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CASE REPORT
Heart failure

Pulmonary hypertension in an adult patient with congenital central hypoventilation syndrome: a case report

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Background Congenital central hypoventilation syndrome (CCHS) is a life-threatening disorder of autonomic respiratory control. Mutations in the paired-like homeobox 2B (PHOX2B) gene impair respiratory drive, causing hypercarbia and hypoxaemia. Most patients with CCHS are diagnosed in the neonatal period; however, a few are diagnosed in adulthood.

Case summary We report a 32-year-old man with a history of unexplained cyanosis 14 days after birth. He presented to our hospital with breathlessness and abnormal electrocardiogram findings discovered in a health check-up. Pulmonary hypertension (PH) was suspected based on electrocardiographic and echocardiographic evidence of right ventricular (RV) overload. Results of pulmonary function tests and chest computed tomography were normal. Arterial blood gas analysis revealed type 2 respiratory failure without a significant alveolar–arterial oxygen gradient, indicating alveolar hypoventilation. Right heart catheterization (RHC) showed pre-capillary PH [pulmonary artery pressure 47/24 (35) mmHg], and a hyperventilation challenge test and a non-invasive positive pressure ventilation (NPPV) treatment during RHC provided drastic improvement in PH [pulmonary artery pressure 28/12 (18) mmHg]. Congenital central hypoventilation syndrome was diagnosed based on genetic testing (20/25 polyalanine repeat expansion mutations in PHOX2B). After NPPV therapy initiation, the RV overload was slightly improved.

Discussion Some patients with CCHS develop mild hypoventilation without overt clinical signs, and PH can be the first clinical manifestation. In our case, the hyperventilation challenge test improved PH. Although CCHS causes chronic alveolar hypoxia and hypoxic pulmonary vasoconstriction with subsequent PH, optimal ventilation therapy can improve pulmonary circulation even in affected adults.

Keywords Congenital central hypoventilation syndrome • Pulmonary hypertension • Hyperventilation challenge test • Non-invasive positive pressure ventilation • Case report

ESC curriculum 6.7 Right heart dysfunction • 9.6 Pulmonary hypertension

Learning points

- Some patients with *PHOX2B* mutations develop mild hypoventilation without overt clinical signs, and pulmonary hypertension can be the initial manifestation.
- In a short time, hyperventilation improves hypoxic pulmonary vasoconstriction and pulmonary hypertension.
- Optimal ventilation therapy can improve pulmonary circulation and prognosis.

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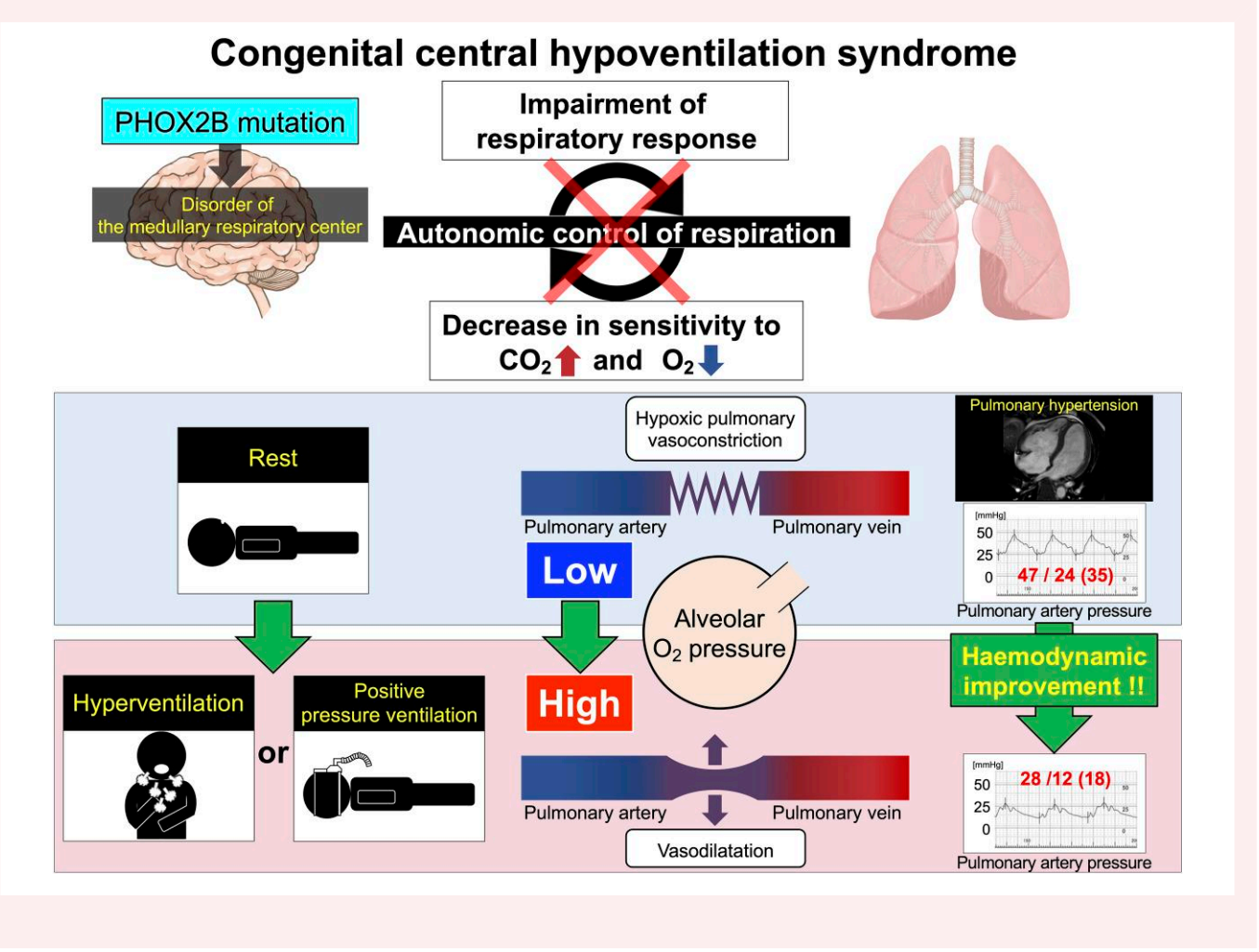
Introduction

Congenital central hypoventilation syndrome (CCHS) is a life-threatening disease that impairs the respiratory response to hypercarbia and hypoxaemia, particularly during sleep. More than 90% of affected individuals have polyalanine repeat expansion mutations (PARM) in the paired-like homeobox 2B (PHOX2B) gene, and polyalanine expansion length is associated with disease severity.[1,2] Congenital central hypoventilation syndrome was first reported by Mellins *et al.*[3] in 1970 in an infant with severe hypoventilation and pulmonary hypertension (PH) who died at 14 months of age due to heart failure. Although most patients with CCHS are diagnosed in the neonatal period, a few are diagnosed in adulthood with pulmonary hypertension.[4] Herein, we present a unique case of PH due to CCHS, diagnosed by right heart catheterization (RHC), with haemodynamic improvement during a hyperventilation challenge.

Summary figure



Case presentation

We report a 32-year-old man with a history of hospitalization at 14 days after birth due to unexplained cyanosis. Although the cause of cyanosis was unknown, his condition was non-fatal, and he was discharged at 9 months of age. He had no severe symptoms or fatal events after discharge without medication and attending hospital.

At age 32 years, he presented to our hospital with breathlessness during exercise and abnormal electrocardiogram findings found in a health check-up. Although he had no clinical signs of PH or right heart failure including a loud pulmonic component of the second heart sound or leg oedema, PH was suspected based on electrocardiographic evidence of right ventricular (RV) overload (*Figure 1A*). Echocardiography (*Figure 2A and B*) showed RV dilatation with a D-shaped left ventricle. Cardiac magnetic resonance (CMR) imaging showed RV dilatation and systolic dysfunction (right ventricular ejection fraction = 16%, right ventricular end-diastolic volume = 143.0 mL, and right ventricular end-systolic volume = 120.4 mL) (*Figure 2C and D*). His haemoglobin level and haematocrit were 20.1 g/dL and 65.4%, respectively. Chest computed tomography showed no interstitial lung disease or thoracic deformation, and pulmonary function tests revealed neither obstructive nor restrictive abnormalities. Lung perfusion scintigraphy results were normal. Arterial blood gas analysis revealed type 2 respiratory failure without a significant alveolar–arterial oxygen gradient, indicating alveolar hypoventilation. Right heart catheterization revealed pre-capillary PH [pulmonary artery wedge pressure, 9 mmHg; pulmonary artery pressure, 47/24 (35) mmHg; and pulmonary vascular resistance, 4.7 Wood units] (*Table 1*).[5]

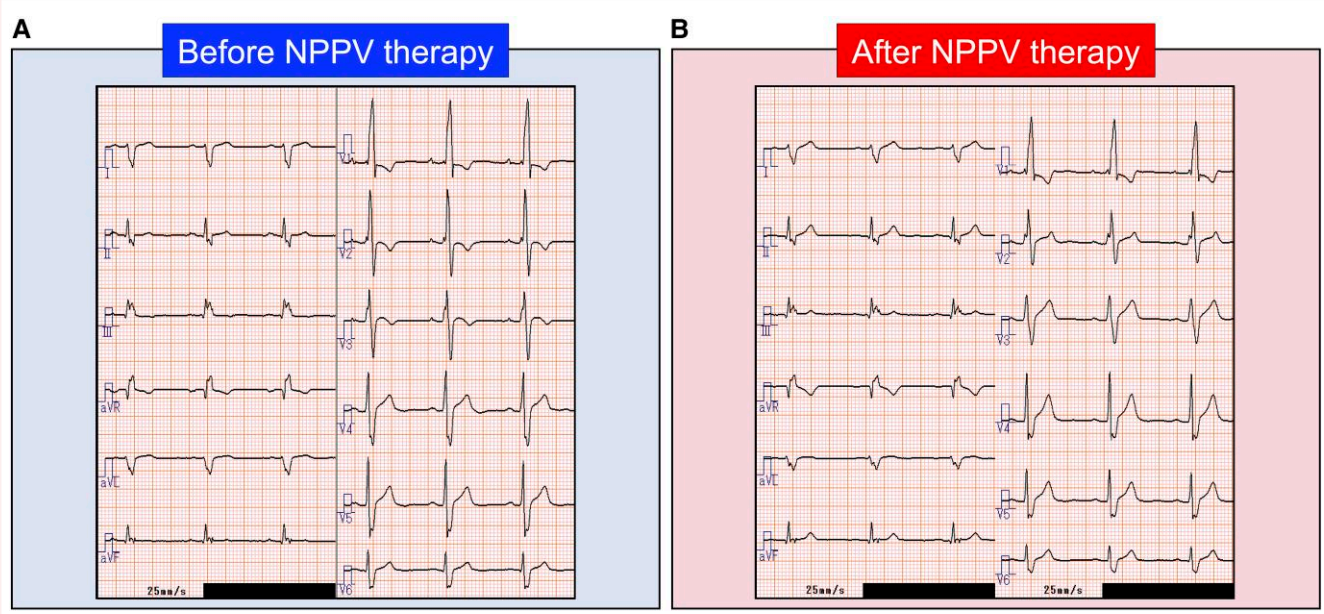


Figure 1 Electrocardiogram findings before and after non-invasive positive pressure ventilation (NPPV) therapy. (*A*) Electrocardiogram before NPPV suggested right ventricular overload, with complete right bundle branch block, right axis deviation, and T-wave inversion in precordial leads V_1–V_3. (*B*) After NPPV, right ventricular overload findings were slightly improved.

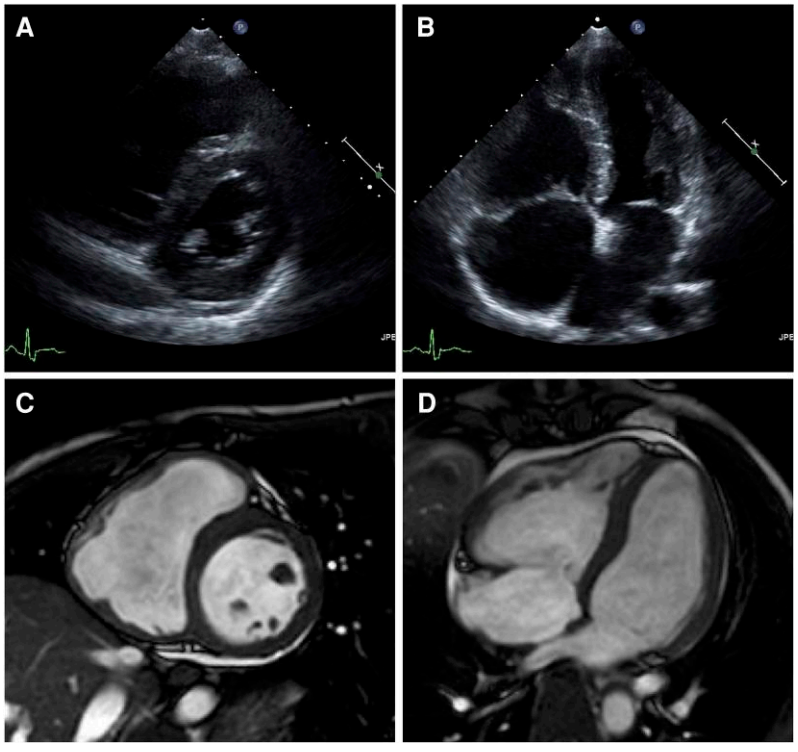


Figure 2 Right ventricular parameters on echocardiography and cardiac magnetic resonance (CMR) imaging. (*A*) and (*B*), both obtained from echocardiography, showed flattening of the interventricular septum at end-systole. (*C*) and (*D*), both obtained from CMR imaging, showed right ventricular dilatation and systolic dysfunction (right ventricular ejection fraction = 16%, right ventricular end-diastolic volume = 143.0 mL, and right ventricular end-systolic volume = 120.4 mL).

Table 1 The findings of right heart catheterization

	Normal reference	Rest	Hyperventilation	Non-invasive positive pressure ventilation
Haemodynamic characteristics				
Pulmonary artery wedge pressure, mmHg	≤15	(9)	(8)	(9)
Pulmonary artery pressure, mmHg	15–30/4–12 (8–20)	47/24 (35)	28/12 (18)	29/14 (20)
Right atrial pressure, mmHg	2–6	(6)	(5)	(7)
Artery, mmHg	120/80	137/81 (99)	135/78 (97)	132/80 (97)
Cardiac output, mL/min	4–8	5.5	3.8	3.8
Systemic vascular resistance, dyne·sec·cm^{-5}		1352	1937	1895
Pulmonary vascular resistance, Wood unit	0.3–2.0	4.7	2.6	2.9
Oxyhaemoglobin saturation (blood sampling site)				
Main pulmonary artery, %	65–80	71.3	81.0	76.5
Left atrium (pulmonary artery wedge samples), %	95–100	89.8	99.5	93.7
Artery, %	95–100	87.5	99.6	98.4
Arterial blood gas analysis				
pH		7.328	7.602	7.479
PaO_2, mmHg		59.6	121.0	99.4
$PaCO_2$, mmHg		73.6	32.6	46.0
$HCO3^-$, mmHg		37.5	32.4	33.8

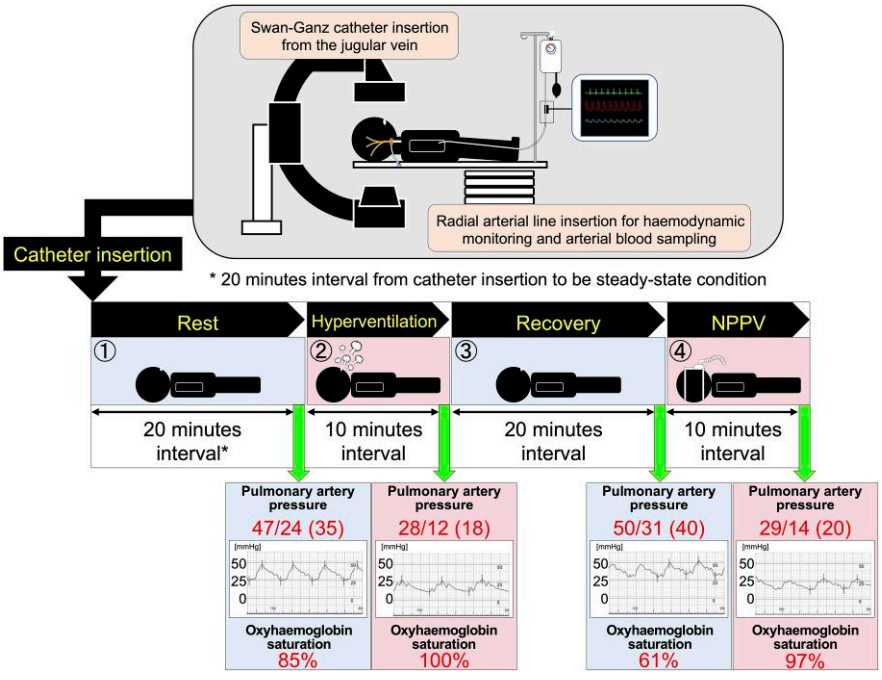


Figure 3 Method and results of hyperventilation challenge and non-invasive positive pressure ventilation (NPPV) during right heart catheterization. A Swan–Ganz catheter was inserted through the right jugular vein for haemodynamic monitoring, and a radial arterial line was inserted for haemodynamic monitoring and arterial blood sampling. Haemodynamic measurement 'at rest' was performed 20 min after catheter insertion to represent steady-state conditions, because external stimuli such as pain caused by puncture and catheter insertion may affect the respiratory drive. Haemodynamic measurement 'at hyperventilation' was performed 10 min after hyperventilation, and hyperventilation was continued until final measurements. The recovery interval before NPPV was 20 min. As in 'at hyperventilation', NPPV was used 10 min before and during haemodynamic measurement 'at NPPV'.

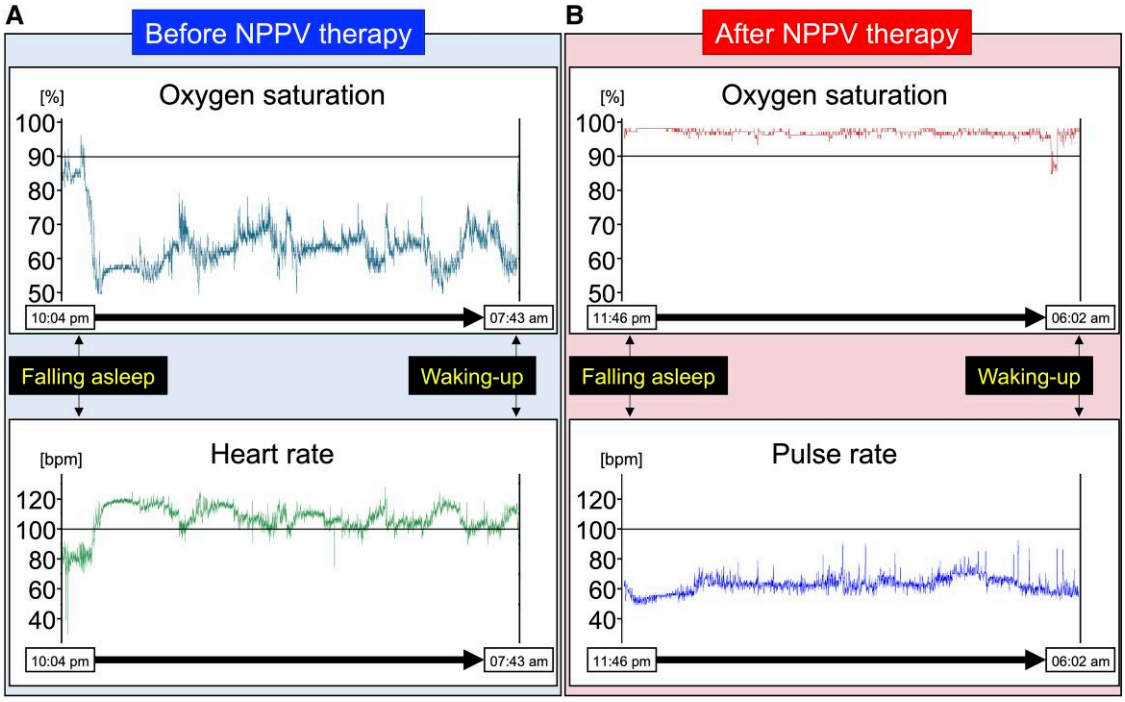


Figure 4 Oxyhaemoglobin saturation and heart (pulse) rate before and after non-invasive positive pressure ventilation (NPPV) therapy. (*A*) Results of polysomnography before NPPV therapy. Central apnoea caused severe hypoxaemia with tachycardia. The mean and minimum oxyhaemoglobin saturation were 64.0% and 46.0%, respectively. (*B*) Results of oxyhaemoglobin saturation monitoring after NPPV therapy. Non-invasive positive pressure ventilation therapy notably improved hypoxaemia and tachycardia.

A hyperventilation challenge and non-invasive positive pressure ventilation (NPPV) were performed during RHC (*Figure 3*). Notably, the hyperventilation challenge drastically improved the oxyhaemoglobin saturation at the left atrium (pulmonary artery wedge samples), PH [pulmonary artery wedge pressure, 8 mmHg; pulmonary artery pressure, 28/12 (18) mmHg; and pulmonary vascular resistance, 2.6 Wood units], and electrocardiographic evidence of RV overload. Twenty minutes elapsed between the end of the hyperventilation challenge and NPPV. During recovery, the pulmonary artery pressure gradually increased to a level greater than that at rest. Furthermore, NPPV produced similar haemodynamic improvements. Polysomnography revealed central apnoea and severe hypoxaemia with tachycardia (*Figure 4A*). Surprisingly, the mean oxyhaemoglobin saturation was 64.0%. Congenital central hypoventilation syndrome was ultimately diagnosed based on genetic test results (20/25 PARM in PHOX2B). This represents a relatively short polyalanine expansion length and causes mild hypoventilation without a requirement for ventilation support during wakefulness. Therefore, NPPV only during sleep was initiated, and the average use of NPPV was 4.8 h per day in 73.3% of the first 30 days. Hypoxaemia and tachycardia notably improved with NPPV (*Figure 4B*). One month after NPPV initiation, the haemoglobin level and haematocrit decreased from 20.1 to 14.4 g/dL and from 65.4% to 45.6%, respectively. Right ventricular overload findings on the electrocardiogram were also slightly improved (*Figure 1B*).

Discussion

To our knowledge, this is the first reported case of PH due to CCHS diagnosed by RHC, with haemodynamic improvement during a hyperventilation challenge. Hypoxic pulmonary vasoconstriction (HPV)—an essential mechanism in this case—is a pulmonary vascular response to alveolar hypoxia,[6] preventing severe hypoxaemia in conditions with significant ventilation–perfusion mismatch. However, the protective effects are limited in cases of short-term hypoxia and involvement of only part of the lung. Long-term alveolar hypoxia involving the entire lung, as in patients with CCHS, increases pulmonary vascular resistance and RV afterload, ultimately causing PH and RV dysfunction. As shown in *Figure 3*, our case demonstrated pre-capillary PH at rest, and hyperventilation for only 10 min inhibited HPV and normalized pulmonary artery pressure. Impressively, pre-capillary PH and oxyhaemoglobin desaturation recurred only 20 min after hyperventilation. Ventilation therapy can improve pulmonary circulation, even in adults with CCHS.

Almost all CCHS patients have PHOX2B anomalies, and PARM are the most frequent. Polyalanine expansion repeats of 24–33 have been reported in PHOX2B, and expansion length is associated with disease severity.[1] Most patients with CCHS and mild hypoventilation have 20/24 or 20/25 PARM in PHOX2B. However, patients with 26 or more PARM develop severe hypoventilation requiring ventilation support even during wakefulness.[7]

The two types of ventilatory support for CCHS are positive pressure ventilation and diaphragm pacing. Positive pressure ventilation is non-invasive but has a risk of self-discontinuation. Diaphragm pacing provides longer ventilation support; however, surgical implantation is necessary, and there are risks of device malfunction and infection. Ventilation support is life-saving for patients with CCHS, and optimal therapy can improve prognosis.[1,8] According to the results of RHC and genetic testing, NPPV therapy only during sleep, and not diaphragm pacing, was applied in the present case. Non-invasive positive pressure

ventilation therapy improved oxyhaemoglobin desaturation during sleep (*Figure 4B*). Furthermore, secondary polycythaemia and electrocardiographic evidence of RV overload were improved 1 month after initiation of NPPV therapy.

In conclusion, electrocardiogram abnormalities and pulmonary hypertension were the first clinical findings in our adult patient with CCHS. A hyperventilation challenge and NPPV drastically improved pulmonary circulation. Certain PHOX2B mutations cause mild hypoventilation without overt clinical signs and a delayed diagnosis. Optimal ventilation therapy is life-saving for patients with CCHS.

Lead author biography

Yosuke Terui is a general cardiologist at Iwate Prefectural Isawa Hospital. His work at Tohoku University Graduate School of Medicine focuses on cardiomyopathy, pulmonary hypertension, and cardio-oncology.

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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 the Committee on Publication Ethics (COPE) guidance.

Conflict of interest: None declared.

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Data availability

All available data are presented within the manuscript.

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