ESC European Society of Cardiology

European Heart Journal - Case Reports (2023) **7**, 1–6
https://doi.org/10.1093/ehjcr/ytad365

CASE REPORT
Heart failure

Acute venodilation properties of low-dose intravenous nitroglycerine in pulmonary veno-occlusive disease: a case report

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Received 29 June 2022; revised 23 June 2023; accepted 31 July 2023; online publish-ahead-of-print 4 August 2023

Background The use of pulmonary vasodilators for pulmonary arterial hypertension (PAH) has led to a favourable prognosis. In contrast, pulmonary veno-occlusive disease (PVOD) is characterized by the possibility of severe pulmonary oedema after specific PAH therapy. Pulmonary oedema presumably develops in association with pulmonary arterial vasodilation without concomitant pulmonary venodilation. The venous circulation maximally dilates with small amounts of nitroglycerine.

Case summary A 59-year-old woman with advanced PVOD was referred to our hospital. We performed a right heart catheterization after administering combination therapy with selexipag and macitentan, and intravenous nitroglycerine at 0.2 and 0.4 μg/kg/min decreased pulmonary arterial wedge pressure (PAWP) and mean pulmonary arterial pressure (PAP) to minimal levels. The final dose of 1 μg/kg/min yielded an ∼20% decrease in mean PAP and pulmonary vascular resistance (PVR).

Discussion Here, we described the acute effect of intravenous nitroglycerine on PAWP and PVR in a patient with PVOD. This case highlights the venodilation response even in advanced PVOD, suggesting the importance of further research into selective venous dilators as potent therapy.

Keywords Pulmonary veno-occlusive disease • Nitroglycerine • Venodilation • Case report

ESC curriculum 9.6 Pulmonary hypertension • 6.7 Right heart dysfunction

Learning points

- Intravenous low-dose nitroglycerine decreased pulmonary arterial wedge pressure and pulmonary vascular resistance in a patient with pulmonary veno-occlusive disease (PVOD).
- These haemodynamic reactions indicate venoconstriction with comorbid structural remodelling even in end-stage PVOD.
- This case highlights the importance of further research into selective venous dilators as potent therapeutic agents for PVOD.

Introduction

Pulmonary veno-occlusive disease (PVOD) is a rare subgroup of pulmonary arterial hypertension (PAH) disorders with a worse prognosis. Idiopathic or familial PAH is caused by the remodelling of small precapillary pulmonary arteries. On the other hand, PVOD manifests as a fibrous intimal proliferation that preferentially involves post-capillary venous pulmonary vessels and results in increased pulmonary capillary

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Handling Editor: Costantino Mancusi/Massimo Mapelli
Peer-reviewers: Aiste Monika Jakstaite; George Giannakoulas; Alessia Gambaro
Compliance Editor: Megha Agarwal

pressure. The use of pulmonary artery dilators for PAH has led to a favourable prognosis. In contrast, PVOD is characterized by the possibility of severe pulmonary oedema following specific PAH therapy.[1,2] Pulmonary oedema presumably develops in association with pulmonary arterial vasodilation without concomitant pulmonary venodilation, increasing transcapillary hydrostatic pressure and fluid transudation into the interstitium and alveoli. There is no established medical therapy for PVOD, only limited reports of incomplete and transient clinical improvement in individual patients with PVOD treated with PAH therapy.[1] The systemic venous circulation appears to maximally dilate with small amounts of nitroglycerine, and no further augmentation with increasing dosage was reported.[3] Moreover, peripheral arterial resistance decreases progressively in response to increasing doses and no distinct plateau is demonstrated.[3] The effect of nitroglycerine in PVOD is unknown. Thus, here, we investigated venodilation reactivity to low-dose nitroglycerine in patients with end-stage PVOD.

Summary figure

−4 years	Exertional dyspnoea
−17 months	Referred to former hospital: first right heart catheterization: diagnosis of PAH
−16 months	Presented pulmonary oedema with epoprostenol use: diagnosis of PVOD
−7 months	Symptom exacerbation
−15 weeks	Hospitalized at former hospital
−11 weeks	Discharged
Respiratory distress, lower extremity oedema, and fatigue	
−8 weeks	Transported to our hospital and admitted
−3 weeks	Discharged
Day 0	Hospitalized: right heart catheterization
+5 weeks	Discharged
+8 weeks	Symptom exacerbation: subsequent hospitalization
+12 weeks	Intubation: death

Case presentation

A 59-year-old Japanese woman had a 4-year history of exertional dyspnoea. The patient was previously diagnosed with coronary vasospastic angina. She was referred to the former hospital 17 months prior to the current presentation, at which time lung perfusion scintigraphy excluded chronic thrombo-embolism. A right heart catheterization demonstrated an elevated mean pulmonary arterial pressure (PAP) of 58 mmHg and pulmonary vascular resistance (PVR) of 928 dynes s^{-1} cm^{-5}, with a normal mean pulmonary arterial wedge pressure (PAWP) of 9 mmHg and cardiac index (CI) of 3.0 L/min/m^2. She was diagnosed with idiopathic PAH, for which treatment with sildenafil and macitentan (10 mg) was initiated, followed by intravenous epoprostenol. On dose escalation of the epoprostenol up to 10 ng/kg/min, her oxygenation worsened and mild pulmonary oedema and pleural effusion developed. The epoprostenol was immediately stopped. On treatment with diuretics, the pulmonary oedema improved. Such a response to pulmonary arterial vasodilation confirmed the clinical diagnosis of PVOD. She was discharged after the careful initiation of low-dose selexipag (0.4 mg).

The patient experienced symptom exacerbation 4 months ago, for which she was hospitalized. The sildenafil was changed to tadalafil (40 mg), and the selexipag dose was slowly increased up to 1.6 mg. She was discharged on home oxygen therapy (3 L/min).

Two months ago, she developed respiratory distress, lower extremity oedema, and fatigue, for which she was transported to our hospital. A thoracic computed tomography (CT) scan revealed mediastinal lymph node enlargement (*Figure 1A and B*), a dilated pulmonary artery (*Figure 1B*), mild pericardial effusion, bilateral pleural effusion (*Figure 1C*), and multiple centrilobular ground-glass opacities and interlobular septal thickening (*Figure 1D–F*). Lung transplantation was deemed not indicated due to her age. Tadalafil withdrawal, incremental oxygen therapy (4 L/min), and mild fluid restriction improved those manifestations. She was subsequently discharged.

The patient was admitted to our hospital for the re-evaluation of pulmonary artery pressure. Her vital signs were as follows: blood pressure 98/46 mmHg, pulse rate 50/min, body temperature 36.3 °C, and O_2 saturation 93% on 4 L of supplemental O_2 via a nasal cannula. A chest radiograph showed enlargement of the right heart and bilateral pulmonary arteries (*Figure 2*). An electrocardiogram demonstrated right axis deviation and right ventricular hypertrophy (*Figure 3*). Echocardiography showed a dilated right ventricle with a flattened interventricular septum leading to a D-shaped left ventricle, mild tricuspid regurgitation, and a tricuspid regurgitation pressure gradient of 65 mmHg (*Figure 4*). She provided written informed consent, and we performed right heart catheterization. All measurements were performed under the patient's spontaneous respiration. Oxygen was administered at 4 L/min throughout the procedure. After determination of her baseline haemodynamics, the nitroglycerine was increased every 5 min, followed by an evaluation of PAP and PAWP. The dose of intravenous nitroglycerine was increased up to 1 μg/kg/min, and a complete haemodynamic evaluation was performed. The results are shown in *Table 1*. Intravenous nitroglycerine at 0.2 and 0.4 μg/kg/min reduced PAWP and mean PAP to the minimal plateau level, respectively. The final dose of 1 μg/kg/min yielded a decrease of ∼20% in mean PAP and PVR and a slight increase in CI.

She had a CT scan before and after on the same day as the right heart catheterization. At 1 h after the intravenous nitroglycerine administration, a repeat thoracic CT scan (*Figure 5E–H*) did not indicate apparent pulmonary oedema or pleural effusion compared with that just before the right heart catheterization the same day (*Figure 5A–D*). Thereafter, the intravenous nitroglycerine was discontinued. No symptoms or signs of deterioration were noted. Neither systemic blood pressure nor oxygen saturation was affected throughout the procedure. After a close examination for persistent low-grade fever, the patient was discharged. Three weeks after discharge, she experienced an exacerbation and was readmitted. Her condition temporarily improved with intensive treatment, but she had a marked exacerbation triggered by defaecation and died 12 weeks after the right heart catheterization.

Discussion

Here, we described the acute effect of intravenous nitroglycerine causing a decrease in both PAWP and PVR and the potential involvement of venoconstriction in PVOD, even at the end stage. The administration of nitroglycerine yielded an ∼20% decrease in mean PAP and PVR without reducing CI. Additionally, her PAWP and PAP immediately decreased to a plateau. Mean PAWP decreased to a plateau with 0.2 μg/kg/min of nitroglycerine, whereas mean PAP decreased with 0.4 μg/kg/min. Ultimately, mean PAWP decreased by 4 mmHg; on the other hand, mean PAP decreased by 9 mmHg. These indicate that the decrease in PAP was not derived solely by the reduction in preload. Her systemic blood pressure was not decreased by the final dose. The patient was simultaneously undergoing combination therapy with selexipag and macitentan, indicating a preceding pulmonary artery dilatation at a level

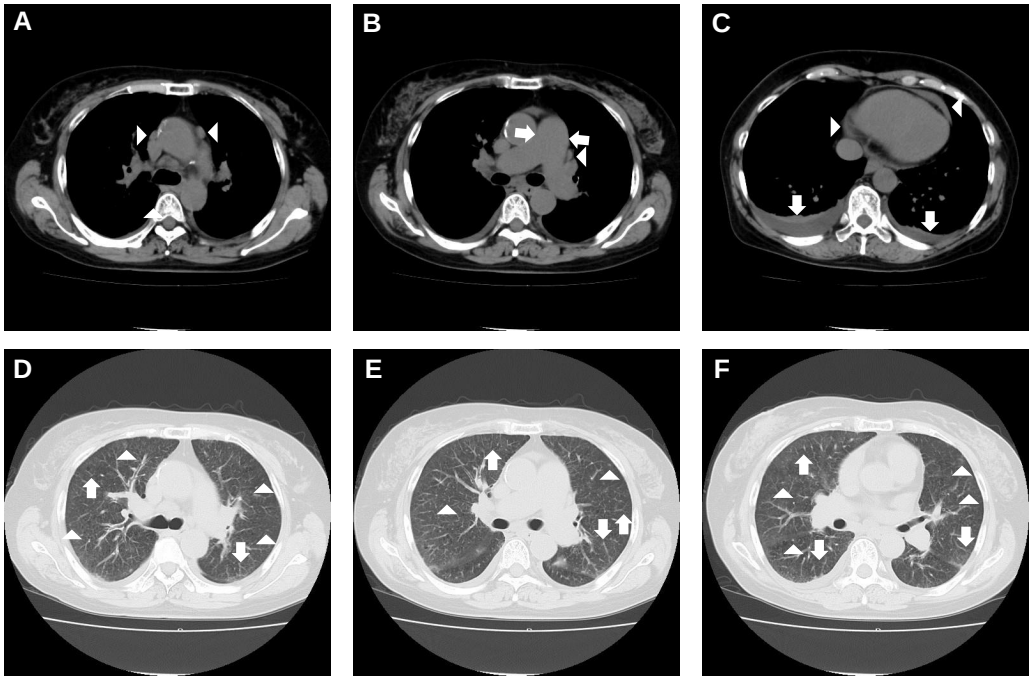

Figure 1 Transverse thoracic computed tomography scan demonstrating mediastinal lymph node enlargement [arrowhead, (*A*, *B*)], a dilated pulmonary artery [arrow, (*B*)], mild pericardial effusion (arrowhead), bilateral pleural effusion (arrow) (*C*), and multiple centrilobular ground-glass opacities (arrowhead) and interlobular septal thickening (arrow) (*D*–*F*).

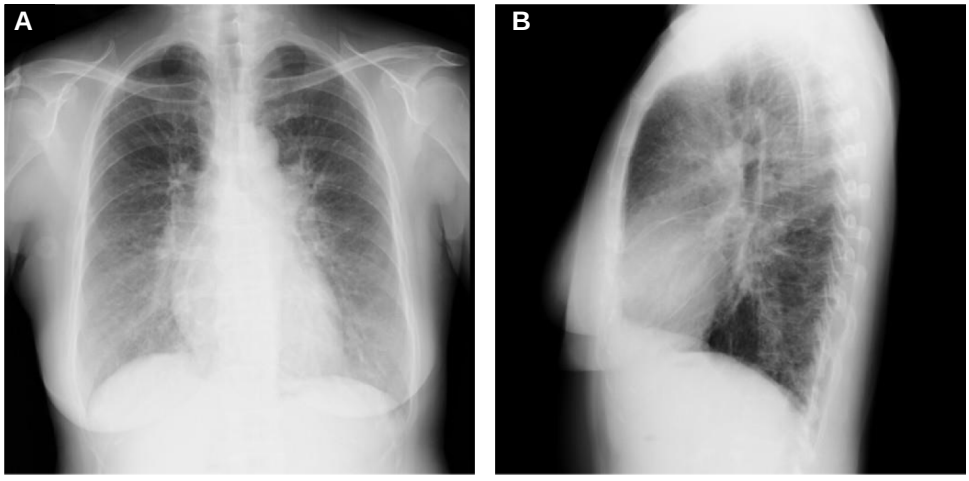

Figure 2 Frontal chest radiograph (*A*) showing enlargement of the right heart and prominent main pulmonary arteries. Lateral chest radiograph (*B*) showing filling of the retrosternal airspace revealing right ventricular dilatation.

that did not cause pulmonary oedema. These haemodynamic reactions suggest the involvement of pulmonary venoconstriction with comorbid structural remodelling.

Although significantly decreased mean PAP and PVR were reported in some PVOD cases,[2] short-acting pulmonary arterial vasodilators, such as inhaled nitric oxide or intravenous epoprostenol, cause acute pulmonary oedema at the time of catheterization.[4,5] Selective pulmonary venodilation properties are preferable to avoid this adverse event,[2] although the properties of PAH-specific vasodilators have been insufficiently evaluated. Nitrates are potent venodilators that ameliorate heart failure by redistributing blood from the central circulation into larger capacitance veins and increasing compliance of the arterial vasculature.[6] Nitrovasodilators have been used extensively in clinical practice, and some clinical trials have shown improved clinical outcomes in patients

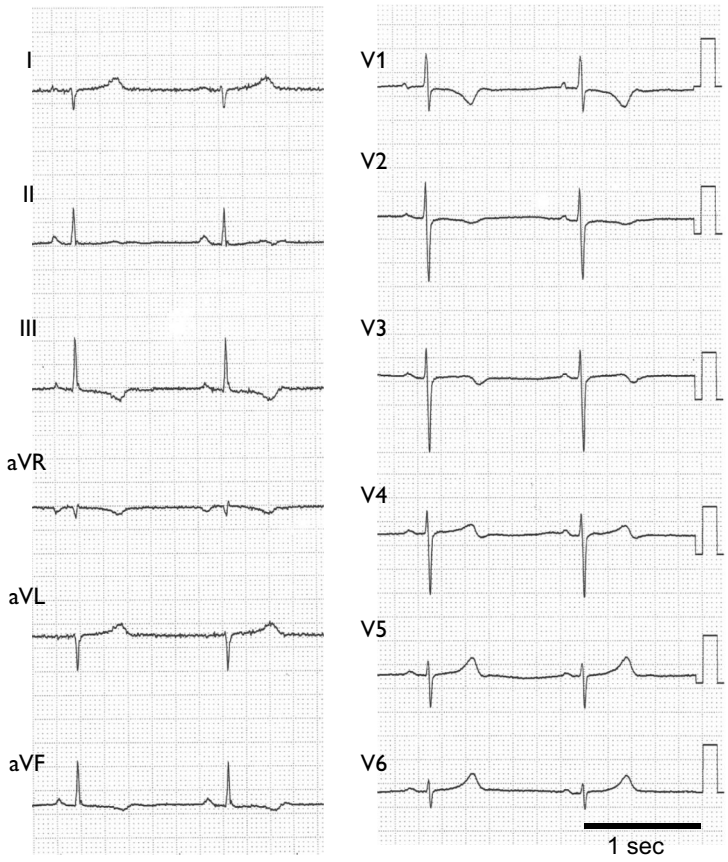

Figure 3 Electrocardiogram demonstrating right axis deviation and right ventricular hypertrophy. 10 mm/mV, 25 mm/s.

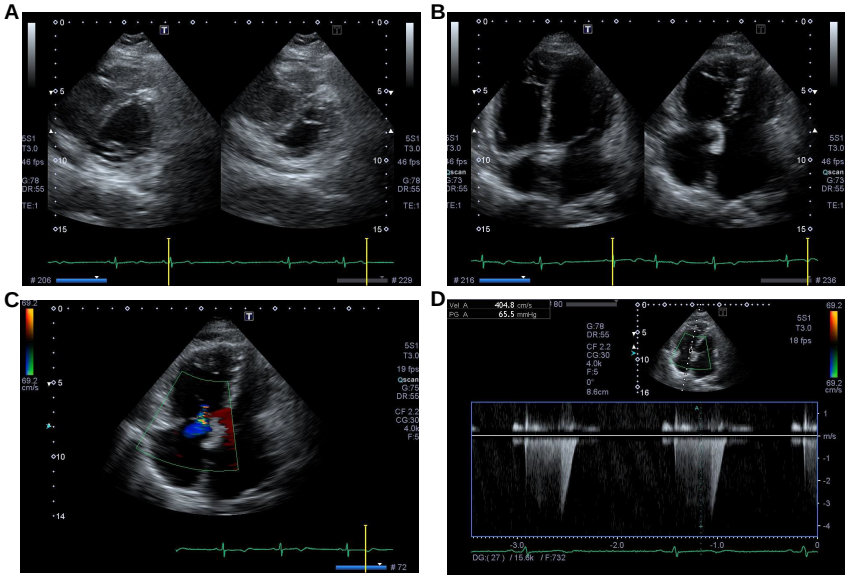

Figure 4 Echocardiography demonstrating a flattened interventricular septum leading to a D-shaped left ventricle in the apical four-chamber view (*A*), a dilated right ventricle in the parasternal short-axis view (*B*), mild tricuspid regurgitation in the apical four-chamber view with colour flow mapping (*C*), and a tricuspid regurgitation pressure gradient of 65 mmHg with continuous wave Doppler signals (*D*).

Table 1 Right heart catheterization data

Nitroglycerine (μg kg^{-1} min^{-1})	0	0.2	0.4	0.6	0.8	1
Mean pulmonary arterial wedge pressure (mmHg)	**12**	**7**	**8**	**8**	**9**	**8**
Systolic pulmonary arterial pressure (mmHg)	70	65	58	53	56	55
Diastolic pulmonary arterial pressure (mmHg)	29	29	26	25	25	24
Mean pulmonary arterial pressure (mmHg)	**43**	**43**	**35**	**35**	**35**	**34**
Right ventricular systolic pressure (mmHg)	76					65
Right ventricular diastolic pressure (mmHg)	4					2
Right ventricular end-diastolic pressure (mmHg)	9					5
Mean right atrial pressure (mmHg)	**5**					**3**
Systolic blood pressure (mmHg)	96	87	100	97	95	102
Diastolic blood pressure (mmHg)	47	50	52	40	44	38
Heart rate (min^{-1})	57	66	67	58	64	62
Arterial oxygen saturation of pulse oximetry (%)	**96**	**98**	**99**	**97**	**97**	**97**
Cardiac index (L min^{-1} m^{-2})	**2.2**					**2.3**
Pulmonary vascular resistance (dynes s^{-1} cm^{-5})	**757**					**607**

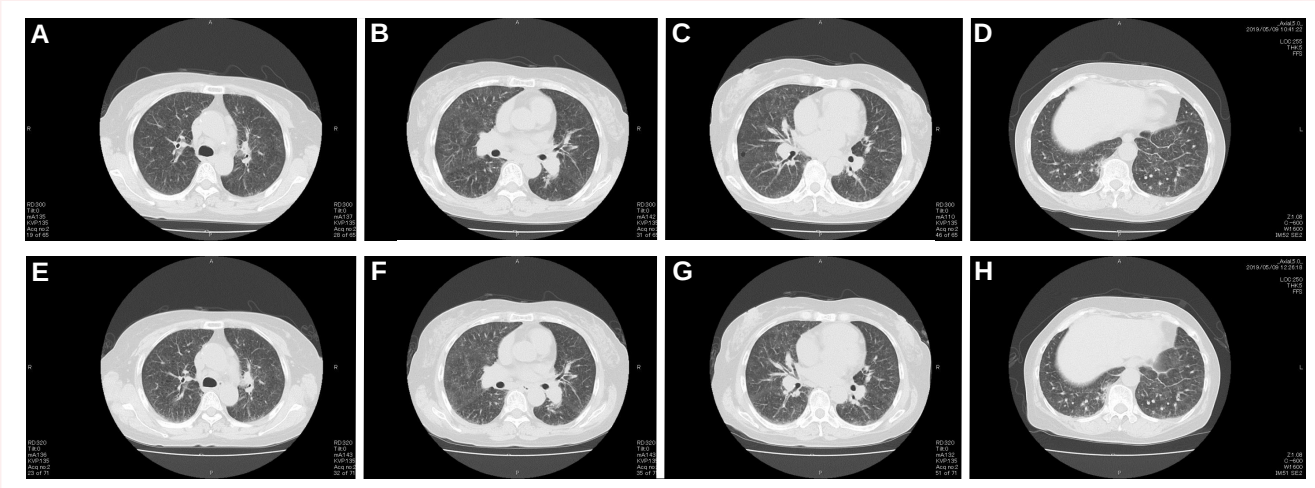

Figure 5 Chest computed tomography scans taken on the day that the intravenous nitroglycerine was administered [before, (*A–D*); 1 h after, (*E–H*)].

with acute heart failure treated with nitroglycerine.[7,8] Small amounts of nitroglycerine dilate the venous circulation maximally to the plateau level, although nitroglycerine decreases peripheral arterial resistance in a dose-dependent manner without reaching a definite plateau.[3] We administered adequately small amounts of nitroglycerine to avoid the apparent arterial dilating effect represented by the systemic blood pressure. Inhaled nitric oxide reportedly increased the PAWP of patients with PAH and PVOD,[9,10] whereas the lowest dose of nitroglycerine decreased the PAWP to the maximal plateau level in the present case. Acute exaggeration of pulmonary oedema or pleural effusion from the administration of intravenous nitroglycerine was not apparent for 1 h. Pulmonary oedema occurred after an acute vasodilator test[4,5] as well as at different intervals after the initiation of specific PAH therapies.[2] Since this intravenous administration was continued only for 1 h, nitroglycerine cannot be credited as a long-term therapy for PVOD.

Here, we described the acute effect of intravenous nitroglycerine on PAWP and PVR in a patient with PVOD. This case highlights the venodilation response despite end-stage PVOD, suggesting the importance of further research into selective venous dilators as potent therapy.

Lead author biography

Hidekazu Maruyama graduated from the Graduate School of Comprehensive Human Sciences at the University of Tsukuba. He is currently working as a cardiologist at the National Hospital Organization Kasumigaura Medical Center since 2018 and as an assistant professor at the University of Tsukuba since 2021.

Acknowledgements

The authors thank Chihiro Ota and Hiroaki Nishimiya for providing excellent technical assistance with the catheterization.

Consent: The authors confirm that written consent for submission and publication of this case report, including images and associated text, was obtained from the patient in line with the Committee on Publication Ethics guidelines.

Funding: None declared.

Conflict of interest: None declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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