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ORIGINAL ARTICLE

Importance of dynamic central venous pressure in Fontan circulation

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Abstract
We tested our hypotheses that central venous pressure (CVP) shows an excessive increase in response to volume overload in Fontan circulation according to the extent of the reduction in venous capacitance (Cv), and that the maximum CVP after volume loading is associated with hepatic congestion. Changes in CVP after angiography (volume loading) were examined in 40 patients with Fontan circulation and 29 controls with biventricular circulation. CVP significantly increased with angiography in both groups, but the changes were much more evident in the Fontan group than in controls (3.3 ± 2.0 vs. 0.9 ± 1.4 mmHg, $p = 0.0003$). Multivariate analysis demonstrated that reduced Cv was the only significant determinant of CVP increase, independent of the amount of injected contrast medium, blood volume, pulmonary resistance, and ventricular diastolic stiffness ($p < 0.05$). Importantly, the use of a venodilator was associated with increased Cv and the resultant suppression of CVP elevation with volume load. In addition, CVP levels both at baseline ($p = 0.02$) and after volume loading ($p = 0.01$) were weakly but significantly correlated with the plasma levels of γ-glutamyl transpeptidase, a marker of hepatic congestion; however, multivariate analysis revealed that the CVP level after volume loading was a more important determinant of hepatic congestion. The results of this study highlight the importance of assessing dynamic in addition to static CVP for a better understanding of Fontan circulation. The potential importance of Cv as a therapeutic target for improving Fontan physiology needs further elucidation.

Keywords Venous capacitance · Dynamic CVP · Fontan circulation

Introduction

Fontan circulation is a right-heart bypass circulation, and thus has an inherent limitation for maintaining ventricular preload [1]. Reduction of venous capacitance (Cv) through venoconstriction appears to be a key adaptive mechanism to compensate for this limitation; however, this effect is achieved at the expense of increased central venous pressure (CVP) [2–4] The reduction of Cv can also result in an increased sensitivity of CVP elevation in response to volume load, and thereby may play an important role in the development of organ congestion [5–7], an important complication after Fontan surgery. However, to date, little information is available about how CVP changes with alterations in volume status, and how CVP variation from the resting baseline condition affects organ congestion in the Fontan circulation. By examining CVP change after volume loading with angiography (injection of contrast medium) during cardiac catheterization, the present study was conducted to test our hypotheses that (1) CVP shows an excessive increase in response to volume overload in Fontan circulation according to the degree of Cv reduction; (2) the use of a venodilator is associated with increased Cv and the resultant suppression of CVP elevation with volume load; and (3) the maximum CVP after volume loading is more significantly associated with hepatic congestion than baseline CVP at rest.

Methods

Patients

We studied 40 consecutive patients who underwent cardiac catheterization for postoperative evaluation of Fontan

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circulation and 29 patients with biventricular circulation who also underwent diagnostic and/or interventional cardiac catheterization. As a general clinical practice in Japan, including at our institution, catheter examination is routinely performed 1 year after Fontan surgery to check the Fontan status, regardless of the presence or absence of symptoms. Furthermore, we subsequently perform catheterization for Fontan evaluation every 5–10 years based on our institutional protocol, with the understanding that a treatable failure process (the so-called failing Fontan) can progress even in asymptomatic patients. Control patients were selected from 30 consecutive patients with biventricular circulation by excluding one patient who had hemodynamics that mimicked Fontan circulation (i.e., severe tricuspid stenosis and regurgitation with an elevated CVP of 16 mmHg). The cardiac catheterization studies were performed after obtaining written informed consent from the parents of all patients. The study was approved by our institutional review board on clinical investigation (nos. 972 and 1632).

Measurements

Serum levels of γ-glutamyl transpeptidase (γ-GTP), as an index of hepatic congestion [8], were measured as a part of the routine blood examination on admission for the catheterization. During cardiac catheterization, after pressure recording and blood sampling for the measurement of oxygen saturation, we assessed the total circulatory blood volume using the dye-dilution technique, with injection of indocyanine green at a dose of 0.4 mg/kg (DDG analyzer; Nihon Kohden, Tokyo, Japan) [9, 10]. Because blood volume is calculated based on the blood concentration of the injected dye after the dye has been evenly distributed throughout the body, the presence of intra- or extra-cardiac shunts does not affect the calculation of blood volume using the dye-dilution method. We also estimated the mean circulatory filling pressure (Pmcf) in patients with Fontan circulation by measuring the simultaneous changes in aortic pressure (AP) and CVP during Valsalva maneuver, as previously reported [11, 12]. After these hemodynamic measurements, angiography or ventriculography was performed as necessary, and the CVP changes after the injection of contrast medium (acute volume loading) were then measured.

Data analysis

The indexed systemic (Qs) and pulmonary (Qp) blood flow values were calculated with the Fick method by using the estimated oxygen consumption. Pulmonary vascular resistance index (Rp) was calculated as (mPAP − PCWP)/Qp, where mPAP is the mean pulmonary arterial pressure and PCWP is the pulmonary capillary wedge pressure. Ventricular diastolic stiffness was assessed as [ventricular end-diastolic pressure − minimal diastolic pressure)/stroke volume index] [13, 14]. Pmcf was estimated as (MAPpost × CVPcon − MAPcon × CVPpost)/(MAPpost − MAPcon + CVPcon − CVPpost) [12], where CVPcon and MAPcon were CVP and the mean AP (MAP) during the control state before Valsalva maneuver, and CVPpost and MAPpost were those after Valsalva maneuver, respectively. The Cv was then calculated by dividing the total circulatory blood volume by Pmcf [10, 12, 15].

Statistical analysis

Comparisons between the two groups were made by an unpaired *t* test. Comparisons of hemodynamics before and after angiography were made with a paired *t* test. Multivariate regression analysis was performed to assess the determinants of CVP change after volume loading, with Cv, amount of injected contrast medium, circulatory blood volume, Rp, and ventricular diastolic stiffness included as independent variables. A p value of < 0.05 was considered statistically significant. All statistical analyses were performed with JMP version 8.2 (SAS, Cary, NC, USA).

Results

Table 1 summarizes the demographic data, underlying cardiac diseases, and medications for each group. Age at catheterization was significantly higher in patients with Fontan circulation than in controls. Fenestration had been created in all patients with Fontan circulation according to our institutional protocol; however, the fenestration was patent in 29 patients at the time of catheterization. There were two patients with protein-losing enteropathy, one patient with liver cirrhosis, and two patients with paroxysmal atrial flutter. Table 2 summarizes the hemodynamic data for each group. As expected, CVP was significantly higher in patients with Fontan circulation than in controls. Hemodynamic data in controls indicate that these patients did not have severe heart failure. Medications were prescribed according to the decision of the attending physician. Eleven patients with Fontan circulation received a venodilator (isosorbide dinitrate).

Changes in CVP after angiography

There was no significant difference in the total amount of contrast medium used for angiography between the two groups (4.1 ± 1.8 mL/kg in the Fontan group and 4.9 ± 3.0 mL/kg in the control group, respectively; $p = 0.279$), and there was no significant change in heart rates after angiography compared with the values at baseline in both groups. Figure 1 shows the comparison of CVP changes

Table 1 Patient characteristics in each group

	Fontan group ($n = 40$)	Control group ($n = 29$)	p value
Age (year)	9.8 ± 7.8	5.4 ± 4.2	< 0.01
Body weight (kg)	26.6 ± 16.4	18.7 ± 12.8	< 0.05
Underlying disease (*N*)			
Univentricular connection of RV type (15)		Tetralogy of Fallot (6)	
Univentricular connection of LV type (2)		TGA (4)	
Double outlet right ventricle (7)		TGA + VSD (2)	
PA IVS (4)		cTGA + VSD + PA (2)	
Tricuspid atresia (5)		CoA complex (2)	
TGA + VSD + PS/PA (3)		Kawasaki disease (2)	
cTGA + VSD + PS (1)		Atrial septal defect (1)	
VSD + hypoplastic RV (1)		Atrioventricular septal defect (1)	
Hypoplastic left heart syndrome (2)		Others (9)	
Type of Fontan surgery		Type of surgery	
Atrio-pulmonary connection (2)		Repair of Tetralogy of Fallot (4)	
Lateral tunnel (4)		Jatene (6)	
Extra-cardiac conduit (34)		Modified Blalock-Taussig shunt (3)	
		EEA of the aorta + repair of VSD (2)	
		Ross (2)	
		Others (6)	
		No surgery (6)	
Medications			
Isosorbide dinitrate (%)	11 (28%)	1 (3%)	< 0.05
Enalapril (%)	23 (58%)	7 (24%)	< 0.05
Torasemide (%)	15 (38%)	6 (20%)	< 0.05
Pimobendan (%)	5 (13%)	1 (3%)	< 0.05
β-Blockers (%)	11 (28%)	5 (17%)	< 0.05
PDE-V inhibitors (%)	17 (43%)	2 (6.9%)	< 0.05
Bosentan (%)	19 (48%)	2 (6.9%)	< 0.05
Aspirin (%)	27 (68%)	9 (31%)	< 0.05
Warfarin (%)	30 (75%)	1 (3%)	< 0.05

p values for medications are for the frequency in use

RV right ventricle, *PA IVS* pulmonary atresia with intact ventricular septum, *PS* pulmonary stenosis, PA pulmonary atresia, *TGA* transposition of the great arteries, *VSD* ventricular septal defect, *c* corrected, *CoA* coarctation of aorta, *EEA* end-to-end anastomosis, *PDE* phosphodiesterase

Table 2 Hemodynamic data in each group

	Fontan group	Control group	p value
Heart rate (bpm)	81.2 ± 18.6	93.3 ± 18.5	0.01
Central venous pressure (mmHg)	10.2 ± 3.1	6.2 ± 3.4	< 0.0001
Mean pulmonary artery pressure (mmHg)	9.7 ± 3.2	16.2 ± 5.2	< 0.0001
Pulmonary capillary wedge pressure (mmHg)	6.0 ± 3.6	8.3 ± 2.8	0.005
Aortic pressure			
Systolic (mmHg)	89.7 ± 19.9	84.3 ± 17.4	0.25
Mean (mmHg)	67.7 ± 15.8	65.9 ± 14.3	0.62
Pulmonary vascular resistance (m^2)	1.7 ± 0.6	1.8 ± 0.6	0.38
Systemic blood flow (L/min/m^2)	3.3 ± 0.8	3.6 ± 0.8	0.12
Circulatory blood volume (mL/kg)	93.6 ± 33.0		
Mean circulatory filling pressure (mmHg)	30.7 ± 8.0		
Brain natriuretic peptide (pg/mL)	21.4 ± 27.2	39.5 ± 63.5	0.13

Blood volume was calculated for Fontan patients only

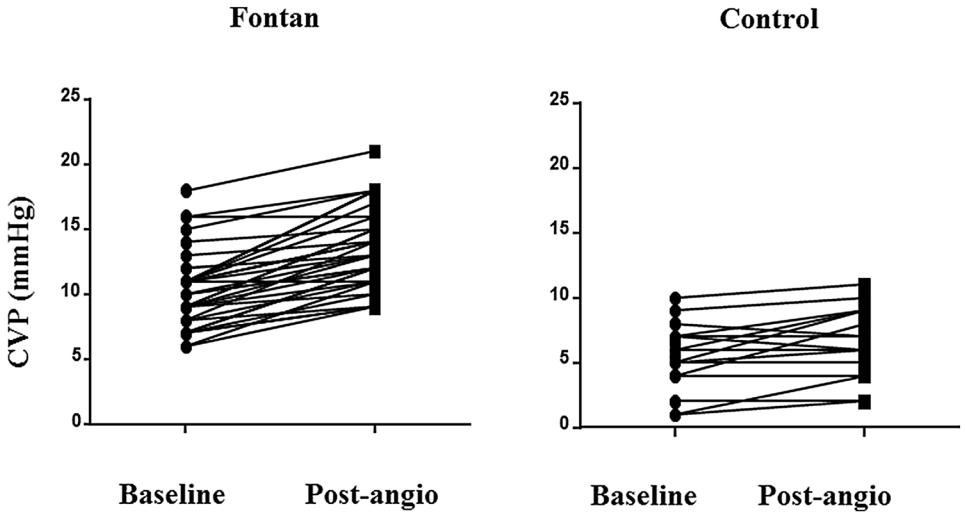

Fig. 1 Comparison of changes in central venous pressure (CVP) with volume loading by angiography between the two groups. Of note, the CVP increase after angiography varied markedly among patients with Fontan circulation despite having similar levels of CVP before angiography

Table 3 Determinants of change in central venous pressure after volume loading

	Coefficient	*p* value
Venous capacitance	− 0.55 (− 0.08 to − 1.02)	0.03
Amount of contrast medium		0.45
Circulatory blood volume		0.91
Pulmonary vascular resistance		0.62
Diastolic stiffness		0.35

Values in parentheses indicate the 95% confidence intervals

Table 4 Univariate and multivariate analyses for the determinant of γ-glutamyl transpeptidase

	Coefficient in multivariate analysis	Univariate		Multivariate	
		R	*p* value	*R*	*p* value
Baseline CVP		0.37	0.02		0.81
Maximum CVP	10.8 (3.5–18.1)	0.45	0.01	0.45	0.01

Values in parentheses indicate the 95% confidence intervals

CVP central venous pressure

with volume loading by angiography between the two groups. The CVP after angiography significantly increased in both groups (from 10.2 ± 3.1 to 13.5 ± 3.1 mmHg in the Fontan group, $p = 0.0001$, and from 5.7 ± 3.4 to 6.1 ± 3.9 mmHg in the control group, $p = 0.003$); however, the changes were much more evident in patients with Fontan circulation than in controls (3.3 ± 2.0 vs. 0.9 ± 1.4 mmHg, $p = 0.0003$), consistent with the decrease in Cv in patients with Fontan circulation. The difference was even more significant after controlling for the amount of the injected contrast medium ($p < 0.0001$). Of note, the CVP elevation after angiography varied markedly among patients with Fontan circulation regardless of the CVP levels before angiography, as indicated by the divergent direction of changes in Fig. 1. Multivariate regression analysis demonstrated that Cv was a significant determinant of CVP increase after angiography independent of the amount of the injected contrast medium, circulatory blood volume, Rp, and ventricular diastolic stiffness (Table 3). Similar results in terms of a more prominent increase in CVP level in patients with Fontan circulation and its association with Cv were obtained even when the analysis was confined to a homogeneous sample of Fontan patients with an extracardiac conduit.

Importantly, Cv was significantly higher in patients with Fontan circulation who received a venodilator (sodium dinitrate) than in those who did not (4.2 ± 2.2 vs. 2.8 ± 0.8 mL kg^{-1} $mmHg^{-1}$, $p < 0.05$). Additionally, the CVP change was significantly lower in patients with Fontan circulation who received a venodilator than in those who did not (2.0 ± 1.1 vs. 3.6 ± 2.1 mmHg, $p < 0.05$).

CVP and hepatic congestion

As shown in Table 4, the CVP levels both at baseline ($p = 0.02$) and after volume loading ($p = 0.01$) were weakly but significantly correlated with the plasma levels of γ-GTP; however, multivariate analysis revealed that CVP after angiography was a more important determinant of hepatic congestion.

Discussion

Numerous studies have indicated the importance of CVP as a key hemodynamic parameter that affects outcome both immediately and in the long term after Fontan surgery [15–18]. However, in all reports, CVP was measured in the resting, mostly sedated, condition during cardiac

catheterization or postoperative intensive care; however, CVP during daily life can change dramatically with volume status and with physical activity when the preload volume is mobilized. This should be particularly true in the Fontan circulation in which the right heart, as a diastolic reservoir pump, is lacking [19]. In fact, diverse clinical outcomes are often recognized among patients with Fontan circulation with similar levels of CVP measured at resting conditions. Despite the recognition of the potential importance of dynamic rather than static CVP, few studies have been conducted to reveal the nature and impact of dynamic changes in CVP in the Fontan circulation. The present study addressed these issues for the first time by examining variations of CVP after volume loading with contrast medium, which is a routine procedure performed with cardiac catheterization.

Changes in CVP and its determinants

Our data clearly demonstrated that volume load with contrast medium injection significantly increased the CVP in patients after Fontan operation, and that the extent of CVP increase was more evident in patients with Fontan circulation than in control patients with two ventricular circulations without apparent symptoms of heart failure. Importantly, the degree of CVP increase in response to the volume load varied largely depending on the Cv value, with lower Cv associated with a greater elevation of CVP. We have previously reported that therapy tailored to increase systemic Cv using venodilators yields a Fontan circulation with a lower CVP than is generally accepted as required for good Fontan circulation [2]. The present study adds further important evidence showing that increased Cv also reduces dynamic CVP elevation. In fact, the use of nitrates was associated with larger levels of Cv and smaller elevation of CVP after volume loading. Although attention has been mostly paid to Rp as a determinant of CVP, our data importantly indicate that in addition to Rp, Cv can be a viable therapeutic target to reduce CVP variation as well as the baseline CVP at rest in patients after Fontan surgery. This notion is also supported by our previous study with computational simulation, which demonstrated marked effects of Cv on CVP variations in the Fontan circulation [15].

Because Pmcf can be accurately estimated using peripheral venous pressure as an arm equilibrium pressure, which is a transient stop-flow forearm arterial and venous equilibrium pressure [20], Cv can be a useful marker for the follow-up of patients after Fontan surgery even in outpatient clinics.

Dynamic CVP and organ congestion in Fontan circulation

Although Fontan surgery has greatly contributed to the improvement of mortality in patients with a single ventricular circulation, high CVP in this circulation causes organ congestion, such as hepatic disorder, renal dysfunction, protein-losing enteropathy, and possibly cerebral malfunction, leading to increased morbidity and mortality with time after the surgery [5, 7, 20–23]. The results of the present study underscored the importance of assessing CVP variations in addition to the resting baseline CVP, because CVP changes variably even with similar levels of resting CVP. The importance of understanding the CVP as dynamic rather than static was further highlighted by the fact that CVP values after volume loading was more significantly associated with hepatic congestion than CVP at baseline before volume loading. Prospective studies investigating the effects of lowering the resting CVP and its variation, by targeting Cv, on the outcome of organ congestion in patients with Fontan circulation are warranted.

Limitation

The clear limitations of this study are its retrospective nature and the limited number of analyzed patients. Owing to these limitations, the age of the patients was significantly different between the two groups. Therefore, we re-analyzed the data by selecting Fontan patients with ages matched to that of the controls (5.5 ± 1.8 years, $n = 22$); however, significantly greater changes in CVP in Fontan patients than in controls (2.8 ± 0.4 vs. 0.9 ± 1.4 mmHg, $p = 0.01$) were noted even after age-matching. Furthermore, analysis of covariance by including age and the amount of the injected contrast medium as covariates still showed a significant difference between the two groups ($p = 0.003$). The heterogeneous nature of the controls was also a limitation, and the mild elevation of brain natriuretic peptide levels in the control group may indicate stress on the ventricle. However, such effects should contribute to reducing Cv for the centralization of blood volume, and thus should strengthen rather than weaken our results. Because Fontan patients were also heterogeneous, we performed multivariate analysis for Cv determinants by including age, failing Fontan status (protein-losing enteropathy, liver cirrhosis, and atrial flutter), CVP, and the use of nitrates as independent variables. Only the use of nitrates had a significant effect on Cv values. This is consistent with an adaptive mechanism of venoconstriction in the Fontan circulation as reported previously [2–4]; however, it does not necessarily exclude the possibility of an association between lower Cv and failing Fontan status, particularly owing to the limited number of the analyzed patients. This issue also remains to be elucidated in future studies.

There may be a concern that the significantly different baseline CVP (10.2 vs. 6.2 mmHg) may itself also influence the Cv value. However, if CVP is reduced by volume depletion, Cv should increase to mobilize the ventricular preload

volume, and vice versa. In addition, our previous study also demonstrated that decrease in CVP induced by veno-dilation was associated with increased Cv [2]. Therefore, a high CVP is likely a result of decreased Cv rather than its cause.

We did not measure Rp or CI after volume loading with angiography. Because the injection of contrast medium may have had some effects on the pulmonary vascular bed, Rp may have been changed after angiography. However, the transpulmonary pressure gradient did not change significantly after angiography (4.2 ± 0.2 vs. 4.7 ± 2.7 mmHg, $p = 0.27$), suggesting that the Rp change after contrast medium injection was minimum and unlikely to affect the CVP increase in patients with Fontan circulation.

Although the present results suggest the importance of Cv as a determinant of CVP variation, we could not find any significant association between the Cv values and the plasma levels of γ-GTP (data not shown). This particularly suggests that not only Cv-related CVP elevation but also other factors that affect CVP variations contribute to the elevation of γ-GTP and, thus, hepatic congestion. The intensity of daily physical activities or dietary habit may be one of such factors; however, this issue needs to be further explored in future studies.

Conclusions

The results of this study may partly explain the often-recognized clinically diverse status of patients with Fontan circulation, even if they have similar CVP levels at resting conditions. The results also highlight the importance of assessing dynamic CVP in addition to static CVP for a better understanding of the Fontan circulation. Checking for this CVP change after angiography is a very easy and useful method, and should be incorporated routinely in catheterization studies of patients with Fontan circulation. Furthermore, the present results also suggest the potential importance of Cv as a therapeutic target for improving Fontan physiology.

Compliance with ethical standards

Conflict of interest We (all authors) declare that we have no conflict of interest.

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