Cardiothoracic Area Ratio Predicts Lethal Pulmonary Venous Obstruction in Patients with Single Ventricle and Total Anomalous Pulmonary Venous Connection

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Abstract

Background and Objectives When single ventricle (SV) is complicated with total anomalous pulmonary venous connection (TAPVC), the pulmonary vein obstruction (PVO) occurs at a high rate.

There are some patients who died from the lethal PVO (l-PVO) which needed PVO release dead due to severe desaturation within 24 hours after birth. The purpose of this study was to find a predictive marker for l-PVO during the fetal period.

Methods We enrolled 21 patients diagnosed with SV associated with TAPVC in the antenatal period. Ten patients had supracardiac, five had cardiac, five had infracardiac, and one had mixed TAPVC. We reviewed fetal echocardiography and measured cardiothoracic area ratio (CTAR) and total cardiac dimension (TCD). We divided 21 cases into l-PVO group (6) and non-l-PVO group (15) and compared the fetal echocardiography findings and postnatal prognoses between the groups.

Results CTAR at the final fetal echocardiography was 16 to 29% (median: 21) in the l-PVO group and 22 to 38% (median: 28) in the non-l-PVO group ($p = 0.01$). TCD/week at the final echocardiography was 0.67 to 1.0 (median: 0.77) in the l-PVO group and 0.78 to 1.2 (median: 0.96) in the non-l-PVO group ($p = 0.02$).

Conclusion Reduced CTAR in the antenatal period is a good predictor of l-PVO after birth.

Keywords
- pulmonary venous obstruction
- single ventricle
- TAPVC
- Fetal echocardiography
- CTAR

Some patients with single ventricle (SV) associated with total anomalous pulmonary venous connection (TAPVC) and pulmonary venous obstruction (PVO) die immediately after birth.[1–5] If these cases can be picked up during the antenatal period, more time can become available for the appropriate planning of treatment after birth and explanation to their parents. Pulmonary venous velocity or flow pattern according to fetal echocardiography had been used to predict these issues.[6–13] However, in clinical practice, more severe PVO is more difficult to identify. Therefore, we aimed to identify the other predictors of lethal PVO (l-PVO) in fetuses with SV.

Methods

Between 2005 and 2015, 21 patients who were diagnosed with SV and TAPVC by fetal echocardiography at our institute were identified. The mothers underwent fetal echocardiography at the Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi, Osaka, Japan. Pre- and postnatal medical records were reviewed to obtain data on clinical parameters, including perinatal outcomes.

We defined l-PVO as the need for PVO treatment within 24 hours after birth or the inability to perform surgery due to severe desaturation or bad general health of the neonate. Six

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patients had l-PVO. The remaining 15 patients had nonlethal PVO (non-l-PVO).

Fetal Echocardiography

Fetal echocardiography with cardiovascular anatomical assessment was performed according to previously described techniques using a variety of echocardiography systems. All images were recorded on DVDs for offline analysis. Three investigators reviewed all fetal echocardiographic findings. The following dimensions were defined: cardiothoracic area ratio (CTAR) and total cardiac dimension (TCD) (►**Fig. 1**). For analysis, we used the values of CTAR, TCD, and Tei index obtained at the final fetal echocardiography, which was performed at gestational age of 34 to 38 weeks (median: 36 weeks). We calculated the combined cardiac output (CCO) of the 6 cases with pulmonary atresia. Three representative heart cycles were traced for the measurement of velocity time integral (VTI). CCO is calculated by using the formula, CCO $= \pi$(aortic diameter (cm)/2)$^2 \times$ VTI (cm) $\times$ heart rate (bpm)/estimated body weight (kg), and the average value was recorded. And we compared CTAR, TCD, Tei index, and CCO between cases with l-PVO and non-l-PVO.

Statistical Analysis

Comparisons between groups were performed using the Mann–Whitney *U* test.

A p-value of < 0.05 was considered statistically significant. The differences between the assessments of the investigators were assessed using interclass correlation coefficients (ICCs).

Results

Patient Profiles

We summarized the 21 patients in ►**Table 1**. Six of the 21 patients suffered from l-PVO. Analysis of the atrial situs revealed that 19 patients had right isomerism (RI); all of the patients with l-PVO had RI. Ten patients had supracardiac TAPVC, five had cardiac TAPVC, five had infracardiac TAPVC, and one had mixed TAPVC. Regurgitation of the atrioventricular valves was more than mild in eight fetuses (l-PVO: 2, non-l-PVO: 6). Body weight at birth was 1,788 to 4,126 g (median: 2,692 g). Five patients required intubation and mechanical ventilator soon after birth, four of whom were in the l-PVO group. All of the four patients who suffered from pneumothorax after birth had l-PVO, while none of the non-l-PVO patients had pneumothorax. Surgery was performed in four of the six patients with l-PVO within 24 hours after birth and two of the four patients died at the 168th and 199th day.

Fetal Echocardiographic Findings

We performed fetal echocardiography multiple times between 22 and 38 weeks of gestation. The final fetal echocardiography was performed at 34 to 38 weeks (median: 36.2 weeks). ►**Fig. 1** shows the method used to measure cardiac size: the ellipse method. ►**Table 2** shows the correlations between echocardiographic findings and prognoses. CTAR in the l-PVO group was significantly lower than that in the non-l-PVO group (16–29% [median: 21%] vs. 22–38% [median: 28%], $p = 0.01$). TCD/week in the l-PVO group was significantly lower than that in the non-l-PVO group (0.67–1.0 [median: 0.77] vs. 0.78–1.2 [median: 0.96], $p = 0.02$). Tei index in the l-PVO group was lower than that in the non-l-PVO group (0.26–0.34 [median: 0.30%] vs. 0.28–0.48% [median: 0.40%], $p = 0.02$). The values of CTAR, TCD/week, and Tei index were significantly lower in the l-PVO group than those in the non-l-PVO group. We were able to calculate the CCO in six patients with pulmonary atresia (l-PVO: 2 [cases 16, 21]; non-l-PVO: 4 [cases 2, 3, 4, 8]). The values were 183 and 250 mL/kg in the l-PVO group and 308 to 589 mL/kg in the non-l-PVO group (►**Fig. 2**).

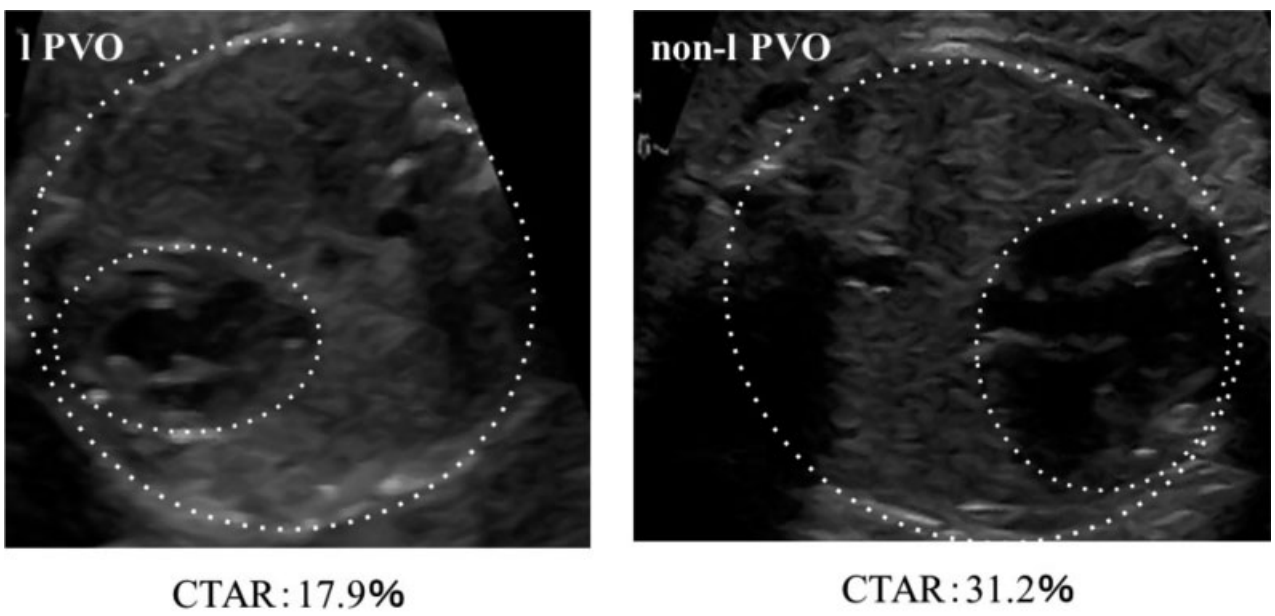

Fig. 1 Procedure for measuring cardio-thoracic area ratio.

Table 1 Patients profiles

Patient no.	Critical PVO	GW at finding	Atrial situs	Diagnosis	Drainage site of PV	BW at birth	GW at birth	APGAR 1/5 min	Highest $PaO_2 < 24h$	Pneumothorax after birth	Intubation after birth	Surgical repair PVO	Outcome
1	No	24	RI	SA, SV, PS	Atrium	2,506	38	8/8	41.7	No	No	No	Alive
2	No	25	RI	SA, SV, PA	SVC	2,692	38	8/8	37.3	No	No	Day 21	Alive
3	No	25	RI	SA, SV, PS	SVC	3,014	39	4/6	44.2	No	No	Day 34	Alive
4	No	26	RI	SA, SV, PA	Inn V	2,972	38	8/8	36.4	No	No	Day 160	Alive
5	No	26	RI	SA, DORV, PS	SVC	1,788	38	2/8	47.5	No	No	Day 91	Alive
6	No	29	RI	SA, SV, PA	Inn V	2,353	39	8/8	43.0	No	No	Day 114	Dead
7	No	29	RI	SA, SV	Portal V	2,496	37	—	—	—	Yes	No	Dead
8	No	29	RI	SA, SV, PA	Portal V	3,258	39	7/7	36.9	No	No	Day 26	Dead
9	No	29	Solitus	SA, SV, PA	Portal V	2,572	38	7/8	41.3	No	No	Day 36	Alive
10	No	29	RI	MA,DORV	SVC	3,200	39	8/8	47.8	No	No	Day 177	Alive
11	No	30	RI	SA, SV, PS	Atrium	2,688	38	8/8	43.3	No	No	No	Alive
12	No	32	RI	SA, SV, CoA	SVC	3,618	38	8/9	60.2	No	No	No	Dead
13	No	33	RI	SA, SV, PA	SVC, Portal V	2,522	38	8/8	43.8	No	No	Day 85	Alive
14	No	34	RI	SA, SV, PS	SVC	2,910	38	8/8	48.5	No	No	Day 116	Alive
15	No	35	Solitus	MA, DORV, PA	Atrium	1,874	38	8/8	44.3	No	No	No	Alive
16	Yes	20	RI	SA, SV, PA	Portal vein	2,948	38	8/9	41.9	No	Yes	4 h	Dead
17	Yes	23	RI	SA, SV, PA	Atrium	2,404	38	7/8	—	No	Yes	4 h	Alive
18	Yes	22	RI	SA, DORV, PS	Portal vein	2,962	38	7/7	30.1	Yes	Yes	8 h	Dead
19	Yes	25	RI	SA, SV, PS	Inn V	4,126	40	8/8	28.8	No	No	13 h	Alive
20	Yes	26	RI	SA, SV	Atrium	2,054	39	3/5	24.7	Yes	Yes	No	Dead
21	Yes	26	RI	SA, SV, PS	SVC	3,126	40	5/5	32.8	Yes	Yes	No	Dead

Abbreviations: APGAR, Appearance, Pulse, Grimace, Activity, and Respiration; BW, body weight; CoA, coarctation; DORV, double outlet right ventricle; GW, gestational week; MA, mitral atresia; PA, pulmonary atresia; PaO_2, arterial partial pressure of oxygen; PS, pulmonary stenosis; PVO, pulmonary venous obstruction; SA, single atrium; SV, single ventricle.

Table 2 Summary of fetal echocardiography before birth (mean ± SD)

	Gestational wk	TCD/GW	CTAR (%)	Tei index	CAVVR (mild)
Critical PVO (+)	38.5 (38–40)	0.77 ± 0.13 (0.67–1.0)	21 ± 4.7 (16–29)	0.30 ± 0.040 (0.26–0.34)	6/15
Critical PVO (–)	38 (37–39)	0.96 ± 0.097 (0.78–1.2)	28 ± 4.2 (22–38)	0.40 ± 0.072 (0.28–0.48)	2/6
P PVO (+) vs. PVO (–)	NS	$p = 0.02$	$p = 0.01$	$p = 0.02$	

Abbreviations: CAVVR, common atrioventricular valve regurgitation; CTAR, cardiothoracic area ratio; GW, gestational week; PVO, pulmonary venous obstruction; SD, standard deviation; TCD, total cardiac dimension.

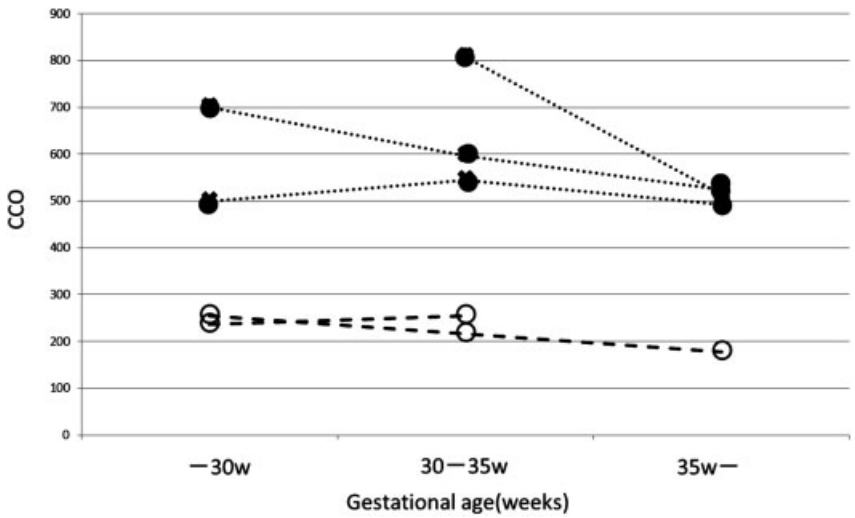

Fig. 2 Changes in cardio-thoracic area ratio (CTAR) by gestational week. The open circle shows the change in patients with lethal pulmonary vein obstruction (l-PVO). The closed circle shows the change in non-l-PVO patients. CTAR gradually decreased in cases of l-PVO with no or trivial regurgitation of the atrioventricular valve.

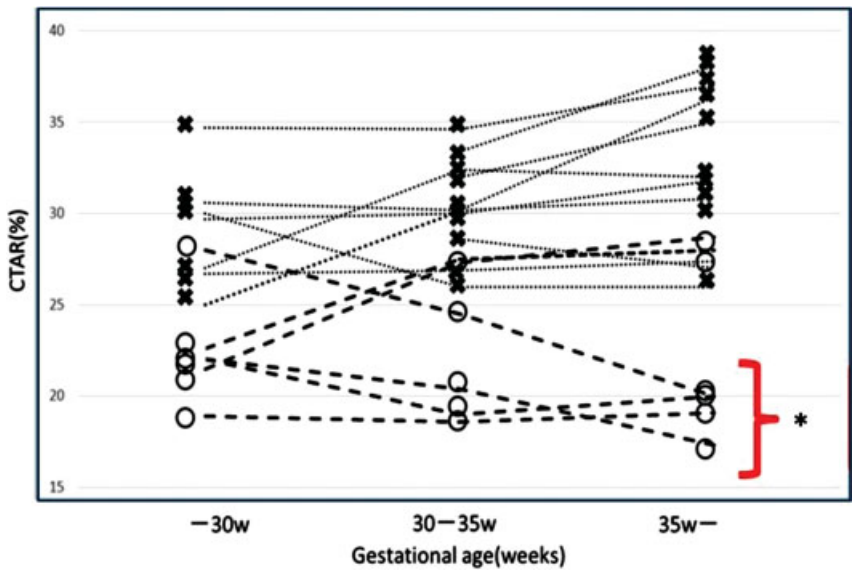

Fig. 3 Changes in combined cardiac output by gestational week showing the CCO of patients with lethal pulmonary vein obstruction (l-PVO) and non-l-PVO with single ventricle, total anomalous pulmonary venous connection, and pulmonary atresia. The open circle shows the CCO of patients with l-PVO. The closed circle shows the CCO of patients with non-l-PVO. CCO; combined cardiac output.

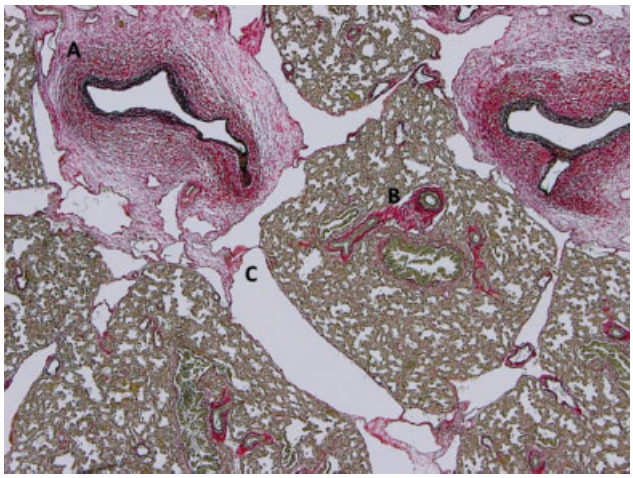

Fig. 4 Histological findings from a lung sample from case 20 (who died 16 hours after birth due to pulmonary vein obstruction). (A) The elastic fiber is hypertrophic, especially in the pulmonary vein. (B) The media of the pulmonary artery is hypertrophic. Heath-Edwards grade = I. (C) The interstitial wall of the pulmonary alveolus is hypertrophic and the lymphatic vessels are dilated. (D) The wall of the pulmonary alveolus is edematous and there are many cellular components and thickening.

Difference between Observers

Three investigators measured the CTAR and TCD based on reviews of findings. For CTAR, the median ICC was 0.88 and the single measures ICC was 0.70 ($p < 0.01$). For TCD, the median ICC was 0.93 and the single measures ICC was 0.82 ($p < 0.01$).

Discussion

The results of this study demonstrated that l-PVO after birth is associated with respiratory failure and pneumothorax. If patients with l-PVO are not diagnosed antenatally, the risk of death increases. If these cases can be identified before birth, it will be possible to prepare treatment strategies and inform their parents about the clinical situation. However, it is difficult to diagnose disorders of the pulmonary vein in the antenatal period, and diagnosis of PVO is particularly challenging.[10,14] In this study, we failed to diagnose TAPVC in 3 of 21 cases. Furthermore, we could diagnose l-PVO in just two of six patients antenatally. Diagnosis is thought to be difficult because pulmonary blood flow decreases in cases of fetal PVO.[7,9,13] Fetal pulmonary blood flow is important for the development of appropriate fetal heart preload in the latter half of the pregnancy.[15] The heart most probably remains small because preload decreases in fetuses with PVO.

The lower values of CTAR can suggest SV and TAPVC associated with l-PVO. The changes in CTAR in the antenatal period observed in this study are shown in ►**Fig. 3**. The CTAR values of patients with l-PVO were lower than those of patients with non-l-PVO. In particular, in the case of no or trivial regurgitation of the atrioventricular valve, the value of CTAR became smaller at any time. In these cases, the cut-off value of CTAR was 22.7% (sensitivity = 100%, specificity = 100%). The CTAR value was lower in the l-PVO group and appeared to represent a good index to predict l-PVO.

We measured the CCO to make sure that the CTAR with l-PVO is smaller. We compared the difference in CCO between the l-PVO and non-l-PVO groups. The CCO in the l-PVO group was lower than that in the non-l-PVO group. These results suggest that pulmonary blood flow volume in patients with l-PVO decreased due to PVO and that heart preload more severely decreased in lethal cases. According to Moss and Adams', which is one of the most common textbooks for pediatric cardiology, the decreased inflow from the left atrial leads to decrease in left ventricular volume in the cases of TAPVC with PVO. Finally, they show that the heart size in the l-PVO group decreased and the value of CTAR got smaller.

The cases of the l-PVO group often suffered from pneumothorax and it is sometimes the cause of death. ►**Fig. 4** shows the histological findings from lung samples from case 20, a patient who died 16 hours after birth due to l-PVO. The findings showed that the elastic fiber is hypertrophic, especially in the pulmonary vein, that the media of the pulmonary artery is hypertrophic, and that the interstitial wall of the pulmonary alveolus is hypertrophic and the lymphatic vessels are dilated.

It means that the lumen of the pulmonary artery and vein was narrower. Moss and Adams' also showed similar findings of the pulmonary vein and lungs due to PVO.

Therefore, we conclude lower preload due to a narrower lung vessel lumen and more severe lung edema contribute to the lower values of CTAR with l-PVO.

Study Limitation

This study has several limitations that should be discussed. First, the number of cases was small, and so the cut-off value for CTAR may be changed. Second, we calculated the CCO in only six cases of pulmonary atresia because the value was not correct due to the fast flow velocity in the cases with pulmonary stenosis. Because of the small sample volume, the data of the CCO may be changed.

In conclusion, in patients with l-PVO of SV and TAPVC, the symptom rerated to PVO rapidly progresses postnatally due to decrease in pulmonary blood flow. The antenatal values of CTAR are lower in patients with l-PVO. Thus, CTAR serves as a good predictor of l-PVO associated with SV and TAPVC.

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