**Ventricular myocardial response to exercise in patients with Fontan circulation**

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**Abstract**

**Background:** Exercise stress echocardiography has been used to assess myocardial reserve in various heart diseases. This study examined the ventricular myocardial response to exercise in Fontan patients using exercise stress echocardiography.

**Methods:** Twenty-five Fontan patients and 19 control subjects underwent semi-supine bicycle exercise stress echocardiography in this prospective, single-center, cross-sectional study. Pulsed-wave Doppler tissue imaging peak systolic (s') and diastolic (e') velocities, longitudinal strain and systolic strain rate, and early diastolic strain rate data at rest and at peak exercise were obtained for the systemic ventricle. The myocardial reserve of functional parameters was calculated as the difference between peak exercise and rest.

**Results:** Inter- and intra-observer reliability were both high for exercise stress echocardiography measurements. Compared with controls, Fontan patients had significantly lower s', e', longitudinal systolic strain and strain rate, and early diastolic longitudinal strain rate at rest and at peak exercise as well as reduced myocardial reserve.

**Conclusions:** Fontan patients have markedly reduced myocardial reserve during exercise.

The use of exercise stress echocardiography assessment may improve the clinical management of Fontan patients.

**Key words: Fontan, exercise stress echocardiography, cardiac reserve, single ventricle**

## Introduction

The Fontan procedure has improved survival in children with functionally univentricular hearts [1]. However, the long-term mortality of Fontan patients remains higher than that of patients with other types of congenital heart disease [2]. The limited exercise capacity of Fontan patients can predict the risk of morbidity and mortality [3]. Abnormal hemodynamic responses to exercise in the Fontan population have a significant impact on exercise capacity [4]. Although myocardial reserve function in response to stress has been associated with exercise capacity in several heart diseases [5], it is not well studied in Fontan patients.

The myocardial response to stress is best estimated under physiologic inotropic and chronotropic conditions in exercise testing [6]. Semi-supine bicycle exercise stress echocardiography is a technique that enables the assessment of echocardiographic and hemodynamic parameters during incremental exercise. There is increasing evidence that exercise stress echocardiography can provide useful information on ventricular function and functional reserve in patients with heart disease [7]. The exercise performed in exercise stress echocardiography is a more physiological way to induce cardiovascular

responses as compared with pharmacologic stress testing [8]. Although exercise stress echocardiography is mainly used for identifying regional myocardial dysfunction in adults with coronary artery disease, its utility has also been recognized in pediatric populations [9-11]. However, information on the myocardial response during exercise in Fontan patients is limited [12].

The aim of this study was to evaluate the myocardial response to exercise in patients with Fontan circulation using exercise stress echocardiography.

## Methods

### Study population and design

This was a prospective, single-center, cross-sectional study. Eligible children, adolescents, and adults who had undergone the Fontan operation were prospectively recruited between August 2015 and January 2018. The exclusion criteria were an inability to perform the bicycle exercise testing, severe cardiac dysfunction, inadequate image quality, arrhythmia during examination, and cardiac translocation. Healthy age- and gender-matched control subjects were recruited from a group of volunteers. Collected patient data included age,

gender, age at Fontan procedure, postoperative time, type of Fontan procedure, fenestration, severity of atrioventricular valve insufficiency, and medication. Ventricular morphology was determined by echocardiography and characterized as dominant left ventricle, dominant right ventricle, or biventricle. The institutional research ethics board approved this study, and all subjects provided informed consent.

**Stress echocardiographic protocol**

A semi-supine bicycle ergometer (Lode BV, Groningen, the Netherlands) was used for all echocardiographic stress studies. A Bruce exercise protocol was employed, with 20 W increment increases every 3 minutes for patients with Fontan circulation and control subjects ≤ 14 years of age and 25 W increment increases for controls >14 years of age. Target heart rate (HR) was defined as 85% of maximal HR. Tests were terminated in cases of patient fatigue, chest pain, arrhythmia, ischemic electrocardiographic changes, progressive fall in systolic blood pressure of >10 mmHg or percutaneous oxygen saturation ($SpO_2$) of >10%, severe hypertension, inadequate image quality, or when the target HR was reached. Patients were monitored by continuous electrocardiography. Blood pressure, oxygen saturation, and HR were recorded every 2 minutes.

**Echocardiographic image acquisition and analysis**

Echocardiography was performed by an experienced pediatric cardiologist using a Vivid E9 echocardiographic system (GE Medical Systems). All images were taken at rest and at the time of peak HR during exercise from the apical four-chamber view and acquired at a frame rate of 64-108 frames/sec. The data were analyzed offline using EchoPAC software (GE Medical Systems).

Ventricular end-systolic area (VESA) and ventricular end-diastolic area (VEDA) were measured, and fractional area change (FAC) was calculated as (VEDA - VESA) / VEDA × 100%. In Fontan patients with biventricle circulation, VESA and VEDA were measured by summing the traced areas of the 2 ventricles. We also obtained pulsed-wave Doppler images of atrioventricular valve inflow velocities for Fontan patients and mitral inflow velocity for controls for determination of E velocities. In Fontan patients with double inlets or 2 atrioventricular valves, we averaged the 2 E wave velocities of each inflow. For Fontan patients, pulsed-wave tissue Doppler imaging (TDI) was obtained of the septum and bilateral atrioventricular valve annulus, whereas for controls, TDI was performed of the interventricular septum and left ventricle lateral wall annulus from the

apical four-chamber view. The systole (s') and early diastole (e') peak velocities were measured by averaging the peak velocities obtained from the annulus and interventricular septum. In single-ventricle cases without a septum, TDI measurements were averaged from peak annular velocities at both lateral annuli. Fusion of the E and A waves in ventricular inflow and e' and a' waves for TDI were measured as E and e', respectively. The E/e' ratio was calculated by dividing the peak E wave velocity by the peak e' velocity. From the apical ventricular view, longitudinal strain and strain rate in the systole and early diastole phases were determined by two-dimensional speckle-tracking echocardiography (STE) as the average of segmental longitudinal strain values obtained in the 6 segments of the single ventricle in Fontan patients and for the left ventricle in controls. In the Fontan patients with biventricle circulation, longitudinal strain and strain rate were measured by tracing the right ventricle wall including the right ventricle lateral and septal walls, tracing the left ventricle wall including the left ventricle lateral and septal walls, and then averaging both values. To determine cardiac reserve ($\Delta$), we calculated the difference of each hemodynamic and echocardiographic measurement between at peak exercise and at rest ($\Delta$ = peak - rest) [12]. All echocardiographic measurements were averaged from 3

consecutive waveforms.

**Inter- and intra-observer reproducibility**

The inter- and intra-observer variability for the analyses of TDI (s', e') and longitudinal strain and strain rate were determined in 20 randomly selected subjects (10 each of patients and controls) using the intraclass correlation coefficient and Bland–Altman analysis by calculating the bias (mean difference) and 1.96 degrees of standard deviation (SD) around the mean difference. To assess inter-observer reproducibility, 2 observers (Yamazaki S and Motoki N) independently analyzed the same data while blinded to the other's measurements. To determine intra-observer reproducibility, measurements were repeated after more than 4 weeks by the same observer (Yamazaki S).

**Statistical analysis**

Categorical variables are expressed as absolute values and percentages and continuous variables are presented as the mean ± SD. Comparisons between groups were performed using Student's *t*-test or Mann–Whitney's *U* test as appropriate. The parameters of 3 groups were compared using the one-way analysis of variance with the Tukey post hoc test or Kruskal-Wallis test with Dunn's multiple comparison test as appropriate. A *P*-

value of <0.05 was considered statistically significant. Statistical calculations were performed using SPSS version 23.0 software (SPSS, Inc., Chicago, IL, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [13].

## Results

### Patient characteristics

Twenty-five patients who had received the Fontan procedure (mean age: 14 ± 3.9 years, range: 8-21 years) and 19 age-matched control subjects were enrolled in this study. The participants' characteristics, including ventricular morphology, type of Fontan, previous operations, and medications, are summarized in Table 1. Age, height, weight, and body surface area were comparable between Fontan patients and controls. There were no fenestrated Fontan patients in the cohort. Atrioventricular valve regurgitation was absent or trivial in 20 patients (80%) and mild in 5 patients (20%).

### Feasibility and reproducibility

The feasibility of s' and e' in Fontan patients were both 100% at rest and 92% at peak

exercise, and parameters derived from STE were obtained in 96% of patients. For controls, the parameters measured by TDI could be measured in all subjects, while strain parameters were feasible in 84-86% of participants. The reproducibility results for this study are summarized in Table 2 and show that the measurements derived from TDI and STE were highly reproducible.

**Arterial oxygen saturation, hemodynamic data, and echocardiography at rest**

The arterial oxygen saturation, hemodynamic data, and echocardiographic measurements at rest and at peak exercise are summarized in Table 3. Arterial oxygen saturation at rest was significantly lower in Fontan patients as compared with controls. At rest, HR in Fontan patients was significantly higher than in controls, while systolic blood pressure was similar between the groups. All systolic and diastolic echocardiographic parameters were significantly lower in Fontan patients versus controls.

**Hemodynamic data and echocardiography at peak exercise and cardiac reserve**

All patients displayed normal sinus rhythm during echocardiographic image acquisition at exercise.

At the timing of peak exercise in exercise stress echocardiography, HR, systolic blood

pressure, and all systolic and diastolic echocardiographic parameters except for E/e' were significantly increased in both groups as compared with at rest. In both controls and Fontan patients, VEDA index (VEDAi) did not change remarkably with exercise load, whereas VESA index (VESAi) decreased significantly from rest to peak exercise. Oxygen saturation, HR, VESAi, and systolic and diastolic parameters at peak exercise were lower in Fontan patients than in controls (Table 3). In terms of reserve, Δoxygen saturation, ΔHR, ΔVESAi, and systolic cardiac function reserve including Δs', Δlongitudinal strain, and Δsystolic strain rate were significantly lower in Fontan patients versus controls. Moreover, diastolic cardiac function reserve parameters assessed by ΔE, Δe', and Δearly diastolic strain rate were also significantly impaired in the Fontan group (Table 4). There were no remarkable differences in exercise stress responses among dominant ventricular morphologies in Fontan patients (Table 5).

**Discussion**

This study evaluated the myocardial response to exercise in Fontan patients using exercise stress echocardiography. Although Fontan patients exhibited significant increases in HR

and systolic and diastolic functional parameters in response to exercise, these were of a lower magnitude than in controls.

**Feasibility and reproducibility**

Several studies have addressed the feasibility and reproducibility of TDI and STE by exercise stress echocardiography in children. Cifra et al. reported acceptable results for biventricular color TDI velocities (s' and e') and longitudinal strain, with the feasibility of color TDI and longitudinal strain at 95-98% [14]. Likewise, Hasan et al. demonstrated good feasibility and reproducibility and showed high successful acquisition rates (90-100%) for pulsed-wave TDI in Fontan patients at rest and during exercise [12]. Our results were similar to those above and thus were considered valid for use.

**Hemodynamic and myocardial response to exercise**

Consistently with previous reports [15, 16], the systolic and diastolic parameters in both Fontan patients and control subjects showed a significant positive myocardial response during exercise in this study, which was likely attributable to physiological changes during exertion. In healthy individuals, cardiac output during exercise increases dramatically due to increased HR, greater preload, increased myocardial contractility, and

reduced afterload [16]. The healthy human myocardium responds to a higher HR by increasing its inotropic activity in a force-frequency relationship. This intrinsic property of cardiac muscle provides greater contractile force and faster relaxation at an elevated HR [17]. As the systolic and diastolic phases progressively shorten at higher HR, positive systolic and diastolic myocardial responses to exercise may help maintain constant stroke volume and ventricular filling volume, thus augmenting cardiac output during exertion [18].

In the present study, Fontan patients exhibited a lower magnitude of myocardial responses to exercise as compared with controls. The factors associated with this observation are likely multifactorial and may include chronotropic incompetence in addition to impaired contractile reserve, reduced filling capacity, limited preload, and less reduced afterload. Similarly to the results of a previous study [19], the response to increased heart rate during exercise in Fontan patients was limited in comparison to that in normal subjects. Cifra et al. described a linear relationship between HR and color TDI velocities, E, and myocardial strain measured by exercise stress echocardiography in healthy children [14]. Thus, the lower myocardial reserve in systolic and diastolic parameters in Fontan patients

might at least be partly explained by chronotropic incompetence.

The force-frequency relationship in Fontan patients is not completely understood. Senzaki et al. evaluated hemodynamics and ventricular function using pressure-volume loops in Fontan patients by separately quantifying ventricular contractility, diastolic function, and loading factors at rest and under heart-stimulating conditions [20]. They demonstrated that ventricular contractility and diastolic function in Fontan patients were comparable to those of control subjects at rest, whereas systolic and diastolic reserve responses to increased HR by atrial pacing were limited versus controls. Additionally, Claessen et al. examined the relationships among HR acceleration during exercise, ventricular filling, and cardiac output using cardiac magnetic resonance imaging in Fontan patients [21]. They suggested that the chronotropic constraint in Fontan patients was more likely a secondary phenomenon caused by inadequate systemic ventricular filling and reduced systolic contractility leading to impaired cardiac output rather than sinoatrial pacemaker dysfunction. Due to the lower peak HR in Fontan patients as compared with controls in the present study, it could not be distinguished clearly whether the lower myocardial response during exercise in Fontan patients was a result of lower

myocardial reserve or chronotropic incompetence. However, taken together with the results of previous studies [20, 21], a diminished force-frequency relationship might have been inherent in the Fontan circulation to diminish myocardial contractile reserve during exercise stress echocardiography.

As differences in loading conditions during exercise could also have a significant impact on the magnitude of TDI, STE, and other echocardiographic measurements [22, 23], limitations in the exercise-induced augmentation of pulmonary vascular flow and ventricular filling in Fontan patients might explain the lower myocardial response to exertion as well. Decreased ventricular preload leading to reduced augmentation of cardiac output during supine bicycle exercise has been demonstrated in Fontan patients [21, 24]. Ventricular afterload during exercise could have similarly affected the myocardial response. Increased vascular resistance in the Fontan circulation could have exerted a significant negative impact on the resting hemodynamics and exercise capacity of Fontan patients [25].

In the present study, cardiac reserve indices obtained by exercise stress echocardiography did not differ notably by ventricular morphology. The influence of ventricular

morphology on prognosis and cardiac function parameters in Fontan patients remains to be determined. Ghelani et al. reported that Fontan patients with right ventricle morphology showed lower global circumferential strain as compared with patients having left ventricle morphology [26]. In contrast, Ishizaki et al. witnessed no differences in ejection fraction or global longitudinal strain on cardiac magnetic resonance imaging among Fontan patients with dominant RV, dominant LV, and biventricular circulations [27]. Further validation and investigation are needed to elucidate the relationship between cardiac reserve indices and ventricular morphology.

The Fontan subjects in this study exhibited arterial saturation at rest, which declined further with exercise. Right-to-left shunting, such as in pulmonary arteriovenous fistulae, venovenous collaterals, and ventilation-perfusion mismatch, are considered major factors causing arterial hypoxia in Fontan patients [28]. Given the strong correlation between arterial saturation at rest and at peak exercise [29], these factors may have deteriorated arterial saturation with exertion in our patients.

**Study limitations**

This study had several limitations. First, it contained a small sample of relatively young

patients and lacked longitudinal data. Additional trials are needed to elucidate whether exercise stress echocardiography parameters can predict prognosis in Fontan populations. The effect of differences in ventricular morphology and muscle architecture should also be addressed in further detail. Second, the results of the present study cannot be extrapolated to Fontan patients with a more severe status since they excluded patients unable to perform exercise stress echocardiography. Third, the two-dimensional STE frame rate was fixed during exercise, which might have resulted in reading errors of strain values at peak exercise due to an insufficient frame rate. Lastly, peak HR was lower in Fontan patients than in controls and might have at least partially contributed to the lower myocardial reserve observed in this study. Continuous image acquisition and the estimation of myocardial contractility by a relatively load-independent echo parameter, such as isovolumic contraction, will help overcome this limitation [7, 14].

**Conclusions**

In conclusion, the magnitude of myocardial response to exercise by exercise stress echocardiography in Fontan patients was remarkably lower than that in healthy controls. Exercise stress echocardiography assessment may be a useful tool in the clinical

management of Fontan patients.

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**Conflict of interest**

Shoko Yamazaki, Yohei Akazawa, Haruka Obinata, Noriko Motoki, Kohta Takei, Satoshi Yasukochi, and Kiyohiro Takigiku declare that they have no conflict of interest.

**Human rights statements and informed consent**

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients for being included in the study.

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**Figure legends**

Figure 1.

Measurements of s' and e' velocities derived from TDI and LS derived from STE at rest and at peak exercise in a Fontan patient (a, 11 years of age) and a control subject (b, 10 years of age). LS=the average of segmental longitudinal strain; LA=left atrium; LV=Left ventricle; RA=right atrium; RV=right ventricle; EC=extracardiac conduit

Figure 2.

Graphs depicting the cardiac reserve of s', LS, systolic strain rate, E, e', and diastolic strain rate in Fontan patients (red) and controls (blue). The horizontal line in the middle of each box indicates the median, the top and bottom borders of the box show the $75^{th}$ and $25^{th}$ percentiles, respectively, and the whiskers mark the $90^{th}$ and $10^{th}$ percentiles. LS=the average of segmental longitudinal strain

**Author contributions**

Concept/design: Shoko Yamazaki and Kiyohiro Takigiku, Data analysis/interpretation: Shoko Yamazaki, Data collection: Shoko Yamazaki and Haruka Obinata, Drafting the article: Yohei Akazawa, Revision of the article: Shoko Yamazaki and Yohei Akazawa, Approval of the article: Kohta Takei and Satoshi Yasokochi, Statistics: Noriko Motoki

**Table 1. Subject characteristics**

| Variable | Fontan (n=25) | Control (n=19) | *P*-value |
|---|---|---|---|
| Age at the study, years (range) | 14 ± 3.9 (8-21) | 14 ± 5.1 (8-21) | 0.66 |
| Female, n (%) | 12 (48%) | 6 (32%) | 0.27 |
| Height (cm) | 151 ± 12.7 | 152 ± 15.5 | 0.79 |
| Weight (kg) | 43.0 ± 8.9 | 44.6 ± 15.6 | 0.68 |
| Body surface area ($m^2$) | 1.4 ± 0.20 | 1.4 ± 0.30 | 0.88 |
| Age at Fontan procedure (years) | 2.8 ± 0.59 | | |
| Postoperative time (years) | 11.5 ± 4.0 | | |
| Dominant ventricular morphology, n (%) | | | |
| LV | 13 (52%) | | |
| RV | 8 (32%) | | |
| BV | 4 (16%) | | |
| Type of Fontan, n (%) | | | |
| APC | 1 (4%) | | |
| IAR | 2 (8%) | | |
| ECR | 22 (88%) | | |
| Procedures prior Fontan, n (%) | | | |
| APS | 13 (52%) | | |
| PAB | 11 (44%) | | |
| Glenn | 24 (96%) | | |
| Fenestrated patent, n (%) | 0 (0%) | | |
| Atrioventricular valve insufficiency, n (%) | | | |
| None or trivial | 20 (80%) | | |
| Mild | 5 (20%) | | |
| Moderate | 0 (0%) | | |
| Severe | 0 (0%) | | |
| Medical therapy, n (%) | | | |
| Diuretic | 6 (24%) | | |
| Anticoagulant | 25 (100%) | | |
| ACEI/ARB | 7 (28%) | | |

| | |
|---|---|
| β-blocker | 2 (8%) |
| Antiarrhythmic | 0 (0%) |

Data are presented as the mean ± SD. LV = left ventricle; RV = right ventricle; BV = biventricle; APC = atriopulmonary connection; IAR = intra-atrial rerouting; ECR = extracardiac rerouting; APS = aortopulmonary shunt; PAB = pulmonary artery banding; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker

**Table 2. Inter- and intra-observer reproducibility**

| Variable | Inter-observer variability | ICC | Intra-observer variability | ICC |
|---|---|---|---|---|
| **Rest** | | | | |
| e' velocity of IVS | -0.094 ± 0.68 | 0.99 | -0.19 ± 0.47 | 0.99 |
| e' velocity of LV lateral wall annulus | 0.59 ± 0.88 | 0.99 | 0.29 ± 0.98 | 0.98 |
| e' velocity of RV lateral wall annulus | -0.13 ± 0.67 | 0.99 | -0.21 ± 0.40 | 0.96 |
| s' velocity of IVS | -0.076 ± 0.54 | 0.96 | -0.058 ± 0.46 | 0.97 |
| s' velocity of LV lateral wall annulus | 0.019 ± 0.56 | 0.99 | -0.21 ± 0.56 | 0.99 |
| s' velocity of RV lateral wall annulus | -0.21 ± 0.84 | 0.98 | -0.065 ± 0.78 | 0.98 |
| Longitudinal strain | 0.14 ± 1.3 | 0.93 | 0.44 ± 0.89 | 0.96 |
| Systolic strain rate | 0.0040 ± 0.087 | 0.91 | 0.032 ± 0.10 | 0.88 |
| Early diastolic strain rate | 0.056 ± 0.19 | 0.95 | 0.019 ± 0.15 | 0.97 |
| **Peak exercise** | | | | |
| e' velocity of IVS | 0.032 ± 1.0 | 0.98 | -0.36 ± 0.96 | 0.98 |
| e' velocity of LV lateral wall annulus | -0.17 ± 1.1 | 0.98 | -0.25 ± 1.2 | 0.98 |
| e' velocity of RV lateral wall annulus | -0.013 ± 1.8 | 0.98 | -1.2 ± 1.9 | 0.98 |
| s' velocity of IVS | 0.046 ± 0.65 | 0.99 | 0.016 ± 0.85 | 0.98 |
| s' velocity of LV lateral wall annulus | 0.086 ± 0.92 | 0.98 | -0.051 ± 0.96 | 0.98 |
| s' velocity of RV lateral wall annulus | 0.30 ± 1.0 | 0.99 | -0.29 ± 0.96 | 0.99 |
| Longitudinal strain | -0.15 ± 1.7 | 0.94 | 0.56 ± 1.2 | 0.96 |
| Systolic strain rate | 0.030 ± 0.20 | 0.94 | 0.049 ± 0.18 | 0.95 |
| Early diastolic strain rate | 0.064 ± 0.24 | 0.96 | -0.030 ± 0.26 | 0.96 |

Data are presented as the mean ± SD.

ICC = intraclass correlation coefficient; IVS = intraventricular septum

**Table 3. Hemodynamic and echocardiographic parameters at rest and at peak exercise**

| | Fontan (n=25) | | Control (n=19) | | *P*-value | *P*-value | *P*-value | *P*-value |
|---|---|---|---|---|---|---|---|---|
| | Resting value | Peak value | Resting Value | Peak value | Fontan rest vs. Peak | Control rest vs. peak | Fontan rest vs. control rest | Fontan peak vs. control peak |
| **Exercise level and hemodynamic parameters** | | | | | | | | |
| Workload (Watts) | | 65 ± 17 | | 96 ± 47 | | | | <0.01 |
| Oxygen saturation (%) | 95.8 ± 1.6 | 93.0 ± 3.4 | 98.3 ± 2.2 | 98.2 ± 1.1 | <0.001 | 1.0 | <0.001 | <0.001 |
| Heart rate (bpm) | 84.3 ±16.0 | 131.1 ± 19.1 | 72.8 ± 15.5 | 144.2 ± 17.1 | <0.001 | <0.001 | 0.015 | 0.024 |
| Systolic pressure (mmHg) | 110.5 ± 14.2 | 157.7 ± 18.4 | 114.1 ± 15.2 | 155.6 ± 26.3 | <0.001 | <0.001 | 0.43 | 0.75 |
| **Systolic parameters** | | | | | | | | |
| FAC (%) | 0.39 ± 0.048 | 0.43 ± 0.070 | 0.42 ± 0.038 | 0.50 ± 0.037 | <0.001 | <0.001 | 0.0068 | <0.001 |
| VEDAi | 15.6 ± 3.5 | 15.4 ± 3.5 | 15.7 ± 2.3 | 15.4 ± 2.3 | 0.49 | 0.15 | 0.97 | 0.99 |
| VESAi | 10.5 ± 2.4 | 9.9 ± 2.2 | 9.0 ± 1.5 | 7.8 ± 1.6 | 0.024 | <0.001 | 0.018 | 0.001 |
| s' (cm/s) | 4.9 ± 1.2 | 7.2 ± 1.7 | 8.3 ± 1.6 | 13.2 ± 2.8 | <0.001 | <0.001 | <0.001 | <0.001 |
| Longitudinal strain (%) | -15.7 ± 2.8 | -18.8 ± 3.4 | -19.9 ± 3.1 | -25.6 ± 1.8 | <0.001 | <0.001 | <0.001 | <0.001 |
| Systolic strain rate (s-1) | -0.94 ± 0.15 | -1.3 ± 0.29 | -1.2 ± 0.23 | -2.2 ± 0.25 | <0.001 | <0.001 | <0.001 | <0.001 |
| **Diastolic parameters** | | | | | | | | |
| E (cm/sec) | 65.2 ± 17.1 | 97.4 ± 28.2 | 84.8 ± 12.3 | 132.5 ± 24.6 | <0.001 | <0.001 | <0.001 | <0.001 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| e' (cm/s) | 6.4 ± 1.8 | 10.1 ± 2.8 | 13.0 ± 2.1 | 18.1 ± 2.3 | <0.001 | <0.001 | <0.001 | <0.001 |
| E/e' ratio | 10.7 ± 3.1 | 10.3 ± 4.3 | 6.6 ± 1.0 | 7.4 ± 0.8 | 0.73 | 0.025 | <0.001 | 0.005 |
| Early diastolic strain rate (s-1) | 1.4 ± 0.43 | 2.3 ± 0.64 | 2.5 ± 0.73 | 3.7 ± 0.57 | <0.001 | <0.001 | <0.001 | <0.001 |

Data are presented as the mean ± SD. FAC = fractional area change; VEDAi = ventricular end-diastolic area index; ESAi = ventricular end-systolic area index

**Table 4. Hemodynamic and myocardial reserve**

| | Fontan (n=25) | Control (n=19) | *P*-value |
|---|---|---|---|
| **Oxygen saturation and hemodynamic parameters** | | | |
| Δ Oxygen saturation (%) | -2.8 ± 2.6 | 0.0 ± 2.1 | <0.001 |
| Δ Heart rate (bpm) | 46.8 ± 17.7 | 71.3 ± 19.2 | <0.001 |
| Δ Systolic pressure (mmHg) | 47.2 ± 23.4 | 42.4 ± 22.4 | 0.50 |
| **Systolic parameters** | | | |
| Δ FAC (%) | 0.040 ± 0.038 | 0.069 ± 0.025 | 0.069 |
| ΔVEDAi | -0.24 ± 1.7 | -0.58 ± 1.6 | 0.53 |
| ΔVESAi | -0.55 ± 1.1 | -1.4 ±0.95 | 0.017 |
| Δ s' (cm/s) | 2.3 ± 1.4 | 4.9 ± 2.4 | <0.001 |
| Δ Longitudinal strain (%) | 3.0 ± 2.2 | 5.6 ± 2.4 | 0.001 |
| Δ Systolic strain rate (s-1) | 0.39 ± 0.21 | 1.0 ± 0.22 | <0.001 |
| **Diastolic parameters** | | | |
| Δ E (cm/sec) | 32.2 ± 20.9 | 47.8 ± 27.3 | 0.038 |
| Δ e' (cm/s) | 3.6 ± 2.4 | 5.1 ± 1.7 | 0.02 |
| Δ E/e' ratio | -0.21 ± 2.9 | 0.79 ± 1.4 | 0.15 |
| Δ Early diastolic strain rate (s-1) | 0.91 ± 0.62 | 1.4 ± 0.68 | 0.027 |

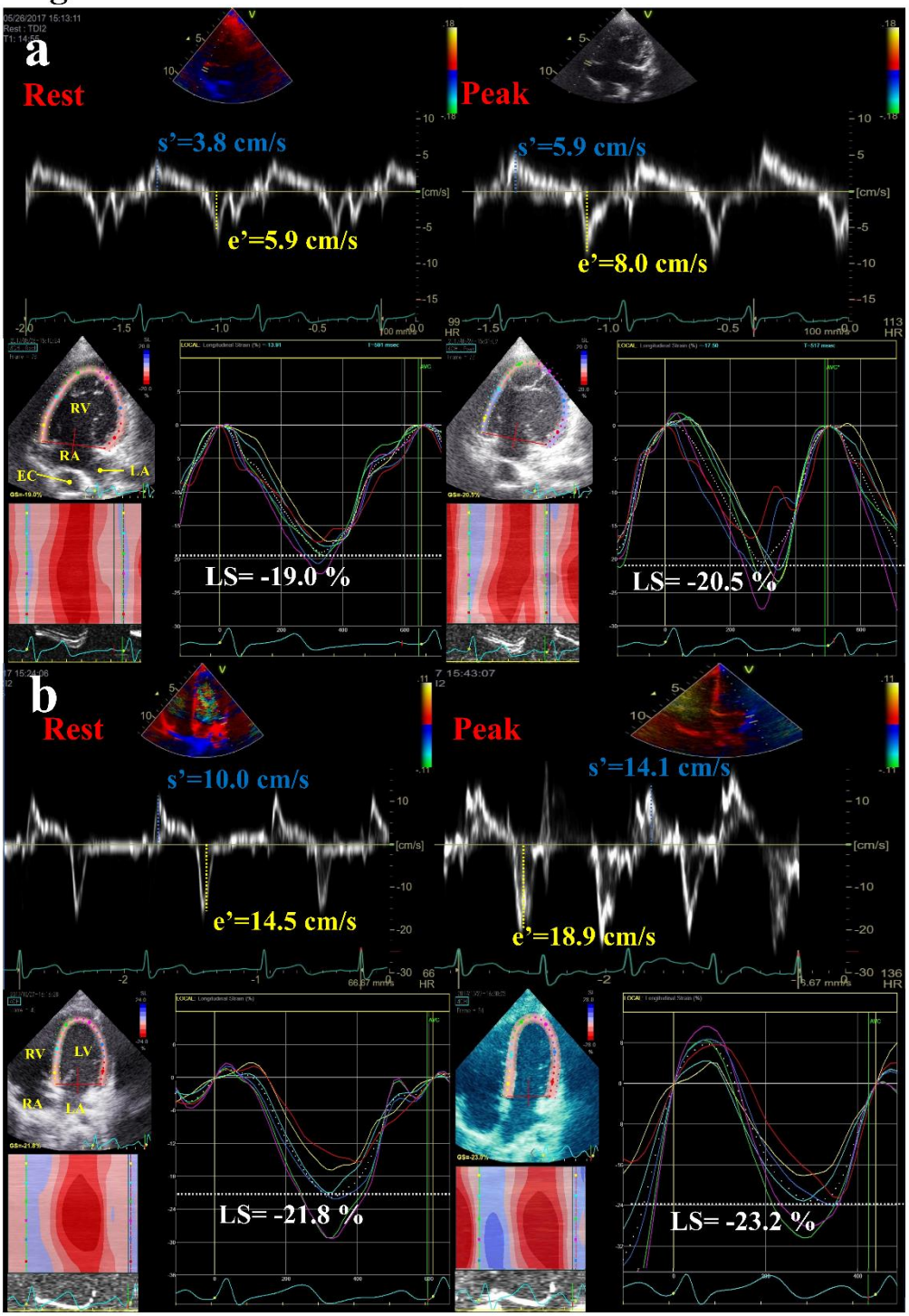
Data are presented as the mean ± SD. Δ = difference of each measurement between at peak exercise and at rest (peak – rest); FAC = fractional area change; VEDAi = ventricular end-diastolic area index; VESAi = ventricular end-systolic area index

**Table 5. Comparison of stress response by dominant ventricular morphology in Fontan group**

| | Dominant RV (n=8) | | | Dominant LV (n=13) | | | Biventricle (n=4) | | | *P*-value | *P*-value | *P*-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Rest | Peak | Δ(peak-rest) | Rest | Peak | Δ(peak-rest) | Rest | Peak | Δ(peak-rest) | Rest | Peak | Δ(peak-rest) |
| Heart rate (bpm) | 85 ± 14 | 132 ± 12 | 48 ± 19 | 85 ± 17 | 131 ± 23 | 46 ± 19 | 80 ± 17 | 128 ± 21 | 48 ± 12 | 0.81 | 0.93 | 0.97 |
| Systolic pressure (mmHg) | 107 ± 12 | 158 ± 19 | 51 ± 25 | 116 ± 13 | 157 ± 19 | 41 ± 17 | 100 ± 18 | 158 ± 22 | 58 ± 37 | 0.085 | 0.99 | 0.40 |
| FAC | 0.37 ± 0.047 | 0.41 ± 0.068 | 0.039 ± 0.034 | 0.38 ± 0.053 | 0.43 ± 0.078 | 0.041 ± 0.043 | 0.42 ± 0.021 | 0.45 ± 0.054 | 0.038 ± 0.037 | 0.37 | 0.67 | 0.99 |
| s' (cm/s) | 5.1 ± 1.1 | 7.2 ± 1.5 | 2.1 ± 1.7 | 4.7 ± 1.3 | 6.9 ± 1.7 | 2.1 ± 1.0 | 5.1 ± 0.8 | 8.2 ± 2.0 | 3.1 ± 1.8 | 0.77 | 0.40 | 0.48 |
| Longitudinal strain (%) | -17.0 ± 3.2 | -20.5 ± 2.9 | 3.5 ± 2.1 | -14.7 ± 2.6 | -17.6 ± 3.6 | 2.8 ± 2.5 | -16.5 ± 1.0 | -19.3 ± 2.1 | 2.9 ± 1.4 | 0.087 | 0.09 | 0.85 |
| Systolic strain rate (s-l) | -0.94 ± 0.1 | -1.3 ± 0.2 | 0.36 ± 0.2 | -0.94 ± 0.2 | -1.4 ± 0.4 | 0.42 ± 0.2 | -0.98 ± 0.1 | -1.3 ± 0.1 | 0.36 ± 0.1 | 0.13 | 0.66 | 0.75 |
| E (cm/sec) | 69 ± 17 | 102 ± 32 | 33 ± 22 | 61 ± 18 | 96 ± 30 | 34 ± 21 | 70 ± 11 | 93 ± 14 | 23 ± 24 | 0.18 | 0.78 | 0.65 |
| e' (cm/s) | 7.2 ± 2.1 | 11.3 ± 3.3 | 4.1 ± 3.5 | 5.6 ± 1.6 | 8.8 ± 1.9 | 3.0 ± 1.4 | 7.2 ± 0.8 | 11.2 ± 2.7 | 4.0 ± 2.2 | 0.12 | 0.10 | 0.59 |
| E/e' ratio | 9.7 ± 1.5 | 9.9 ± 4.2 | 0.16 ± 3.4 | 11.5 ± 3.9 | 11.2 ± 5.0 | -0.076 ± 2.6 | 9.9 ± 2.4 | 8.6 ± 1.6 | -1.3 ± 2.9 | 0.41 | 0.59 | 0.64 |
| Early diastolic strain rate (s-l) | 1.5 ± 0.7 | 2.5 ± 0.5 | 1.0 ± 0.6 | 1.3 ± 0.2 | 2.1 ± 0.7 | 0.80 ± 0.7 | 1.3 ± 0.2 | 2.3 ± 0.4 | 1.0 ± 0.5 | 0.60 | 0.37 | 0.71 |

Data are presented as the mean ± SD. FAC = fractional area change

**Figure 1.**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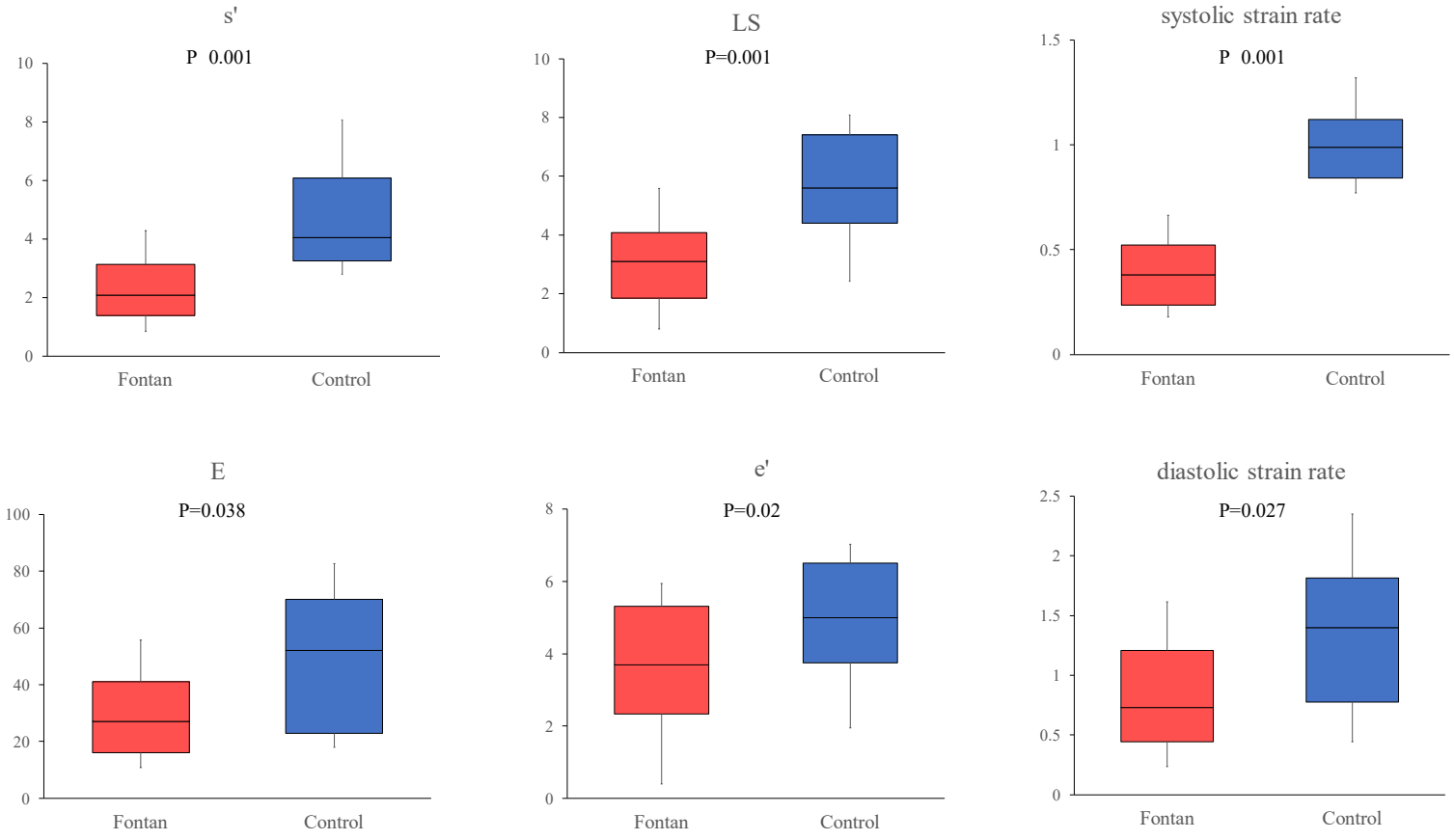
e'=5.9 cm/s
Peak
s'=5.9 cm/s
e'=8.0 cm/s
RV
RA
EC
LA
LS= -19.0 %
LS= -20.5 %
b
Rest
s'=10.0 cm/s
e'=14.5 cm/s
Peak
s'=14.1 cm/s
e'=18.9 cm/s
RV
LV
RA
LA
LS= -21.8 %
LS= -23.2 %

**Figure .**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6
4
2
0
Fontan
Control
LS
P=0.001
10
8
6
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2
0
Fontan
Control
systolic strain rate
P 0.001
1.5
1
0.5
0
Fontan
Control
E
P=0.038
100
80
60
40
20
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Fontan
Control
e'
P=0.02
8
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Control
diastolic strain rate
P=0.027
2.5
2
1.5
1
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Fontan
Control