Induction of aggressive arterial and venous dilation therapy in addition to pulmonary dilation therapy (super-Fontan strategy) improves Fontan circulation both at rest and during treadmill exercise

Check for updates

Shoichi Ishikawa, MD,[a] Shun Matsumura, MD, PhD,[b] Akiko Yana, MD,[b] Clara Kurishima, MD,[b] Yoichi Iwamoto, MD, PhD,[a,b] Hirotaka Ishido, MD, PhD,[b] Satoshi Masutani, MD, PhD, FAHA,[b] Ryo Nakagawa, MD, PhD,[a] and Hideaki Senzaki, MD, PhD, FAHA[a]

ABSTRACT

Objective: Fontan circulation maintains preload and cardiac output by reducing venous capacitance and increasing central venous pressure (CVP). The resultant congestive end-organ damage affects patient prognosis. Therefore, a better circulatory management strategy to ameliorate organ congestion is required in patients with Fontan circulation. We sought to verify whether aggressive arterial and venous dilation therapy in addition to pulmonary dilation (super-Fontan strategy) can improve Fontan circulation and reduce congestion.

Methods: Patients after Fontan surgery who received the super-Fontan strategy in a single center were recruited. Participants were examined using medical records between 2010 and 2018. We retrospectively analyzed the changes in hemodynamics at rest and during treadmill exercise before and after the introduction of this therapy.

Results: The therapy significantly increased venous capacitance (3.21 ± 1.27 mL/kg/mm Hg to 3.79 ± 1.30 mL/kg/mm Hg, $P = .017$) and decreased total pulmonary resistance, leading to significantly reduced CVP (11.7 ± 2.4 mm Hg to 9.7 ± 2.2 mm Hg, $P < .001$) and increased cardiac index (CI) (3.09 ± 1.01 L/min/m^2 to 3.54 ± 1.19 L/min/m^2, $P = .047$). Furthermore, this strategy significantly reduced the elevations in CVP (19.6 ± 5.3 mm Hg to 15.4 ± 2.7 mm Hg, $P = .002$) with preserved CI in response to exercise. CVP at rest and during exercise was significantly positively correlated with serum markers of hepatic congestion and fibrosis, respectively.

Conclusions: The super-Fontan strategy is a therapy that turns the heart failure condition of Fontan circulation into a more physiological condition. However, whether the strategy improves long-term prognosis warrants further studies. (JTCVS Open 2022;11:388-97)

The super-Fontan strategy improved Fontan hemo-dynamics at rest and during exercise.
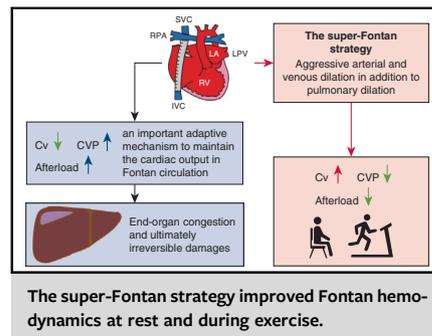
CENTRAL MESSAGE

The adaptive mechanism that maintains a high central venous pressure (CVP) causes chronic complications after Fontan surgery. The super-Fontan strategy reduces the elevation of CVP.

PERSPECTIVE

CVP at rest and during exercise is significantly correlated with the serum markers of hepatic congestion and fibrosis, respectively. Because high CVP is a key driver of organ dysfunction due to chronic congestion, the super-Fontan strategy may help delay or prevent long-term complications in patients with Fontan circulation.

▶ Video clip is available online.

Reducing venous capacitance (Cv) by constricting the venous vasculature is an important adaptive mechanism to maintain ventricular preload and thereby the cardiac output in Fontan circulation, in which the pulmonary ventricle is lacking.[1-4] However, this adaptation inevitably causes elevations in central venous pressure (CVP) both at rest and under volume loading conditions,[5] leading to end-organ congestion[6-8] and ultimately irreversible damages during a long period after Fontan surgery.[9] We have previously demonstrated that chronically antagonizing this adaptive mechanism during the first year after Fontan surgery through the aggressive dilation of the systemic veins and arteries, while optimizing pulmonary vascular resistance (Rp) and cardiac function (super-Fontan strategy), lowers CVP levels beyond those expected for "normal" Fontan circulation and close to those of the normal 2-ventricle circulation.[2] In the present study, we further tested the generality of the efficacy of this strategy by introducing it to patients who had undergone Fontan surgery several years previously. In addition, because it is potentially important to suppress venous congestion during exercise, when CVP can increase much more than at rest with preload mobilization, we also tested the effects of the super-Fontan strategy on exercise hemodynamics. We hypothesized that the super-Fontan strategy can improve chronic Fontan hemodynamics by increasing Cv and optimizing the systemic and pulmonary circulation not only at rest but also during exercise.

METHODS

Among the 52 patients who were followed up at the outpatient clinic at Saitama Medical Center after Fontan surgery, we retrospectively analyzed those who received the super-Fontan strategy using medical records from April 2010 to February 2018. Patients who had already received the super-Fontan strategy just after the Fontan completion were excluded. Isosorbide dinitrate (Frandol tape: 0.8-2.5 mg/kg; Katakura, TOA EIYO LTD) was administered once daily to increase the Cv. The angiotensin-converting enzyme inhibitor (ACEI) enalapril (0.1-0.2 mg/kg) was concurrently administered to those who were not taking an ACEI or an angiotensin type II receptor blocker (ARB). These medications were titrated and adjusted during the outpatient follow-up, and the presence of their side effects was carefully monitored, especially in those associated with hypotension. Medications for maintaining a low Rp and ventricular contractility, if needed (targeting an ideal Rp of at least less than 2 Rum^2 and ejection fraction of more than 50%), were also administered.

Changes in hemodynamics, including CVP, blood pressure (BP), heart rate (HR), cardiac index (CI), mean circulatory filling pressure (MCP), circulatory blood volume (BV), and Cv were examined before and after the introduction of this therapy. We evaluated CVP and MCP using peripheral venous pressure (PVP), as previously reported.[10] To summarize, CVP was estimated according to the known relationship between CVP and PVP,[10] and MCP was measured as equilibrated PVP during rapid inflation of a BP cuff to 200 mm Hg (Video 1). CI and BV were calculated using the dye-dilution technique (DDG analyzer; Nihon Kohden) with injection of indocyanine green (0.4 mg/kg). The DDG analyzer provided an accurate and reproducible time course of the blood concentration of the injected indocyanine green.[11] Thereafter, Cv was calculated by dividing the BV by the MCP. Systemic vascular resistance (Rs) was computed as mean BP minus CVP divided by CI. The total pulmonary resistance (TPR), which incorporates both Rp and ventricular diastolic function, was also calculated as CVP divided by CI.

In addition to the hemodynamic changes at the resting condition, we also evaluated the effects of the super-Fontan strategy on dynamic changes in Fontan hemodynamics during treadmill exercise testing before and after the induction of the therapy. In addition to changes in BP and HR, changes in CVP were estimated by continuously monitoring PVP, and changes in CI were continuously measured using impedance cardiography (AESCULON mini; Osypka Medical), which provides instantaneous CI values.[12,13] Treadmill exercise testing was performed according to a modified Bruce protocol at our institution: 30 seconds for each stage, considering that children tend to stop exercise because of lower-extremity fatigue before reaching their maximum cardiopulmonary functional capacity. CVP changes during exercise have not been well recognized in patients with Fontan circulation. Therefore, to better understand the effects of the super-Fontan strategy on hemodynamic changes during exercise in patients with Fontan circulation, changes in hemodynamics during treadmill exercise with the same protocol in patients with isolated paroxysmal ventricular contraction but with normal cardiac function were analyzed as control data and compared with the data of patients with Fontan circulation.
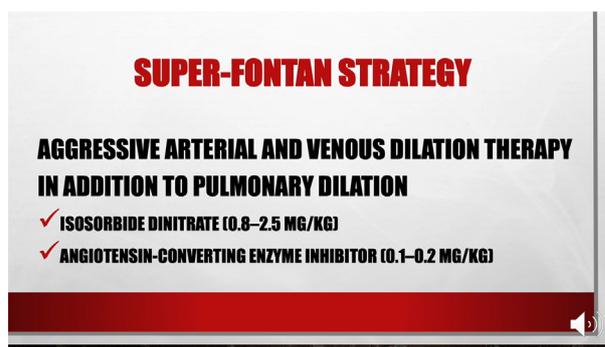
VIDEO 1. Summary of The Super-Fontan Strategy. #4 slide is re-used from our previous publication in *JTCVS* with a permission from Elsevier publisher.[10] Video available at: https://www.jtcvs.org/article/S2666-2736(22)00298-4/fulltext.

TABLE 1. Characteristics of patients who received the super-Fontan strategy

Characteristics	Pre–super-Fontan	Post–super-Fontan	N, mean ± SD, P value
n			30
Sex (male:female)			21:9
Age, y			
Fontan surgery			2.8 ± 1.2
Evaluation before the super-Fontan strategy			8.9 ± 4.4
Introduction of the super-Fontan strategy			9.1 ± 4.4
Evaluation after the super-Fontan strategy			11.4 ± 4.4
Underlying disease, n			
Single left ventricle			3
Single right ventricle			12
Tricuspid atresia			3
Pulmonary atresia/intact septum			6
Hypoplastic left heart syndrome			3
Others			3
Asplenia/polysplenia			6/1
Fenestration	22 (73)	20 (67)	.57
Medications, n (%)			
Diuretics	18 (60)	20 (67)	.592
ACEI/ARB	22 (73)	29 (97)	.011
β-Blockers	11 (36)	12 (40)	.822
Pulmonary dilators	25 (83)	27 (90)	.448
Bosentan, mg/kg/d	16 (4.0 ± 0.7)	14 (4.1 ± 0.7)	
Macitentan, mg/kg/d	5 (0.19 ± 0.02)	9 (0.21 ± 0.03)	
Sildenafil, mg/kg/d	1 (3.5)	1 (3.7)	
Tadalafil, mg/kg/d	18 (1.1 ± 0.2)	20 (4.0 ± 0.7)	
Digoxin	2 (7)	2 (7)	1.000
Warfarin/aspirin	28 (93)	30 (100)	.150
Antiarrhythmics	2 (7)	2 (7)	1.000
Nitrates	0 (0)	30 (100)	<.001

SD, Standard deviation; *ACEI*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin type II receptor blocker.

The institutional review board or equivalent ethics committee of the Saitama Medical Center (no. 2360, June 4, 2020) and the International University of Health and Welfare (no. 20-Nr-097, March 31, 2021) approved the study protocol and publication of data. The patients provided informed written consent for the publication of the study data.

Statistical Analysis

Data are summarized as mean ± standard deviation. Data before and after the super-Fontan strategy were compared by performing the paired *t* test, and data between the patients with Fontan circulation and controls during exercise were compared using the unpaired *t*-test.

RESULTS

We found 30 patients who received the super-Fontan strategy more than a year after the Fontan surgery, and they were enrolled in this study. The patient characteristics are summarized in Table 1. The mean time since surgery for the patients who received the super-Fontan strategy was 6.6 ± 4.3 years. Enalapril or an ARB (candesartan) had already been prescribed in 22 patients (73%). Thus, enalapril was added for the remaining patients, except for 1 patient with allergic reactions to enalapril and candesartan. Table 2 summarizes the effects of the super-Fontan strategy on resting hemodynamics. CVP and BP significantly decreased without changes in HR (78.7 ± 16.0 beats per minute vs 80.4 ± 17.1 beats per minute, *P* = .816). CI and oxygen saturation also significantly improved after the induction of the super-Fontan strategy. These hemodynamic improvements were accompanied by changes in venous characteristics, represented by a significant increase in Cv. In addition, TPR was also significantly reduced after the therapy, whereas Rs showed a borderline reduction.

Table 3 summarizes the characteristics of both Fontan (n = 25) and control (n = 28) patients who performed treadmill exercise testing. The ages were similar between the 2 groups. As expected, CI was lower and CVP was greater in patients with Fontan circulation than in controls. The maximum exercise stage was significantly lower in patients with Fontan circulation before the initiation of the therapy than in controls. As shown in Figure 1, patients with Fontan circulation showed an augmented increase in CVP (18.9 ± 4.1 mm Hg vs 11.1 ± 2.2 mm Hg, *P* < .001) compared with control patients at peak exercise despite a significantly lower maximum exercise stage. BP also showed

TABLE 2. Hemodynamic changes with the super-Fontan strategy

	Pre-	Post-	*P* value
CVP, mm Hg	11.7 ± 2.4	9.7 ± 2.2	<.001
mBP, mm Hg	73.5 ± 14.1	67.8 ± 9.8	.009
HR, bpm	78.7 ± 16.0	80.4 ± 17.1	.816
CI, L/min/m^2	3.09 ± 1.01	3.54 ± 1.19	.047
SpO$_2$, %	87.7 ± 7.9	91.4 ± 5.3	<.001
BV, mL/kg	92.0 ± 22.7	101.9 ± 33.5	.328
Cv, mL/kg/mm Hg	3.21 ± 1.27	3.79 ± 1.30	.017
MCP, mm Hg	29.6 ± 12.7	27.8 ± 7.8	.088
TPR, RUm^2	4.28 ± 1.65	2.92 ± 0.93	.006
Rs, RUm^2	22.3 ± 8.7	17.0 ± 6.4	.078

CVP, Central venous pressure; *mBP*, mean blood pressure; *HR*, heart rate; *bpm*, beats per minute; *CI*, cardiac index; *SpO₂*, oxygen saturation; *BV*, blood volume; *Cv*, venous capacitance; *MCP*, mean circulatory filling pressure; *TPR*, total pulmonary resistance; *Rs*, systemic vascular resistance.

an augmented increase (130.8 ± 9.5 mm Hg vs 94.4 ± 16.6 mm Hg, $P = .021$). CI and HR were lower throughout all exercise stages in patients with Fontan circulation than in control patients. In 18 patients with Fontan circulation, treadmill exercise testing was repeated after the super-Fontan strategy was introduced. As summarized in Table 4, the super-Fontan strategy significantly reduced the elevations in CVP, BP, and HR with preserved CI in response to treadmill exercise, and tended to increase the maximum exercise stage ($P = .051$). More importantly, CVP increase during exercise was significantly and negatively correlated with changes in Cv (Figure 2) but not with Rp, suggesting that venodilation effectively reduced CVP not only at rest but also during exercise when the preload volume was mobilized.

Figure 3 shows the relationship between CVP and markers of liver function in Fontan patients. CVP at rest was significantly positively correlated with gamma-glutamyl transpeptidase, an index of hepatic congestion, whereas maximum CVP during exercise was significantly and positively correlated with a liver fibrosis marker (type 4 collagen 7S).

This therapy did not result in any major complications, including hypotension, arrhythmia, or heart failure, except in 2 patients who complained of headaches only at the initiation of the therapy.

DISCUSSION

The present study investigated the effects of aggressive arterial and venous dilation therapy in addition to pulmonary dilation therapy (86% of patients before the therapy and 90% after the therapy were taking a pulmonary dilator), or the super-Fontan strategy, on chronic Fontan circulation both at rest and during exercise. We found that (1) the therapy, introduced in patients about 10 years after the Fontan surgery, effectively lowered CVP with improvement of other hemodynamic variables; (2) patients with Fontan circulation exhibited exaggerated increases in CVP and BP during exercise compared with age-matched control participants; (3) the super-Fontan strategy effectively suppressed CVP, BP, and HR elevations during exercise while preserving the peak exercise level and CI; and (4) CVP at rest and during exercise significantly correlated with serum markers of

TABLE 3. The characteristics of patients with Fontan circulation (before the initiation of the therapy) and the control patients who underwent treadmill exercise testing

	Fontan (n = 25) (pre–super-Fontan)	Control (n = 28) (biventricle)	*P* value
Sex (male:female)	19:6	17:11	.234
Age, y	10.1 ± 3.7	11.6 ± 4.7	.209
Hemodynamics at rest			
CVP, mm Hg	10.3 ± 1.6	6.1 ± 1.2	<.001
BP systolic, mm Hg	111 ± 13	109 ± 13	.540
BP diastolic, mm Hg	64 ± 11	60 ± 14	.262
CI, L/min/m^2	2.91 ± 0.71	3.75 ± 0.79	<.001
Max stage, treadmill	4.5 ± 1.4	5.9 ± 1.2	<.001

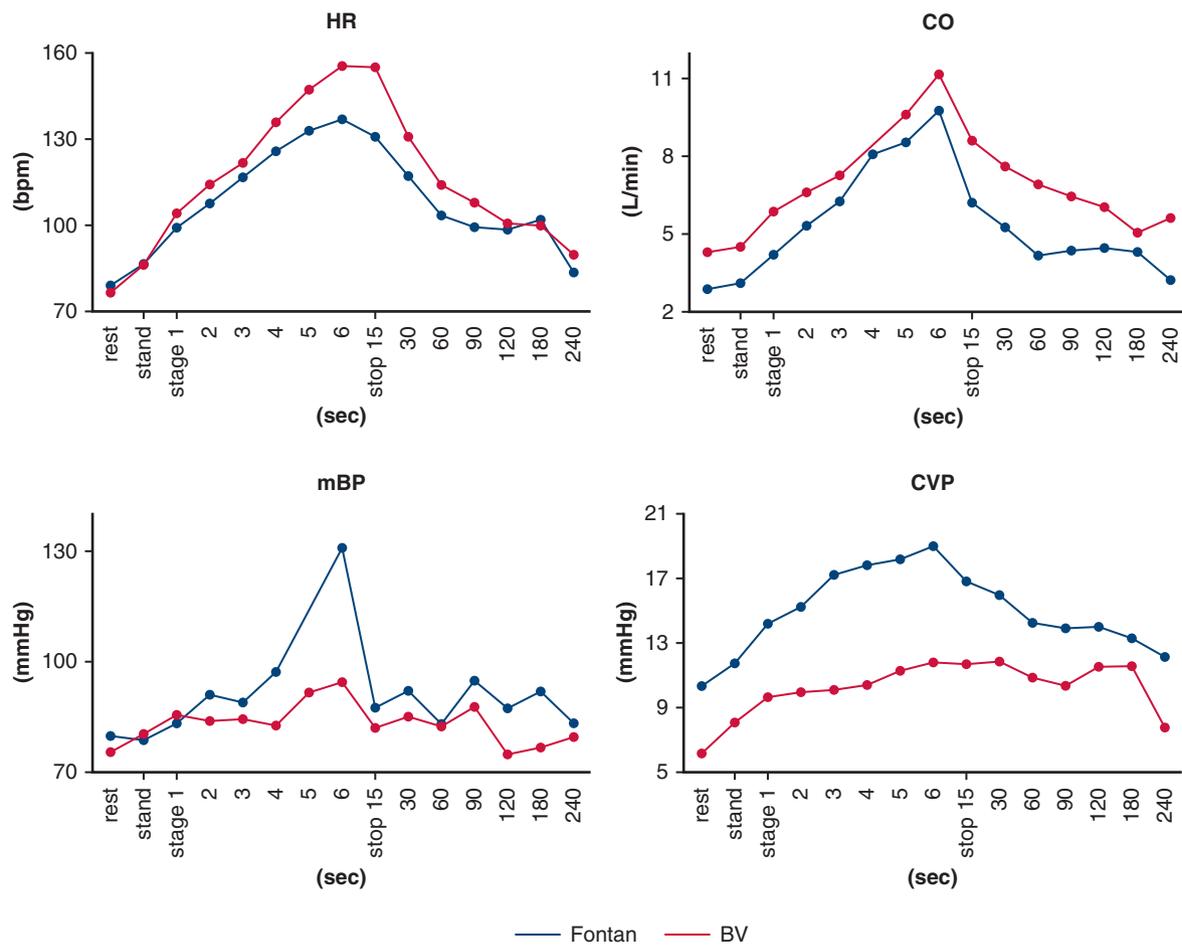*CVP*, Central venous pressure; *BP*, blood pressure; *CI*, cardiac index.

FIGURE 1. Changes in hemodynamics during exercise. During exercise, patients with Fontan circulation had limited increases in HR and CO, whereas mBP significantly increased compared with controls. CVP significantly increased during exercise in both groups, although the degree of CVP elevation was much greater in patients with Fontan circulation than in control. *bpm*, Beats per minute; *HR*, heart rate; *CO*, cardiac output; *BV*, biventricular; *mBP*, mean blood pressure; *CVP*, central venous pressure.

hepatic congestion and fibrosis, respectively. These results suggest that this therapeutic strategy may help prevent or delay organ dysfunction and improve the prognosis of patients with Fontan circulation (Figures 4 and 5).

Effects on Resting Hemodynamics

In our previous study conducted in young patients (average age 3 years), the strategy introduced just after the Fontan completion achieved significantly lower and close to normal levels of CVP at catheter examination 1 year after the surgery compared with a control group of patients with Fontan circulation who were not treated with this therapy.[2] The reduction of CVP was accompanied by significantly greater values of Cv together with significantly lower levels of Rs. The present study adds further evidence showing that the super-Fontan strategy can be a viable therapy for improving Fontan hemodynamics, which are key drivers of postoperative complications and long-term outcomes, by showing that the therapy effectively lowered Fontan

pressure with an increase in Cv in school-aged patients who have not been treated with this therapy for years after the surgery. The therapy also significantly reduced TPR with a borderline decrease in Rs, leading to increased CI. The reason why the magnitude of the therapeutic effects on Rs differs from that reported in the previous study could be because nearly three-fourths of the present patients had already received ACEI/ARB before the therapy induction (Table 1), whereas only 17% of the control patients with Fontan circulation in the previous study had received ACEI/ARB. More importantly, although our previous study did not show a reduction in Rp with this therapy, the present study clearly demonstrated a significant decrease in TPR. Because pulmonary dilators were newly prescribed in only 2 patients (Table 1), the effects could mostly be attributed to the pharmacologic actions of nitrates. Khambadkone and colleagues[14] reported on pulmonary endothelial dysfunction that was partly related to a lack of pulsatility in the Fontan pulmonary circulation, and observed that Rp

TABLE 4. The effects of the super-Fontan strategy during exercise

	Pre-	Post-	*P* value
n (male:female)	18 (13:5)		
Age, y	10.6 ± 4.0	11.9 ± 4.1	<.001
Max stage	4.2 ± 1.3	4.9 ± 1.3	.051
Max METS	13.3 ± 3.5	14.8 ± 3.0	.115
Hemodynamics at rest			
CI, L/min/m^2	2.82 ± 0.63	3.18 ± 0.81	.175
CVP, mm Hg	8.7 ± 2.3	8.0 ± 1.4	<.001
mBP, mm Hg	81 ± 11	78 ± 11	.235
HR, bpm	75 ± 19	75 ± 17	.881
Cv, mL/kg/mm Hg	2.37 ± 1.01	3.46 ± 0.62	.006
TPR, Rum^2	3.45 ± 0.92	2.82 ± 1.19	.009
Rs, Rum^2	28.9 ± 7.6	24.3 ± 8.5	.405
Hemodynamics at peak exercise			
CI, L/min/m^2	7.21 ± 2.42	7.59 ± 1.15	.939
CVP, mm Hg	19.6 ± 5.3	15.4 ± 2.7	.002
mBP, mm Hg	99 ± 17	89 ± 14	.010
HR, bpm	150 ± 25	139 ± 20	.029
TPR, RUm^2	3.19 ± 1.59	2.03 ± 0.55	.032
Rs, Rum^2	12.6 ± 3.9	10.2 ± 2.1	.047

METS, Metabolic equivalent; *CI*, cardiac index; *CVP*, central venous pressure; *mBP*, mean blood pressure; *HR*, heart rate; *bpm*, beats per minute; *Cv*, venous capacitance; *TPR*, total pulmonary resistance; *Rs*, systemic vascular resistance.

decreased with exogenous nitric oxide (NO) late after Fontan surgery (median of 9 years postoperatively). Therefore, it is possible that pulmonary endothelial dysfunction became more evident over time after Fontan completion, and nitrates may have served as an NO donor, thereby reducing Rp in the present patients with Fontan circulation (about 10 years after the surgery) but not in the young patients just after Fontan completion in the previous study. Alternatively, because the calculated TPR included ventricular diastolic function, nitrates may have improved diastolic function through possible improvements in coronary perfusion. The detailed mechanism of action for improving the TPR warrants further investigation by exploring the pulmonary endothelial function and/or differentiating ventricular diastolic function. In addition, the difference in the effects between nitrite only and a combination of nitrate and systemic and pulmonary dilators should be clarified.

Exercise Physiology of Fontan Circulation and Effects of the Super-Fontan Strategy

The present study also provides novel information about the exercise physiology of Fontan circulation and its modulation by the super-Fontan strategy. By continuously monitoring hemodynamic parameters, we demonstrated for the first time that Fontan circulation is associated with
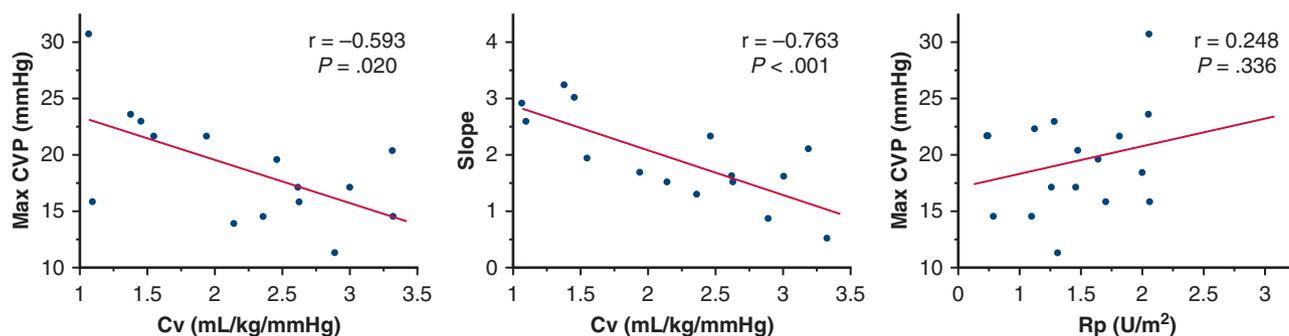

FIGURE 2. Relationships of maximum central venous pressure during exercise with venous capacitance and pulmonary resistance in patients with Fontan circulation. Max CVP and the slope of CVP elevation during exercise in the Fontan group was negatively correlated with Cv, but not with Rp. These results suggest that CVP elevation during exercise depends on Cv rather than Rp. Slope was defined as the difference between pre-exercise (standing) CVP and maximum CVP divided by the maximum exercise stage. *Max CVP*, Maximum central venous pressure; *CVP*, central venous pressure; *Cv*, venous capacitance; *Rp*, pulmonary resistance.
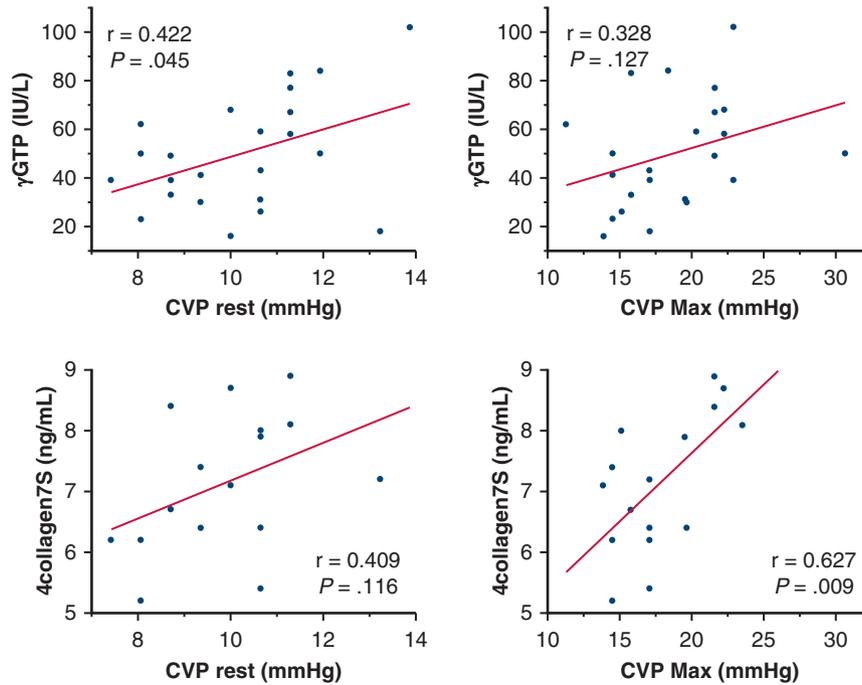
FIGURE 3. Relationships between liver function markers and central venous pressure. CVP at rest and maximum CVP were significantly and positively correlated with γ-GTP and type 4 collagen 7S (r = 0.422, P = .045 and r = 0.627, P = .009, respectively). These results indicate that suppressing the elevation of CVP not only at rest but also during exercise may greatly contribute to the improvement of organ congestion and maintenance of function. *γ-GTP*, Gamma-glutamyl transpeptidase; *CVP*, central venous pressure; *CVP Max*, maximum central venous pressure.

augmented increases in CVP and BP during exercise compared with the normal 2-ventricle circulation in age-matched healthy participants. Reduced Cv, a characteristic of Fontan circulation, implies a greater CVP alteration in response to a given change in volume. Indeed, we have previously reported an amplified increase in CVP after

angiography in patients with Fontan circulation compared with patients with 2-ventricle circulation.[5] A similar mechanism should underlie the augmented increase in venous pressure in patients with Fontan circulation during exercise, when the preload volume is mobilized. This was supported by the significant association of maximum CVP during
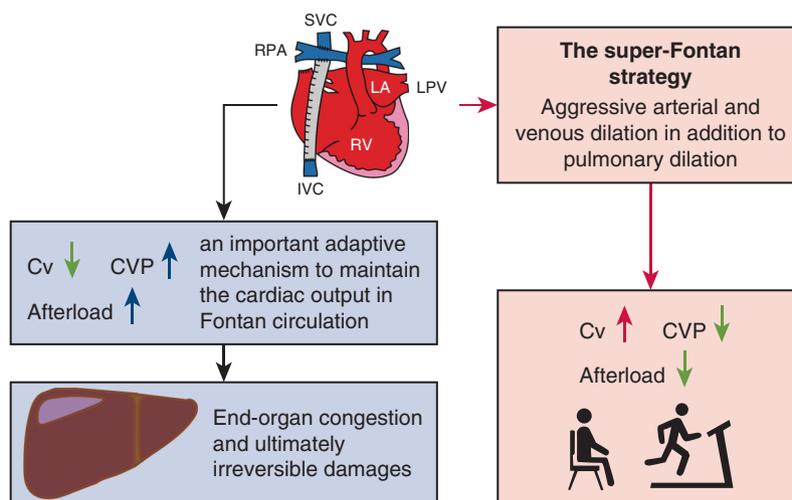

FIGURE 4. A decrease in Cv is an important adaptive mechanism to maintain the cardiac output in the Fontan circulation. However, it causes an increase in CVP that leads to end-organ damages. The afterload is also increased in Fontan circulation, contributing to a decrease in cardiac output. The super-Fontan strategy increases the Cv and decreases afterload, thereby improving the Fontan hemodynamics at rest and during exercise. *SVC*, Superior vena cava; *RPA*, right pulmonary artery; *LA*, left atrium; *LPV*, left pulmonary vein; *RV*, right ventricle; *IVC*, inferior vena cava; *Cv*, venous capacitance; *CVP*, central venous pressure.
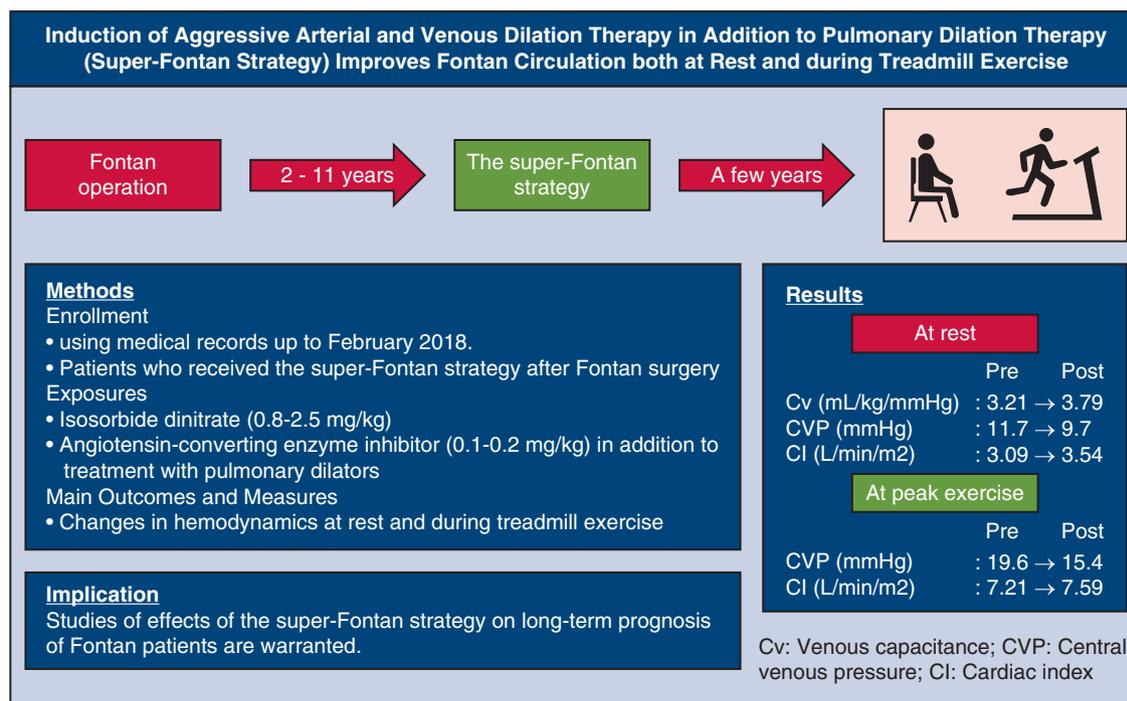
FIGURE 5. Graphical abstract depicting the study's methods, results, and implications. *Cv*, Venous capacitance; *CVP*, central venous pressure; *CI*, cardiac index.

exercise with Cv, as shown in Figure 2. In addition, the nonpulsatile nature of pulmonary blood flow may also contribute to the amplified increase in CVP during exercise due to pulmonary endothelial dysfunction.[15] In fact, an elegant study by Van De Bruaene and colleagues[16] reported a reduction in TPR and augmentation of pulmonary blood flow during exercise with improved endothelial function induced by sildenafil. The augmented increase in CVP during exercise in patients with Fontan circulation highlights the importance of assessing dynamic CVP in addition to static CVP for a better understanding of Fontan circulation. The results may also partly explain the often-recognized clinically diverse status of patients with Fontan circulation, even if they have similar CVP levels at resting conditions.

The increased response of BP in patients with Fontan circulation may be partly due to characteristic changes in both nonpulsatile and pulsatile properties of the arterial bed in patients with Fontan circulation.[17-19] Increased sympathetic nerve activity during exercise in patients with Fontan circulation may also be a contributing factor.[20] Regardless of the mechanisms of the exaggerated response in CVP and BP, a more intense increase in CVP and BP during exercise should serve to further exacerbate resting venous congestion and afterload on the ventricle in patients with Fontan circulation. The significant associations of CVP at rest and during exercise with serum markers of hepatic congestion and fibrosis (Figure 3) may partly support this notion. Therefore, suppression of these untoward

responses would become an important therapeutic strategy to improve the long-term outcome after Fontan surgery. Notably, our super-Fontan strategy effectively suppressed the increase in CVP and BP together with an increase in HR (Table 4). In addition to the increased Cv, our data importantly showed that improvements in TPR and Rs with this therapy contributed to the improvements in exercise physiology of patients with Fontan circulation, suggesting the relevance of the pulmonary and systemic arterial beds as well as the venous bed as therapeutic targets for optimizing Fontan circulation. Numerous studies have revealed that in addition to decreased Cv,[3,5] Fontan circulation has other unique but disadvantageous hemodynamic characteristics, including increased afterload with ventricular contractile mismatch[17,18,21] and abnormal pulmonary circulation.[19,21,22] Increased afterload is a well-known cause of heart failure,[23] and heart failure development is recognized as an important cause of Fontan failure.[24,25] Thus, decreasing afterload should be an important therapeutic strategy to improve the prognosis of patients with Fontan circulation. Although a previous study involving the use of ACEI for 10 weeks failed to demonstrate a beneficial effect of afterload reduction in terms of hemodynamics and exercise performance in patients with Fontan circulation,[26] our data clearly showed that the combination of ACEI and venous dilators in addition to pulmonary dilators suppressed CVP elevation and increased afterload, both at rest and during exercise. Thus, our therapeutic strategy

may also provide beneficial effects from the viewpoint of preventing heart failure development in patients after Fontan surgery.

In addition, recent studies have reported an important role of pulmonary vascular disease as an independent risk factor for Fontan failure and emphasized the importance of maintaining a very low Rp in the treatment and prevention of Fontan failure.[27] It should be considered that even patients with Fontan circulation with a seemingly good clinical status have pulmonary vascular abnormalities and that Rp can be lowered to further optimize Fontan circulation. In fact, recent studies have demonstrated that pulmonary dilators, including NO,[14] endothelin receptor antagonists,[28,29] or phosphodiesterase V inhibitors,[16,30,31] improved hemodynamics and exercise capacity even in the setting of marginally elevated baseline Rp in patients with Fontan circulation. Notably, our present results were obtained in a setting in which most of the patients were taking pulmonary dilators. To achieve the best possible Fontan circulation, venous physiology, pulmonary vascular bed, ventricular function, and afterload need to be optimized. Taking our results together with those of previous studies indicating the beneficial effects of pulmonary dilators on Fontan circulation, we recommend that the super-Fontan strategy, aimed at obtaining the best possible Fontan circulation to improve prognosis, should include aggressive pulmonary artery dilation in addition to arterial and venous dilation. Moreover, because it is known that longer periods of hemodynamic burden on the end organs can cause more damage to their function, it may be better to initiate the strategy as early as possible to shorten the periods of hemodynamic burden.

Cordina and colleagues[32] recently reported that there were some physically superior Fontan patients with normal or even supranormal exercise capacity. They called such patients as super-Fontans. Augmented peripheral muscle pump and thoracic bellows associated with regular physical activity might be the underlying mechanism.[32] The combination of our pharmacologic strategy and lifestyle modification that augments muscle pump and respiratory function might help establish a more robust super-Fontan circulation and condition. However, further investigation is warranted.

Limitations

The study was primarily limited by its retrospective nature and the relatively small number of participants; thus, large-scale prospective randomized studies with the control group (patients with Fontan circulation without treatment) are needed to further confirm our results. In addition, our studied population was consisted of school-aged patients at an average age of 9.1 years after the surgery. It should be clarified whether the therapy can also confer beneficial effects in adult patients with Fontan circulation in whom failing Fontan circulation with or without associated complications are more prevalent as late sequelae; however,

we infer that, for the nitrates to work, the therapy should be started at least before the venous function is lost in these patients.[33] CI measurements during exercise using the AESCULON mini may have been inaccurate as previously reported.[12] However, we believe that the trends in the CI changes were true because the measurement error should have been equally applied to all patients. In addition, even if the errors existed, the effects of the super-Fontan strategy on the CI changes during exercise may have been even more evident, considering the significant changes in Rs and TPR. Due to the noninvasive measurements using PVP and calculations on the assumption of tight correlations between PVP and CVP, our results on TPR may still have errors. However, the comparison of TPR based on PVP and those from invasive data in 13 patients from the study cohort, in whom simultaneous invasive data could be obtained during catheterization, showed excellent correlation (y = 0.98x + 0.07, R^2 = 0.86). Thus, our measurements and assumption appeared valid. Lastly, although we did not observe serious complications with the therapy in the present study, careful monitoring of potential adverse effects was important for the safe application of this medical regimen in the long term.

CONCLUSIONS

Fontan circulation per se is a heart failure condition. The super-Fontan strategy is a therapy that turns the condition into a more physiological one. Prospective studies examining whether hemodynamic improvements result in an improvement of long-term prognosis are highly warranted.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

References

1. Kelley JR, Mack GW, Fahey JT. Diminished venous vascular capacitance in patients with univentricular hearts after the Fontan operation. *Am J Cardiol*. 1995; 76:158-63.
2. Kurishima C, Saiki H, Masutani S, Senzaki H. Tailored therapy for aggressive dilatation of systemic veins and arteries may result in improved long-term Fontan circulation. *J Thorac Cardiovasc Surg*. 2015;150:1367-70.
3. Liang F, Senzaki H, Kurishima C, Sughimoto K, Inuzuka R, Liu H. Hemodynamic performance of the Fontan circulation compared with a normal biventricular circulation: a computational model study. *Am J Physiol*. 2014;307: H1056-72.
4. Ursino M, Antonucci M, Belardinelli E. Role of active changes in venous capacity by the carotid baroreflex: analysis with a mathematical model. *Am J Physiol*. 1994;267:H2531-46.
5. Kim J, Kuwata S, Kurishima C, Iwamoto Y, Ishido H, Masutani S, et al. Importance of dynamic central venous pressure in Fontan circulation. *Heart Vessels*. 2018;33:664-70.
6. Kuwata S, Takanashi M, Hashimoto M, Iwamoto Y, Ishido H, Masutani S, et al. Thyroid function in patients with a Fontan circulation. *Am J Cardiol*. 2019;123:979-83.

7. Saiki H, Kurishima C, Masutani S, Senzaki H. Cerebral circulation in patients with Fontan circulation: assessment by carotid arterial wave intensity and stiffness. *Ann Thorac Surg*. 2014;97:1394-9.

8. Wilson TG, d'Udekem Y, Winlaw DS, Cordina RL, Celermajer DS, Wheaton GR, et al. Hepatic and renal end-organ damage in the Fontan circulation: a report from the Australian and New Zealand Fontan Registry. *Int J Cardiol*. 2018;273:100-7.

9. Rychik J, Goldberg D, Rand E, Semeao E, Russo P, Dori Y, et al. End-organ consequences of the Fontan operation: liver fibrosis, protein-losing enteropathy and plastic bronchitis. *Cardio Young*. 2013;23:831-40.

10. Masutani S, Kurishima C, Yana A, Kuwata S, Iwamoto Y, Saiki H, et al. Assessment of central venous physiology of Fontan circulation using peripheral venous pressure. *J Thorac Cardiovasc Surg*. 2017;153:912-20.

11. Belin de Chantemele E, Gauquelin-Koch G, Duvareille M, Pellet N, Gharib C, Custaud MA. Blood volume measurement: the comparison of pulse dye densitometry and Dill and Costill's methods. *Life Sci*. 2006;78:1564-9.

12. Beck R, Milella L, Labellarte C. Continuous non-invasive measurement of stroke volume and cardiac index in infants and children: comparison of Impedance Cardiography NICaS® vs CardioQ® method. *Clin Ter*. 2018;169:e110-3.

13. Petter H, Erik A, Bjorn E, Goran R. Measurement of cardiac output with non-invasive Aesculon impedance versus thermodilution. *Clin Physiol Funct Imaging*. 2011;31:39-47.

14. Khambadkone S, Li J, de Leval MR, Cullen S, Deanfield JE, Redington AN. Basal pulmonary vascular resistance and nitric oxide responsiveness late after Fontan-type operation. *Circulation*. 2003;107:3204-8.

15. Zongtao Y, Huishan W, Zengwei W, Hongyu Z, Minhua F, Xinmin L, et al. Experimental study of nonpulsatile flow perfusion and structural remodeling of pulmonary microcirculation vessels. *Thorac Cardiovasc Surg*. 2010;58:468-72.

16. Van De Bruaene A, La Gerche A, Claessen G, De Meester P, Devroe S, Gillijns H, et al. Sildenafil improves exercise hemodynamics in Fontan patients. *Circ Cardiovasc Imaging*. 2014;7:265-73.

17. Senzaki H, Masutani S, Kobayashi J, Kobayashi T, Sasaki N, Asano H, et al. Ventricular afterload and ventricular work in Fontan circulation: comparison with normal two-ventricle circulation and single-ventricle circulation with Blalock-Taussig shunts. *Circulation*. 2002;105:2885-92.

18. Senzaki H, Masutani S, Ishido H, Taketazu M, Kobayashi T, Sasaki N, et al. Cardiac rest and reserve function in patients with Fontan circulation. *J Am Coll Cardiol*. 2006;47:2528-35.

19. Senzaki H, Isoda T, Ishizawa A, Hishi T. Reconsideration of criteria for the Fontan operation. Influence of pulmonary artery size on postoperative hemodynamics of the Fontan operation. *Circulation*. 1994;89:266-71.

20. Ohuchi H, Tasato H, Sugiyama H, Arakaki Y, Kamiya T. Responses of plasma norepinephrine and heart rate during exercise in patients after Fontan operation and patients with residual right ventricular outflow tract obstruction after definitive reconstruction. *Pediatr Cardiol*. 1998;19:408-13.

21. Nogaki M, Senzaki H, Masutani S, Kobayashi J, Kobayashi T, Sasaki N, et al. Ventricular energetics in Fontan circulation: evaluation with a theoretical model. *Pediatr Int*. 2000;42:651-7.

22. Yun TJ, Im YM, Jung SH, Jhang WK, Park JJ, Seo DM, et al. Pulmonary vascular compliance and pleural effusion duration after the Fontan procedure. *Int J Cardiol*. 2009;133:55-61.

23. Masutani S, Kuwata S, Kurishima C, Iwamoto Y, Saiki H, Sugimoto M, et al. Ventricular-vascular dynamics in pediatric patients with heart failure and preserved ejection fraction. *Int J Cardiol*. 2016;225:306-12.

24. Griffiths ER, Kaza AK, Wyler von Ballmoos MC, Loyola H, Valente AM, Blume ED, et al. Evaluating failing Fontans for heart transplantation: predictors of death. *Ann Thorac Surg*. 2009;88:558-63; discussion 563-4.

25. Stout KK, Broberg CS, Book WM, Cecchin F, Chen JM, Dimopoulos K, et al. Chronic heart failure in congenital heart disease: a scientific statement from the American Heart Association. *Circulation*. 2016;133:770-801.

26. Kouatli AA, Garcia JA, Zellers TM, Weinstein EM, Mahony L. Enalapril does not enhance exercise capacity in patients after Fontan procedure. Clinical trial randomized controlled trial. *Circulation*. 1997;96:1507-12.

27. Egbe AC, Connolly HM, Miranda WR, Ammash NM, Hagler DJ, Veldtman GR, et al. Hemodynamics of Fontan failure: the role of pulmonary vascular disease. *Circ Heart Fail*. 2017;10:e004515.

28. Hebert A, Mikkelsen UR, Thilen U, Idorn L, Jensen AS, Nagy E, et al. Bosentan improves exercise capacity in adolescents and adults after Fontan operation: the TEMPO (treatment with endothelin receptor antagonist in Fontan patients, a randomized, placebo-controlled, double-blind study measuring peak oxygen consumption) study. Randomized controlled trial. *Circulation*. 2014;130:2021-30.

29. Agnoletti G, Gala S, Ferroni F, Bordese R, Appendini L, Napoleone CP, et al. Endothelin inhibitors lower pulmonary vascular resistance and improve functional capacity in patients with Fontan circulation. *J Thorac Cardiovasc Surg*. 2017; 153:1468-75.

30. Mori H, Park IS, Yamagishi H, Nakamura M, Ishikawa S, Takigiku K, et al. Sildenafil reduces pulmonary vascular resistance in single ventricular physiology. Clinical Trial Multicenter Study. *Int J Cardiol*. 2016;221:122-7.

31. Sabri MR, Zolfi-Gol A, Ahmadi A, Haghjooy-Javanmard S. Effect of tadalafil on myocardial and endothelial function and exercise performance after modified Fontan operation. *Pediatr Cardiol*. 2016;37:55-61.

32. Cordina R, du Plessis K, Tran D, d'Udekem Y. Super-Fontan: is it possible? *J Thorac Cardiovasc Surg*. 2018;155:1192-4.

33. Valente AM, Bhatt AB, Cook S, Earing MG, Gersony DR, Aboulhosn J, et al. The CALF (congenital heart disease in adults lower extremity systemic venous health in Fontan patients) study. *J Am Coll Cardiol*. 2010;56:144-50.

Key Words: congenital heart disease, Fontan, central venous pressure, hemodynamics