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Case report

# Inhaled nitric oxide mitigates need for extracorporeal membrane oxygenation in a patient with refractory acute hypoxemic respiratory failure due to cardiac and pulmonary shunts

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ABSTRACT

We present a case of refractory acute hypoxemic respiratory failure due to influenza B pneumonia with concomitant large intra-atrial shunt (IAS) and severe pulmonary regurgitation in a patient with Saethre-Chotzen syndrome with prior pulmonary homograft placement. Our patient's hypoxemia improved with inhaled nitric oxide as an adjunct to mechanical ventilation without requiring extracorporeal membrane oxygenation, and eventually a percutaneous closure with a 30 mm CardioSeal patent foramen ovale closure device was accomplished. However, his peri-procedural hospital course was complicated by occluder device migration, which was retrieved with eventual surgical closure of the PFO. Nitric oxide has not demonstrated any statistically significant effect on mortality and only reported to transiently improved oxygenation in patients with hypoxemic respiratory failure. Our case demonstrates that inhaled nitric oxide may have a role in acute hypoxemic respiratory failure in a case with significant cardiac and pulmonary shunts.

## 1. Introduction

The use of inhaled nitric oxide (iNO) has long been used within the pediatric population with congenital heart disease in order to mitigate right-to-left shunts. Inhaled NO has also been proposed for pulmonary hypertension (PH), and is occasionally used as a rescue therapy for severely hypoxemic patients both with and without an established diagnosis of PH.

## 2. Case presentation

A 30 year-old gentleman with Saethre-Chotzen syndrome with a prior history of open surgical pulmonic valvotomy and pulmonary outflow homograft patch presented to a community hospital with shortness of breath, abdominal pain, nausea and vomiting. Briefly, Saethre-Chotzen syndrome is associated with autosomal dominant mutation in the TWIST, FGFR2, or FGFR3 genes, characterized by craniosynostosis, limb anomalies, and a spectrum of septal defects [1]. His other relevant past history included gastric bypass for morbid obesity (admission BMI to the hospital of 42), recent treatment for bilateral lower extremity swelling with antibiotics and steroids by his primary care physician with some resolution. Admission vitals included: HR of 90; BP of 140/80 mmHg; RR 27 breaths per minute; Pulse Oximetry of 92%. He was initiated on antibiotics, nasal cannula oxygen and intravenous fluids as a maintenance therapy. Chest x-ray showed low lung volumes. Venous duplex study demonstrated an acute left lower extremity superficial thrombophlebitis in the upper greater saphenous vein. CT angiography of his chest demonstrated no evidence of acute pulmonary embolism. He had significant cardiomegaly and central pulmonary artery enlargement. Abdominal scan demonstrated cholelithiasis with nephrolithiasis and left intrarenal calculus. He additionally had low attenuation in the lower pole of the right kidney diagnosed to be a wedge-shaped infarct. He was also noted to have a small cerebellar infarct.

Due to worsening hypoxemia, he was transferred to the intensive care unit, where non-invasive ventilation in the form of BiPAP was

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**Table 1**
Ventilator setting and arterial blood gas (ABG) at the outside hospital. Inhaled Nitric Oxide doses included.

| Date | Outside Hospital Day 3 | Outside Hospital Day 4 | Outside Hospital Day 5 | Outside Hospital Day 6 | Outside Hospital Day 7 | Our Hospital Day 1 | Our Hospital Day 1 |
|---|---|---|---|---|---|---|---|
| Time | 4:17 | 4:17 | 15:07 | 11:16 | 9:51 | 14:43 | 16:54 |
| iNO (ppm) | 0 | 0 | 0 | 0 | 0 | 40 | 40 |
| pH | 7.427 | 7.38 | 7.383 | 7.362 | 7.403 | 7.395 | 7.388 |
| pCO2 | 36.6 | 37.8 | 39.5 | 39.3 | 41.4 | 39.3 | 40.5 |
| PO2 | 68.7 | 58.8 | 62.9 | 59.2 | 42.2 | 58.7 | 65.9 |
| HCO3 | 24.6 | 22.5 | 23.2 | 22.5 | 24.9 | 23.7 | 23.9 |
| Base excess | 0.3 | −2.1 | −1.4 | −2.1 | 0.9 | −0.6 | −0.6 |
| O2 sat | 95 | 90.7 | 93.8 | 93.2 | 79.0 | 92.7 | 94.8 |
| Temp | 37 | 37 | 37 | 37 | 37 | 37 | 37 |
| FiO2 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| vent mode | BIPAP | BIPAP | BIPAP | BIPAP | AC | AC | PCV |
| Rate | 12 | 12 | 12 | 12 | 28 | 28 | 18 |
| TV | | | | | 500 | 500 | 500 |
| CPAP/PEEP | 10 | 10 | 10 | 10 | 16 | 20 | 20 |
| A-a gradient | 578 | 585.2 | 508.3 | 584 | 600.9 | 584.6 | 574.1 |
| Hgb | 18.4 | | 17.9 | 16.5 | 15.7 | 15.9 | 15.6 |
| O2-Hgb | 90.5 | | 92.6 | 90.7 | 81.3 | 89.8 | 92 |
| Met-Hgb | 0.8 | | 0.9 | 1.2 | 1.2 | 1.5 | 1.4 |
| CO Hgb | 1.6 | | 1.5 | 1.5 | 1.5 | 1.6 | 1.6 |

initiated. Despite this, he continued to decline in the following days and he was intubated and placed on mechanical ventilation on day seven post-admission. Lung protective ventilation was initiated in the belief that he had acute respiratory distress syndrome (ARDS). High PEEP strategy was used. Low mean arterial pressure (MAP) < 60 led to initiation of norepinephrine and vasopressin as vasoactive agents. Despite FiO2 of 1.0 and PEEP of 16, his arterial blood gases (ABG) showed pH of 7.4, pCO2 41, paO2 42. Failure of mechanical ventilation to improve hypoxemic respiratory failure was noted and our institution was contacted for mobile ECMO team activation and transport with initiation of veno-venous extracorporeal membrane oxygenation. Interestingly, a CT scan of his chest was done was done at the community hospital, and was not suggestive of bilateral opacities (primary requirement) for diagnosis of ARDS per the Berlin definition [2]. No echocardiography was done at the outside institution. Due to the chest CT findings, decision was made to initiate inhaled nitric oxide therapy prior to transfer. 40 parts per million (40 ppm) dose was used. Patient's oxygen saturation improved to 94% from 79% and paO2 was noted to be 65.9 (Table 1).

With these changes, decision was made to transfer him to our institution on iNO and ECMO therapy was not initiated. A transesophageal echocardiogram was performed and revealed a large intra-atrial (Fig. 1a) bidirectional shunt with right-to-left flow during systole and left-to-right flow during diastole (Fig. 1b). This represented a large patent foramen ovale due to right-sided chamber enlargement due to severe pulmonary regurgitation and dilatation of the pulmonary arteries with bi-direction flow. Severe pulmonary regurgitation was demonstrated on Doppler assessment (Fig. 2). Furthermore, the thick septum primum and thin septum secundum support this over an atrial septal defect (Fig. 3). He was also noted to have an enlarged pulmonary artery measuring 4.9 cm and severe pulmonary valve regurgitation (supplemental video 1). An incidental absent left main and separate ostial connections of the left anterior descending and left circumflex coronary arteries to the sinus of Valsalva were noted.

He underwent bronchoscopy which showed significant secretions in the right bronchial lower lobe which was noted to be positive for influenza B per the broncho-alveolar lavage sent. A pulmonary artery catheter was placed and the hemodynamic and arterial blood gas profile changes are noted in the table (Table 2). It was felt that both pulmonary regurgitation and IAS required correction; however, due to concern for sepsis (need for vasopressors, although no bacteremia was noted) and these procedures were initially deferred. He was continued on iNO, judicious diuresis along with vasopressor wean for a mean arterial pressure > 60. Of note, drop in his MAP < 60 led to increased

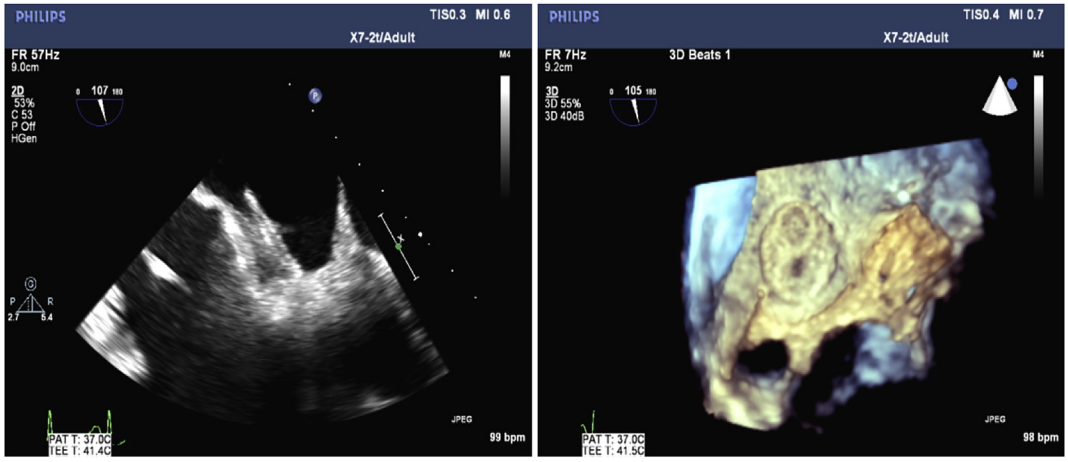


**Fig. 1.** a (left) and b. Fig. 1a is a mid-esophageal view at 115° and demonstrates left to right flow during diastole through the intra-atrial shunt. Fig. 1b: This color M-mode is displayed across the intra-atrial septum and shows bi-directionality dependent upon cardiac cycle. Red arrows indicate the septum secundum. Green arrows indicate septum primum.

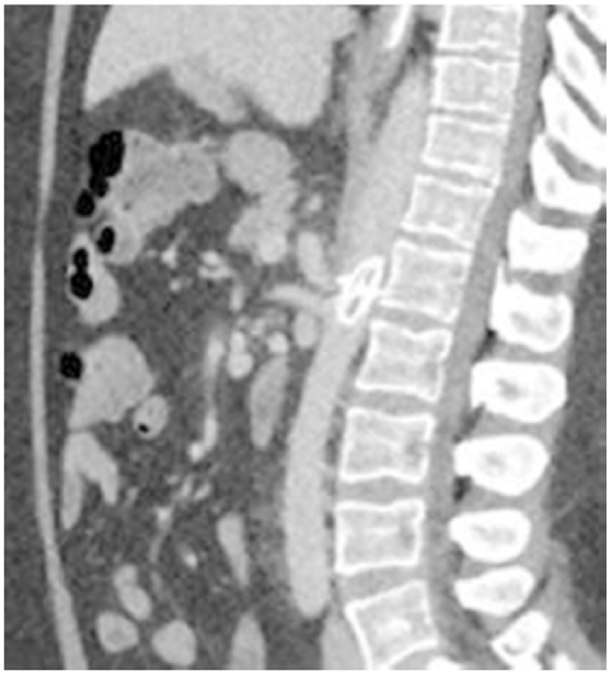

**Fig. 2.** Continuous wave Doppler demonstrates dense diastolic flow with rapid deceleration consistent with fast equilibration of the right ventricle and pulmonary artery and to-and-fro flow through the pulmonary valve consistent with severe pulmonary regurgitation. Blue double arrow is systolic forward flow and orange arrow is diastolic regurgitant flow.

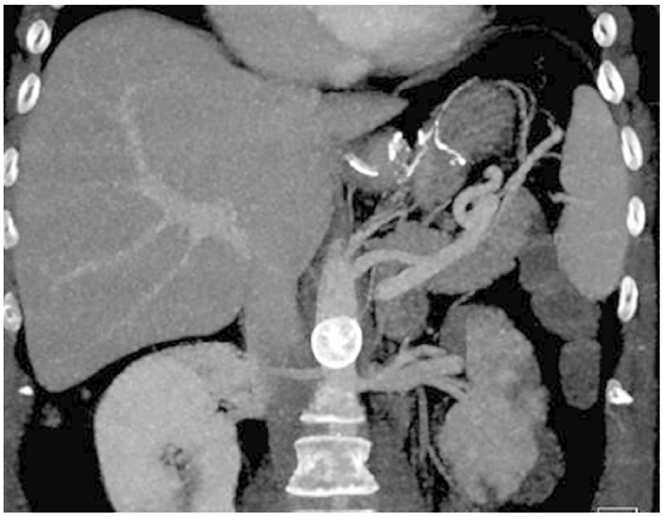

**Fig. 3.** 2D and 3D TEE images showing ASD closure device in place before migration.

hypoxemia while on inhaled nitric oxide.

Day four after admission, he was taken to the cardiac catheterization laboratory, where a 30 mm CardioSeal patent foramen ovale closure device was placed. (Fig. 3). During the closure procedure, the IAS was crossed with a multi-purpose catheter and then we used a balloon to measure flow stop diameter. This measurement was approximately 18 mm by echo and 16 mm by fluoroscopy. Following balloon occlusion of the IAS, oxygen saturation improved acutely. A 30 mm cribriform ASD occluder device was placed and adequate rims of tissue were captured all around. His oxygen saturations and arterial oxygen pressure initially decreased, and then improved modestly subsequent to the procedure and he was able to be weaned off inhaled nitric oxide on day 10 (Table 2). Interval echocardiography on day 10 did show residual R-L shunt and continued severe pulmonary regurgitation. On day twelve a tracheostomy was performed and continued ventilator wean was attempted subsequently with weaning of PEEP and FiO2. On ICU day fifteen, follow-up CT scans revealed persistence of left cerebellar vermis infarct, improved interstitial edema of the lung and migration of the CardioSeal device to the abdominal aorta at the level of the celiac trunk and SMA (Fig. 4). He had not been overtly hypoxic during this time. However, the device migration required angiographic removal by vascular surgery using gooseneck snare and endobronchial forceps. Ultimately, on hospital day nineteen, his mechanical ventilation was discontinued, and he was maintained on supplemental oxygen delivery via a tracheostomy collar. Ultimately, he was discharged to an acute rehabilitation unit with 2–4L home oxygen.

Following hospital discharge, he returned in 6 months and underwent primary closure of left atrial septal defect with 2-layer Prolene suture closure and pulmonic valve replacement with pulmonic outflow patch graft reconstruction of the pulmonary artery using bovine pericardial patch and a porcine heart valve Medtronic Hancock II size 29 mm. .

Intraoperative pressure and oxygenation measurements are as follows: Prior to Closure: Pulmonary artery 46/22 mmHg with a mean of 31 mmHg. The pulmonary capillary wedge pressure 28. The right atrial mean pressure was 22 mmHg. The mean left atrial pressure was 24 mm Hg. By oximetry, the left upper pulmonary vein 96.8% and the pulmonary artery pre-closure was 54%. The post closure measurements for the pulmonary artery were 42/18 mmHg, mean of 28 mmHg. The pulmonary artery saturation was 52%.

At the end of the procedure, transesophageal echocardiogram demonstrated normal prosthetic pulmonary valve function. The atrial septal defect was closed, and a negative bubble study was demonstrated by transesophageal echocardiogram. He is currently being followed in the outpatient cardiology clinic and doing well.

## 3. Discussion

Our case has several unique and valuable learning points. Further, there was an uncommon complication of IAS closure device migration, which has seldom been reported in the literature before [3–6]. Of the cases that have been reported, predictive factors include hypermobile septum primum and thick septum secundum. Typically, device migration happens in less than 1% of cases and occurs within the first 48 hours of intervention, which was likely the case with our patient, as evidenced by prominent thrombus formation on the retrieved device. Our patient had a thick septum secundum. His IAS was large, and greater than 1cm in diameter, also likely compromising device anchoring.

Of further note, the discussion to be had surrounding his hypoxic respiratory failure is rich. Acute hypoxic respiratory failure may be due to different etiologies causing ventilation-perfusion mismatch-notably dead space and intra-alveolar shunt. A cardiac shunt should always be in the differential diagnosis. In our patient, the acute hypoxic respiratory failure was as a result of intra-alveolar shunt from infiltrates caused by influenza B pneumonia, interstitial pulmonary edema caused by fluid resuscitation and atelectasis in a morbidly obese patient exacerbated by intra-atrial shunt. Hypoxemia was worsened by systemic vasodilation from presumed sepsis and use of sedative agents. Systemic vasodilation led to increased cardiac output, which in the setting of large intra-atrial shunt and severe pulmonary regurgitation, increased the R-L shunt (Supplemental Video 2). Inhaled nitric oxide was able to mitigate this by improving pulmonary arterial blood flow and reducing the R-L shunt. Inhaled nitric oxide is also thought to selectively dilate the vasculature in open airways following inhalation, thereby improving V/Q mismatch [7].

It would be important to remember that not all acute hypoxic respiratory failure is due to ARDS. ARDS, as per the Berlin definition, requires bilateral pulmonary opacities on imaging, absence of cardiogenic pulmonary edema and a P/F ratio < 300 as a diagnostic criteria

**Table 2**
Ventilator setting and arterial blood gas (ABG) throughout the hospital stay at our facility. Inhaled Nitric Oxide doses included.

| HD | HD1 | HD1 | HD2 | HD3 | HD4 | HD5 | HD5 | HD6 | HD6 | HD6 | HD7 | HD8 | HD9 | HD10 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time | 2000- | 2200- | 0230- | 2100- | 500 | 100 | 1600 | 300 | 1130 | 1200 | 400 | 300 | 345 | 330 |
| NO | 40 | 40 | 20 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 30 | 1.4 | 2 | 0.5 |
| CVP | 22 | 17 | 12 | 14 | 17 | 18 | 14 | 13 | | | 15 | 16 | 12 | 11 |
| PAS/PAD | 44/21 | 36/15 | 26/12 | 34/14 | 36/18 | 30/14 | | | | | | | | |
| PAM | 33 | 26 | 19 | 24 | 26 | 23 | | | | | | | | |
| CO | 8.1 | 8.2 | 7 | 7.3 | 6.9 | 5.2 | | | | | | | | |
| CI | 2.9 | 2.9 | 2.5 | 2.6 | 2.5 | | | | | | | | | |
| SVO2 | 74 | 80 | 75 | 77 | 68 | 60 | | | | | | | | |
| SPO2 | 96 | 93 | 92 | 90 | 88 | 80 | 85 | 85 | 87 | 87 | 90 | 85 | 88 | 85 |
| BP | 141/68 | 133/60 | 106/53 | 118/60 | 124/60 | 119/70 | 105/58 | 137/68 | | | 153/80 | 137/73 | 133/71 | 117/60 |
| NO | 40 | 40 | 20 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 20 | 1 | 2 | 1 |
| pH | 7.227 | 7.347 | 7.446 | 7.394 | 7.365 | 7.292 | 7.38 | 7.293 | 7.325 | 7.329 | 7.409 | 7.471 | 7.444 | 7.473 |
| PaCO2 | 56.6 | 37.6 | 34.5 | 41.2 | 45.7 | 45.1 | 40.5 | 48.3 | 48 | 40 | 44 | 40 | 39.6 | 39 |
| PaO2 | 106.5 | 68.7 | 64.9 | 67.1 | 61.6 | 49.5 | 52 | 61.5 | 50 | 57 | 57 | 55 | 55 | 51 |
| HCO3 | 23 | 20.2 | 23.2 | 24.6 | 25 | 21.3 | 23.6 | 22.9 | 24 | 20 | 27 | 29 | 26 | 28 |
| P:F | 106 | 85 | 81 | 83 | 61 | 49 | 52 | 61 | 50 | 57 | 57 | 55 | 55 | 55 |
| FIO2 | 1 | 0.8 | 0.8 | 0.8 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| SaO2 | 97 | 93 | 93 | 92 | 90 | 81 | 86 | 89 | 82 | 87 | 88 | 89 | 87 | 86 |
| VENT | | | | | | | | | | | | | | |
| MODE | simv vc | simv vc | simv vc | simv vc | simv vc | simv pc | bilevel | ac pc | ac pc | ac pc | simv pc | simv pc | simv pc | simv pc |
| RATE | 24 | 24 | 24 | 16 | 16 | 16 | 20 | 16 | 18 | 18 | 14 | 14 | 14 | 14 |
| VT | 600 | 600 | 600 | 600 | 600 | 632 | 650 | 619 | 538 | 538 | 597 | 466 | 808 | 526 |
| PC | | | | | | 12 | 12 | 18 | 18 | 18 | 14 | 12 | 12 | 12 |
| PS | 12 | 12 | 12 | 12 | 12 | 12 | | | | | 14 | 12 | 12 | 12 |
| PEEP | 12 | 12 | 12 | 12 | 10 | 15 | | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| FIO2 | 100 | 80 | 80 | 80 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| PPLAT | 29 | 29 | 29 | 29 | 27 | 25 | 28 | 29 | 29 | 29 | 26 | 20 | 26 | 26 |
| PEAK | 29 | 29 | 27 | 33 | 33 | 30 | 34 | 31 | 31 | 31 | 28 | 26 | 26 | 26 |

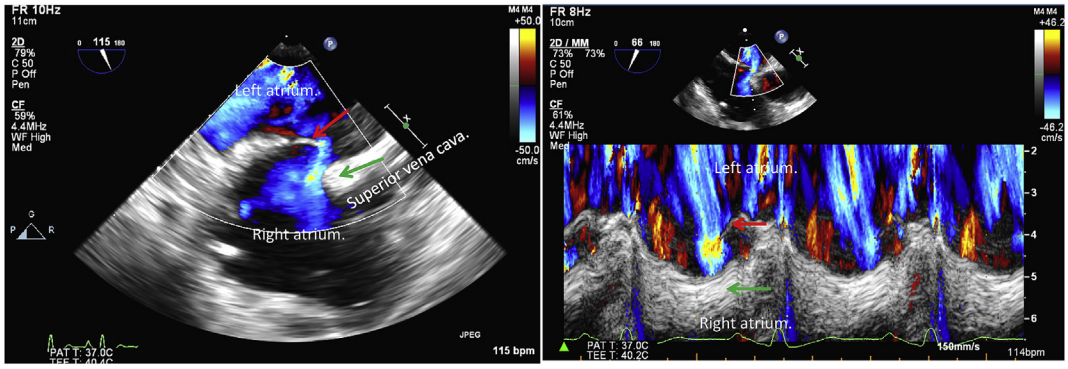


**Fig. 4.** a: Arterial sagital and b: arterial coronal MIP view demonstrating ASD closure device within the abdominal aorta.

[2]. We were asked to review the patient for VV-ECMO initiation for severe ARDS due to inability to oxygenate the patient despite maximal conventional mechanical ventilation support. A high PEEP strategy was applied in the referring institution. This may have been deleterious in our patient due to severe pulmonary regurgitation and increased right ventricular pressure overload. Mechanical ventilation strategies should not be, merely, lung protective, but also RV protective. Assessment of the cardiac function by bedside echocardiography is paramount in this setting to optimize cardiopulmonary interactions.

The current ELSO guidelines indicate that in acute hypoxic respiratory failure due to any cause (primary or secondary) ECLS should be considered when the risk of mortality is 50% or greater (P/F ratio < 150 on FiO2 > 90%), and is indicated when the risk of mortality is 80% or greater (P/F ratio < 100 on FiO2 > 90%) despite optimal care for 6 hours or more. Our ECMO transport team was called on day seven post-admission to the hospital and day one post-intubation. Delays in ECMO initiation in severe acute respiratory failure are associated with worse outcomes and current recommendations indicate initiation of VV-ECMO within 48 hrs. Typically, these guidelines are applicable to those patients with ARDS. A cardiac assessment is critical in all patients with acute hypoxic respiratory failure to elucidate the cause of hypoxemia.

Initiation of VV-ECMO in our patient would be challenging with the oxygenated ECMO blood flow along with the native flow mixing in the right atrium and likely shunting across to the left atrium, with resultant no/minimal improvement in oxygenation. Peripheral VA-ECMO would also have been problematic due to high output vasodilatory state (initial CI 3.2) which would have competed with native hypoxemic blood flow from the left ventricle. Only central VA-ECMO may have mitigated patient's hypoxemia by returning oxygenated blood to the root of the aorta (by open or percutaneous cannulation techniques). Nitric oxide in the setting of acute hypoxemic respiratory failure has been questioned with no improvement in survival outcomes [8,9]. However, we argue that inhaled nitric oxide is beneficial in the setting of significant RV dysfunction and cardiac shunt as a cause of acute hypoxemic respiratory failure and use needs to be individualized to patients. Prior studies have also reported beneficial outcomes in select group of patients [10–12].

Nitric oxide has also been used in safe transport of patients to a tertiary care center in severe hypoxemic respiratory failure [13]. Our case indicates that an inhaled nitric oxide tank may be considered in mobile ECMO transport team's armamentarium. We were handicapped

by lack of CT images from the referring center prior to initiating transport. Viewing the images on arrival made us suspect the cause of acute hypoxemic respiratory failure to be different from ARDS. However, bedside echocardiography was difficult with poor images obtained by using the Sonosite due to patient's body habitus and high ventilatory pressures. A formal TEE was unavailable at the referring center at the late hours of the ECMO team arrival. Use of inhaled nitric oxide enabled us to mitigate need for ECMO and transfer the patient to our tertiary center where a formal TEE confirmed our suspicions.

As the use of extracorporeal membrane oxygenation increases, it is important to know when ECMO may be contra-indicated, and if indicated, appropriate cannulation strategies (VV vs VA or hybrid modes). Through a careful review of the real-time pathologic drivers of our patient's hypoxemia, we were able to abrogate the need for ECMO, and ultimately pursue shunt-directed management, and thereby avoid cannulation. We posit that iNO is contextually of benefit in R-L shunt physiology, and may be an appropriate temporizing strategy when determining if patient's need ECMO.

## Financial disclosures

None.

## Conflicts of interest

None.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmcr.2018.03.017.

## References

[1] L. Clauser, M. Galie, A. Hassanipour, O. Calabrese, Saethre-Chotzen syndrome: review of the literature and report of a case, J. Craniofac. Surg. 11 (2000) 480–486.
[2] A.D.T. Force, V.M. Ranieri, G.D. Rubenfeld, et al., Acute respiratory distress syndrome: the Berlin definition, J. Am. Med. Assoc. 307 (2012) 2526–2533.
[3] H. El-Said, S. Hegde, S. Foerster, et al., Device therapy for atrial septal defects in a multicenter cohort: acute outcomes and adverse events, Cathet. Cardiovasc. Interv. 85 (2015) 227–233.
[4] S.S. Goel, O. Aksoy, E.M. Tuzcu, R.A. Krasuski, S.R. Kapadia, Embolization of patent foramen ovale closure devices: incidence, role of imaging in identification, potential causes, and management, Tex. Heart Inst. J. 40 (2013) 439–444.
[5] F. Martin, P.L. Sanchez, E. Doherty, et al., Percutaneous transcatheter closure of patent foramen ovale in patients with paradoxical embolism, Circulation 106 (2002) 1121–1126.
[6] J. Moore, S. Hegde, H. El-Said, et al., Transcatheter device closure of atrial septal defects: a safety review, JACC Cardiovasc. Interv. 6 (2013) 433–442;
[7] N.S. Hill, I.R. Preston, K.E. Roberts, Inhaled therapies for pulmonary hypertension, Respir. Care 60 (2015) 794–802 discussion -5.
[8] O. Karam, F. Gebistorf, J. Wetterslev, A. Afshari, The effect of inhaled nitric oxide in acute respiratory distress syndrome in children and adults: a Cochrane Systematic Review with trial sequential analysis, Anaesthesia 72 (2017) 106–117.
[9] F. Gebistorf, O. Karam, J. Wetterslev, A. Afshari, Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults, Cochrane Database Syst. Rev. (2016) CD002787.
[10] R.A. Helmers, K. Chandrasekaran, Nitric oxide therapy for post-laparoscopic surgery associated patent foramen ovale: incidence, mechanisms, diagnosis and therapy, Heart Lung 43 (2014) 155–157.
[11] P. Estagnasie, G. Le Bourdelles, L. Mier, F. Coste, D. Dreyfuss, Use of inhaled nitric oxide to reverse flow through a patent foramen ovale during pulmonary embolism, Ann. Intern. Med. 120 (1994) 757–759.
[12] M.T. Chua, T.B. Sim, I. Ibrahim, Not all unexplained hypoxia is pulmonary embolism, Singap. Med. J. 56 (2015) e32–e35.
[13] N.R. Teman, J. Thomas, B.S. Bryner, et al., Inhaled nitric oxide to improve oxygenation for safe critical care transport of adults with severe hypoxemia, Am. J. Crit. Care 24 (2015) 110–117.