We should note that lower pressure of pulmonary capillary wedge than we expected lifts up central venous pressure in Fontan circulation

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【 Background 】

In patients with bi-ventricle who have chronic heart failure increased post-capillary pressure, such as high pressure of pulmonary capillary wedge (PCWP), provokes pulmonary hypertension. High PCWP are induced by decreased left-cardiac functions. In Fontan patients with mono-ventricle high central-venous pressure (high CVP) impair Fontan circulation. We predicted that increased PCWP in Fontan heart also induced high central-venous pressure (high CVP), and that high PCWP was caused by various factors which subsisted before Fontan procedure.

【 Objective 】

We investigated values of PCWP which caused high CVP in Fontan patients and backgrounds for high PCWP.

【 Methods 】

Subjects and examinaions. The medical records of 174 Fontan patients were reviewed from 2 yrs to 18 yrs. They underwent cardiac catheterizations and blood tests between 2010 and 2015.
Comparative methods. We defined CVP 16 mmHg or over as high CVP (CVP ≥ 16 mmHg: n=27). First, we examined whether the area under a receiving operating characteristics curve (AUROC) was described meaningfully by PCWP for predicting high CVP. Second, we sought minimum PCWP which was connected with high CVP. Using minimum PCWP we calculated following values with a standard formula to predict high CVP, such as positive and negative predictive values, sensitivity, and specificity. In addition, cardiac factors were searched for by AUROCs which were related to minimum PCWP. Third, We searched for clinical factors which made PCWP rising.

Table 1. Clinical characteristics 174 Fontan patients

Cath. age (yrs)	14.7±11.2, 7.0 (1.7- 42.9)
Fontan age (yrs)	7.8±8.9, 3.0 (1.0 – 39.7)
Right isomerism (%)	26/174 (14)
Ventricle type (n)	Right (48) Left (36) Bi-ventricle (90)
1st strategy (n)	Shunting to PA (84) PA banding (56) Native PS (12) Norwood (21)
TAPVC repair	10/174 (5)
AVV repair	35/174 (20)
PTA	57/174 (63)
Coil embolization	111/174 (32)
Fenestrated Fontan	39/174 (22)
Internal medicine	
Diuretics (%)	51/174 (29)
ACEI/ARB (%)	85/174 (48)
B-blocker (%)	134/174 (77)
Pul. Vasodilatation (%)	58/174 (33)
Warfarin (%)	164/174 (94)

Table 2. Hemodynamic parameters 174 Fontan

Cardiac indexes	
%SVEDV (%)	107±46, 96 (36 - 378)
%SVESV (%)	52±28, 44 (11 - 209)
SVEF (%)	51±10, 53 (10 - 70)
SVEDP (mmHg)	9±5, 8.0 (2 - 36)
SVESP (mmHg)	91±18, 88 (59 - 155)
Qs (L/min/m2)	3.4±1.0, 3.4 (1.1 - 7.0)
Rs (U・m2)	3.4±1.0, 3.4 (1.1 - 7.0)
AVVR	0 (82) I (65) II (24) III (3)
AR	0 (133) I (37) II (4)
Pulmonic indexes	
CVP (mmHg)	12±3, 12 (6 - 30)
Rp (U・m2)	7±3, 7 (2 - 26)
PAI (mm/m2)	241±80, 239 (75 - 464)
PAI (mm/m2)	241±80, 239 (75 - 464)
AoSatO2 (%)	92±4, 93 (63 - 98)

Table 3. AUROC for predicting CVP ≥ 16 mmHg by PCWP in 174 post-Fontan patients

	AUROC	95%CI	p value
PCWP	0.824	0.713 -0.934	< 0.001

AUROC: Area under receiver characteristic operator curves

Table 4. Patient-rates with a change in PCWP between high CVP and non-high CVP

	CVP≥ 16 mmHg (n=27)	CVP< 16mmHg (n=147)	p value
PCWP ≥ 4 mmHg	26/27 (96)	136/147 (92)	0.76
PCWP ≥ 5 mmHg	25/27 (92)	115/147 (78)	0.14
PCWP ≥ 6 mmHg	23/27 (85)	96/147 (65)	0.069
PCWP ≥ 7 mmHg	23/27 (85)	64/147 (43)	0.00016
PCWP ≥ 8 mmHg	20/27 (74)	47/147 (31)	<0.0001
PCWP ≥ 9 mmHg	20/27 (74)	25/147 (17)	<0.0001
PCWP ≥ 10 mmHg	18/27 (66)	13/147 (8)	<0.0001
PCWP ≥ 11 mmHg	16/27 (59)	6/147 (4)	<0.0001
PCWP ≥ 12 mmHg	13/27 (48)	2/147 (1)	<0.0001
PCWP ≥ 13mmHg	11/27 (40)	1/147 (1)	<0.0001
PCWP ≥ 14 mmHg	7/27 (25)	1/147 (1)	<0.0001

Table 5. Optimal value of PCWP for predicting CVP ≥ 16 mmHg

	CVP≥ 16 mmHg	CVP< 16mmHg	
PCWP ≥ 7 mmHg	23	64	87
PCWP < 7 mmHg	4	83	87
	27	147	174

Sensitivity: 85% (23/(23+4))
Specificity: 47% (83/(83+64))
Positive predictive value: 26% (23/(23+64))
Negative predictive value: 95% (4/(83+4))

Table 6. AUROC for predicting PCWP ≥ 7 mmHg by cardiac parameters in 174 post-Fontan patients

Factors	AUROC	95%CI	p value
SVEDP (mmHg)	0.830	0.772 - 0.889	< 0.001
SVESP (mmHg)	0.599	0.515 - 0.683	0.024
SVEDV (%)	0.587	0.661 - 0.907	0.048
SVESV (%)	0.580	0.495 - 0.665	0.068
SVEF (%)	0.484	0.398 - 0.571	0.724
Systolic Ao (mmHg)	0.568	0.482 - 0.654	0.123
Rs (U・m2)	0.478	0.388 - 0.568	0.631
PAI (mm/m2)	0.478	0.392 - 0.564	0.617

Table 7. Related factors to increasing PCWP in 174 post-Fontan patients

	PCWP (mmHg)	p value
Right isomerism	9.2 vs. 6.9	0.0019
Other than SLV	7.6 vs. 5.7	0.0033
AR (+)	7.8 vs. 7.0	0.20
AVVR (+)	7.7 vs. 6.9	0.055
AVVR ≥ II	9.4 vs. 6.8	0.00033
Repair of AVV	8.9 vs. 6.8	0.0015
Repair of TAPVC	8.7 vs. 7.1	0.18
Coil embolization	7.4 vs. 7.0	0.47
PTPA	7.4 vs. 7.1	0.67

【Results】

Table 3. AUROC for predicting CVP ≥ 16 mmHg by PCWP.
We drew the AUROC for predicting high CVP by PCWP to gain quite a positive one（0.824: 95%C.I.0.713~0.934）.
Table 4. Patient-rates with a change in PCWP.
We sought minimum value of PCWP which induces CVP 16 mmHg or over in Fontan patients. The rate of patients with PCWP ≥ 12 mmHg in high CVP group was higher than that in non-high CVP group (48% vs. 1%: p<0.00001). We got similar results for PCWP ≥ 13 mmHg and PCWP ≥ 14 mmHg. Moreover, significant patient-rate differences between high CVP and non-high CVP were obtained by PCWP ≥ 11 mmHg, PCWP ≥ 10mmHg (66% vs. 8%: p＜0.00001), and by lower pressures. Significant differences were not obtained by PCWP ≥ 6 mmHg, and by lower pressures. Minimum value of PCWP was 7 mmHg which was potentially connected with high CVP (85% vs. 43%: p=0.00016).
Predicting CVP ≥ 16 mmHg by minimum PCWP (Table 5).
We calculated negative and positive predictive value, sensitivity, and specificity, to predict high CVP by minimum PCWP in 174 Fontan patients. Negative predictive value was very high (95%); sensitivity was high (85%). In contrast, negative predictive value was quite low (26%); specificity was low (47%).
AUROC for predicting PCWP ≥ 7 mmHg (Table 6).
What kind of factors are related to PCWP ≥ 7mmHg in Fontan patients? AUROCs were calculated about each cardiac performance for predicting minimum PCWP. We obtained significant AUROCs for predicting this PCWP ≥ 7 mmHg by 3 cardiac performances, such as end-diastolic ventricular pressure (0.832), end-diastolic ventricular volume (0.587), and end-systolic ventricular volume (0.599). We gained, namely, especially large AUROCs for predicting PCWP ≥ 7 mmHg by means of end-diastolic ventricular pressure. Ventricular ejection fraction and pulmonary artery index were not related to predicting PCWP ≥ 7 mmHg.
Related factors to increasing PCWP (Table 7).
Then, what kind of factors raise PCWP in Fontan patients? We searched for clinical factors which made PCWP rising. Rising PCWP was significantly related to clinical factors, such as right single ventricle or bi-ventricle, right isomerism, moderate regurgitation of atrio-ventricular valve, and history of atrio-ventricular valve repair.

【 Discussion】

Major findings.
First, AUROC for predicting high CVP was fairly large by means of PCWP in Fontan circulation. The values of 7 mmHg was possibly the minimum PCWP which would make CVP ≥16 mmHg. Second, this PCWP ≥ 7 mmHg was the value that derived very high negative predictive-value (95%) to predictive CVP ≥ 16 mmHg. Third, ventricular overload, particularly elevated SVEDP, were related to minimum PCWP. Clinical factors, which were associated PCWP increasing, were flollows; ventricular type, isomerism heart, and valve regurgitation.
High CVP and PCWP elevation in Fontan patients.
Our study showed that AUROC was very high (AUROC=0.824, 95% C.I.: 0.71-0.93) for predicting CVP ≥ 16 mmHg by PCWP. This indicated that high CVP was mightily associated with PCWP elevation. Cardiac functions would be connected with PCWP elevation. Practically, we found minimum PCWP, which pushed up CVP levels, were provoked by various cardiac overloads, such as SVESP elevation, SVEDV expansion, and particularly SVEDP elevation. We have to choose strategies before Fontan procedure which are able to avoid these cardiac overloads. In addition, this study showed structural factors could induce PCWP elevation, such as major right ventricle, right isomerism, and strong valve regurgitation of atrio-ventricular valve. We should mind PCWP elevation in Fontan candidate patients with these structural factors.
Minimum PCWP related to high CVP.
This study showed minimum PCWP was 7 mmHg which was connected with high CVP. This value was lower than that we expected. We actually do not take notice of this PCWP value. However, we obtained high sensitivity for predicting high CVP by means of this minimum PCWP. Because we gain highly false positive-rate (74%), we can not suspect high CVP at once by means of this minimum PCWP. However, as very low false negative-value (5%) we get, we can exclude possibility of high CVP in Fontan patients with PCWP 7 mmHg below.

Conclusion.
In Fontan circulation PCWP which would make CVP rising is not so higher than we expect. We should employ the strategy avoiding high PCWP in Fontan candidate patients to acquire adequate CVP after procedure.