ESC European Society of Cardiology

European Heart Journal - Case Reports (2022) **6**, 1–4
https://doi.org/10.1093/ehjcr/ytac351

CASE REPORT
Other

Pulmonary arterial hypertension sensitive to calcium channel blocker, but not advanced pulmonary hypertension treatment: a case report

Kyoko Hirakawa [1,2], Tatsuo Aoki[1], Akihiro Tsuji[1], and Takeshi Ogo [1,3]*

[1]Division of Pulmonary Circulation, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Centre, 6-1, Kishibe-Shimmachi, Suita, Osaka 564-8565, Japan; [2]Department of Cardiovascular Medicine, Kumamoto University, Kumamoto 860-8556, Japan; and [3]Department of Advanced Medicine in Pulmonary Hypertension, National Cerebral and Cardiovascular Centre, Osaka 564-8565, Japan

Received 19 December 2021; first decision 21 January 2022; accepted 17 August 2022; online publish-ahead-of-print 22 August 2022

Background Calcium channel blockers (CCB), the first accepted treatment, is effective only in a small number of idiopathic pulmonary arterial hypertension (I-PAH) patients with vasoreactivity [these patients are identified by a positive acute pulmonary vasoreactive test (AVT) response]. While the majority of I-PAH patients is non-vasoreactive and CCB non-responders, modern advanced pulmonary hypertension (PH)-specific therapies, which act on one of the three different mechanistic pathways—endothelin, nitric oxide (NO), and prostacyclin pathways, are effective. Treatment response to advanced PH-specific vasodilators in PAH patients with vasoreactivity is unknown.

Case summary A 30-year-old woman with I-PAH was referred to our centre with worsening symptoms and deteriorating PH. She was being administered oral triple combination of advanced PH-specific treatment including a phosphodiesterase-5 inhibitor, an endothelin receptor antagonist, and a long-acting prostacyclin analogue. The patient showed positive AVT with NO inhalation while on these advanced PH-specific drugs. We added high-dose CCB, which dramatically normalized her pulmonary blood pressure without further symptoms, and she has remained stable for 5 years.

Discussion Our case describes a PAH patient with vasoreactivity, who was resistant to three different types of advanced PH-specific vasodilators but was exclusively sensitive to CCB treatment. Some CCB responders may have a specific CCB-sensitive PAH phenotype refractory to other pulmonary vasodilators. This case highlights the role of identifying CCB responders in this era of use of modern, advanced PH-specific vasodilators. The investigation of the mechanisms underlying CCB sensitivity in PAH is necessary.

Keywords Calcium channel blocker responder • Idiopathic pulmonary arterial hypertension • Acute pulmonary vasoreactivity test • Case reports

ESC Curriculum 6.7 Right heart dysfunction • 9.6 Pulmonary hypertension

* Corresponding author. Tel: +81 6 6170 1070, Fax: +81 6 6833 5126, Email: tak@ncvc.go.jp
Handling Editor: Davide Stolfo
Peer-reviewers: Aiste Monika Jakstaite; Claudio Picariello
Compliance Editor: Reshma Amin
Supplementary Material Editor: Katharine Kott

Leaning points

- Some calcium channel blocker (CCB) responder may theoretically have a specific CCB-sensitive phenotype refractory to other pulmonary vasodilators.
- This report suggests that identifying CCB responders by acute vasodilatation test in this era of modern pulmonary hypertension-specific therapy is important.

Introduction

Idiopathic pulmonary arterial hypertension (I-PAH) is a chronic incurable condition characterized by pulmonary hypertension (PH) without clear causes, leading to right heart failure and death. A small proportion of PAH patients with vasoreactivity, who are identified by positive acute pulmonary vasoreactivity test (AVT), exhibit excellent clinical response to long-term high-dose calcium channel blocker (CCB) treatment[1–3] and are called CCB responders. Meanwhile, majority of patients with I-PAH, who are non-vasoreactive at AVT, do not benefit from CCB but benefit from modern advanced PH-specific pulmonary vasodilators, which act each on three different pathways—endothelin, nitric oxide (NO), and prostacyclin pathways. Modern advanced PH-specific therapies as well as CCB may be beneficial in treating PAH patients with vasoreactivity. However, the outcome of treatment of PAH with vasoreactivity with advanced PH-specific vasodilators is unknown. We report a case of a IPAH vasoreactive patient who was resistant to three different types of advanced PH-specific vasodilators but was exclusively sensitive to CCB with favourable long-term outcome.

Timeline

Before admission: exertional dyspnoea

September 2011
- Patients were hospitalized due to syncope and dyspnoea
- Echocardiography showed suspicion of PH, leading to the right heart catheterization (RHC)
- Right heart catheterization shows severe PH and low cardiac output [mean pulmonary arterial pressure (PAP) was 40 mmHg; pulmonary vascular resistance (PVR) was 9.3 wood unit; and cardiac index (CI) was 1.7 L/min/m^2]. Pulmonary hypertension due to left heart disease and lung disease were ruled out by echocardiogram, computed tomography, and spirometry. Chronic thromboembolic PH was ruled out by ventilation/perfusion scan and enhanced computed tomography. Finally, I-PAH was diagnosed by ruling out other pulmonary arterial hypertension by clinical history, laboratory examination, and drug history according to current PH guideline
- The patient was maintained on upfront triple oral combination therapy (beraprost 300 μg/day, sildenafil 60 mg/day, and bosentan 250 mg/day)

2012
- Haemodynamics were improved (mean PAP: 23 mmHg, PVR: 2.4 wood unit, CI: 2.99 L/min/m^2)

Continued

Continued

Before admission: exertional dyspnoea

2013
- Right heart catheterization showed the deterioration of haemodynamics (mean PAP: 41 mmHg, PVR 7.3 wood unit, CI: 2.41 L/min/m^2) after 2 years of treatment

March 2014
- Right heart catheterization demonstrated slight worsening haemodynamics and her symptom was progressive
- Sildenafil (60 mg/day) was switched to tadalafil (40 mg/day)

September 2015
- Right heart catheterization demonstrated slight worsening haemodynamics and her symptom was progressive
- Bosentan (250 mg/day) was switched to macitentan (10 mg/day)

July 2016
- The patient was referred to our centre
- Right heart catheterization demonstrated worsening haemodynamics, and acute pulmonary vasoreactivity test was performed
- We prescribed calcium blocker (nifedipine 160 mg/day) addition to her existing targeted therapy, and her dyspnoea resolved immediately

June 2017
- The patient's symptom remained World Health Organization functional class (WHO-FC) I and the RHC demonstrated mean PAP, PVR, and CI values of 23 mmHg, 2.4 wood unit, and 3.03 L/min/m^2

June 2019
- Pulmonary hypertension remained almost normalized without symptoms

June 2021
- Pulmonary hypertension remained almost normalized without symptoms

Case report

A 31-year-old woman was hospitalized due to syncope and dyspnoea (WHO-FC III) 5 years prior to presentation. The patient had no medical history or drug therapy. Pulmonary hypertension with right heart failure was suspected by echocardiography and confirmed by RHC. Pulmonary hypertension associated with left heart disease (Group 2) and lung disease (Group 3) was ruled out by echocardiography, computed tomography, and spirometry. Chronic thromboembolic PH (Group 4) was ruled out by ventilation/perfusion scan. Finally, I-PAH was diagnosed after excluding other PAH by clinical history, laboratory examination, and drug history according to current PH guideline. At diagnosis, her serum brain natriuretic peptide level was 9.5 pg/mL

(normal range <5.8 pg/mL); 6 min walking distance was 175 m; mean PAP was 40 mmHg; PVR was 9.3 wood unit; and CI was 1.7 L/min/m^2 (*Table 1*). An AVT was not performed at the time. A triple upfront oral therapy with beraprost, bosentan, and sildenafil was started. Her symptoms improved from WHO-FC III to WHO-FC II on targeted therapy. After 1 year, haemodynamics were improved (mPAP: 23 mmHg, PVR: 2.4 wood unit, CI: 2.99 L/min/m^2). However, the RHC showed the deterioration of haemodynamics (mean PAP: 41 mmHg, PVR 7.3 wood unit, CI: 2.41 L/min/m^2) after 2 years of treatment. She developed progressive dyspnoea after 3 years of PH-specific treatment and sildenafil (60 mg/day) was switched to tadalafil (40 mg/day). After 4 years of treatment, bosentan (250 mg/day) was switched to macitentan (10 mg/day). The patient's clinical parameters and haemodynamic status during the 5-year follow-up are shown in *Figure 1*.

Table 1 Haemodynamic changes during the acute vasoreactivity test

	Baseline	Nitric oxide at 20 ppm
PAP [Systolic/diastolic (mean)] (mmHg)	84/32 (48)	34/11 (21)
PAWP (mmHg)	12	10
RAP (mmHg)	13/9 (7)	7/4 (3)
Blood pressure (mmHg)	114/68 (79)	99/59 (70)
SvO_2/SaO_2 (%)	78.6/97.9	75.1/97.0
CO/CI (L/min/m^2)	4.81/2.75	4.24/2.42
SVR (wood unit)	15.0	15.8
PVR (wood unit)	7.5	2.6

PA, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; RAP, right atrial pressure; SVO_2, mixed venous oxygen saturation; SaO_2, arterial oxygen saturation; CO, cardiac output; CI, cardiac index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

The patient was referred to our institution for the introduction of intravenous epoprostenol due to the failure of oral combination PH-specific treatment. Right heart catheterization confirmed a worsening risk haemodynamics pattern (*Table 1*) (mean PAP: 48 mmHg, PVR: 7.5 wood unit, CI: 2.75 L/min/m^2). An AVT was performed for the first time in the patient with 20 ppm of NO administered for 10 min, and the patient demonstrated dramatic haemodynamic improvement (mean PAP: 21 mmHg, PVR: 2.8 wood unit, CI: 2.4 L/min/m^2) (*Table 1*). The AVT was diagnosed as positive based on the current PAH treatment guidelines, which defined a positive AVT as a reduction in the mean PAP ≥10 mmHg to reach an absolute value ≤40 mmHg in the setting of increased or unchanged cardiac output.[4] We prescribed a high-dose CCB (nifedipine 160 mg/day) in addition to her existing PH-specific therapy instead of initiating intravenous epoprostenol, and her dyspnoea resolved to WHO-FC I. After 1-year of CCB treatment, the patient's symptom remained WHO-FC I and the RHC demonstrated mean PAP, PVR, and CI values of 23 mmHg, 2.4 wood unit, and 3.03 L/min/m^2, respectively. After 3 and 5 years of CCB treatment, symptom was resolved, and PH remained almost normalized with macitentan, tadalafil, beraprost, and nifedipine (*Figure 1*).

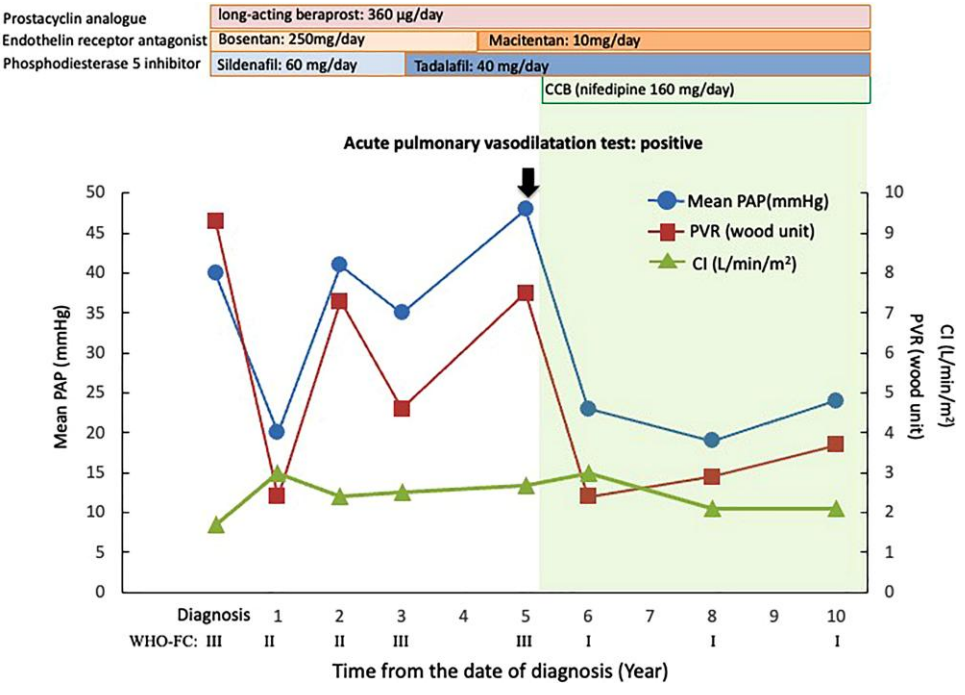


Figure 1 Clinical course and treatment in this patient. This patient was refractory to combination pulmonary hypertension-specific therapy during 5 years on targeted therapy. After positive results of an acute vasoreactivity test with nitric oxide inhalation, she was initiated on CCB therapy, which provided near-normalization of her haemodynamics with World Health Organization functional Class I. This patient remained stable for another 5 years.

Discussion

Our case illustrated that modern advanced PH-specific therapy was not beneficial in a high-dose CCB responder PAH patient with vasoreactivity.

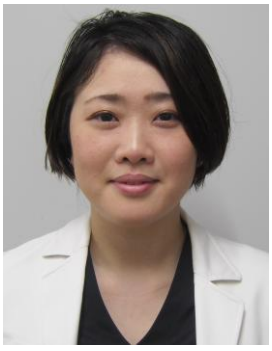
This patient may have a specific phenotype sensitive to CCB treatment. Sitbon *et al.*[2] reported that only 6.8% of patients (with positive AVT) with PAH demonstrated a favourable, long-term clinical response to CCBs. These patients have the vasoreactive phenotype, suggesting that not only CCB but also any vasodilators may be beneficial to them. However, this patient showed excellent haemodynamic and clinical improvement exclusively with CCB but not with three other pulmonary vasodilators. One of the possible underlying mechanisms of CCB-sensitive PAH may be an abnormality in the calcium channel pathway. The activation of calcium channel-receptor pathway can cause an excessive influx of calcium via calcium channel receptor, which could induce excessive pulmonary vasoconstriction and PH.[5] Calcium channel blockers may be effective by blocking active calcium channel receptors and inhibiting excessive calcium inflow directly, whereas advanced PH-specific vasodilators may not sufficiently dilate pulmonary vessels. Gain-of-function mutation in the calcium channel receptor is a possible underlying mechanism of this phenotype. However, such genetic abnormality has not yet been identified. Investigations for the underlying mechanism of PH in CCB responders such as next generation genomic analysis may be warranted.

Tolerance to PH-specific vasodilators may be another possible mechanism of poor response to PH-specific vasodilators in vasoreactive PAH. Dose escalation of intravenous epoprostenol is recommended in cases of tolerance. This patient improved after 1 year of PH-specific vasodilator treatment but deteriorated gradually, which suggests that the patient developed tolerance to advanced PH-specific medications. High-dose CCB treatment may have sustained effectiveness without tolerance in vasoreactive PAH patients.

The AVT with NO inhalation demonstrated a positive result, despite the patient's being on a combination therapy that included phosphodiesterase 5 inhibitors (PDE5-I). Even if risky on top of a triple oral therapy (it could be considered off label at this stage), AVT was performed to better understand vasoreactive pulmonary status of the patient. A previous study showed that NO is reduced in PAH.[6] Nitric oxide inhalation may open pulmonary vessels more than PDE5-I, which are NO dependent vasodilators, if there is reduced NO. Riociguat, a NO non-dependent vasodilator, might be more effective than PDE5-I in this patient. Furthermore, NO inhalation will directly act on smooth muscle cells while PDE5-I acts by cyclic guanosine monophosphate inhibition in endothelial cells. There may be endothelial dysfunction, which attenuates the effect of oral vasodilators working via endothelial cells. Although acute vasodilatation test with CCB was previously performed,[1] now it is discouraged due to potential severe risk such as hypotension.[7]

This case described a PAH patient with vasoreactivity, who was resistant to three different types of advanced PH-specific vasodilators, was exclusively sensitive to CCB, and had a favourable long-term outcome. High-dose CCB may be more beneficial than advanced PH-specific vasodilators in a PAH patient with positive acute vasoreactivity test. At the initial diagnosis of PAH, AVT is recommended to identify long-term CCB responders before initiating PH-specific vasodilators in the current PAH treatment guidelines.[6] However, 24% of I-PAH patients are initiated on targeted therapy without AVT[3] because CCB responders are rare. Calcium channel blockers responder PAH may be underdiagnosed and mistreated with advanced PH-specific vasodilators. This case highlighted the importance of identifying CCB responders in this era of modern advanced PH-specific vasodilator treatment. The investigation of the mechanism underlying CCB sensitivity including genetic analysis is necessary.

Lead author biography



Dr Kyoko Hirakawa obtained doctor of Medicine degree at Kumamoto University in Japan, where she worked on research into pulmonary circulation. She is now an assistant professor of cardiovascular medicine at Kumamoto University Hospital.

Supplementary material

Supplementary material is available at *European Heart Journal—Case Reports* online.

Acknowledgements

We sought the services of Editage for English language editing.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

Funding: This research did not receive any grants from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Rich S, Kaufmann E, Levy PS. Effect of high doses of calcium-channel blockers on survival in patients with primary pulmonary hypertension. *N Engl J Med* 1992;**327**:76–81.
2. Sitbon O, Humbert M, Jais X, Ioos V, Hamid AM, Provencher S, Garcia G, Parent F, Herve P, Simonneau G. Long-term response to calcium channel blockers in patients with idiopathic pulmonary arterial hypertension. *Circulation* 2005;**111**:3105–3111.
3. Thenappan T, Shah SJ, Rich S, Gomberg-Maitland M. A USA-based registry for pulmonary arterial hypertension: 1982–2006. *Eur Respir J* 2007;**30**:1103–1110.
4. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 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* 2016;**37**:67–119.
5. Kuhr FK, Smith KA, Song MY, Levitan I, Yuan JXJ. New mechanisms of pulmonary arterial hypertension: role of Ca^{2+} signaling. *Am J Physiol Heart Circ Physiol* 2012;**302**:H1546–H1562.
6. Tonelli AR, Alnuaimat H, Mubarak K. Pulmonary vasodilator testing and use of calcium channel blockers in pulmonary arterial hypertension. *Respir Med* 2010;**104**:481–496.
7. Milger K, Felix JF, Voswinckel R, Sommer N, Franco OH, Grimminger F, Reichenberger F, Seeger W, Ghofrani HA, Gall H. Sildenafil versus nitric oxide for acute vasodilator testing in pulmonary arterial hypertension. *Pulm Circ* 2015;**5**:305–312.