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ORIGINAL ARTICLE

Pulmonary vasodilators can lead to various complications in pulmonary "arterial" hypertension associated with congenital heart disease

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Abstract
Congenital heart disease-associated pulmonary arterial hypertension (CHD-PAH) is one of the major complications in patients with CHD. A timely closure of the left-to-right shunt will generally result in the normalization of the pulmonary hemodynamics, but a few patients have severe prognosis in their early childhood. We hypothesized that wide-ranging pathological mechanism in PAH could elucidate the clinical state of severe CHD-PAH. Using electronic medical records, we retrospectively analyzed six infants with severe CHD-PAH who had treatment-resistant PH. All patients were born with congenital malformation syndrome. After starting on a pulmonary vasodilator, five of the six patients developed complications including pulmonary edema and interstitial lung disease (ILD), and four patients had alveolar hemorrhage. After steroid therapy, the clinical condition improved in four patients, but two patients died. The autopsy findings in one of the deceased patients indicated the presence of recurrent alveolar hemorrhage, pulmonary venous hypertension, ILD, and PAH. Based on the clinical course of these CHD-PAH in patients and the literature, CHD-PAH can occur with pulmonary vascular obstructive disease (PVOD)/pulmonary capillary hemangiomatosis (PCH), ILD, and/or alveolar hemorrhage. The severity of CHD-PAH may depend on a genetic disorder, respiratory infection, and upper airway stenosis. Additionally, pulmonary vasodilators may be involved in the development of PVOD/PCH and ILD. When patients with CHD-PAH show unexpected deterioration, clinicians should consider complications associated with PVOD/PCH and/or pulmonary disease. In addition, the choice of upfront combination therapy for pediatric patients with CHD-PAH should be selected carefully.

Keywords Congenital heart disease-associated pulmonary arterial hypertension · Pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis · Interstitial lung disease · Alveolar hemorrhage

Introduction

Pulmonary arterial hypertension (PAH) is a severe, progressive disorder characterized by a high pulmonary arterial pressure [1]. Pulmonary veno-occlusive disease (PVOD)/pulmonary capillary hemangiomatosis (PCH) is a rare type of pulmonary hypertension (PH) defined by increased pulmonary vascular resistance caused by capillary or postcapillary disorder [2, 3]. PAH and PVOD/PCH can overlap pathologically and genetically [4, 5]. In addition, PVOD/PCH was reclassified as "PAH with overt features of venous/capillary (PVOD/PCH) involvement" in the latest World Symposium on Pulmonary Hypertension (WSPH) in 2018 [6]. The revised classification reveals that PAH has a more extensive clinical course than previously anticipated. We describe six pediatric patients with severe, treatment-resistant, congenital heart disease-associated PAH (CHD-PAH), and analyze their clinical conditions based on the WSPH statement and previous literature. We hypothesized that a wide-ranging pathological mechanism in PAH could elucidate the clinical state of severe CHD-PAH.

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Patients and methods

Based on the electronic medical records, we retrospectively reviewed CHD-PAH patients whose systolic pulmonary arterial pressure was estimated to be equal to or higher than systemic systolic blood pressure and in whom specific pulmonary vasodilator was not effective, in Hokkaido University Hospital and Fukuoka Children's Hospital from January 2008 to December 2018.

The Institutional Review Board (IRB) of Hokkaido University Hospital for clinical research approved this study (IRB approval no. 019-0003). The IRB of Fukuoka Children's Hospital for clinical research also approved the study (IRB approval no. 2019-13). Information regarding the present study was disclosed on Hokkaido University website for an opt out of approval, because three of the patients died. Informed consent for the living patients was waived due to the retrospective nature of the study.

Illustrative cases

Six infants were included in this analysis. Four patients were born with trisomy 21, one with trisomy 18, and one with VACTERL association (the last patient had cardiac malformation, anal atresia, and limb anomaly) (Table 1). The median age (range) at PH progression was 5 months (3 months to 1 year and 4 months). As shown in Table 2, all the patients had an estimated systolic pulmonary arterial pressure that was equal to or higher than the systemic systolic blood pressure. Before PH progression, patient 3 had a mycoplasma infection, and patient 6 developed respiratory syncytial virus infection. All patients were diagnosed as having CHD-PAH progression, and a variety of pulmonary vasodilators were used (Table 3). After initiation of this treatment, patients developed alveolar hemorrhage, interstitial lung disease (ILD), acute respiratory distress syndrome, and so on. The median value (range) of the maximum serum KL-6 level was 2219 (1987–6273) U/mL (reference range < 400 U/mL). Clinical condition of four of the patients improved, while the remaining two patients died, and the cause of death was related to CHD-PAH. Here, we describe the detailed clinical courses of CHD-PAH in patient 2 and patient 3 as representative patients.

Patient 2

A girl was born at 38 weeks of gestation with a birth weight of 3.0 kg. At 1-month-old medical checkup, she had poor weight gain, poor feeding, and a specific appearance suggestive of trisomy 21. The chromosomal examination confirmed trisomy 21. She was referred to the pediatric cardiology outpatient clinic, and was diagnosed with complete atrioventricular septal defect, patent ductus arteriosus (PDA), and PH. Cardiac catheterization was performed at 56 days of age; her left-ventricular pressure (systolic/end-diastolic) was 51/8 mmHg, right-ventricular pressure (systolic/end-diastolic) was 53/7 mmHg, main pulmonary arterial pressure (systolic/diastolic/mean) was 49/14/31 mmHg, pulmonary-to-systemic flow ratio was 1.91, and pulmonary vascular resistance was 4.81 Wood units·m^2. At 64 days of age, intracardiac repair and PDA ligation were performed. Postoperatively, her right-ventricular pressure estimated by ultrasonic echocardiography was still very high and almost equal to the left-ventricular pressure. She required nitric oxide (NO) inhalation even after endotracheal extubation at 77 days of age. At 95 days of age, NO inhalation was stopped and she had a cough and labored breathing. Decreasing the amount of milk feeding and increasing the dose of diuretics improved her respiration only temporarily. Her chest X-ray showed interstitial markings, so intravenous prednisolone was started at 110 days of age, and her respiratory status dramatically improved. We switched intravenous prednisolone to oral prednisolone on the next day. However, we suspected that severe PAH still remained, so at 113 days of age, oral bosentan was started. At 120 days of

Table 1 Characteristics of all patients

Patient number	Sex	Genetic disorder	Complication of CHD	Former surgical procedure (age at operation)
1	Female	Trisomy 21	PA, VSD	ICR (4 m)
2	Female	Trisomy 21	cAVSD, PDA	ICR (2 m)
3	Male	Trisomy 21	VSD, AP window	AP window repair (6 d)
4	Male	Trisomy 21	cAVSD, PDA, ASD type II	PAB and PDA ligation (2 d), ICR (5 m)
5	Female	Trisomy 18	VSD, ASD, PDA, DCRV	PAB and PDA ligation (7 m)
6	Male	VACTERL association	VSD, PAPVC	None

CHD congenital heart disease, *PA* pulmonary atresia, *VSD* ventricular septal defect, *ICR* intracardiac repair, *cAVSD* complete atrioventricular septal defect, *PDA* patent ductus arteriosus, *AP window* aortopulmonary window, *ASD* atrial septal defect, *DCRV* double-chambered right ventricle, *PAB* pulmonary artery banding, *PAPVC* partial anomalous pulmonary venous connection

Table 2 Hemodynamic parameters in patients

Patient number	Measurement period	PAP: systolic/diastolic/mean (mmHg)	mRAP (mmHg)	CI (L/min/m^2)	PVR (wood units/m^2)	mPAWP (mmHg)	Systolic systemic BP (mmHg)	Qp/Qs	eRVSP (mmHg)
1	Before ICR	–	2	5.47	3.4	–	74	2.31	–
	After ICR and PH progression[a]	45/14/29	3	4.2	5.76	7	89	1.03	–[b]
2	Before ICR	49/14/31	–	–	4.81	–	51	1.91	–
	After ICR and PH progression	–	–	–	–	–	–	–	75
3	Before vasodilator induction	–	–	–	–	–	–	–	–[b]
	After vasodilator induction	–	–	–	–	–	–	–	–[b]
4	Before pH progression	–	–	–	–	–	–	–	–[b]
	After PH progression[c]	65/36/50	–	–	–	7[d]	69	2.4	–[b]
5	Before vasodilator induction	–	–	–	–	–	–	–	–[b]
	After vasodilator induction	–	–	–	–	–	–	–	–[b]
6	Before PH progression	–	–	–	–	–	–	–	–[e]
	After PH progression	–	–	–	–	–	–	–	–[f]

–, not available, *mPAP* mean pulmonary arterial pressure, *RAP* right atrial pressure, *CI* cardiac index, *PVR* pulmonary vascular resistance, *mPAWP* mean pulmonary artery wedge pressure, *BP* blood pressure, *Qp/Qs* pulmonary blood flow-to-systemic blood flow ratio, *eRVSP* estimated right-ventricular systolic pressure, *ICR* intracardiac repair, *PH* pulmonary hypertension

[a]The catheterization was performed with 10 L/min oxygen and nitric oxide 5 ppm inhalation

[b]The pressure in the RV was estimated to be almost equal to that of the LV by interventricular septum shape

[c]The catheterization was performed with intubated state (fraction of inspiratory oxygen 0.4)

[d]The mean pulmonary vein pressure is displayed

[e]A left-to-right shunt flow in ventricular septal defect was detected

[f]A right-to-left shunt flow in ventricular septal defect was detected

age, prominent labored breathing and hypoxemia started. Intravenous dexamethasone improved her condition temporally, but labored breathing and hypoxemia remained. At 139 days of age, she developed acute bronchitis and underwent endotracheal intubation. Intravenous dexamethasone and ampicillin improved her condition temporally. Her chest high-resolution computed tomography (HRCT) showed panlobular ground-glass opacity and interlobular septal thickening (Fig. 1). At 176 days of age, her respiratory status deteriorated further, so we started methylprednisolone pulse therapy in the intensive-care unit. Subsequently, she developed alveolar hemorrhage and hypovolemic shock and died at 181 days of age.

A lung autopsy was performed after obtaining informed consent from her parents. Histopathological findings showed narrowing and obstructive small pulmonary arteries with medial thickening, hemosiderin deposition, lymphangiectasia, many emphysematous bullae, fibrous thickening of the cell walls, and intimal fibrous thickening of almost 50% of the pulmonary veins (Fig. 2a–d). These findings indicated the presence of recurrent alveolar hemorrhage, pulmonary venous hypertension, ILD, and PAH.

Patient 3

A boy was suspected of having CHD in his fetal stage. He was born at 36 weeks of gestation with a birth weight of 2.8 kg. Just after birth, he was diagnosed as having ventricular septal defect (VSD) and aortopulmonary window (AP window). At 6 days of age, he underwent AP window repair. At that time, we did not perform VSD closure or pulmonary artery banding (PAB) because the main pulmonary artery was hypoplastic and seemed to restrict pulmonary arterial flow. The chromosomal examination revealed that he had trisomy 21. He was discharged at 76 days of age. However, during regular visits, the ultrasound cardiogram revealed reduction in pulmonary artery flow velocity, and progression of PH was suspected. Therefore, at 156 days of age, oral bosentan and home oxygen therapy were started. Bosentan was switched to macitentan at 160 days of age. Subsequently, he developed cyanosis and respiratory failure, and was admitted to the hospital as an emergency at 166 days of age. He required tracheal intubation and ventilator management, which temporarily improved his respiratory status. We considered PH crisis followed by an upper airway obstruction, so we

Table 3 Outcome of all patients after PH progression

Patient number	Age at PH progression	Antecedent infection	Vasodilators added at PH progression	Result after adding vasodilators	Treatment for the status listed in the left-hand column	Maximum serum KL-6 (U/mL)	Lung biopsy	Outcome
1	5 months	None	Sildenafil, bosentan	Pulmonary edema, interstitial pneumonia, ARDS	Prednisolone, dexamethasone, methylprednisolone pulse therapy, intensive care	2110	None	Death
2	3 months	None	Bosentan	Pulmonary edema, ILD, alveolar hemorrhage, pulmonary venous hypertension	Prednisolone, dexamethasone, methylprednisolone pulse therapy, intensive care	2210	Autopsy	Death
3	5 months	Mycoplasma infection	Tadalafil, bosentan (switched to macitentan), selexipag, NO inhalation	Alveolar hemorrhage, lung hemosiderosis, ILD	Intensive care, withdrawal of vasodilators, methylprednisolone pulse therapy, ICR	2227	None	Improved
4	5 months	None	Tadalafil, macitentan, selexipag	ILD	Methylprednisolone pulse therapy	6273	None	Improved
5	1 year 4 months	None	Sildenafil, bosentan, epoprostenol, NO inhalation	Alveolar hemorrhage	Withdrawal of vasodilators, dexamethasone, intensive care	1987	None	Improved
6	6 months	RSV infection	Sildenafil, macitentan	Alveolar hemorrhage, ILD	Methylprednisolone pulse therapy, intensive care	3183	None	Improved

PH pulmonary hypertension, *ARDS* acute respiratory distress syndrome, *ILD* interstitial lung disease, *NO* nitric oxide, *ICR* intracardiac repair

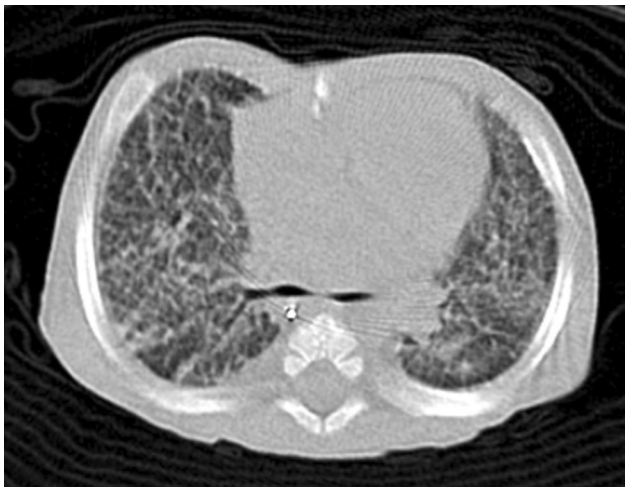

Fig. 1 Chest HRCT scan of patient 2. At 145 days of age, patient 2's lung HRCT image shows panlobular ground-glass opacity and interlobular septal thickening. *HRCT* high-resolution computed tomography

started selexipag at 168 days of age and NO inhalation at 171 days of age. He often had deep desaturation when sucking phlegm or crying, and the amount of bloody sputum increased from 176 days of age; thus, he was admitted to the intensive-care unit. His bloody sputum increased further despite strict ventilator management and administration of a hemostatic agent and fresh-frozen plasma. At 181 days of age, his serum KL-6 level increased to 2227 U/mL. His chest computed tomography (CT) scan indicated complication with ILD and alveolar hemorrhage (Fig. 3a). Methylprednisolone pulse therapy was started, but his condition did not improve. A mycoplasma infection was confirmed by the particle agglutination method, and azithromycin was started. Despite these therapies, his bloody sputum continued, and hemosiderin was found in his intratracheal-suctioned phlegm. His second CT scan revealed dilated pulmonary arteries, proximally to distally (Fig. 3b).

We considered that the high flow status was caused by VSD and that pulmonary vasodilators induced alveolar hemorrhage and respiratory failure; accordingly, we stopped the vasodilators gradually and performed PAB at 199 days of age. Postoperatively, the amount of bloody sputum gradually reduced, and the follow-up CT scan showed a dramatic improvement over the previous findings (Fig. 3c). He was successfully extubated at 216 days of age, and steroid therapy was slowly tapered and stopped at 223 days of age. However, at 241 days of age, his respiratory status deteriorated again. Although methylprednisolone therapy was restarted, it did not improve his respiratory failure. The chest X-ray revealed worsening of the ILD, and his serum KL-6 level increased up to 3036 U/mL. To control the pulmonary artery flow, he underwent VSD patch closure at 275 days of age. His respiratory status was dramatically improved postoperatively. At 305 days of age, he was discharged from the hospital with home oxygen therapy, oral prednisolone, and budesonide inhalation therapy.

Figure 4 reveals the chest CT image of the other patients. Patients 1, 4, and 6 (Fig. 4a, b, d) had reference findings of PVOD/PCH; panlobular ground-glass opacity, interlobular septal thickening, and funicular shadows

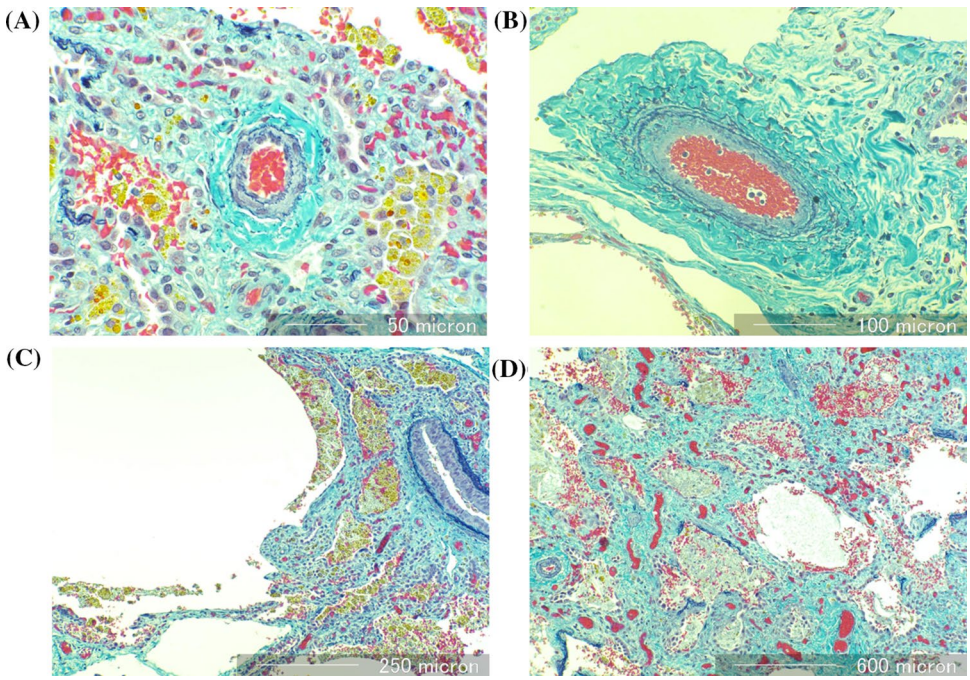

Fig. 2 Histopathological findings of the lung autopsy for patient 2 at 181 days of age. **a** Small pulmonary arteries with a diameter of 50 μm have a medial thickness. Yellowish hemosiderin deposition is also found. **b** Almost 50% of the pulmonary veins have intimal fibrous thickening. **c** There are many emphysematous bullae and hemosiderin deposits. **d** Fibrous thickening of the wall of a pulmonary alveolus is revealed. The central white area is lymphangiectasia

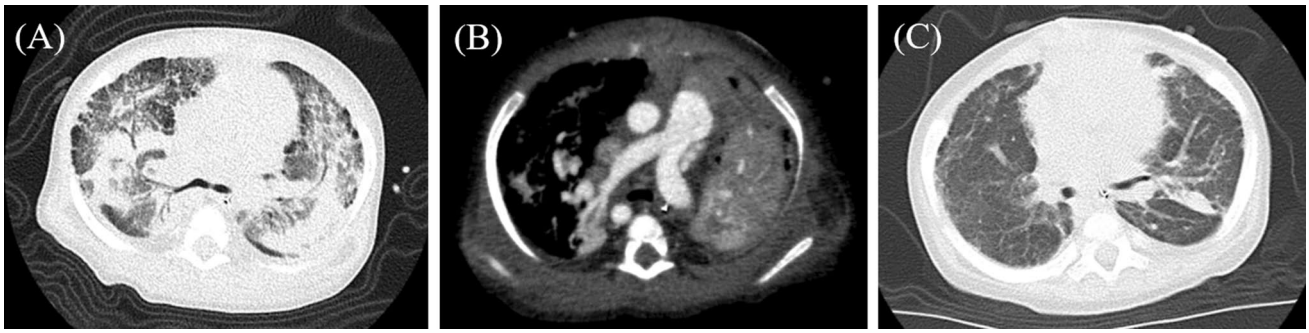

Fig. 3 Chest HRCT scan of patient 3 illustrating fibrosis and alveolar hemorrhage. **a** At 188 days of age, patient 3's lung HRCT image shows honeycomb cysts involving the subpleural area, alveolar hemorrhage, and parenchymal opacification consisting of consolidation and ground-glass opacities. **b** At 197 days of age, the HRCT scan revealed dilated pulmonary arteries totally. **c** At 210 days of age, the follow-up HRCT scan after steroid treatment, cessation of pulmonary vasodilators, and pulmonary artery banding shows marked improvement of the previous findings. *HRCT* high-resolution computed tomography

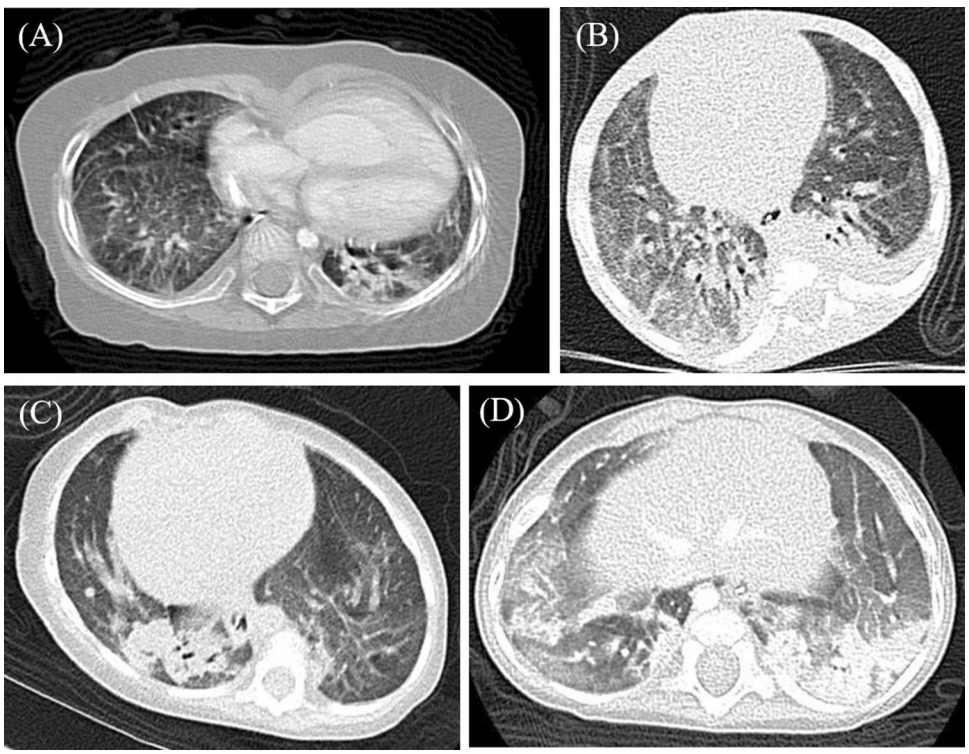

Fig. 4 Chest HRCT image of the others. **a** The HRCT image of patient 1 reveals interlobular septal thickening and interlobar pleura thickening. **b** The HRCT image of patient 4 shows panlobular ground-glass opacity, mild interlobular septal thickening, and funicular shadows. **c** In patient 5 image, only atelectasis and funicular shadows are shown. **d** Patient 6 image demonstrates ground-glass opacity, interlobular septal thickening, air space consolidation, and atelectasis. *HRCT* high-resolution computed tomography

Discussion

The present study revealed that CHD-PAH could be complicated by PVOD/PCH, ILD, and/or alveolar hemorrhage.

The 6th WSPH statement indicated that decreasing diffusing capacity of the lung for carbon monoxide and severe hypoxia on exercise are useful biomarkers for diagnosing PVOD/PCH. However, it is difficult to assess these biomarkers in children. Although HRCT is also known to be useful for diagnosing PVOD/PCH, the characteristic findings are not present in all cases of PVOD/PCH. In addition, it is challenging to diagnose PVOD/PCH in children, because the lung volume is relatively small for HRCT analysis. However, we consider that the HRCT and pathological findings in our cases may indicate the possibility of PVOD/PCH coexistence. Besides, in our CHD-PAH cases, we used specific pulmonary vasodilators for deteriorating conditions; their clinical conditions worsened, and they developed pulmonary edema. This phenomenon strongly indicated PVOD/PCH. Muneuchi et al. also reported an infant with CHD-PAH; she died of unexpected deterioration of PH, and lung autopsy proved the existence of PVOD [7]. The frequency of pediatric PAH with

PVOD/PCH is not clear, because there are a few reports, so further investigation is necessary.

In addition to the clinical conditions similar to that reported by Muneuchi et al., our patients were also complicated with alveolar hemorrhage and ILD. To clarify the mechanism, several issues need to be taken into consideration.

1. Complication with congenital malformation syndrome: Trisomy 21 is frequently associated with chronic upper respiratory tract obstruction, sleep apnea syndrome, and hypoxia, caused by infection. These can also be associated with alveolar capillary dysplasia and peripheral lung cysts, and the condition can cause lung dysplasia [8, 9]. Emphysematous lesions and interstitial lesions can destroy the pulmonary vessels, with deterioration of PH. In addition to trisomy 21, trisomy 13; trisomy 18; DiGeorge syndrome; VACTERL association; and Noonan syndrome also tend to be complicated with CHD-PAH [10, 11]. CHD-PAH in combination with these genetic syndromes can cause deterioration of a patient's clinical condition. However, there are a few reports about CHD-PAH with congenital malformations besides trisomy 21. Further pathological analysis is necessary.
2. Overlap of pathology with PH: The findings of PVOD/PCH can be seen in patients with idiopathic pulmonary fibrosis or combined pulmonary fibrosis and emphysema [12, 13]. PVOD can also induce fibrosis of lung interstitium [2]. Similar to the relationship between PAH and PVOD/PCH, that between ILD and PVOD/PCH may be less distinct than we think.
3. Relationship between PH and alveolar hemorrhage: It has been reported that hemosiderin-laden macrophages in the sputum of patients with PVOD is found significantly at higher rates compared with the other forms of PH [14]. Lederer et al. argued that engorgement of the capillaries in PVOD leads to occult alveolar hemorrhage. Additionally, pulmonary edema can cause diffuse alveolar hemorrhage, and repetitive alveolar hemorrhages can induce interstitial fibrosis of the lung [15]. Furthermore, pulmonary vasodilators may cause alveolar hemorrhage. It has been revealed that epoprostenol, with anticoagulant therapy, increases one's risk of lung hemorrhage, and sildenafil can induce pulmonary hemorrhage [16–19]. Physicians should be cautious about the risk of alveolar hemorrhage and ILD when treating patients with PAH and PVOD/PCH.
4. Relationship between pulmonary vasodilators and ILD: Several studies have reported that epoprostenol induces ILD [20–22]. Furthermore, the ARTEMIS study was terminated early, because ambrisentan deteriorated the condition of PAH patients with idiopathic pulmonary fibrosis [23]. Moreover, riociguat increased the death rate and deterioration of respiratory status in the RISE-IIP trial, which was terminated early [24]. In the 6th WSPH, these 2 aforementioned drugs were determined to be contraindicated for each of these medical statuses [25]. The mechanism of why pulmonary vasodilators can induce or deteriorate ILD is unclear; thus, further investigation is necessary.

Taken together, we illustrate the mechanism of fatal CHD-PAH in Fig. 5. Namely, CHD-PAH, PVOD/PCH, ILD, and alveolar hemorrhage can overlap each other, based on congenital malformation syndrome, respiratory infection, upper airway obstruction, pulmonary vasodilators, and so on. Pulmonary vasodilators can induce pulmonary edema in patients with PVOD/PCH and cause deterioration of PVOD/PCH and ILD. Physicians should consider that pediatric patients with severe CHD-PAH may be complicated with congenital malformation syndrome, other forms of PH caused by PVOD/PCH, or pulmonary disease, and select their treatment carefully. Making a differential diagnosis is sometimes difficult, especially in severe cases. Based on our experience, HRCT and the serum KL-6 level are useful for supporting the diagnosis. The serum KL-6 level is a serum marker for ILD, but it is known to increase in patients with diffuse alveolar hemorrhage. Kida et al. reported that patients with diffuse alveolar hemorrhage whose serum KL-6 level was higher than 700 U/mL had a significantly poorer prognosis than other patients [26].

In severe cases of CHD-PAH, NO inhalation can be safer than the other oral or intravenous pulmonary vasodilators. Unlike those pulmonary vasodilators, NO does not reach a region with a low-ventilation perfusion ratio and dilate only vessels in a region with a high-ventilation perfusion ratio. It has the advantage of improving general hypoxia. Furthermore, it was reported that in experiments on animals, NO inhalation decreased pulmonary arterial resistance and pulmonary vein resistance [27]. In addition, NO inhalation decreased pulmonary vein resistance and pulmonary capillary pressure in patients with acute respiratory distress syndrome [28, 29]. These reports suggest that NO inhalation is useful for PVOD/PCH.

When the medical status of patients with CHD-PAH deteriorates even if pulmonary vasodilators are started or the dose is increased, physicians should consider not only the possibility of the limited efficacy of pulmonary vasodilators but also complications of other clinical conditions, such as PVOD/PCH, ILD, and alveolar hemorrhage. The therapeutic strategy of combining multiple pulmonary vasodilators, the so-called combination therapy, is recognized as the standard treatment for adult patients with PAH. Based on the current study, however, careful judgment is needed when choosing combination therapy,

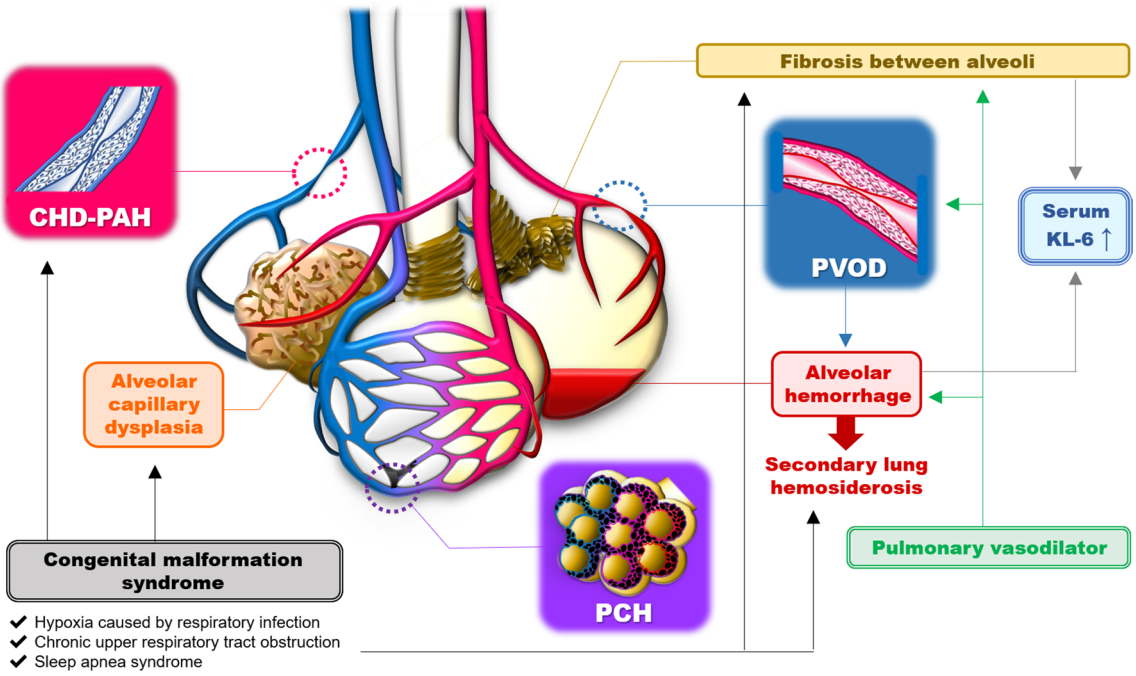

Fig. 5 Estimated mechanism of severe CHD-PAH. *CHD-PAH* congenital heart disease-associated pulmonary arterial hypertension, *PVOD* pulmonary veno-occlusive disease, *PCH* pulmonary capillary hemangiomatosis

especially upfront combination therapy for CHD-PAH, because it may deteriorate the patient's medical status. Further discussion is necessary to determine the proper use of upfront combination therapy for CHD-PAH, and the conclusion should be clearly described in the guideline for managing childhood PH.

In our cases, lung biopsy was not performed to make a definite diagnosis of PVOD/PCH, ILD, and/or alveolar hemorrhage, except in patient 2 who had lung autopsy, and it was difficult to make a definite diagnosis of PVOD/PCH and/or other forms of PH. However, lung biopsy is not usually recommended because of the risk of hemorrhage, pneumothorax, and air embolism. Nevertheless, we believe that our clinical inspection policy for our patients was appropriate.

In conclusions, CHD-PAH can occur concomitantly with PVOD/PCH, ILD, and/or alveolar hemorrhage. In such a clinical situation, the use of pulmonary vasodilators may be harmful, so we should consider optimal treatments including avoiding combination therapy.

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Compliance with ethical standards

Conflict of interest Authors have nothing to disclose.

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