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ORIGINAL ARTICLE

# Stroke volume ratio derived from magnetic resonance imaging as an indicator of interventricular dyssynchrony predicts future cardiac event in patients with biventricular Fontan circulation

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## Abstract

The prognostic factors in patients with biventricular heart who underwent Fontan surgery remain unclear. This study wanted to assess the hypothesis that interventricular dyssynchrony evaluated by cardiac magnetic resonance imaging (MRI) can predict future cardiac events in patients with biventricular heart who have undergone Fontan surgery. We prospectively enrolled consecutive patients with biventricular Fontan circulation from 2003 to 2016, and performed protocolized cardiac MRI. We determined the stroke volume ratio (SVr) using the following formula to assess interventricular dyssynchrony: (stroke volume (SV) of the two whole ventricles)/(SV of the right ventricle + SV of the left ventricle), by tracing cine MRI data. If interventricular dyssynchrony existed, blood flowed and returned to each ventricle through the ventricular septal defect; therefore, the SVr in this instance should be less than 1.0. We enrolled 40 patients. SVr ranged from 0.81 to 1.0 (median 0.95). Low SVr (< 0.95) was associated with worse New York Heart Association functional class, longer QRS duration, right bundle branch block, low biventricular indexed stroke volume, and low biventricular ejection fraction. During the follow-up period (median 53.5 months), 10 cardiac events occurred (six cases of acute exacerbation of heart failure, three cases of supraventricular tachycardia, and one case of exacerbation of protein-losing enteropathy). Univariate analysis showed four clinical predictors: SVr < 0.95 [hazard ratio (HR) 9.3, 95% confidential interval (CI) 1.7–171.5]; biventricular ejection fraction < 0.45 (HR 9.4, 95% CI 2.2–65.3); left ventricular indexed end-diastolic volume > 73 mL/m$^2$ (HR 4.5, 95% CI 1.1–15.7); and the presence of the aorta directly arising from the right ventricular conus (HR 5.8, 95% CI 1.1–106). SVr derived from MRI can predict future cardiac events in Fontan patients with biventricular hearts.

**Keywords** Fontan · Biventricular heart · Dyssynchrony · Stroke volume ratio · Prognostic factors

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## Abbreviations

| | |
|---|---|
| BiV | Biventricular |
| CRT | Cardiac resynchronization therapy |
| DKS | Damus–Kaye–Stansel |
| ED | End-diastolic |
| EDV | End-diastolic volume |
| EF | Ejection fraction |
| ES | End-systolic |
| ESV | End-systolic volume |
| LBBB | Left bundle branch block |
| LV | Left ventricle |
| MRI | Magnetic resonance imaging |
| NYHA | New York Heart Association |
| RBBB | Right bundle branch block |
| ROC curve | Receiver-operating characteristic curve |
| RV | Right ventricle |
| $SpO_2$ | Percutaneous oxygen saturation |
| SV | Stroke volume |

SVr Stroke volume ratio
VSD Ventricular septal defect

## Introduction

Fontan-type surgery is commonly performed in patients with congenital anomalous hearts, wherein only one functional ventricle exists. However, it is occasionally performed in patients with biventricular hearts that cannot be surgically separated because of straddling of the atrioventricular valve, remote-type ventricular septal defect (VSD), or other complex conditions. In biventricular Fontan circulation, the anatomically and physiologically different two ventricles, the left and right ventricles (LV and RV), have to work cooperatively as "one systemic ventricle". Therefore, focusing on "one systemic ventricle", interventricular dyssynchrony between the LV and RV corresponds to intraventricular dyssynchrony in the normally structured heart. In this challenging population, interventricular dyssynchrony can cause to-and-fro flow via the VSD and is associated with impaired cardiac function [1]. Only a few studies have reported on this subject to date. And, there has been no widely accepted method has been established to quantify interventricular dyssynchrony severity. Moreover, the relationship between interventricular dyssynchrony and cardiac events remains unclear. Although Yamamura et al. proposed biventricular Fontan dyssynchrony on ventriculography derived by cardiac catheterization [1], no examination via magnetic resonance imaging (MRI) has been performed yet. This study aimed to calculate the stroke volume ratio (SVr) by cine MRI in patients with biventricular Fontan circulation and tested the hypothesis that SVr is associated with deteriorating cardiac function and is a predictive factor of future cardiac events.

## Materials and methods

### Patients

We prospectively enrolled 47 consecutive patients with biventricular Fontan circulation and performed protocolized cardiac MRI from 2003 to 2016. The hearts meeting the following criteria were defined as "biventricular Fontan" in nature: these were hearts with two ventricles present after Fontan surgery, with both ventricles having an inlet portion, and the end-diastolic volume of the smaller ventricle being > 25% of the larger ventricle. The exclusion criteria were as follows: poor image quality, single ventricle, and/or history of ischemic heart disease. In addition, patients with moderate or severe valvular disease (regurgitation or stenosis) of the atrioventricular or aortic valve were excluded, because significant valvular disease can affect the ventricular stroke volume. We evaluated atrioventricular valvular and aortic regurgitation by cardiac MRI and defined moderate or severe regurgitation as a regurgitant fraction > 30%. On the other hand, we evaluated atrioventricular valvular stenosis by echocardiography and defined moderate or severe stenosis as a mean pressure gradient > 5 mmHg [2]. In patients who underwent more than one study, only data from the last study were analyzed.

### MRI measurements

All MRI examinations were performed using a 1.5 T MRI scanner (Intera; Philips Healthcare, Best, The Netherlands) with a five-element phased array cardiac coil. Cine steady state-free precession sequences were utilized on horizontal-axis views, encompassing two whole ventricles, with 0 mm gaps between images. Cine sequences with retrospective electrocardiogram gating were used with the following parameters: cardiac phase = 20, TR/TE = 2.9/1.5 ms, slice thickness = 10 mm, gapless between slices, flip angle = 55°, matrix = 192 × 256, and field of view = 380 × 380 mm. All examinations were transferred to a dedicated workstation (Z400; AZE, Tokyo, Japan) for subsequent image analysis. The end-diastolic (ED) and end-systolic (ES) frames of LV, RV, and the two whole ventricles were visually individually selected, while contours were drawn manually by tracing the endocardial borders in each slice at both ED and ES. Contour tracing was aided by reviewing multiple phase scans in the movie mode. The location of the VSD (border between the LV and the RV) was determined as an extension line of interventricular septum on each horizontal-axis view. Traced contours were used for the quantification of end-diastolic volumes (EDV), end-systolic volumes (ESV), stroke volume (SV), and ejection fraction (EF). EF was calculated as the percentage of difference between EDV and ESV with respect to EDV.

We calculated SVr using the following formula (Figs. 1, 2, 3):

Stroke volume ratio (SVr)
= (SV of the two whole ventricles)
/(SV of RV + SV of LV).

Notably, when there is no interventricular dyssynchrony, SVr must be 1.0. Otherwise, when interventricular dyssynchrony exists, SVr should be < 1.0 and inversely correlate with interventricular dyssynchrony severity. We also measured SV and cardiac output using the phase-contrast method.

We divided the patients into two groups: the low SVr group (SVr < 0.95) and the high SVr group (SVr > 0.95). The

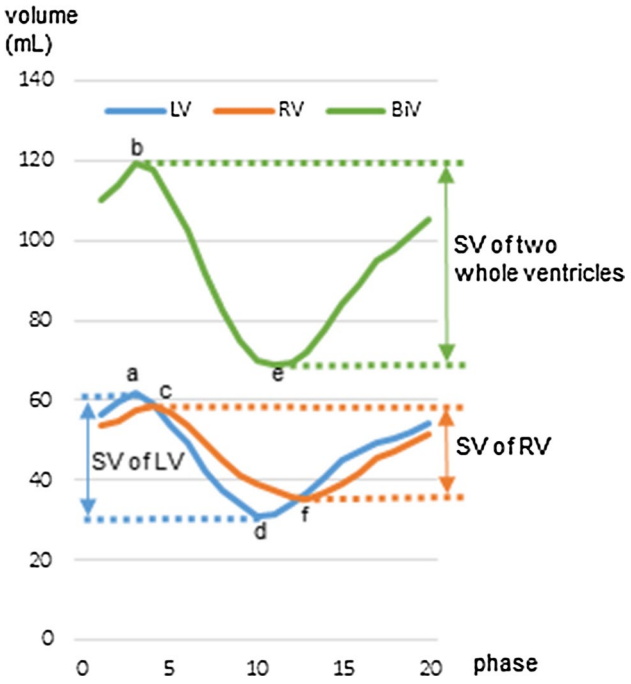


**Fig. 1** Schematic illustration of methods of analysis of the SVr. Cardiac cycle was divided into 20 phases. The volumes of each RV and LV were added to obtain the volume of two whole ventricles. In the heart with interventricular dyssynchrony, the stroke volume of two whole ventricles is less than the sum of the stroke volume of the RV and LV obtained independently because the timing of the maximum and minimum phases of each of the two ventricular volumes are not simultaneous. The more severe the interventricular dyssynchrony becomes, the greater the difference between the SVs, and the smaller the SVr become. The characters "a–f" correspond to the schema of Fig. 2. *LV* left ventricle, *RV* right ventricle, *SV* stroke volume, *SVr* stroke volume ratio

cutoff value was determined based on a previous report [1]. We compared SVr with other MRI parameters.

### Clinical data

Based on data from the patients' medical records, we investigated QRS duration, six-minute walk test, and New York Heart Association (NYHA) classification. Patients with percutaneous oxygen saturation ($SpO_2$) of < 90% (four patients) were excluded from the analysis of the NYHA class and six-minute walk test, because desaturation may affect activities of daily living and exercise capacity. The reasons for a low $SpO_2$ were venovenous collaterals (two cases), baffle leak (one case), and pulmonary arteriovenous fistula (one case). Two of the four were NYHA class I; the other two were class II. We compared SVr with the clinical data.

Patients were followed up with until the occurrence of a cardiovascular event involving acute (exacerbation of) heart failure, clinically significant arrhythmia, thromboembolism, or protein-losing enteropathy occurred. Acute exacerbation of heart failure was defined as heart failure requiring admission. Arrhythmia requiring emergent defibrillation, pacemaker implantation, or hospitalization for antiarrhythmic drug adjustment was defined as clinically significant.

### Statistical methods

Statistical analysis was performed using JMP Pro version 12 (SAS Institute, Cary, NC, USA). Data are presented as mean with standard deviations or median with ranges where appropriate. We used the Chi square test to compare the proportions of categorical variables between the groups. A Student's *t* test or the Mann–Whitney *U* test was used for continuous variables. Pearson or Spearman rank correlation was performed for regression analysis. Receiver operating characteristic (ROC) curves were analyzed to determine the optimal cutoff values. The effect of factors across time on cardiac event data was analyzed using a Cox proportional hazard model.

The survival curve during the follow-up for cardiac event was analyzed using the Kaplan–Meier method, and the statistical assessment was performed using the log-rank test. A $P$ value < 0.05 was considered statistically significant (two-tailed).

## Results

### Patient characteristics

Of the 47 patients, seven patients (four with moderate or severe atrioventricular valvular regurgitation, one with severe atrioventricular valvular stenosis, one with history of myocardial infarction, and one with poor image quality due to body motion during MRI study) were excluded, leaving a total of 40 study participants.

The diagnosis was double-outlet right ventricle in 19 patients, complete atrioventricular septal defect in 13 patients, criss-cross heart in four patients, complete transposition of the great arteries in three patients, and anatomically corrected malposition of the great arteries in one patient.

Fontan surgery was performed at a median of 5 years old (range 0–27 years old), and cardiac MRI study was performed at 15 years (range 2–25 years) after the Fontan procedure.

Right bundle branch block (RBBB) was seen in 12 of the 40 (30%) patients, while no patients with left bundle branch block (LBBB) were observed.

SVr was 1.0 in seven of the 40 (17.5%) patients without detectable interventricular dyssynchrony. In 14 of the 40

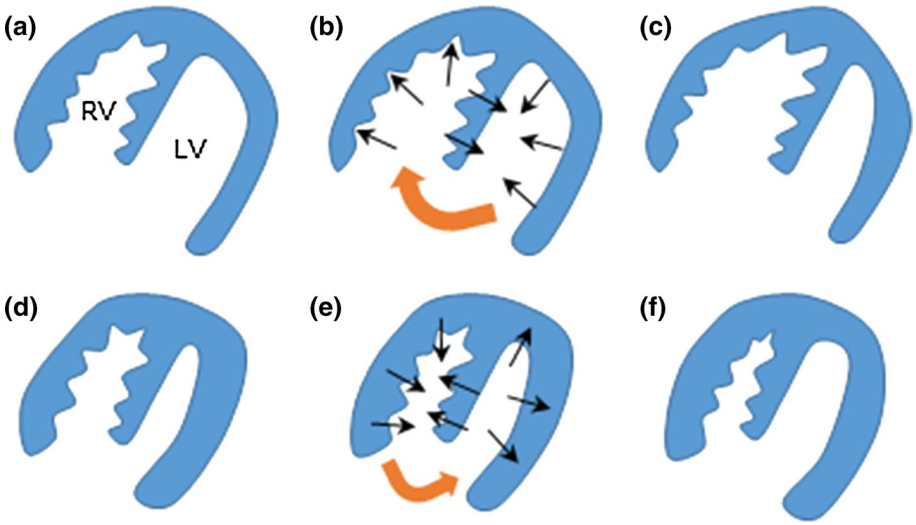


**Fig. 2** Hypothetical schematic illustration of the heart with interventricular dyssynchrony. **a–c** End-diastolic phase. **a** The LV volume is maximum before the RV. **b** The volume of whole two ventricle volume is maximum. Although the RV cavity is still expanding, the LV has already started to contract, and the blood flow from the LV to the RV via the VSD is seen. **c** The RV volume is maximum. From this point, the two ventricles begin to contract coordinately. **d–f** End-systolic phase. **d** The LV volume is minimum. **e** The volume of the whole two ventricles is minimum. Opposite to **b**, the RV is still contracting and the LV is already expanding, hence, blood flow from the RV to the LV via the VSD is seen. **f** The RV volume reached to minimum. *LV* left ventricle, *RV* right ventricle, *VSD* ventricular septal defect

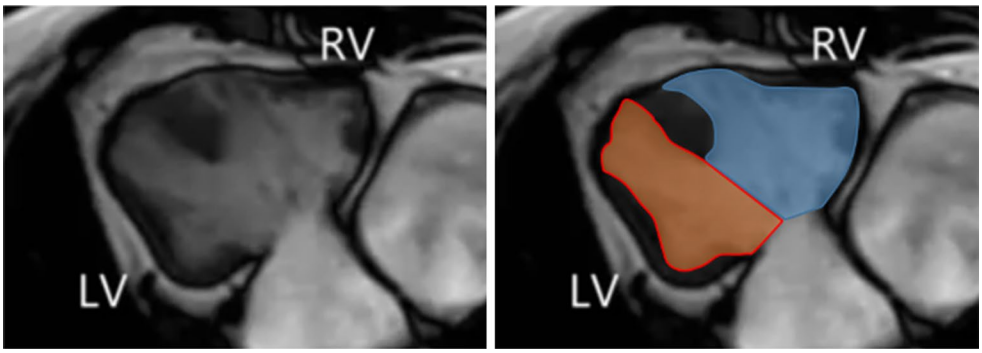


**Fig. 3** Magnetic resonance imaging used to evaluate end-diastolic volumes (EDV) of the right ventricle (RV) and left ventricle (LV)

(35%) patients, the LV preceded the RV both in the early systolic and diastolic periods.

In 16 of the 40 (40%) patients, the LV started to relax earlier than the RV but also started to contract simultaneously. In another three (12.5%) patients, the RV preceded the LV in both the contraction and relaxation phases (Table 1).

SV values derived from the cine steady state–free precession sequence and the phase-contrast method were well-correlated ($R = 0.56$, $P < 0.002$).

## Low SVr group/high SVr group

Just half of patients were categorized into the low SVr group (SVr < 0.95, $n = 20$, 50%) and the rest were categorized into high SVr group (SVr > 0.95, $n = 20$, 50%). SVr did not differ with respect to patient sex. Low SVr was significantly associated with NYHA class ≥ II, long QRS duration, RBBB, heart with aorta that arises from RV conus, high indexed biventricular end-systolic volume, and low EF of the RV and biventricle (Table 2). In addition, the SVr had a negative correlation with QRS duration ($R = 0.77$, $P < 0.0001$) and a positive correlation with biventricular EF ($R = 0.57$, $P = 0.0001$) (Fig. 4).

## Cardiac events

During the follow-up period (median; 53.5 months, range 6–114 months), 10 cardiovascular events occurred (six cases of acute exacerbation of heart failure, three cases of

**Table 1** Patient characteristics

| | |
|---|---|
| *N* | 40 |
| Age at MRI (years) | 20 (7–45) |
| Age at Fontan surgery (years) | 5 (0–27) |
| Sex, male/female | 17/23 |
| APC/TCPC | 27/13 |
| DORV/cAVSD/CCH/others[a] | 19/13/4/4 |
| Atrioventricular connection | |
| Two valves | |
| Normal alignment | 13 |
| Criss-crossing | 4 |
| Straddling | 10 |
| Unilateral AVV atresia | 0 |
| CAVV | 13 |
| Ventriculoarterial connection | |
| Aortic override (−) | |
| Ao arises from RV (conus) | 28 |
| Ao arises from LV | 0 |
| Aortic override (+) | 9 |
| p-DKS | 3 |
| Earlier start contraction | |
| RV | 3 |
| LV | 14 |
| Simultaneously | 23 |
| Earlier start relaxation | |
| RV | 3 |
| LV | 30 |
| Simultaneously | 7 |
| Bundle branch block | |
| RBBB | 12 |
| LBBB | 0 |
| No BBB | 28 |
| SVr | 0.95 (0.81–1.0) |

*Ao* aorta, *AVV* atrioventricular valvular, *APC* atriopulmonary connection Fontan-type surgery, *BBB* bundle branch block, *cAVSD* complete atrioventricular septal defect, *CAVV* common atrioventricular valve, *CCH* criss-cross heart, *p-DKS* post Damus–Kaye–Stansel anastomosis, *DORV* double-outlet right ventricle, *LBBB* left bundle branch block, *LV* left ventricle, *MRI* magnetic resonance imaging, *RBBB* right bundle branch block, *RV* right ventricle, *SVr* stroke volume ratio, *TCPC* total cavo-pulmonary connection

[a]Complete transposition of the great arteries 3, anatomically corrected malposition of the great arteries 1

supraventricular tachycardia, and one case of exacerbation of protein-losing enteropathy). Table 3 shows univariate Cox hazard analyses of predictors of cardiac events. The cutoff values were derived from the ROC curve.

Figure 5 shows the Kaplan–Meier curves. Patients with an SVr < 0.95 had significantly lower event-free survival probability than those with an SVr > 0.95 ($P = 0.01$).

## Discussion

The number of Fontan patients is increasing steadily all over the world, and ensuring a precise prognosis prediction is important to treat them adequately [3]. In a systematic review of 6707 cases, Alsaied et al. enumerated eight major predictive risk factors of late mortality in Fontan patients and advocated that the most attributive risk factor was "moderate/severe ventricular dysfunction or moderate/severe atrioventricular valve regurgitation" [4]. Moreover, they revealed that the most major direct cause of late mortality in these patients was heart failure [5]. For this reason, it is significantly important to elucidate the detailed mechanisms of ventricular dysfunction and heart failure in Fontan patients. Especially in patients with biventricular Fontan circulation, interventricular dyssynchrony is thought to induce cardiac dysfunction; however, there is not sufficient evidence about the relationship of interventricular dyssynchrony and heart failure or future cardiac events.

This is the first MRI study to assess the relationship between interventricular dyssynchrony and cardiac events in patients with biventricular Fontan circulation, wherein the LV and RV act as a "single systemic ventricle". SVr can be easily calculated using classical cine MRI data and can quantitate mechanical interventricular dyssynchrony simply. SVr derived by ventriculography was studied and discussed previously, but obtaining cine ventriculography is invasive to patients [1]. However, SVr derived from MRI is noninvasive and thought to provide a more precise measurement.

### Interventricular dyssynchrony and intrinsic ventricular characteristics

In the normally structured heart, the start of the LV contraction is earlier than that of the RV by 20 ms [6]. In addition, over the long term, the RV is more susceptible to the afterload of systemic pressure than the LV [7] and is prone to be affected by cardiac dysfunction following intraventricular conduction delay [8]. In the biventricular Fontan heart, the intrinsic characteristics of both the RV and LV are almost the same as the ventricles of a normally structured heart. In addition, therefore, the RV contracts/relaxes after the LV contraction/relaxation in many cases in this study. The fact that a relationship was found between RBBB and low SVr reinforces this hypothesis.

### Interventricular dyssynchrony and anatomy of outflow tract

Higaki et al. elucidated the relationship among interventricular dyssynchrony and to-and-fro flow through the VSD and

**Table 2** Comparison between low and high SVr groups

| | Low SVr (< 0.95) | High SVr (> 0.95) | *P* value |
|---|---|---|---|
| *N* | 20 (50%) | 20 (50%) | |
| Age at MRI (years) | 27 (7–45) | 17.5 (8–40) | 0.21 |
| Age at Fontan surgery (years) | 6.5 (1–27) | 3.5 (0–18) | 0.2 |
| Male | 10/20 (50%) | 13/20 (65%) | 0.52 |
| APC | 16/20 (80%) | 11/20 (55%) | 0.09 |
| NYHA class[a] | | | |
| I | 9 (25%) | 14 (39%) | |
| ≥ II | 10 (28%) | 3 (8%) | 0.03 |
| 6mwt (m)[a] | 460 (380–530) | 472.5 (430–680) | 0.17 |
| QRS duration (ms) | 100 (65–136) | 89 (67–106) | 0.0003 |
| RBBB | 11/20 (55%) | 1/20 (5%) | 0.001 |
| BNP (pg/mL) | 60.1 (4–151.8) | 52.5 (6.5–447.8) | 0.61 |
| AVV | | | |
| Two valves | 12 (30%) | 15 (38%) | |
| CAVV | 8 (20%) | 5 (13%) | 0.51 |
| Ao arises from | | | |
| RV conus | 17 (43%) | 11 (28%) | |
| Others | 3 (8%) | 9 (23%) | 0.04 |
| Indexed end-diastolic volume (L/m$^2$) | | | |
| RV | 53.9 (29.7–104.3) | 53.1 (30.9–94.1) | 0.68 |
| LV | 40.5 (19.4–103.9) | 36.3 (15.6–69.7) | 0.26 |
| BiV | 105.0 (50.8–154.0) | 96.9 (64.1–150.3) | 0.37 |
| Indexed end-systolic volume (L/m$^2$) | | | |
| RV | 28.4 (12.4–57.8) | 28.7 (14.5–51.2) | 0.77 |
| LV | 21.7 (8.8–61.1) | 18.0 (5.7–45.2) | 0.07 |
| BiV | 61.0 (27.7–96.8) | 47.7 (23.4–79.4) | 0.0048 |
| Indexed stroke volume (L/m$^2$) | 46.4 (23.0–65.2) | 47.9 (33.6–75.8) | 0.14 |
| Cardiac Index (L/min/m$^2$) | 3.21 (1.54–4.87) | 3.19 (2.28–4.98) | 0.52 |
| Ejection fraction | 0.44 (0.30–0.55) | 0.49 (0.42–0.66) | 0.0008 |
| RVEDV/BiVEDV | 0.54 (0.30–0.84) | 0.57 (0.38–0.80) | 0.33 |

[a]Four patients with $SpO_2$ of < 90% were excluded from the analysis of the NYHA class and 6mwt

*Ao* aorta, *APC* atriopulmonary connection Fontan-type surgery, *AVV* atrioventricular valve, *BiV* biventricle, *BiVEDV* biventricular end-diastolic volume, *BNP* B-type natriuretic peptide, *CAVV* common atrioventricular valve, *MRI* magnetic resonance imaging, *NYHA* New York Heart Association, *LV* left ventricle, *RBBB* right bundle branch block, *RV* right ventricle/right ventricular, *RVEDV* right ventricular end-diastolic volume, *$SpO_2$* percutaneous oxygen saturation, *SVr* stroke volume ratio, *6mwt* six-minute walk test

aortic valvular opening in detail using ventriculography and pulsed Doppler echocardiography in a biventricular Fontan heart with the aorta arising from the RV conus as follows: blood ejected from the LV pools into the RV until the start of RV contraction and aortic valvular opening in the early systolic phase, resulting in RV volume overload. After the RV contraction starts, the aortic valve finally opens and blood is ejected from the heart. In the early diastolic phase, LV relaxation begins earlier than RV relaxation, and causes blood regurgitation from the RV to the LV, resulting in LV volume overload and loss of cardiac output [9].

We hypothesized about biventricular Fontan with other type of outflow tract anatomy. For example, the aortic valve directly arises from both the RV and LV in a heart with an overriding aorta. This explains why blood ejected from the LV directly opens the aortic valve and immediately passes the valve in the early systolic phase, resulting in less interventricular dyssynchrony. Three patients underwent Damus–Kaye–Stansel (DKS) anastomosis. The aortic or pulmonary valve had overridden the interventricular septum in all three of these patients; hence, we categorized them into an Ao override group.

The relationship of outflow tract anatomy to interventricular dyssynchrony must result in lower SVr and higher cardiovascular event rates in cases with RV conus. DKS anastomosis is usually added to minimize the risk of systemic ventricular outflow tract obstruction and is related to good outcomes [10, 11], but it may also reduce interventricular

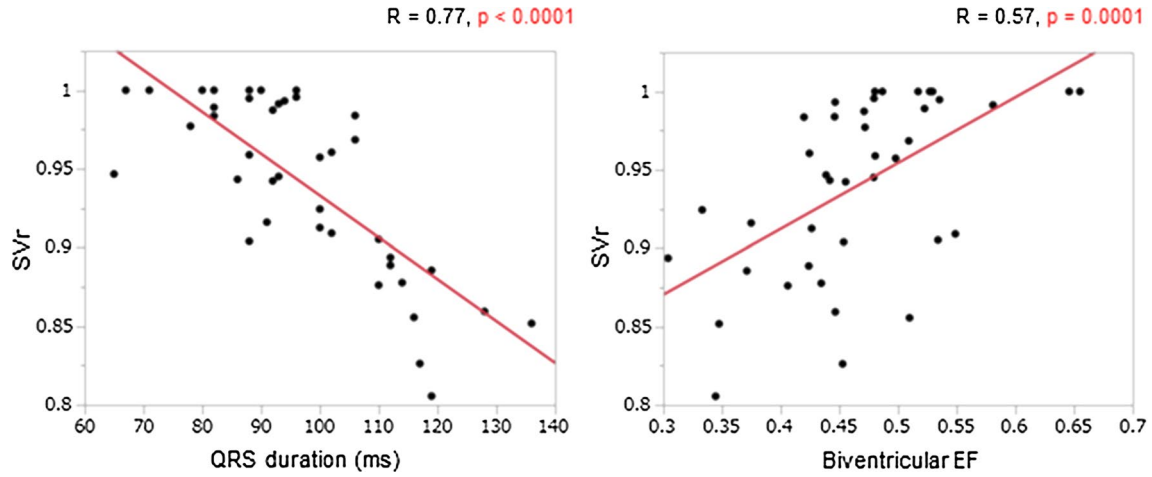


**Fig. 4** The correlation between stroke volume ratio (SVr) and variables that showed significant difference. SVr is negatively correlated with QRS duration and positively correlated with biventricular ejection fraction. *EF* ejection fraction, *SVr* stroke volume ratio

**Table 3** Univariate factors predicting future cardiac events

| | HR | 95% CI | *P* value |
|---|---|---|---|
| Age at MRI > 38 (years) | 4.3 | 0.63–18.7 | 0.07 |
| Age at Fontan surgery > 13 (years) | 1.9 | 0.40–6.8 | 0.39 |
| Female | 1.5 | 0.41–6.9 | 0.57 |
| NYHA class ≥ II | 3.2 | 0.90–12.4 | 0.07 |
| QRS duration > 110 (ms) | 3.5 | 0.96–12.6 | 0.06 |
| RBBB | 1.4 | 0.36–49 | 0.61 |
| BNP > 38 (pg/mL) | 4.4 | 0.81–81.5 | 0.09 |
| Ao arises from RV conus | 5.8 | 1.07–106 | 0.04 |
| Heart rate > 72 (bpm) | 2.5 | 0.71–9.9 | 0.15 |
| Indexed end-diastolic volume (mL/m$^2$) | | | |
| RV > 36 | 1.8 | 0.33–32.4 | 0.57 |
| LV > 73 | 4.5 | 1.1–15.7 | 0.03 |
| BiV > 120 | 2.5 | 0.68–8.9 | 0.16 |
| Indexed end-systolic volume (mL/m$^2$) | | | |
| RV > 25 | 2.6 | 0.64–17.3 | 0.19 |
| LV > 21 | 3.3 | 0.83–22.0 | 0.10 |
| BiV > 62 | 2.8 | 0.79–11.0 | 0.12 |
| Indexed stroke volume > 53 (mL/m$^2$) | 2.3 | 0.66–9.1 | 0.19 |
| Cardiac index > 3.1 (L/min/m$^2$) | 2.1 | 0.53–14.1 | 0.31 |
| Ejection fraction < 0.45 | 9.4 | 2.2–65.3 | 0.002 |
| RVEDV/BiVEDV < 0.37 | 2.9 | 0.75–10.3 | 0.11 |
| SVr < 0.95 | 9.3 | 1.7–171.5 | 0.006 |

*Ao* aorta, *BiV* biventricle, *BiVEDV* biventricular end-diastolic volume, *BNP* B-type natriuretic peptide, *CI* confidence interval, *HR* hazard ratio, *LV* left ventricle, *MRI* magnetic resonance imaging, *NYHA* New York Heart Association, *RBBB* right bundle branch block, *RV* right ventricle/right ventricular, *RVEDV* right ventricular end-diastolic volume, *SVr* stroke volume ratio

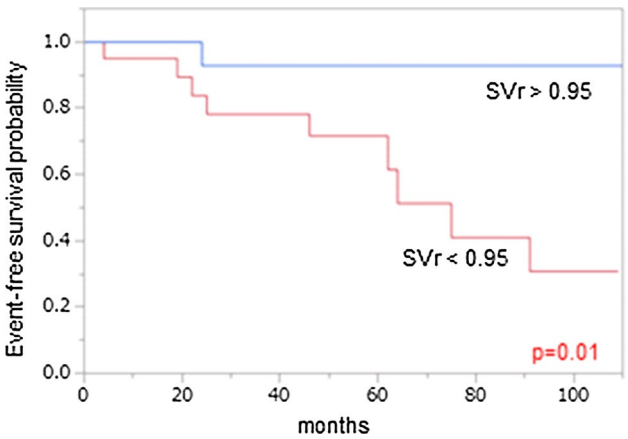


**Fig. 5** Kaplan–Meier curve for event-free survival probability. Survival curves were calculated using the Kaplan–Meier method and analyzed by the log-rank test. *SVr* stroke volume ratio

dyssynchrony. In contrast, atrioventricular valve and inlet anatomy have no significant relationship with interventricular dyssynchrony. Because we excluded the single ventricle heart, both the RVs and LVs of all cases received direct blood inflow through the atrioventricular valve, and no significant difference existed in the inlet anatomy between the cases.

## SVr and clinical features

Low SVr was related to high indexed biventricular ESV, low biventricular EF, and high NYHA class. In echocardiography studies, vortex flow in the LV has been known to be associated with increased EDV and ESV, as well as reduced EF [12] and adverse clinical outcomes [13] in a normally structured heart. Flow energy loss derived from cardiac MRI

is also associated with clinical status in patients with dilated cardiomyopathy [14]. Furthermore, an echocardiography study reported that left ventricular energy loss in VSD was associated with a high RV pressure and a vortex flow in the LV [15]. In the participants of our study, to-and-fro blood flow, which crosses the VSD, is considered to create a vortex flow in the ventricles and produce energy loss. Not only was volume overload to both the RV and LV as mentioned above noted, but also increased energy loss may play an important role in increased ventricular volume, reduced EF, and impaired NYHA class.

In our study, the SVr had quite a good inverse correlation with QRS duration, and this relationship reveals that mechanical interventricular dyssynchrony is related with electrical conduction delay in patients with biventricular Fontan circulation without a history of ischemic heart disease.

### SVr and cardiac events

Also, in our study, SVr predicts future cardiac events. This means that interventricular dyssynchrony plays a very important role in cardiac prognosis.

In a PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease, patients with an anatomical presentation of single ventricle with an EF of < 45% are indicated for the implantation of cardiac resynchronization therapy (CRT) (class IIa); however, what to do in the presence of interventricular dyssynchrony in a biventricular Fontan circuit is not mentioned in the statement [16]. SVr of < 0.95 might be a good indication of CRT, but further studies are required.

### Quantification of interventricular dyssynchrony

Interventricular dyssynchrony is generally considered a contraction delay between the RV and the LV. Interventricular dyssynchrony in congenital heart disease is based on the "time lag" between two ventricles of peak strain using speckle tracking [17] or feature tracking MRI [18], or of peak intraventricular pressure derived from cardiac catheterization [19]. Miyazaki et al. evaluated interventricular dyssynchrony using ventriculography in a single RV with a rudimentary LV [20]. A tagging MRI study recently reported that interventricular dyssynchrony predicts RV dysfunction in adult congenital heart disease [21]. On the other hand, a Doppler echocardiography study reported that interventricular dyssynchrony is defined as the difference between systemic and pulmonary ventricular pre-ejection intervals > 40 ms derived from pulse Doppler focused on each outflow tract [22]. However, in biventricular Fontan patients, it is impossible to apply the above criteria because both ventricles eject blood towards the same blood vessel (the aorta).

Yamamura et al. first advocated SVr as a marker of interventricular dyssynchrony using cine ventriculography, which can quantitate futile systolic volume through the VSD. The new index differs from the simple time lag between the two ventricles. We think that SVr is applicable for Fontan patients with biventricular type because the futile systolic volume directly reduces the true cardiac output toward the aorta.

Our method also has the advantage of using cine MRI. The measurement of ventricular volumes using ventriculography in Yamamura's method is assumed to be a normally structured heart; hence, the volume of structural complicated ventricles in a Fontan candidate cannot be measured accurately. In contrast, our method always precisely evaluates even structurally complicated ventricles because cine MRI has no blind areas such as echocardiography and is noninvasive unlike ventriculography.

## Limitations

This study has several limitations. First, the included sample size was small. Next, further studies comparing other modalities (e.g., speckle tracking echo or tagging of MRI) are needed for precise quantifications of interventricular dyssynchrony.

## Conclusions

Interventricular dyssynchrony is associated with both low EF of the whole ventricle and worse NYHA in Fontan patients with a biventricular heart. The SVr on MRI can be predictive of future cardiac events in Fontan patients with biventricular hearts.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The ethical committee in our hospital also gave approval, and all subjects provided their informed consent for cardiac MRI.

**Human and animal rights statement** This article does not contain any studies with animals performed by any of the authors.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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