1.8	-13.5 ± 2.5	-13.6 ± 2.6	0.40	0.01	0.02
E wave velocity, cm/sec	103 ± 26	103 ± 27	98 ± 24	95 ± 21	0.37	0.24	0.31
A wave velocity, cm/sec	54 ± 23	58 ± 25	56 ± 23	55 ± 22	0.93	0.56	0.12
E/A ratio	2.1 ± 0.9	2.1 ± 1.3	2.0 ± 1.1	1.9 ± 0.8	0.63	0.93	0.65
e’ velocity, cm/sec	11.6 ± 3.7	11.3 ± 3.8	12.5 ± 3.7	11.6 ± 2.9	0.57	0.08	0.36
E/e' ratio	11.6 ± 3.7	11.3 ± 3.8	8.9 ± 5.0	9.1 ± 5.6	0.07	0.52	0.40
Stroke volume, mL	75 ± 20	82 ± 19	76 ± 19	75 ± 18	0.60	<0.01	<0.01
HR, bpm	65 ± 12	67 ± 12	67 ± 9	69 ± 8	0.51	0.07	0.89
Cardiac output, L/min	4.8 ± 1.5	5.5 ± 1.8	5.1 ± 1.4	5.2 ± 1.4	0.93	<0.01	<0.01
Parameters of RV							
RVEDA, cm^2	27 ± 6	29 ± 7	30 ± 7	30 ± 7	0.36	<0.01	0.14
RVESA, cm^2	17 ± 5	17 ± 5	18 ± 6	18 ± 6	0.65	0.18	0.17
RVFAC, %	39 ± 9	41 ± 9	41 ± 9	42 ± 9	0.53	0.02	0.96
TAPSE, mm	15 ± 4	16 ± 5	18 ± 3	19 ± 3	<0.01	0.19	0.93
S’, cm/sec	9 ± 2	9 ± 2	10 ± 2	10 ± 2	0.02	0.65	0.72

RV-GLS, %	-12.2 ± 3.1	-13.5 ± 3.1	-12.5 ± 4.0	-12.1 ± 5.1	0.66	0.24	0.04
E wave velocity, cm/sec	80 ± 16	80 ± 15	65 ± 12	63 ± 15	<0.01	0.38	0.82
A wave velocity, cm/sec	42 ± 22	44 ± 16	47 ± 19	45 ± 14	0.66	0.62	0.41
E/A ratio	2.3 ± 1.1	2.0 ± 0.7	1.6 ± 0.8	1.5 ± 0.6	0.04	0.05	0.45
TR-PG, mmHg	31 ± 13	32 ± 15	33 ± 16	33 ± 16	0.66	0.45	0.88
Ventricular interaction							
Eccentricity index	1.06 ± 0.07	1.11 ± 0.10	1.09 ± 0.16	1.14 ± 0.17	0.53	<0.01	0.54

All abbreviations as in Table 1.

Table 5

Univariate and multivariate logistic regression analysis for prediction of the lack of preload reserve

	Univariate analysis			Multivariate analysis		
	Odds ratio	**95% CI**	***P* value**	**Odds ratio**	**95% CI**	***P* value**
Age (per 5 years)	0.94	0.771-1.153	0.70			
Sex (Female)	0.69	0.205-2.295	0.54			
LVEF (per 5% decrease)	1.32	0.777-2.243	0.29			
E/e' (per 1 unit increase)	0.95	0.841-1.076	0.42			
LV-GLS (per 1% increase)	0.96	0.696-1.333	0.82			
RVEDA (per 1cm^2 increase)	1.06	0.961-1.160	0.25			
FAC (per 5% decrease)	1.12	0.791-1.586	0.52			
TAPSE (per 1mm decrease)	1.28	1.042-1.572	0.01	1.12	0.842-1.502	0.46
S' (per 1cm/sec decrease)	1.53	1.080-2.169	0.01	1.43	0.832-2.445	0.20
Restrictive physiology	0.83	0.255-2.724	0.76			
RV-GLS (per 1% increase)	1.01	0.841-1.218	0.90			
Eccentricity index (per 0.1 unit increase)	1.19	0.706-2.009	0.49			
Presence of PS	2.38	0.511-11.05	0.26			
Significant TR	1.58	0.237-10.52	0.63			
Significant PR	3.85	1.086-13.66	0.03	4.57	1.048-19.90	0.04

CI, confidence interval. All other abbreviations as in Table 1.