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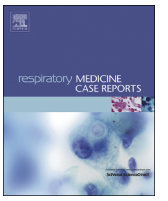

Case Report

# Single-institution experience of extracorporeal membrane oxygenation for near-fatal asthma

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ABSTRACT

Near-fatal asthma (NFA) is the most severe presentation of asthma. It is characterized by hypoxemic and hypercapnic respiratory failure requiring ventilatory assistance, including non-invasive ventilation and mechanical ventilation. However, NFA has a high mortality rate despite conventional therapy. Extracorporeal membrane oxygenation (ECMO) is a treatment modality that is increasingly being utilized as rescue therapy in patients with NFA that is refractory to mechanical ventilation. Prior analyses of the international Extracorporeal Life Support Organization (ELSO) registry data showed a survival rate of over 83% in patients placed on venovenous (VV) ECMO for NFA, but with notable rate of hemorrhagic complications. We report seven cases of adults with NFA requiring ECMO support at our large quaternary care institution between the years 2019 and 2022. All seven patients presented with respiratory failure in the setting of asthma exacerbation that progressed despite standard pharmacotherapy and mechanical ventilation. All patients survived to hospital discharge after ECMO support without hemorrhagic complications, highlighting the effectiveness and safety of ECMO when appropriately used in this population.

**Abbreviations**

| | |
|---|---|
| ABG | Arterial blood gas |
| BiPAP | Bilevel positive airway pressure |
| ECLS | Extracorporeal life support |
| ED | Emergency Department |
| ELSO | Extracorporeal Life Support Organization |
| FiO2 | Fraction of inspired oxygen |
| ICU | Intensive Care Unit |
| LABA-ICS | long-acting beta-agonist-inhaled corticosteroid |
| LAMA | long-acting muscarinic antagonist |
| MV | Mechanical ventilation |
| NFA | Near-fatal asthma |

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pCO2 partial pressure of carbon dioxide
PEEP Positive end-expiratory pressure
PIP Peak inspiratory pressure
RR Respiratory rate
SNF Skilled nursing facility
SpO2 Oxygen saturation
URI Upper Respiratory Infection
USA: United States of America
VAV-ECMO Veno-arterial-venous extracorporeal membrane oxygenation
VBG Venous blood gas
Vt Tidal volume
VTE Venous thromboembolism
VV ECMO Venovenous extracorporeal membrane oxygenation

## 1. Introduction

Asthma is relatively common in the United States of America (USA), with 8% of adults reporting a history of asthma in 2019 [1]. Approximately 40% of patients with asthma experience asthma exacerbations, with 3346 deaths related to asthma exacerbations reported in 2019 [1]. Despite advances in outpatient asthma management, patients can still present with severe asthma exacerbations. Near-fatal asthma (NFA) is a life-threatening presentation of severe asthma and is characterized by respiratory failure and arrest, profound respiratory acidosis, and the need for intubation and mechanical ventilation (MV) [2]. Globally, approximately 30% of NFA cases result in significant morbidity and mortality [3,4].

Mechanical ventilation of patients with severe asthma exacerbations can be challenging. Severe hyperinflation and air trapping can occur, both due to patient breath stacking and suboptimal expiration time [5]. This leads to the development of intrinsic positive end-expiratory pressure (PEEP), which can result in barotrauma and hypotension. Deep sedation and sometimes neuromuscular blockade are needed to allow patient-ventilator synchrony for controlled hypoventilation. Maximizing expiratory time and minimizing inspiratory time on the ventilator will reduce intrinsic PEEP and associated complications [5]. These methods result in a certain degree of hypercapnia and respiratory acidosis.

Despite optimal ventilation techniques and pharmacotherapy for asthma, some patients with NFA still worsen. The severity of their bronchospasm leads to elevated peak inspiratory pressures (PIP) and inability to effectively ventilate, which results in severe respiratory acidosis, hyperinflation, and air trapping [6]. The use of venovenous extracorporeal membrane oxygenation (VV ECMO), a type of extracorporeal life support (ECLS), in these patients can be life-saving. We present a case series of seven adult patients at our large quaternary care institution who were placed on VV ECMO for NFA refractory to optimal therapy between 2019 and 2022. Optimal therapy provided to each patient included: 100mg of intravenous methylprednisolone in the Emergency Department, followed by methylprednisolone 40 mg every 6 hours, continuous albuterol 5 mg/hour, intravenous magnesium, MV with volume control and tidal volume 6–8 mL/kg of ideal body weight with an inspiratory flow rate of 90–110 L/minute, and sedation with Richmond Agitation-Sedation Score goal −4 with addition of paralytics as needed for ventilator asynchrony and/or refractory auto-PEEP. Informed consent was provided, and the study was approved as exempt by the Temple Institutional Review Board (IRB; protocol number 29093) on 7/11/2022. Procedures were followed in accordance with the ethical standards of the Western IRB and the Helsinki Declaration of 1975. Patient characteristics are seen in Table 1, and clinical characteristics and ECMO details are seen in Table 2. ECMO outcomes are seen in Table 3.

## 2. Case descriptions

### 2.1. Patient 1

A 43-year-old male with history of asthma presented in severe respiratory distress in the setting of an asthma exacerbation. Initial venous blood gas (VBG) showed respiratory acidosis (Table 2, Figs. 1 and 2). Despite bilevel positive airway pressure (BiPAP) and optimal medical therapy, his oxygen saturation (SpO2) dropped to the 70 s, prompting intubation. Post-intubation, breath-stacking and

**Table 1**
Demographics.

| Demographic | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
|---|---|---|---|---|---|---|---|
| Age (years) | 43 | 27 | 37 | 38 | 44 | 29 | 24 |
| Sex | Male | Female | Male | Female | Female | Male | Male |
| Outpatient ICS Use | No | No | No | No | Yes | No | No |
| Number of exacerbations in previous 1 year | 0 | 0 | 1 | 10 | 1 | 5 | 0 |
| Past exacerbations requiring NIV/MV | none | none | none | Yes - NIV, MV | Yes - NIV | none | none |

ICS: Inhaled Corticosteroid, MV: Mechanical Ventilation, NIV: Non-Invasive Ventilation, PIP: Peak Inspiratory Pressure, VV ECMO: Venovenous ECMO.
In addition to changes in arterial pH and pCO2, all patients had reductions in peak inspiratory pressures and minute ventilation after VV ECMO cannulation. While patients had complications, none were specifically related to VV ECMO cannulation.

**Table 2**
Clinical and ECMO characteristics.

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
|---|---|---|---|---|---|---|---|
| Trigger | seasonal allergies | weather change | construction materials | unknown | Viral URI | Viral URI | Viral URI |
| Time to mechanical ventilation (hours) from presentation | 3 | 1 | 1.5 | 5 | 26 | 12 | 3 |
| Presentation pH and PaCO2 (mmHg) | 7.26/63 | 7.23/67 | 7.27/60 | 7.43/45 | 7.40/34 | 7.19/76 | 7.29/57 |
| Immediate Pre-ECMO pH and PaCO2 (mmHg) | 7.18/63 | 6.84/181 | 6.86/212 | 7.13/101 | 7.27/103 | 7.12/95 | 7.11/59 |
| Immediate Pre-ECMO Ventilator Settings | 28/450/40/5 | 12/300/40/5 | 12/350/100/5 | 14/400/100/10 | 16/400/50/5 | 16/500/100/5 | 18/500/40/5 |
| Cannula Insertion Technique | Percutaneous | Percutaneous | Percutaneous | Percutaneous | Percutaneous | Percutaneous | Percutaneous |
| ECMO Modality and Configuration | VV (Right IJ 19 Fr return cannula, Right femoral 25 Fr drainage cannula) | VV (Right IJ 17 Fr return cannula, Right femoral 21 Fr drainage cannula) | VV (Right IJ 17 Fr return cannula, R femoral 21 Fr drainage cannula), then VAV(additional right femoral artery 15 Fr cannula) | VV (Right IJ 19 Fr return cannula, Right femoral 25 Fr drainage cannula) | VV (Left IJ 17 Fr return cannula, Right femoral 21 Fr drainage cannula) | VV (Right IJ 19 Fr return cannula, Right femoral 25 Fr drainage cannula) | VV (Right IJ 17 Fr return cannula, Right femoral 25 Fr drainage cannula) |
| ECMO Settings (Flow, Sweep, FiO2) | 4.3 L/min, 7 L/min, 100% | 3.4 L/min, 6 L/min, 40% | VV:<br>VAV: 4.8 L/min, 3 L/min, 100% | 5 L/min, 5.5 L/min, 100% | 3 L/min, 6 L/min, 100% | 4.1 L/min, 6 L/min, 100% | 4.1 L/min, 2 L/min, 100% |
| Anticoagulation Strategy and Agent | VTE prophylaxis with heparin | VTE prophylaxis with heparin | Continuous heparin while on VAV, PTT goal 60-90 | Continuous heparin for history of VTE, PTT goal 60-90 | VTE prophylaxis with heparin | VTE prophylaxis with heparin | VTE prophylaxis with heparin |
| Immediate Post-ECMO pH and PaCO2 (mmHg) | 7.21/55 | 7.4/34 | 7.3/74 | 7.47/41 | 7.62/41 | 7.35/48 | 7.25/46 |
| Pre-ECMO PIP ($cmH_2O$) | 80 | 90 | 67 | 60 | 55 | 50 | 58 |
| Post-ECMO PIP ($cmH_2O$) | 40 | 41 | 40 | 55 | 40 | 30 | 40 |
| Pre-ECMO Minute ventilation (L/min) | 12.6 | 3.6 | 4.2 | 5.6 | 6.4 | 8 | 11 |
| Post-ECMO Minute ventilation (L/min) | 2.4 | 1.1 | 3.5 | 3 | 3 | 5.4 | 6.4 |

ECMO: Extracorporeal membrane oxygenation, Fr: French, IJ: Internal Jugular, PaCO2: partial pressure of carbon dioxide, PIP: peak inspiratory pressure, PTT: Partial thromboplastin time, URI: Upper respiratory infection, VTE: Venous thromboembolism.

auto-PEEP were noted on the ventilator with peak pressures above 60 $cmH_2O$. Minute ventilation on the ventilator was decreased for controlled hypoventilation. Sodium bicarbonate infusion was utilized to target a pH > 7.2. Despite these measures, PIP remained elevated at >70 $cmH_2O$ and respiratory acidosis worsened. Immediate pre-ECMO ventilator settings were volume control with respiratory rate (RR) 28 bpm, tidal volume (Vt) 450 mL, fraction of inspired oxygen ($FiO_2$) 100%, and PEEP 5 $cmH_2O$. VV ECMO was initiated to allow for further lung rest and CO2 clearance, with improvement of peak pressures to 40 s and improvement in respiratory acidosis (Table 2). Initial VV ECMO settings are seen in Table 2. After 11 days on VV ECMO, bronchospasm, peak pressures and respiratory acidosis improved significantly, and he was decannulated. He was extubated the next day and discharged to a skilled nursing facility (SNF) after a 35-day hospitalization (Table 3). He established outpatient pulmonary care with significant improvement in asthma control on medium-dose long-acting beta-agonist (LABA)-inhaled corticosteroid (ICS) inhaler.

### *2.2. Patient 2*

A 27-year-old female with history of moderate persistent asthma without history of intubation presented with 1 day of dyspnea. She was in severe respiratory distress, requiring BiPAP. Arterial blood gas (ABG) showed respiratory acidosis (Table 2, Figs. 1 and 2). Despite optimal therapy, she became progressively hypoxemic and encephalopathic, leading to intubation. Upon intubation, she was noted to have PIP of 75 $cmH_2O$ and tidal volumes approximately 40 mL. Disconnecting the ventilator to reverse possible auto-PEEP did not improve ventilation or high peak pressures. Post-intubation ABG showed severe respiratory acidosis (Table 2). Her PIPs remained greater than 90 $cmH_2O$ with delivered tidal volumes around 100 mL. Immediate pre-ECMO ventilator settings were volume control with RR 12 bpm, Vt 300 mL, $FiO_2$ 40%, and PEEP 5 $cmH_2O$. She was placed on VV ECMO, with initial settings seen in Table 2.

**Table 3**
Outcomes.

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
|---|---|---|---|---|---|---|---|
| Hours on ventilator, Pre-ECMO | 24 | 16 | 4 | 46 | 98 | 12 | 17 |
| Days on ECMO | 11 | 3 | 4 VAV, 11 VV | 7 | 7 | 5 | 5 |
| Days on ventilator, Post-ECMO | 1 | <1 | 11 until trach | 6 | 1 | 3 | <1 |
| Length of Stay (days) | 35 | 9 | 44 | 22 | 21 | 13 | 8 |
| Complications | Acute renal failure, culture negative aspiration pneumonia | H. Flu VAP | bilateral pneumothoraces leading to hypoxic arrest, cavitary aspergillosis | MSSA and Enterobacter VAP | MSSA VAP and bacteremia | Klebsiella VAP | none |
| Hemorrhagic Complications | None | None | None | None | None | None | None |
| Number of blood transfusions | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Survive to Discharge | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

ECMO: Extracorporeal membrane oxygenation, H. Flu: Haemophilus influenzae, MSSA: methicillin sensitive *Staphylococcus aureus*, VAP: ventilator associated pneumonia.

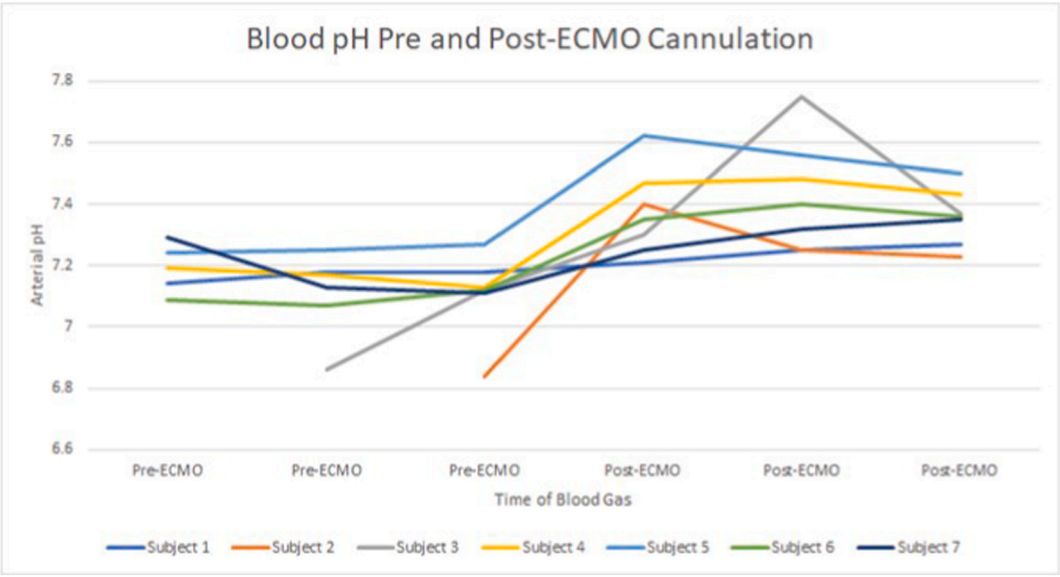


**Fig. 1.** Blood pH Pre- and Post-ECMO ECMO: Extracorporeal membrane oxygenation.

Ventilator settings were changed to assist-control pressure-control (AC/PC) 10/25/5/40% (respiratory rate/inspiratory pressure/PEEP/fraction of inspired oxygen). After 3 days, respiratory acidosis completely resolved, and bronchospasm and peak pressures improved on minimal ECMO settings. She was decannulated from VV ECMO and extubated on the same day (Table 3). She was eventually discharged home after 9 days in the hospital. She established outpatient pulmonary care with significant improvement in asthma control on high-dose LABA-ICS inhaler.

### *2.3. Patient 3*

A 37-year-old male with history of tobacco use and asthma presented with shortness of breath triggered during his work in roofing/construction. His only history of asthma exacerbation documented was a 20-day hospitalization for asthma a few months prior, for which he did not require intubation. Upon arrival to the ED, he was saturating >95% on room air, but VBG showed respiratory acidosis (Table 1, Figs. 1 and 2). Despite optimal therapy, he quickly decompensated with increased work of breathing, hypoxemia, and worsening encephalopathy requiring intubation. Post-intubation ABG showed profound respiratory acidosis (Table 2). Peak pressures were elevated to 70 $cmH_2O$, while receiving tidal volumes less than 100 mL. Immediate pre-ECMO ventilator settings were volume control with RR 12 bpm, Vt 350 mL, $FiO_2$ 100%, and PEEP 5 $cmH_2O$. Given persistent inability to ventilate and life-threatening acidosis, he was placed on VV ECMO; settings are seen in Table 2. He then experienced pulseless electrical activity; he was found to have bilateral pneumothoraces requiring chest tubes in the setting of elevated peak pressures and associated barotrauma. He was resuscitated for approximately 30 minutes until VV ECMO was switched to a veno-arterial-venous (VAV) ECMO for hemodynamic support. Ventilator settings were adjusted to AC/VC 14/250/60%/5 with improvement of peak pressures to 30 $cmH_2O$. Course was com-

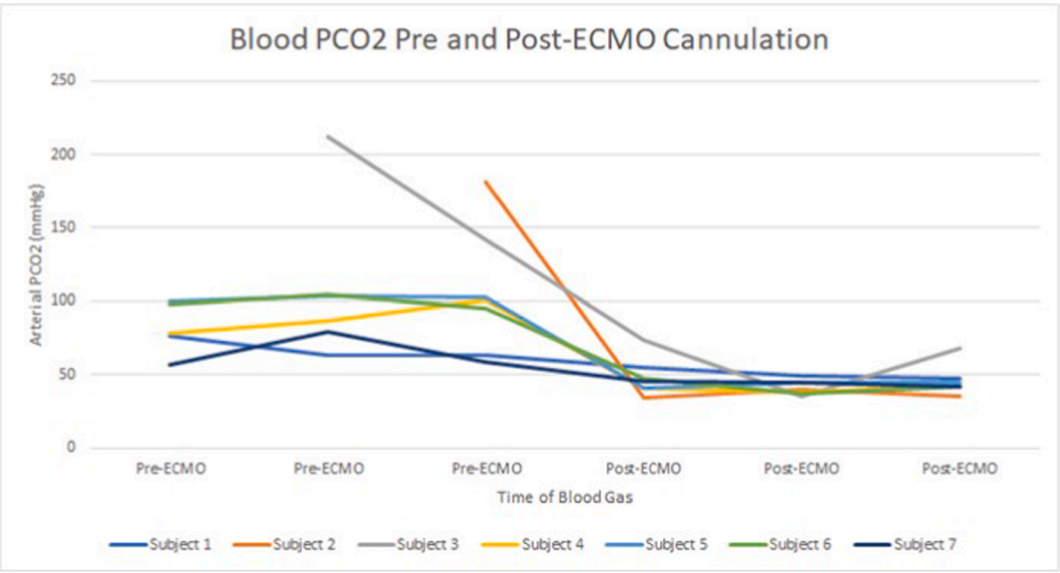


**Fig. 2.** Blood PCO2 Pre- and Post-ECMO Cannulation PCO2: Partial Pressure of Carbon dioxide, ECMO: Extracorporeal membrane oxygenation.

plicated by methicillin-sensitive *Staphylococcus aureus* (MSSA) and *Klebsiella pneumoniae* pneumonia. VAV-ECMO was converted back to VV ECMO after 2 days. By hospital day 9, VV ECMO settings were minimal, tolerating AC 18/470/80/5 with peak pressure of 35 and was decannulated from ECMO. He required tracheostomy placement given difficulty with ventilator liberation. During his time on ECMO, he was transfused 1 unit of blood for hemoglobin $<7$ g/dL, though there was no active bleeding. By the end of his 44-day hospitalization, his tracheostomy was decannulated prior to discharge home (Table 3). He established outpatient pulmonary care with significant improvement in asthma control on high-dose LABA-ICS inhaler and benralizumab biologic therapy.

### 2.4. Patient 4

A 38-year-old female with history of severe persistent asthma presented with dyspnea. She was non-compliant with her home albuterol and had 10 prior admissions the same year for asthma exacerbations. Although initial VBG did not show respiratory acidosis, she required intubation due to worsening encephalopathy and respiratory muscle fatigue despite BiPAP. She developed worsening hypoxemia and PIPs above 60 $cmH_2O$ due to significant bronchospasm and auto-PEEP from breath-stacking. Minute ventilation was decreased on the ventilator. Post-intubation ABG showed severe respiratory acidosis (Table 2). Despite 2 days of appropriate asthma therapy and MV, she had persistent bronchospasm, elevated peak pressures approximately 60 $cmH_2O$, and worsening respiratory acidosis. Immediate pre-ECMO ventilator settings were volume control with RR 14 bpm, Vt 400 mL, $FiO_2$ 100%, and PEEP 5 $cmH_2O$. She was placed on VV ECMO; initial settings are seen in Table 2. After 7 days on VV ECMO, bronchospasm improved significantly; PIP was 33 $cmH_2O$. She was decannulated with ventilator settings of AC/VC 23/400/80%/5. Six days after decannulation from VV ECMO, she was extubated to high flow nasal cannula 30 L FiO2 50%, which was quickly weaned to room air in the following days (Table 3). She was eventually discharged home after 22 days in the hospital. She established outpatient pulmonary care with significant improvement in asthma control on medium-dose LABA-ICS inhaler.

### 2.5. Patient 5

A 44-year-old female with history of asthma presented with an asthma exacerbation. She had no prior history of intubation. Initial VBG did not show respiratory acidosis (Table 2). She developed worsening dyspnea, wheezing, and increased work of breathing requiring BiPAP initiation, despite optimal therapy. Respiratory status worsened requiring intubation. She had persistent bronchospasm despite these measures with difficulty in ventilation; pCO2 ranged from 80 s to 100 s. Attempts to increase minute ventilation led to elevation in peak pressures in the 50 s and auto-PEEP. ABG at this time showed persistent respiratory acidosis (Table 2). Given progressive hypercapnia, the decision was made on hospital day 6 to initiate VV ECMO. Immediate pre-ECMO ventilator settings were volume control with RR 16 bpm, Vt 400 mL, $FiO_2$ 50%, and PEEP 5 $cmH_2O$. Initial ECMO settings are seen in Table 2. Her course was complicated by MSSA pneumonia and bacteremia. By hospital day 12 she was tolerating minimal ECMO settings and was subsequently decannulated. She was extubated to high flow nasal cannula the next day. She was discharged to acute rehab after 21 days of hospitalization (Table 3). She established outpatient pulmonary care with significant improvement in asthma control on high-dose LABA-ICS inhaler, long-acting muscarinic antagonist (LAMA) inhaler, and benralizumab biologic therapy.

### 2.6. Patient 6

A 29-year-old male with history of asthma presented with asthma exacerbation. He had 5 prior presentations to the emergency department within the past year for asthma exacerbations, although he never required intubation previously. He was only using a rescue albuterol inhaler. He was admitted to an outside hospital where he received optimal therapy and admitted to the medical floor. Respi-

ratory viral PCR returned positive for rhinovirus/enterovirus. He was initiated on BiPAP for increased work of breathing, which was later replaced with nasal cannula. The next morning, he was noted to have worsening work of breathing which was refractory to re-initiation of BiPAP with worsening hypercapnia and acidemia (Table 1, Figs. 1 and 2). He was transferred to the ICU and intubated; PIP was greater than 50 $cmH_2O$. Bronchoscopy was performed without any mucus plugs noted. ABG showed worsening respiratory acidosis (Table 2). Immediate pre-ECMO ventilator settings were volume control with RR 16 bpm, Vt 500 mL, $FiO_2$ 100%, and PEEP 5 $cmH_2O$. Our institution's mobile ECMO team was dispatched to the outside hospital where the patient was cannulated for VV ECMO with improvement in PIP to 30 $cmH_2O$. Initial ECMO settings are seen in Table 2. He was decannulated 5 days later. He remained intubated for 3 days due to worsening hypoxemia due to ventilator-associated pneumonia (VAP) and eventually discharged home (Table 3). He established outpatient pulmonary care with significant improvement in asthma control on high-dose LABA-ICS inhaler and dupilumab biologic therapy.

### 2.7. Patient 7

A 24-year-old man with history of asthma presented with asthma exacerbation in the setting of URI symptoms. Upon presentation to the emergency department, initial VBG showed respiratory acidosis (Table 1, Figs. 1 and 2). He was started on BiPAP but developed encephalopathy, hypoxemia, and worsened work of breathing, prompting intubation. Despite mechanical ventilation, he developed worsening mixed respiratory and metabolic acidosis (pH 7.13, pCO2 79, bicarbonate 22), severe bronchospasm and elevated peak pressure (58 $cmH_2O$). Attempts to decrease minute ventilation led to worsening acidosis despite IV fluid resuscitation. Notably, lactic acid was elevated to 8.9, likely in the setting of continuous albuterol as no infection was found. Immediate pre-ECMO ventilator settings were volume control with RR 18 bpm, Vt 500 mL, $FiO_2$ 40%, and PEEP 5 $cmH_2O$. Given life-threatening acidosis and elevated peak pressures, he was placed on VV ECMO; initial settings are shown in Table 2. Minute ventilation was decreased on the ventilator. Post-cannulation ABG showed improved acidosis. Peak pressure decreased to 40 $cmH_2O$. He was decannulated from VV ECMO after 5 days as bronchospasm and PIP improved. He then self-extubated the same day as decannulation, saturating well on room air in no respiratory distress. He was discharged home 3 days later (Table 3). He established outpatient pulmonary care with significant improvement in asthma control on medium-dose LABA-ICS inhaler.

## 3. Discussion

The indications for extracorporeal life support (ECLS) such as VV ECMO include hypercapnic respiratory failure (pH $<$ 7.25) despite optimal MV (respiratory rate $\leq$35 breaths/minute and plateau pressure $\leq$30 $cmH_2O$) and severe asthma [7]. Prior to consideration of VV ECMO cannulation, attempts should have been made to optimize I:E ratio with a respiratory rate 10–14 bpm; high inspiratory flow rates ($\geq$100 L/min) and square waveform can also shorten inspiration and prolong expiration [6]. VV ECMO provides adequate gas exchange during acute respiratory failure and can help prevent ventilator-induced lung injury due to excessive MV [8]. In severe exacerbations of asthma refractory to standard pharmacotherapy and MV, life-threatening levels of respiratory acidosis and dangerously elevated peak and plateau pressures can occur. The elevated peak and plateau pressures can result in barotrauma and hemodynamic instability. This was seen in one of our patients, who developed bilateral pneumothoraces and cardiac arrest. In these instances, VV ECMO can be a life-saving intervention.

Technical advances have made VV ECMO a promising organ support option for NFA while patients receive appropriate pharmacotherapy [8,9]. There have been two larger cohort studies analyzing the international Extracorporeal Life Support Organization (ELSO) registry data. In 2009, Mikkelson et al. analyzed 24 patients from the registry who were placed on VV ECMO for status asthmaticus and found an 83.3% survival rate. They also found that status asthmaticus, as an indication for ECLS in adult respiratory failure, seemed to be associated with greater survival than other indications for ECLS [8]. In 2017, Yeo et al. analyzed 272 patients from the registry who were placed on VV ECMO for NFA and found an 83.5% survival rate. They also found significant improvements in PIP and mean airway pressure; however, they noted a high complication rate, with 28.3% of patients experiencing hemorrhagic complications, the majority of which were cannula site hemorrhage [9].

We have amassed a case series of seven patients - 3 females, 4 males - who were admitted to our large urban quaternary care center from November 2019 to June 2022 who required VV ECMO for NFA despite maximum pharmacotherapy and MV; this included deep sedation, neuromuscular blockade, continuous nebulized treatment, systemic corticosteroids, magnesium, and controlled hypoventilation. Our study is unique in that we experienced a 100% survival rate among our cohort, as compared to approximately 83% survival rate with high incidence of hemorrhagic complications seen in prior ELSO registry analyses [8,9]. The time to ECMO cannulation in our cohort was shorter than that seen in ELSO registry analyses. On average, patients in this cohort spent 31 hours on MV prior to ECMO cannulation, as compared to 65.2 hours on MV prior to ECMO cannulation in Mikkelsen et al.'s ELSO registry analysis [8]. Yeo et al. found that organ failure and hemorrhage constituted the majority of death in NFA patients reported in the ELSO registry [9]. Earlier ECMO cannulation may prevent worsening organ failure, life-threatening acidosis, and barotrauma, which could account for our higher observed survival. The shortened time to ECMO cannulation was facilitated by our ECMO team, composed of cardiothoracic surgeons, that is always present in the hospital or on-call and able to cannulate at outside facilities, avoiding delays in ECMO cannulation prior to transfer to our institution.

Our study is further unique in that we experienced no hemorrhagic complications. One patient received one blood transfusion for hemoglobin $<$7 g/dL without any active hemorrhage. The lack of hemorrhagic complications is attributable to a conservative anticoagulation strategy; therapeutic anticoagulation was administered only if patients had a separate indication for anticoagulation, such as history of venous thromboembolism (VTE), or if they were supported with VAV ECMO. If the ECMO flow was sufficient, VTE prophylaxis with subcutaneous heparin was administered. The use of VTE prophylaxis alone with sufficient ECMO flow of 3–3.5 L/min

has been shown to result in no circuit thrombosis and significantly less gastrointestinal bleeding and blood transfusions than with the use of therapeutic anticoagulation [10]. It is unclear if the ECMO centers in the ELSO registry utilized a similar conservative strategy. As compared to other case reports and case series of ECMO utilization in adults with NFA, our patients tended to have a shorter time on MV prior to ECMO cannulation and/or a conservative anticoagulation strategy [11–17].

The most common reasons for cannulation to VV ECMO were elevated PIPs leading to low tidal volumes, hypercapnia, and acidosis. These patients clearly had a reversible cause of their respiratory failure - exacerbation of their asthma - and no contraindications to ECMO as defined by ELSO [7]. VV ECMO was utilized given cardiac and hemodynamic stability, except for the one patient who suffered cardiac arrest. Given cardiac arrest and hemodynamic instability, VAV ECMO was utilized. Mean PIP prior to VV ECMO cannulation was 65.7 $cmH_2O$, which improved in each subject post-cannulation to a mean PIP of 40.9 $cmH_2O$.

All patients experienced a significant reduction in PaCO2 and improvement in respiratory acidosis immediately following cannulation. Mean PaCO2 prior to ECMO cannulation was 116.3 mmHg which improved to 48.4 mmHg at first ABG post-cannulation (Fig. 2). Care should be taken to not lower pCO2 too rapidly; a previous large retrospective analysis showed increased risk of neurological complications, specifically intracranial hemorrhage with a large relative decrease in pCO2 following ECMO cannulation [18]. This can be achieved by minimizing minute ventilation and by setting a low sweep on the ECMO circuit. Mean time on ECMO was 7.6 days, which is in line with prior ELSO cohort studies [8,9]. Early extubation following ECMO decannulation was common; four of the seven patients were extubated within one day of decannulation. In addition to no hemorrhagic complications, no patients required surgical exploration or unplanned dressing changes of the cannula sites.

## 4. Conclusion

We have shown a cohort of seven patients with NFA refractory to MV who required cannulation of VV ECMO. Our case series is unique in that we experienced a 100% survival in this group with no hemorrhagic complications, despite similar time on ECMO as seen in prior cohort analyses of asthma patients within the ELSO registry. These analyses showed approximately 83% survival and high incidence of hemorrhagic complications in patients managed with VV ECMO for NFA. Our outcomes are attributable to our shorter time on MV pre-ECMO cannulation, the rapid availability of our ECMO team, and conservative anticoagulation strategy. This case series highlights the effectiveness and safety of VV ECMO in NFA that worsens despite optimal pharmacotherapy and MV.

## Author contributions

SG and SD contributed data analysis/interpretation, drafting of the article. EK contributed data collection and drafting of the article. MG and KS contributed critical revision of the article and approval of the article. PD contributed concept and design of the study, critical revision of the article, and approval of the article.

## Declaration of competing interest

The authors have no conflicts of interest to disclose. This manuscript has no relevant disclosures in the form of grants, gifts, or other forms of financial support. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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