Contents lists available at ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Original article

# Use of vasodilators for the treatment of pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis: A systematic review

*Aiko Ogawa*[a,*], *Seiichiro Sakao*[b], *Nobuhiro Tanabe*[b,c], *Hiromi Matsubara*[a], *Koichiro Tatsumi*[b]

[a]*Department of Clinical Science, National Hospital Organization Okayama Medical Center, 1711-1 Tamasu, Kita-ku, Okayama 701-1192, Japan*
[b]*Department of Respirology, Graduate School of Medicine, Chiba University, Chiba, Japan*
[c]*Department of Advanced Medicine in Pulmonary Hypertension, Graduate School of Medicine, Chiba University, Chiba, Japan*

ARTICLE INFO

*Article history:*
Received 26 July 2018
Received in revised form
2 October 2018
Accepted 18 October 2018
Available online 23 November 2018

*Keywords:*
Hemodynamics
Pulmonary hypertension
Treatment
Vasodilator
Pulmonary edema

ABSTRACT

*Background:* There are several medications available to treat pulmonary arterial hypertension (PAH): PAH-targeted drugs. However, in patients with pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis (PVOD/PCH), rare diseases that cause pulmonary hypertension, the effectiveness and safety of vasodilators, including PAH-targeted drugs, are unclear.
*Methods:* We searched English-language publications listed in three electronic databases (PubMed, Cochrane Library, and the Japan Medical Abstracts Society). Reports with efficacy outcomes (survival, improvement in 6-minute walk distance, and pulmonary vascular resistance) and data on development of pulmonary edema after administration of vasodilators to patients with PVOD/PCH were selected (1966 to August 2015).
*Results:* We identified 20 reports that met our criteria. No randomized controlled or prospective controlled studies were reported. The survival time ranged from 71 minutes to 4 years or more after initiation of vasodilators. Most of the reported cases showed an improvement in the 6-minute walk distance and pulmonary vascular resistance. Pulmonary edema was reported in 15 articles, some cases of which were lethal.
*Conclusions:* The present study demonstrates the potential efficacy and difficulties in the use of vasodilators in patients with PVOD/PCH; however, drawing a firm conclusion was difficult because of the lack of randomized controlled trials. Further research is needed to ascertain if vasodilator use is beneficial and safe in patients with PVOD/PCH.



Abbreviations: PVOD/PCH, pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis; PAH, pulmonary arterial hypertension; ERAs, endothelin receptor antagonists; 6MWD, 6-minute walk distance; PVR, pulmonary vascular resistance; GRADE, Grading of Recommendations Assessment, Development and Evaluation

*Corresponding author. Fax: +81-86-294-9255.
E-mail addresses: aiko-oky@umin.ac.jp (A. Ogawa), sakaos@faculty.chiba-u.jp (S. Sakao), ntanabe@faculty.chiba-u.jp (N. Tanabe), tatsumi@faculty.chiba-u.jp (K. Tatsumi).

https://doi.org/10.1016/j.resinv.2018.10.004
2212-5345/

## 1. Introduction

Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis (PVOD/PCH) are rare forms of pulmonary hypertension that are characterized by increased pulmonary vascular resistance leading to right heart failure and death [1,2]. Currently, there are three main medication classes used for the treatment of pulmonary arterial hypertension (PAH): prostacyclins and a prostacyclin-receptor agonist; endothelin receptor antagonists (ERAs); and phosphodiesterase type 5 inhibitors/soluble guanylate cyclase stimulators. These PAH-targeted drugs have been shown to improve dyspnea, exercise capacity, and pulmonary hemodynamics in patients with PAH, and the prognosis for patients with PAH has improved over the last 2 decades following the development of these drugs [3–6]. However, in patients with PVOD/PCH, PAH-targeted drugs are known to cause pulmonary edema, which can be lethal [2,7–10]. Conversely, some case reports have suggested the possible effectiveness of these drugs when used for patients with PVOD/PCH [11–14]. It is unclear whether PAH-targeted drugs improve exercise capacity, hemodynamics, or survival of patients with PVOD/PCH. The aim of this systematic review is to evaluate the efficacy and safety of vasodilators including PAH-targeted drugs for PVOD/PCH.

## 2. Materials and methods

### 2.1. Literature search

We used PubMed/MEDLINE, the Cochrane Database of Systematic Reviews, and the Japan Medical Abstracts Society Database from 1966 through August 2015 to search for the key words "pulmonary veno-occlusive disease" or "pulmonary capillary hemangiomatosis," and "vasodilator." We manually searched the relevant studies according to our selection criteria.

### 2.2. Selection criteria

We selected studies regarding the efficacy and safety of vasodilators in PVOD/PCH. Only peer-reviewed publications of human studies with an abstract in English were selected, and reviews and editorials were excluded. We included reports meeting the following criteria: (1) patients were primarily adults with clinically diagnosed or pathologically diagnosed PVOD/PCH at the time of autopsy or lung biopsy, or when a surgically removed lung specimen was available; (2) interventions comprised vasodilators, including calcium channel blockers and all FDA-approved PAH-targeted drugs, including prostanoids (beraprost sodium, treprostinil, iloprost, and epoprostenol), the selective prostacyclin-receptor agonist (selexipag), ERAs (bosentan, ambrisentan, and macitentan), phosphodiesterase type 5 inhibitors (sildenafil and tadalafil), and the soluble guanylate cyclase stimulator (riociguat); and (3) outcomes included any efficacy outcomes (survival, improvement in 6-minute walk distance [6MWD], and improvement in pulmonary vascular resistance [PVR]) and development of pulmonary edema.

### 2.3. Systematic review team

Two reviewers (S.S. and A.O.) independently searched the databases using the same key words and evaluated each study using a standard form. Any disagreements were resolved by discussion. Selected articles then underwent full-text screening by two independent reviewers to determine eligibility. Fig. 1 shows the study selection flow chart. All data were extracted from the text, tables, and figures.

### 2.4. Data extraction

Using pre-specified inclusion and exclusion criteria, the titles and abstracts were examined for potential relevance by two independent reviewers. We extracted the data for demographics, interventions, outcomes (mortality/survival, 6MWD, or PVR), and occurrence of pulmonary edema.

### 2.5. Quality assessment

The study quality was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE), and the number of patients (studies), study design, limitations, inconsistency, indirectness, imprecision, and publication bias risk in observational studies were evaluated by GRADE [15,16].

## 3. Results

### 3.1. Search results

Database searches yielded 47 studies regarding treatment of patients with PVOD/PCH with vasodilators (Fig. 1). An additional six records were identified through other sources by conducting a manual search of the Guidelines for Treatment of Pulmonary Hypertension (Japanese Circulation Society 2012) [17] and the 2015 European Society of Cardiology/European Respiratory Society Guidelines for the diagnosis and treatment of pulmonary hypertension [18]. From reviewing these two guidelines, two records reporting treatment with continuous intravenous prostacyclin in patients with PVOD/PCH were found [8,19]. Two other original articles were chosen from the above-mentioned records from database searches [20,21].

There were no duplicates and a total of 53 records were screened. Thirty records were excluded because they were review articles, did not include a major outcome, or had different aims of the study. As a result, 23 full-text articles were assessed for eligibility and three full-text articles were excluded due to only reporting acute vasodilator testing results. Finally, 20 studies with 64 patients who received vasodilator therapy were included in qualitative synthesis (Fig. 1, Table 1) [7,8,10–14,19,21–32], and there were no studies were included in quantitative synthesis (meta-analysis) because all articles were case reports or case series.

### 3.2. Quality assessment

In the quality assessment of selected articles, serious limitations related to non-randomized controlled trials were

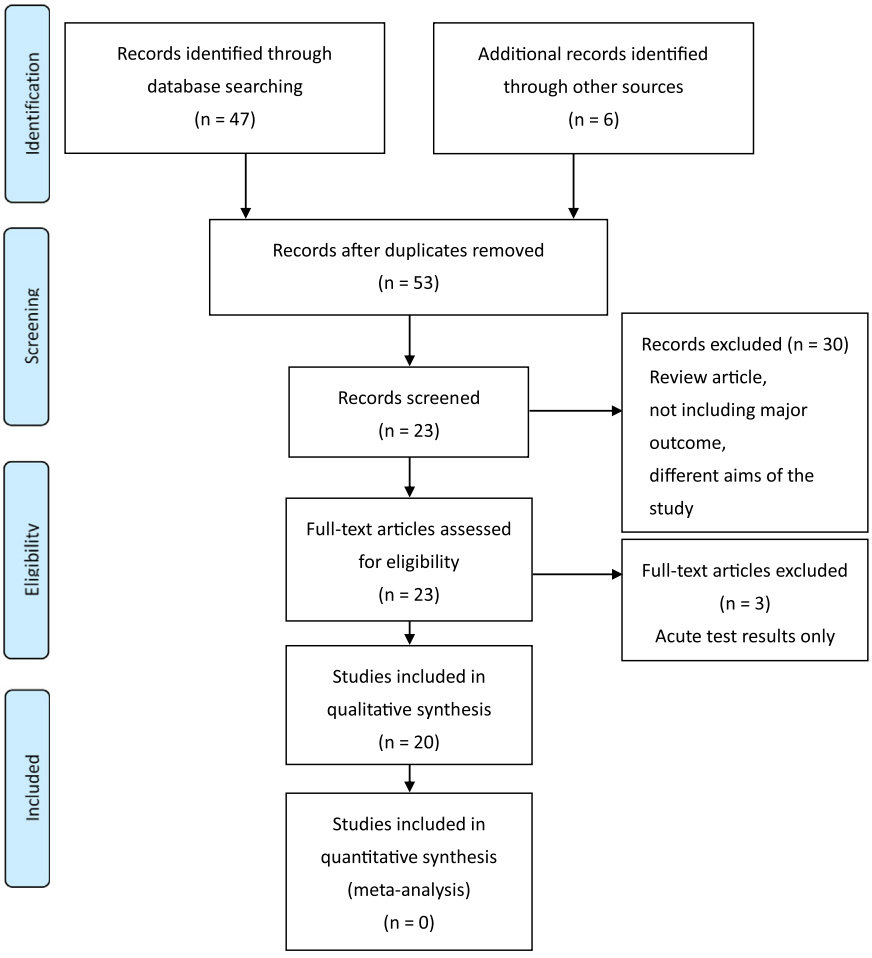


**Fig. 1 – Study flowchart.**

observed including serious inconsistency, indirectness, and imprecision (Table 2).

### 3.3. *Mortality/Survival*

There were no prospective studies or randomized controlled trials and the survival time period was only described in 18 reports (Table 1) [7,8,10–12,14,19,21–29,31,32]. Palevsky et al. reported three patients with PVOD who underwent acute testing using vasodilators including a calcium channel blocker and α blockers [23]. Two of these patients received chronic vasodilator therapy with prazosin. Of these patients, one lived for at least 72 months and the other deteriorated after several months of relative well-being, and then died due to progressive heart failure 23 months after the vasodilator therapy. The patient who did not receive chronic vasodilator therapy died due to heart failure after 6 months. The rest of the 17 reports included chronic treatment of patients with PVOD/PCH with calcium channel blockers or PAH-targeted drugs. The survival time ranged from 71 minutes after initiation of epoprostenol to 4 years or more (Table 1). In some cases, survival or mortality were reported [10,14,19,29], but the time frames vary, from diagnosis to death [14], from diagnosis to death/lung transplantation [10,19], or from initiation of epoprostenol therapy until death/lung transplantation [29]. In two cases, patients were reported to live for at least 4 years with vasodilator therapy [22,31]. In two other cases, patients successfully underwent lung transplantations while receiving vasodilator therapy [11,30]. In a relatively larger case series, the one-year survival was reported to be 83% and the two-year survival was 50% with intravenous epoprostenol therapy [19].

### 3.4. *Improvement in the 6MWD*

Improvement in the 6MWD was reported in seven reports (Table 1) [11,13,19,21,25,29,31]. Because all of studies were single case reports or case series, the 6MWD was evaluated at various times after the initiation of several different drugs with varying doses. Five case reports demonstrated an increase in the 6MWD for a single case [11,13,21,25,31]. In two case series, the 6MWD before and after initiation of vasodilators was statistically evaluated. One report of 12 cases of PVOD patients who were treated with epoprostenol for 3–4 months showed an increase in the 6MWD from 281 ± 162 to 322 ± 160 m, but this did not reach statistical significance ($p = 0.11$) [19]. Another report of eight patients with PVOD or PCH who received epoprostenol (for 387.3 ± 116.3 days) alone or with other PAH-targeted drugs demonstrated a statistically significant increase in the 6MWD (from 97.5 ± 39.2 to 329.4 ± 34.6 m, [$p < 0.001$]) [29].

**Table 1 – Twenty selected studies for final analysis.**

| | First author, year [Reference] | No. of patients treated | Diagnosis | Intervention | Survival | Improvement of 6MWD | Improvement of PVR | Pulmonary edema |
|---|---|---|---|---|---|---|---|---|
| 1 | Salzman 1989 [22] | 1 | PVOD (biopsy) | nifedipine | 4Y (alive) | NR | 11.7 to 7.8 WU (2Y) | (−) |
| 2 | Palevsky 1990 [23] | 2 | PVOD (autopsy) | prazosin | 72 M (alive), 23 M | NR | NR | (−) (2/2) |
| 3 | Davis 1995 [24] | 1 | PVOD (biopsy) | epo | 1 M | NR | 18.3 to 8.0 WU | (+) |
| 4 | Humbert 1998 [8] | 2 | PCH (autopsy) | epo | a few days | NR | NR | (+) (2/2) |
| 5 | Palmer 1998 [7] | 1 | PVOD (autopsy) | epo | 71 min | NR | NR | (+) |
| 6 | Hoeper 1999 [25] | 1 | PVOD (biopsy) | ilo | 9 weeks | 200 to 320 m | 8.9 to 7.0 WU | (−) |
| 7 | Holcomb 2000 [14] | 10 | PVOD (biopsy or autopsy [9], clinical [2]) | CCB (8), epo (3) | 1 Y mortality: 72% | NR | NR | (+) (CCB [6/8], epo [0/3]) |
| 8 | Gugnani 2000 [26] | 1 | PCH (autopsy) | epo | 1 M | NR | 23.4% reduction | (+) |
| 9 | Okumura 2002 [21] | 1 | PVOD (autopsy) | epo | 2Y | 90 to 450 m (4 M) | NR | (+) |
| 10 | Barreto 2005 [13] | 1 | PVOD (biopsy) | sil | NR | 112 to 408 m (1Y) | NR | (−) |
| 11 | Kuroda 2006 [27] | 1 | PVOD (biopsy) | epo + sil | 18 M | NR | NR | (+) |
| 12 | Creagh-Brown 2008 [12] | 1 | PVOD (biopsy) | epo + sil | 9 M | NR | NR | (+) |
| 13 | Overbeek 2008 [28] | 1 | PVOD (clinical) | epo | 28 M (alive) | NR | NR | (+) |
| 14 | Montani 2008 [10] | 16 | PVOD (autopsy [14], biopsy [3], explanted lung [7] for all 24 patients) | epo (11), ilo (3), bos (6), CCB (2) | 11.8 ± 16.4 M* (diagnosis-death/lung transplantation) | NR | NR | (+) (7/16) |
| 15 | Montani 2009 Nov [11] | 1 | PVOD (explanted lung) | bos + sil | 8 M (lung transplantation) | 363 to 338 m (bos, 6 M) | PVRi: 9.6 to 17.0 ($WU/m^2$) (bos, 6 M) | (+) |
| 16 | Montani 2009 Dec [19] | 12 | PVOD (explanted lung [10], clinical [2]) | epo (4), bos + epo (8) | 1Y survival: 83%, 2Y survival: 50% | 281 ± 162 to 322 ± 160 m ($p=0.11$) | PVRi: 28.4 ± 8.4 to 17 ± 5.2 ($WU/m^2$) ($p<0.01$) | (+) (1/12) |
| 17 | Ogawa 2012 [29] | 8 | PVOD [6], PCH [2] (explanted lung or autopsy) | epo (5), epo + sil (1), epo + bos (1), epo + sil + bos (1) | 387.3 ± 116.3 days (epo-death/lung transplantation) | 97.5 ± 39.2 to 329.4 ± 34.6 m ($p<0.001$) | 18.1 ± 2.4 to 13.7 ± 2.5 WU (NS) | (+) (8/8) |
| 18 | Masters 2013 [30] | 1 | PVOD (explanted lung) | sil, epo | NR | NR | NR | (+) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 19 | Sourla 2013 [31] | 1 | PVOD (biopsy) | bos, sil, epo, ilo | 4Y (alive) | 225 to 560 m (bos + sil, 1.5Y) | NR | (+) | |
| 20 | Adachi 2014 [32] | 1 | PCH (autopsy) | bos + sil + epo | 2.6Y | NR | NR | (+) | |

M: months
Y: years
NA: not applicable
NR: not reported
NS: not significant
PVOD: pulmonary veno-occlusive disease
PCH: pulmonary capillary hemangiomatosis
CCB: calcium-channel blocker
epo: epoprostenol
ilo: iloprost
sil: sildenafil
bos: bosentan
6MWD: 6-minute walk distance
PVR: pulmonary vascular resistance
PVRi: pulmonary vascular resistance index
WU: wood units
*n = 22, including patients who did not receive vasodilator therapy

### 3.5. *Improvement in PVR*

PVR was only reported in seven reports (Table 1) [11,19,22,24–26,29]. Five case reports demonstrated an improvement in PVR in a single case [11,22,24–26]. One report of 12 cases of patients with PVOD who were treated with epoprostenol for 3–4 months showed a statistically significant improvement in the PVR index from 28.4 ± 8.4 to 17 ± 5.2 WU/m$^{-2}$ ($p < 0.01$) [19]. Another report of eight patients with PVOD or PCH who received epoprostenol alone or with other PAH-targeted drugs (for 387.3 ± 116.3 days) showed a tendency toward an improvement in PVR (18.1±2.4 to 13.7±2.5 WU [not significant]) [29].

### 3.6. *Pulmonary edema*

Pulmonary edema is the most severe adverse event associated with vasodilator therapy in patients with PVOD/PCH and can be fatal. Pulmonary edema after treatment with vasodilators was reported in 15 articles (Table 1) [7,8,10–12,14,19,21,26–32]. Again, because all the included articles are case reports, the type of drugs and doses varied. The treatment period from the initiation of treatment to the onset of pulmonary edema also varied. In the most severe case, the patient died 71 minutes after initiation of epoprostenol treatment, because of severe pulmonary edema [7]. In contrast, in some cases, vasodilator therapy worked as a bridge to lung transplantation [11,30] or patients lived for years [28,32]. We have summarized the data regarding each treatment regimen and occurrence of pulmonary edema reported in 20 selected articles in Table 3. The number of cases reported was small and some reports did not include details specifying the treatment regimen at the time of pulmonary edema. Hence, ascertaining which drug was more likely to cause pulmonary edema, or whether combination therapy was more likely to induce pulmonary edema compared to monotherapy, was not possible. It seems that epoprostenol and combination therapy tended to induce pulmonary edema more frequently, although publication bias was not negligible.

## 4. Discussion

This systematic review focused on the efficacy and safety of vasodilators in patients with PVOD/PCH. Although it is well known that vasodilators, including calcium channel blockers and PAH-targeted drugs, are effective in improving exercise capacity, pulmonary hemodynamics, and survival in patients with PAH, the prognosis of patients with PVOD/PCH has not improved over the last 2 decades following the emergence of these medications. In the clinical guidelines, there are no established medical therapies for PVOD/PCH [18]. In PVOD/PCH, PAH-targeted drugs are known to cause pulmonary edema, which sometimes can be lethal [2,7–10], although there are some reports indicating the effectiveness of these drugs in the treatment of PVOD/PCH. In this systematic review, we evaluated the effectiveness and safety of vasodilators, including PAH-targeted drugs, for the treatment of PVOD/PCH.

This systematic review includes 20 studies. Fourteen studies were reports of a single case and no randomized

**Table 2 – Quality assessment.**

| Number of studies | Design | Limitations | Inconsistency | Indirectness | Imprecision | Publication bias |
|---|---|---|---|---|---|---|
| Outcome 1: Improvement of mortality/survival | | | | | | |
| 18 | Non RCT | Serious | Serious | Serious | Serious | Unlikely |
| Outcome 2: Improvement in 6MWD | | | | | | |
| 7 | Non RCT | Serious | Serious | Serious | Serious | Unlikely |
| Outcome 3: Improvement in PVR | | | | | | |
| 7 | Non RCT | Serious | Serious | Serious | Serious | Unlikely |
| Outcome 4: Pulmonary edema | | | | | | |
| 15 | Non RCT | Serious | Serious | Serious | Serious | Unlikely |

RCT: randomized controlled trial; 6MWD: 6-minute walk distance; PVR: pulmonary vascular resistance.

**Table 3 – Treatment regimen and occurrence of pulmonary edema in 20 selected studies.**

| Treatment | Pulmonary edema (+) (n) | Pulmonary edema (−) (n) | [Reference] |
|---|---|---|---|
| Monotherapy | | | |
| epoprostenol | 13 | 4 | [7,8,14,18,21,24,26–30] |
| iloprost | 0 | 1 | [25] |
| sildenafil | 1 | 2 | [12,13,30] |
| bosentan | 0 | 2 | [11,31] |
| Combination therapy | | | |
| sildenafil + epoprostenol | 2 | 1 | [12,27,29] |
| sildenafil + bosentan | 2 | 0 | [11,31] |
| bosentan + epoprostenol | 1 | 0 | [29] |
| sildenafil + bosentan + epoprostenol | 2 | 0 | [29,32] |
| Details of treatment regimen unknown | | | |
| details of treatment regimen not reported (epoprostenol, iloprost, bosentan, calcium channel blocker) | 7 | 9 | [10] |
| epoprostenol or bosentan+epoprostenol | 1 | 11 | [19] |
| sildenafil + bosentan + epoprostenol or epoprostenol only | 1 | 0 | [31] |
| sildenafil + bosentan + iloprost or iloprost only | 0 | 1 | [31] |

controlled trials were found. There were four relatively large case series including 8–16 patients treated with vasodilators [10,14,19,29]. Most of the reported cases showed improvements in the 6MWD and PVR. PVOD/PCH is a rare disease and the overall survival rate has not been evaluated on a large scale, even before vasodilators became available. The survival time of patients with PVOD/PCH is reported to be approximately two years after diagnosis [14]. In this systematic review, two cases were reported to live for at least 4 years with vasodilator therapy [22,31]. In a relatively larger case series, the one-year survival was reported to be 83% and the two-year survival was 50% with intravenous epoprostenol therapy [19]. This survival rate appears to be better compared with the previously reported survival of patients with PVOD/PCH. Nevertheless, a larger scale prospective trial is needed to confirm the beneficial effects of PAH-targeted drugs in this population.

Despite the possible efficacy of vasodilators, there is great concern regarding the use of vasodilators in patients with PVOD/PCH, because of the risk of pulmonary edema [7,8]. Detailed hemodynamic measurements have shown that microvascular pressures initially increased during an infusion of no more than 6 ng/kg/min of epoprostenol, but at higher doses, cardiac output increased and the calculated pulmonary vascular resistance decreased [24]. If the dose of epoprostenol is slowly increased in a step-wise manner and diuretics or inotropes are used as necessary, the transcapillary hydrostatic pressure is decreased and fatal pulmonary edema can be avoided [29]. Therefore, therapy for PVOD/PCH should be undertaken only at centers with extensive experience in the management of pulmonary hypertension [18]. The only curative therapy for PVOD/PCH is lung transplantation. Eligible patients with PVOD/PCH should be referred to a transplant center for evaluation as soon as the diagnosis is established. Furthermore, there are some other possible drugs to treat PVOD/PCH, including imatinib and sorafenib [28,33,34]. Further studies are needed to determine whether these drugs are beneficial for patients with PVOD/PCH.

Our study had several limitations. Most of the bias has been described in the Results section. Although we attempted to carry out a systematic review, no randomized controlled trials focused on this issue, and baseline confounding

and selection bias were serious problems. Most of the selected articles were single case reports, and the quality of the analysis was inadequate because there was no control. Moreover, there may have been serious publication bias.

## 5. Conclusion

We aimed to carry out a systematic review to evaluate the efficacy and safety of vasodilators, including PAH-targeting drugs, for PVOD/PCH; however, drawing a firm conclusion was difficult because of the lack of randomized controlled trials involving large numbers of patients. Based on selected case reports, vasodilator use may be effective in improving the 6MWD, PVR, and survival in some cases, but is associated with the risk of causing pulmonary edema in many cases. The present study demonstrates the possible efficacy and difficulties in vasodilator use in patients with PVOD/PCH. Further work is needed to ascertain if vasodilator use is beneficial and safe in patients with PVOD/PCH.

## Acknowledgments

This study was supported in part by grants from the Intractable Respiratory Diseases and Pulmonary Hypertension Research Group, the Ministry of Health, Labour and Welfare, Japan (H29-027), and the Pulmonary Hypertension Research Group from the Japan Agency for Medical Research and Development, AMED (17ek0019127h0003).

## Conflict of interest

Dr. Ogawa received research funding from Nippon Shinyaku Co., Ltd. Dr. Sakao received honoraria from Actelion Pharmaceuticals Japan Ltd., Bayer Yakuhin Ltd., and Nippon Shinyaku Co., Ltd. Dr. Tanabe received honoraria from Actelion Pharmaceuticals Japan Ltd., Bayer Yakuhin Ltd., Bristol Myers Squibb K.K., Daiichi Sankyo Co., Ltd., Nippon Shinyaku Co., Ltd., research funding from Nippon Shinyaku Co., Ltd., and belonged to an endowed department from Actelion Pharmaceuticals Japan, Ltd. Dr. Matsubara received honoraria from Actelion Pharmaceuticals Japan Ltd., AOP Orphan Pharmaceuticals AG, Bayer Yakuhin Ltd., Nippon Shinyaku Co., Ltd., and Pfizer Japan Inc. and research funding from Nippon Shinyaku Co., Ltd. Dr. Tatsumi reports no conflicts of interest.

## REFERENCES

[1] Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62:D34–41.
[2] Montani D, Girerd B, Jais X, Levy M, Amar D, Savale L, et al. Clinical phenotypes and outcomes of heritable and sporadic pulmonary veno-occlusive disease: a population-based study. Lancet Respir Med 2017;5:125–34.
[3] Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 2010;122:156–63.
[4] Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest 2012;142:448–56.
[5] Ogawa A, Satoh T, Tamura Y, Fukuda K, Matsubara H. Survival of Japanese patients with idiopathic/heritable pulmonary arterial hypertension. Am J Cardiol 2017;119:1479–84.
[6] Tamura Y, Kumamaru H, Satoh T, Miyata H, Ogawa A, Tanabe N, et al. Effectiveness and outcome of pulmonary arterial hypertension-specific therapy in Japanese patients with pulmonary arterial hypertension. Circ J 2017;82:275–82.
[7] Palmer SM, Robinson LJ, Wang A, Gossage JR, Bashore T, Tapson VF. Massive pulmonary edema and death after prostacyclin infusion in a patient with pulmonary veno-occlusive disease. Chest 1998;113:237–40.
[8] Humbert M, Maitre S, Capron F, Rain B, Musset D, Simonneau G. Pulmonary edema complicating continuous intravenous prostacyclin in pulmonary capillary hemangiomatosis. Am J Resp Crit Care 1998;157:1681–5.
[9] Ogawa A, Takahashi Y, Matsubara H. Clinical prediction score for identifying patients with pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis. J Cardiol 2018;72:255–60.
[10] Montani D, Achouh L, Dorfmuller P, Le Pavec J, Sztrymf B, Tcherakian C, et al. Pulmonary veno-occlusive disease: clinical, functional, radiologic, and hemodynamic characteristics and outcome of 24 cases confirmed by histology. Medicine 2008;87:220–33.
[11] Montani D, Jais X, Dorfmuller P, Simonneau G, Sitbon O, Humbert M. Goal-oriented therapy in pulmonary veno-occlusive disease: a word of caution. Eur Respir J 2009;34:1204–6.
[12] Creagh-Brown BC, Nicholson AG, Showkathali R, Gibbs JS, Howard LS. Pulmonary veno-occlusive disease presenting with recurrent pulmonary oedema and the use of nitric oxide to predict response to sildenafil. Thorax 2008;63:933–4.
[13] Barreto AC, Franchi SM, Castro CR, Lopes AA. One-year follow-up of the effects of sildenafil on pulmonary arterial hypertension and veno-occlusive disease. Braz J Med Biol Res 2005;38:185–95.
[14] Holcomb Jr BW, Loyd JE, Ely EW, Johnson J, Robbins IM. Pulmonary veno-occlusive disease: a case series and new observations. Chest 2000;118:1671–9.
[15] Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. ⟨https://gdt.gradepro.org/app/handbook/handbook.html⟩ 2013. [Accessed June 2018].
[16] Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence–study limitations (risk of bias). J Clin Epidemiol 2011;64:407–15.
[17] Guidelines for Treatment of Pulmonary Hypertension (JCS2012). ⟨http://www.j-circ.or.jp/guideline/pdf/JCS2012_nakanishi_h.pdf⟩. 2013. Japanese. [Accessed June 2018].
[18] Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: association for

European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2015;2016(37):67–119.
[19] Montani D, Jais X, Price LC, Achouh L, Degano B, Mercier O, et al. Cautious epoprostenol therapy is a safe bridge to lung transplantation in pulmonary veno-occlusive disease. Eur Respir J 2009;34:1348–56.
[20] Pietra GG, Edwards WD, Kay JM, Rich S, Kernis J, Schloo B, et al. Histopathology of primary pulmonary hypertension. A qualitative and quantitative study of pulmonary blood vessels from 58 patients in the National Heart, Lung, and Blood Institute, Primary Pulmonary Hypertension Registry. Circulation 1989;80:1198–206.
[21] Okumura H, Nagaya N, Kyotani S, Sakamaki F, Nakanishi N, Fukuhara S, et al. Effects of continuous IV prostacyclin in a patient with pulmonary veno-occlusive disease. Chest 2002;122:1096–8.
[22] Salzman GA, Rosa UW. Prolonged survival in pulmonary veno-occlusive disease treated with nifedipine. Chest 1989;95:1154–6.
[23] Palevsky HI, Pietra GG, Fishman AP. Pulmonary veno-occlusive disease and its response to vasodilator agents. Am Rev Respir Dis 1990;142:426–9.
[24] Davis LL, deBoisblanc BP, Glynn CE, Ramirez C, Summer WR. Effect of prostacyclin on microvascular pressures in a patient with pulmonary veno-occlusive disease. Chest 1995;108:1754–6.
[25] Hoeper MM, Eschenbruch C, Zink-Wohlfart C, Schulz A, Markworth S, Pohl K, et al. Effects of inhaled nitric oxide and aerosolized iloprost in pulmonary veno-occlusive disease. Respir Med 1999;93:62–4.
[26] Gugnani MK, Pierson C, Vanderheide R, Girgis RE. Pulmonary edema complicating prostacyclin therapy in pulmonary hypertension associated with scleroderma: a case of pulmonary capillary hemangiomatosis. Arthritis Rheum 2000;43:699–703.
[27] Kuroda T, Hirota H, Masaki M, Sugiyama S, Oshima Y, Terai K, et al. Sildenafil as adjunct therapy to high-dose epoprostenol in a patient with pulmonary veno-occlusive disease. Heart Lung Circ 2006;15:139–42.
[28] Overbeek MJ, van Nieuw Amerongen GP, Boonstra A, Smit EF, Vonk-Noordegraaf A. Possible role of imatinib in clinical pulmonary veno-occlusive disease. Eur Respir J 2008;32:232–5.
[29] Ogawa A, Miyaji K, Yamadori I, Shinno Y, Miura A, Kusano KF, et al. Safety and efficacy of epoprostenol therapy in pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis. Circ J 2012;76:1729–36.
[30] Masters K, Bennett S. Pulmonary veno-occlusive disease: an uncommon cause of pulmonary hypertension. BMJ Case Rep 2013;2013.
[31] Sourla E, Paspala A, Boutou A, Kontou P, Stanopoulos I, Pitsiou G. A case of pulmonary veno-occlusive disease: diagnostic dilemmas and therapeutic challenges. Ther Adv Respir Dis 2013;7:119–23.
[32] Adachi S, Hirashiki A, Kondo T, Nakaguro M, Ogawa A, Miyaji K, et al. Imatinib is partially effective for the treatment of pulmonary capillary hemangiomatosis. Intern Med 2014;53:603–7.
[33] Ogawa A, Miyaji K, Matsubara H. Efficacy and safety of long-term imatinib therapy for patients with pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis. Respir Med 2017;131:215–9.
[34] Kataoka M, Yanagisawa R, Fukuda K, Yoshino H, Satoh T. Sorafenib is effective in the treatment of pulmonary veno-occlusive disease. Cardiology 2012;123:172–4.