Use of inhaled nitric oxide prognosticates poor survival in severe ARDS with venovenous ECMO: a retrospective analysis

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Abstract

Background

Inhaled nitric oxide (iNO) has not been sufficiently evaluated in adult patients with severe acute respiratory distress syndrome (ARDS) under venovenous extracorporeal membrane oxygenation (VV ECMO) support.

Objectives

This study aims to assess survival in patients with severe ARDS under VV ECMO with iNO.

Methods

Of the 657 patients under ECMO, 292 under VV ECMO were evaluated. Outcomes in the iNO group (n = 55) were compared with those of the propensity-matched (based on age, sex, height, and sequential organ failure assessment score at admission) control cohort (55 patients under VV ECMO without iNO). Median survival was analyzed using the Kaplan–Meier method, whereas the hazard ratio for in-hospital mortality with iNO use was analyzed using the proportional hazards model.

Results

Weaning failure from VV ECMO was higher in the iNO group (69.7% vs. 47.3%, p = 0.0033). Thirty percent of patients responded sufficiently to iNO, showing a lower pulmonary arterial pressure. Survival was lower in the iNO group compared with the control cohort (22 vs. 109 days, p = 0.0222). The length of stay in the intensive care unit (ICU) (23 vs. 33 days, p = 0.0186) and total hospital stay (27 vs. 35 days, p = 0.0085) were shorter with iNO use. Survival was lower and the risk of mortality (hazard ratio, 1.8; 95% CI 1.1–3.0, p = 0.027) was higher in patients with iNO administration.

Conclusions

Inhaled NO in patients under VV ECMO is a strong predictor of shorter median time of survival and in-house mortality.

Background

Inhaled nitric oxide (iNO) has been widely used as a selective pulmonary vasodilator to treat pulmonary arterial hypertension (PAH) and right heart failure (RV failure) (1). iNO is only distributed to ventilated lung regions and exerts the unique property of selectively inducing smooth muscle relaxation in the pulmonary vasculature in the said regions (1, 2). Thus, iNO improves blood oxygenation, decreases intrapulmonary shunting, and enhances blood flow distribution to improve alveolar ventilation (2, 3). The high affinity of nitric oxide (NO) to oxyhemoglobin in red blood cells leads to the rapid formation of nitrate and methemoglobin; this mechanism limits the vasodilation effects to the pulmonary vasculature and thereby avoids systemic arterial hypotension.
iNO concentrations of up to 80 parts per million (ppm) have been administered safely without unfavorable systemic side effects (6–8).

Patients suffering from acute respiratory distress syndrome (ARDS) frequently present with PAH whereas increased intrapulmonary shunting caused by perfusion of non-aerated alveoli contributes to severe arterial hypoxemia (9, 10). Moreover, elevated pulmonary artery pressure raises transcapillary pressure and thereby increases the risk of alveolar edema, which may aggravate ARDS (11, 12). In addition, PAH may lead or contribute to RV failure and is an independent risk factor for mortality in patients with ARDS (13, 14). Given its pharmacological properties, iNO may lower pulmonary artery pressure, thereby reducing the risk of RV failure and intrapulmonary shunting (15–17). Although randomized controlled trials (RCTs) on iNO use have shown both improved oxygenation and hemodynamics in the acute phase of ARDS in adults, all studies thus far have failed to demonstrate any clinically significant benefit of iNO on survival or ventilator-free days (18, 19).

Venovenous extracorporeal membrane oxygenation (VV ECMO), widely considered a life-saving procedure, may restore oxygenation and eliminate carbon dioxide accumulation when conventional mechanical ventilation fails to ensure a sufficient gas exchange in severe ARDS (20–22).

Patients with severe ARDS who are placed on VV ECMO support with concomitant iNO administration represent a very specific and limited cohort. Data that elucidate the use of iNO in this specific cohort are lacking; therefore, little is known about survival and mortality in this population. Thus, whether iNO would offer prognostic value in determining survival and risk of mortality in a propensity-matched cohort of patients with ARDS, PAH, and/or RV failure undergoing VV ECMO support was investigated.

**Methods**

**Study design**

This retrospective observational propensity-matched cohort study was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology statement.

**Objectives**

The primary objective was to evaluate the benefit of iNO on in-hospital survival in patients with severe ARDS, PAH, and/or RV failure under VV ECMO support despite respiratory optimization.

The secondary objectives were:

- To describe iNO treatment in terms of indication, dosing, and duration;
- To measure the iNO ability to lower mean pulmonary artery pressure (PAP) in patients under VV ECMO who are responders and nonresponders to iNO.
- To describe the clinical characteristics of the propensity-matched cohort, such as time on mechanical ventilation, weaning from VV ECMO, and organ dysfunction, as defined using the sequential organ failure assessment (SOFA) score (23);
- To measure outcome parameters, such as survival rate, in-hospital mortality, and long-term survival; and
- To calculate the rate of in-hospital mortality with the length of iNO administration.
Study population

Data on all ECMO procedures that were performed at the quaternary level of the University Hospital, Bonn, Germany, between May 2015 and May 2021 were collected.

Inclusion criteria

- Age > 18 years old;
- Electronic medical records available, including VV ECMO run parameters, vital parameters, and laboratory measurements (both point-of-care and laboratory diagnostics);
- VV ECMO support;
- ARDS following the Berlin definition (20); and
- iNO administration.

Exclusion criteria

- Venoarterial ECMO support.

Indication for ECMO

Indications for VV ECMO support complied with the Extracorporeal Life Support Organization General Guidelines (24). Indications included treatment of severe hypoxemia and hypercapnia and prevention of harmful mechanical ventilation (i.e., prolonged use of exceedingly high peak inspiratory pressures or driving pressure > 15 cmH₂O) to ensure sufficient gas exchange. All decisions for initiating VV ECMO support were based on the consensus between at least two experienced senior critical care physicians on the ARDS/ECMO team of the current study.

Indication for iNO delivery and definition of PAH and RV failure

iNO was administered at the treating physician’s discretion after bedside evaluation of pulmonary hemodynamics and right heart function, as indicated by invasive pulmonary hemodynamics (assessed using a Swan–Ganz catheter) and/or transesophageal echocardiography. A mean PAP (mPAP) ≥ 25 mmHg was used as a cutoff value for iNO application (25). A positive response to iNO was determined as an mPAP reduction ≥ 6 mmHg. Other indicators, such as pulmonary vascular resistance or cardiac index, were not used due to insufficient data regarding their validity during extracorporeal life support.

The echocardiographic definition of RV dysfunction is still debated. Recently, Vieillard-Baron et al. (26) suggested that in severe ARDS, acute cor pulmonale or severe RV dilatation accurately reflects RV failure, particularly when right atrial pressure is increased. In the present study, RV failure is defined by transesophageal echocardiography, as suggested by Vieillard-Baron et al.

Ethical approval /informed consent

Ethical approval for the current study was provided by the ethics committee (no. 492/20) of the University Hospital of Bonn, Germany, and the need for informed consent was waived.
Statistical analyses

For comparison with iNO-treated patients, a corresponding control cohort was assembled using propensity score matching as described by Randolph et al. (27). This was performed using the treatment-independent variables (i.e., age, sex, weight, height, and SOFA score) recorded at ECMO initiation. First day of VV ECMO support is considered as timepoint zero for both groups.

All data are presented as the median and interquartile range (IQR) for non-normally distributed variables or mean ± standard deviation for normally distributed continuous variables, as appropriate, and frequency distributions with percentages for categorical variables. The paired $t$-test was used to analyze group differences in normally distributed variables, whereas the Wilcoxon test was used for non-normally distributed variables. Nominal variables were assessed using McNemar’s test for 2 × 2 tables.

The Kaplan–Meier method and the stratified log-rank test were performed to analyze survival (28). A conditional logistic regression model was used to determine the individual hazard ratios (HRs) with 95% confidence intervals (CI) for iNO treatment (29, 30). All analyses were performed on R version 4.1.2 (31).

All tests were two-sided, and $p < 0.05$ was determined as the cutoff for significance. No adjustments were made for multiple tests, and $p$ values should be interpreted as exploratory only.

Results

Identification and characteristics of the eligible study cohort

To identify the eligible study cohort, 657 patients under ECMO were screened during the study period. Patients with complete electronic medical records were analyzed (Fig. 1). In addition, 292 patients who underwent VV ECMO support were identified as the eligible study cohort, which included 55 individuals with known PAH and/or RV failure administered with iNO and 237 not administered with iNO and without compromised pulmonary hemodynamics or RV dysfunction. The characteristics of all cohorts are provided in Tables 1 and 2.
Table 1  
Baseline characteristics – of both the total and propensity-matched cohorts.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TOTAL (n = 110)</th>
<th>with iNO (n = 55)</th>
<th>without iNO (n = 55)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age – (mean ± SD) [years]</td>
<td>55.01 ± 11.73</td>
<td>54.55 ± 11.61</td>
<td>55.48 ± 11.93</td>
<td>0.6392</td>
</tr>
<tr>
<td>Male sex – n (%) [male]</td>
<td>76 (69.1)</td>
<td>40 (72.7)</td>
<td>36 (65.5)</td>
<td>0.5403</td>
</tr>
<tr>
<td>Weight – (mean ± SD) [kg]</td>
<td>106.7 ± 38.97</td>
<td>107.92 ± 40.16</td>
<td>105.41 ± 38.06</td>
<td>0.7372</td>
</tr>
<tr>
<td>Height – (mean ± SD) [cm]</td>
<td>174.74 ± 9.54</td>
<td>175.76 ± 8.5</td>
<td>173.71 ± 10.45</td>
<td>0.2588</td>
</tr>
<tr>
<td>BMI – (mean ± SD)</td>
<td>34.94 ± 12.68</td>
<td>34.84 ± 12.66</td>
<td>35.02 ± 12.82</td>
<td>0.9392</td>
</tr>
<tr>
<td>Primary cause of ARDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral pneumonia – n (%)</td>
<td>38 (34.5)</td>
<td>22 (40)</td>
<td>16 (29.1)</td>
<td></td>
</tr>
<tr>
<td>Bacterial pneumonia – n (%)</td>
<td>20 (18.2)</td>
<td>8 (14.5)</td>
<td>12 (21.8)</td>
<td></td>
</tr>
<tr>
<td>Others – n (%)</td>
<td>52 (47.3)</td>
<td>25 (45.5)</td>
<td>27 (49.1)</td>
<td></td>
</tr>
<tr>
<td>Indication for iNO administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary arterial hypertension (PAH) – no. [%]</td>
<td>26 (47)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right heart failure (RHF) – no. [%]</td>
<td>20 (36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAH and RHF – no. [%]</td>
<td>9 (16)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

iNO: inhaled nitric oxide. SD: standard deviation. BMI: body mass index. ARDS: acute respiratory distress syndrome. PAH: pulmonary arterial hypertension. RV failure: right ventricular failure. p < 0.05 considered to be significant.
Table 2
Clinical characteristics - of both the total and propensity-matched cohorts.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TOTAL (n = 110)</th>
<th>with iNO (n = 55)</th>
<th>without iNO (n = 55)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive mechanical ventilation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total time on mechanical ventilation – (median (IQR)) [days]</td>
<td>31 (16–48.75)</td>
<td>24 (14–41.5)</td>
<td>32 (20.5–58)</td>
<td>*0.0281</td>
</tr>
<tr>
<td>Time on mechanical ventilation prior to ECMO support – (median (IQR)) [days]</td>
<td>2 (1–7)</td>
<td>2 (0.79–8)</td>
<td>2 (1–6)</td>
<td></td>
</tr>
<tr>
<td>Tracheostomy – n (%)</td>
<td>47 (42.7)</td>
<td>21 (38.2)</td>
<td>26 (47.3)</td>
<td></td>
</tr>
<tr>
<td><strong>ECMO</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of ECMO support – (median (IQR)) [days]</td>
<td>13 (8–19)</td>
<td>13.6 (9–19.9)</td>
<td>12.5 (8–17.75)</td>
<td></td>
</tr>
<tr>
<td>Weaning failure from ECMO support – n (%)</td>
<td>52 (57.3)</td>
<td>37 (67.3)</td>
<td>21 (38.2)</td>
<td>*0.0033</td>
</tr>
<tr>
<td><strong>Adjunctive therapies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRRT prior to ECMO – n (%)</td>
<td>33 (30.0)</td>
<td>19 (34.5)</td>
<td>14 (25.4)</td>
<td></td>
</tr>
<tr>
<td>Proning prior to ECMO</td>
<td>46 (41.8)</td>
<td>21 (38.2)</td>
<td>25 (45.5)</td>
<td></td>
</tr>
<tr>
<td>Proning during ECMO</td>
<td>59 (53.6)</td>
<td>30 (54.5)</td>
<td>29 (52.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Organ dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA-score – (mean ± SD)</td>
<td>7.95 ± 2.97</td>
<td>8.49 ± 2.96</td>
<td>7.42 ± 2.92</td>
<td></td>
</tr>
<tr>
<td>RESP-score – (mean ± SD)</td>
<td>-0.74 ± 3.9</td>
<td>-0.59 ± 3.65</td>
<td>-0.73 ± 3.95</td>
<td></td>
</tr>
<tr>
<td>No CPR prior to ECMO – n (%)</td>
<td>110 (100.0)</td>
<td>55 (100.0)</td>
<td>55 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Sepsis – n (%)</td>
<td>16 (15.8)</td>
<td>7 (14)</td>
<td>9 (17.6)</td>
<td></td>
</tr>
</tbody>
</table>

iNO: inhaled nitric oxide. SD: standard deviation. IQR: interquartile range. ECMO: extracorporeal membrane oxygenation. CRRT: continuous renal replacement therapy. SOFA: sequential organ failure assessment. RESP: Respiratory ECMO Survival Prediction. CPR: cardiopulmonary resuscitation. *p < 0.05 considered to be significant.

Propensity score matching (1:1) generated 55 individuals without iNO who were included for further analyses as the control cohort. The baseline characteristics of the propensity score-matched cohort (demographics and etiology of ARDS) are presented in Table 1. Variables that were used for propensity score matching (i.e., demographics and SOFA score) showed no differences between both cohorts (Tables 1 and 2). To further describe both the total and propensity-matched cohorts, all known medical histories of conditions indicated by the Charlson Comorbidity Index (32) are presented in Supplemental Table S1. The total time on mechanical ventilation – (median (IQR)) [days].
ventilation, time on mechanical ventilation before VV ECMO support, duration of VV ECMO support, weaning failure from VV ECMO, and rate of tracheostomy are presented in Table 2.

**Indication, dosing, and duration of iNO treatment in patients under VV ECMO**

To evaluate whether patients under VV ECMO support may benefit from iNO administration, transesophageal echocardiography, and/or invasive monitoring using a pulmonary artery catheter were performed before the start of iNO. Subsequently, three groups of indications were identified for the use of iNO in patients undergoing VV ECMO (Table 1): PAH, right heart failure, or a combination of both pathologies.

In addition, the iNO doses administered in the VV ECMO patient cohort were investigated (Fig. 2A). iNO was administered at an average dose of 14.5 ± 5.5 ppm (ranging from a minimum dose of 6.9 ppm to a maximum of 20 ppm). The duration of treatment was 3 days (IQR, 1.76–4.41; Fig. 2B).

**Ability of iNO to lower mean PAP in responder and nonresponder patients**

As mentioned in the Methods section, a positive response to iNO was defined as a mPAP decrease ≥ 6 mmHg. Responder patients with ARDS under VV ECMO showed a significant decrease in mPAP when iNO was administered (mPAP before iNO [40.1 ± 5.6 mmHg] vs. mPAP during iNO [30.5 ± 5.0 mmHg]; p < 0.0001; Fig. 2C). In contrast, nonresponder patients with ARDS did not show a significant decrease in mPAP during iNO treatment (mPAP before iNO [36.9 ± 8.1 mmHg] vs. mPAP during iNO [35.9 ± 8.2 mmHg]; p = 0.1873; Fig. 2D).

**Organ failure, ECMO circuit weaning, and rate of tracheostomy**

Weaning failure from VV ECMO support occurred with a significantly higher rate in iNO-treated patients compared with those without iNO treatment (n = 37 [67.3%] vs. n = 21 [38.2%]; p = 0.0033). Consecutively, the total time on mechanical ventilation was shorter in patients with concomitant iNO compared with iNO nonusers (24 vs. 32 days, p = 0.0281). No difference was found in the time on mechanical ventilation before VV ECMO, duration of VV ECMO, and rate of tracheostomy between patients treated with or without iNO (Table 2).

No differences in adjunctive therapies, i.e., continuous kidney replacement therapy and prone positioning before or during VV ECMO, were noted between the groups (Table 2). Apart from the SOFA score on hospital admission, the severity of further organ failure was assessed using the cardiopulmonary resuscitation rate before ECMO and the rate of sepsis, as defined by SEPSIS-3 (33). However, the values obtained did not differ between the groups.

**Standard ventilation parameters and blood gas analyses both on days 1, 3, and 7 during VV ECMO**

To avoid the onset of PAH and/or RV failure, optimizing respiratory conditions in patients with ARDS is strongly recommended because a driving pressure ≥ 18 cmH₂O, arterial partial pressure of carbon dioxide (PₐCO₂) ≥ 48 mmHg, and PₐO₂/FiO₂ < 150 mmHg have been reported as risk factors (34).

Ventilation parameters and blood gas analyses were both recorded on days 1, 3, and 7 during VV ECMO with or without iNO treatment (Table 3). These findings showed no differences in minute ventilation, positive end-
expiratory pressure (PEEP), or peak inspiratory pressure between the groups. Ventilation parameters, as well as blood gas analyses, showed results that comply with the respective ARDS guidelines on mechanical ventilation (35).

### Table 3
Ventilation parameters and blood gas analysis - of both the total and propensity-matched cohorts over time.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>with iNO (n = 55)</th>
<th>without iNO (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 3</td>
</tr>
<tr>
<td><strong>Ventilation parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minute ventilation – (median (IQR)) [l/min]</td>
<td>2.04 (1.68)</td>
<td>2.21 (2.25)</td>
</tr>
<tr>
<td>PEEP – (median (IQR)) [mbar]</td>
<td>20 (2)</td>
<td>20 (3.23)</td>
</tr>
<tr>
<td>Peak inspiratory pressure – (median (IQR)) [mbar]</td>
<td>26 (3)</td>
<td>26 (3)</td>
</tr>
<tr>
<td><strong>Blood gas analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO$_2$ – (median (IQR)) [mmHg]</td>
<td>103 (7)</td>
<td>102 (40.1)</td>
</tr>
<tr>
<td>PaCO$_2$ – (median (IQR)) [mmHg]</td>
<td>38.4 (7.37)</td>
<td>39.3 (7.13)</td>
</tr>
<tr>
<td>pH – (median (IQR))</td>
<td>7.30 (0.09)</td>
<td>7.34 (0.09)</td>
</tr>
<tr>
<td>PaO$_2$/FIO$_2$ – (median (IQR))</td>
<td>83.5 (37.5)</td>
<td>92 (36.2)</td>
</tr>
<tr>
<td>Minimal FIO$_2$ of a 24 hrs period</td>
<td>80 (20)</td>
<td>70 (25)</td>
</tr>
</tbody>
</table>


### Outcomes

Table 4 presents the data on the length of ICU and hospital stay, in-hospital mortality rate, and median survival time.
Table 4
Survival analysis - of both the total and propensity-matched cohorts.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TOTAL (n = 110)</th>
<th>with iNO (n = 55)</th>
<th>without iNO (n = 55)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Length of ICU stay – (median (IQR)) [days]</td>
<td>27.20 (14.30–49.82)</td>
<td>23.3 (13.55–39.1)</td>
<td>32.5 (17.95–62.45)</td>
<td>*0.0186</td>
</tr>
<tr>
<td>Length of hospital stay – (median (IQR)) [days]</td>
<td>29.60 (15.25–53.53)</td>
<td>27.1 (13.75–40)</td>
<td>34.5 (18–66.9)</td>
<td>*0.0086</td>
</tr>
<tr>
<td>In-hospital death – n(%)</td>
<td>68 (61.8)</td>
<td>38 (69.1)</td>
<td>30 (54.5)</td>
<td></td>
</tr>
<tr>
<td>Median survival time – [95% CI] [days]</td>
<td>33 [23;81]</td>
<td>22 [14; 37]</td>
<td>109 [31;1469]</td>
<td>*0.0222</td>
</tr>
</tbody>
</table>

iNO: inhaled nitric oxide. ICU: intensive care unit. IQR: interquartile range. CI: confidence interval. *p < 0.05 considered to be significant.

The length of ICU stay (23 vs. 33 days, p = 0.0186) and total hospital stay (27 vs. 35 days, p = 0.0086) were significantly shorter in the iNO group. The in-hospital mortality rate was higher in the iNO group (38/55) than in the control group (30/55). Median survival was significantly shorter in the iNO group compared with the control group (22 [95% CI, 14,37] vs. 109 [95% CI, 31,1469] days; p = 0.0222; Table 4). As the Kaplan–Meier curve in Fig. 3A shows, iNO use was linked to a lower long-term survival rate (p = 0.0222).

To evaluate whether survival may depend on the ability of iNO to lower elevated mPAP, a subgroup analysis of the survival rates was performed in the iNO responder and nonresponder groups. Figure 3B shows that the survival in the iNO group differed between iNO responders (36.4%) and nonresponders (23.1%), albeit not statistically significant (p = 0.0623).

**iNO administration is linked to an increased risk of mortality**

Cox proportional hazards analysis using the time point of iNO administration and in-hospital mortality as the independent and dependent variables, respectively, revealed that iNO during VV ECMO increased the risk of mortality by 1.8 (HR 1.1–3.0; p = 0.019; Fig. 4). iNO before or after ECMO support was not associated with an increased risk of in-hospital demise. However, patient numbers in the two groups were too small to draw relevant conclusions for the respective treatment timepoints.

**Discussion**

The main finding of this propensity-matched cohort study is reduced survival probability and an increased hazard ratio for in-hospital mortality despite iNO administration in patients with severe ARDS under VV ECMO.

Pulmonary vascular dysfunction is one of the pathophysiological hallmarks of ARDS and ultimately leads to a certain degree of PAH (36). Recent data suggest that PAH and subsequent RV failure are medical burdens that occur in every second patient with moderate to severe ARDS and are independently associated with the risk of mortality (36, 37). In ARDS, multiple pathophysiological mechanisms that directly cause injury to pulmonary circulation include endothelial dysfunction, distal pulmonary vascular occlusion at the capillary level, pulmonary
vasoconstriction, extrinsic vessel occlusion by alveoli distention, and, ultimately, vascular remodeling (38). These mechanisms lead to increased pulmonary vascular resistance, precapillary pulmonary hypertension, and increased RV afterload (38). The uncoupling between pulmonary circulation and the right heart ultimately leads to the breakdown of oxygen delivery.

Various strategies, including limiting volume loading and correcting blood pressure by infusing norepinephrine, have been suggested to decrease RV wall stress and RV end-diastolic pressure, thereby improving RV stroke volume (39). The patients of the current study received a restrictive fluid regimen and norepinephrine to avoid hypotension, as described previously (35).

Both hypoxia and hypercapnia strongly increase pulmonary vasoconstriction and contribute to PAH (40). Severe ARDS per se is associated with profound hypoxia, which may be accompanied by hypercapnia (41). Hypercapnia is the consequence of protective ventilatory strategies designed to reduce ventilator-induced lung injury. It also reflects increased dead space due to alveolar overdistension and ARDS severity (42).

Higher PEEP levels are frequently required in severe ARDS to avoid life-threatening hypoxia. However, transpulmonary pressure, despite low tidal ventilation when lung compliance decreases due to alveolar collapse, may be associated with increased end-inspiratory airway pressure (43). Consequently, pulmonary capillaries become stretched and their caliber is reduced, resulting in increased pulmonary vasoconstriction (44, 45).

By controlling arterial oxygenation and decarboxylation, even during ultraprotective ventilation (41), VV ECMO suppresses the major factors that increase pulmonary vascular resistance and cause PAH in severe ARDS, thereby sufficiently unloading the RV (46). In this study cohort, VV ECMO was indicated to correct hypoxemia and hypercapnia, as well as allow ultraprotective ventilation, to prevent peak inspiratory (> 27 cmH₂O) and/or driving (> 15 cmH₂O) pressure (Table 3). Although VV ECMO initiation in the current study resulted in adequate arterial oxygenation and normocapnia at a peak inspiratory and driving pressures < 25 cmH₂O and < 10 cmH₂O, respectively, PAH with or without RV failure persisted in 23% of the patients with severe ARDS.

Although iNO in ARDS has been widely abandoned by intensivists because RCTs and meta-analyses have demonstrated no benefits for survival despite temporal improvement in oxygenation (18, 19), it may be an option for decreasing RV afterload by lowering PAH (36). Intriguingly, however, this specific cohort presented with significantly reduced survival probability and an increased hazard ratio for in-hospital mortality with iNO administration.

These findings raise the question of whether iNO itself or the persisting PAH or RV failure may be the contributing factor. iNO use in ARDS has been widely studied over the last decades, and no evidence of direct NO toxicity has been observed at clinically relevant doses below 20 ppm (47). However, conflicting evidence has been reported on whether iNO contributes to increased acute kidney injury (48, 49). CKRT in this study did not indicate an increased rate of acute kidney injury before or during VV ECMO (Table 2). Thus, the potentially detrimental effects of iNO on kidney function can be excluded as a cause of increased mortality.

The optimal dose and time of iNO treatment in ARDS remains controversial. A European expert recommendation on the use of iNO in adults with ARDS suggested that toxic side effects (e.g., methemoglobinemia and the formation of relevant nitrogen dioxide levels) are less likely when inhaled NO doses stay < 20 ppm (47).
Initiating iNO treatment as early as 24–72 h after the onset of ARDS has been suggested because iNO is mainly effective during the early onset of ARDS. In this study, an average iNO dose of 14.5 ppm was administered, and iNO delivery was performed for a median duration of 3 days. iNO was initiated within 24 h after the diagnosis of either PAH and/or RV failure. In most of the patients, iNO was initiated during VV ECMO, as opposed to before or after VV ECMO, as administered in a small cohort. The current analyses revealed an increased hazard ratio for in-hospital mortality when iNO was used during VV ECMO support. In contrast, iNO administration before or after VV ECMO did not significantly affect the hazard ratio for in-hospital mortality. However, the number of included patients in both subgroups was too small to draw relevant conclusions in terms of in-hospital mortality. Intriguingly, a positive response to iNO was observed in only 30% of the patients of the current study. Similar findings were reported by Manktelow (50) on severe ARDS with septic shock. These studies were conducted before the widespread availability of VV ECMO and ultraprotective ventilator strategy. The data of the current study confirm the validity of this observation despite the use of current protective treatment regimens.

Other cofactors that may have contributed to the reduced survival probability and increased risk in the study cohort, i.e., age, sex, and disease severity at the time of VV ECMO initiation (indicated by SOFA score), were adjusted through propensity score matching. However, the iNO itself neither can be proven to reduce survival nor increase the risk of mortality due to the retrospective nature of the data collection.

Overall, the indication for iNO in this specific patient cohort (severe ARDS and VV ECMO) can be concluded to be a negative predictive variable for survival and risk of mortality. This cohort suffers from multiple comorbidities, all of which will worsen the clinical course of the patient regardless of iNO administration. Of note, the current study demonstrated that both groups did not differ in terms of comorbidities as indicated by the Charlson Comorbidity Index. This is further supported by the implementation of iNO in these patients as rescue therapy. The RCT conducted in the late 1990s that first described the use of iNO was performed in patients with mild to moderate ARDS. Thus, iNO administration in critically ill patients with severe ARDS under VV ECMO support should be very carefully discussed because beneficial effects are more than questionable in this specific patient cohort.

A limitation of this study is the retrospective and monocentric nature of the analyses. The availability of RCTs involving patients with severe ARDS is limited after initial RCTs failed to demonstrate any beneficial effects of iNO on survival and mortality. To further improve the significance of the current analyses, a propensity-matched approach in a large cohort of 479 patients under ECMO support was selected. The use of SOFA as a severity of illness matching estimate may not capture the true severity of illness in each group. However, none of the established ECMO outcome prediction scores is able to represent an additional treatment option (such as iNO) during ECMO support. The RESP-Score did not differ between groups. Nevertheless, retrospective analyses allow for an unbiased selection process of patients. All included patients were analyzed depending on treatment and thus were not subjected to selection bias for iNO treatment.

The possibility that RV failure *per se* contributed to the reduced survival probability cannot be excluded because the iNO treatment itself can only be analyzed. Intriguingly, no signs of PAH or RV failure were found in the propensity-matched cohort without iNO. Hence, iNO use indicates reduced survival probability but most likely does not cause it.
In summary, iNO administration in patients with severe ARDS and concomitant VV ECMO support was demonstrated to be a negative predictive variable of survival probability and risk of mortality. iNO in this specific cohort was concluded to only be recommended as a rescue therapy with questionable outcomes when all other options fail.

**Abbreviations**
<table>
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<tr>
<th>Abbr.</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>iNO</td>
<td>inhaled nitric oxide</td>
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<tr>
<td>ARDS</td>
<td>acute respiratory distress syndrome</td>
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<td>VV</td>
<td>venovenous</td>
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<td>ECMO</td>
<td>extracorporeal membrane oxygenation</td>
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<td>ICU</td>
<td>intensive care unit</td>
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<td>PAH</td>
<td>pulmonary arterial hypertension</td>
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<td>RV failure</td>
<td>right heart failure</td>
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<td>ppm</td>
<td>parts per million</td>
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<td>RCTs</td>
<td>randomized controlled trials</td>
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<td>PAP</td>
<td>pulmonary arterial pressure</td>
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<td>SOFA</td>
<td>sequential organ failure assessment</td>
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<td>mPAP</td>
<td>mean pulmonary arterial pressure</td>
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<td>IQR</td>
<td>interquartile range</td>
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<td>CI</td>
<td>confidence intervals</td>
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<tr>
<td>PEEP</td>
<td>positive end-expiratory pressure</td>
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<td>SD</td>
<td>standard deviation</td>
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<td>BMI</td>
<td>body mass index</td>
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<td>CRRT</td>
<td>continuous renal replacement therapy</td>
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<td>CPR</td>
<td>cardiopulmonary resuscitation</td>
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<td>PaO₂</td>
<td>arterial partial pressure of oxygen</td>
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<tr>
<td>PaCO₂</td>
<td>arterial pressure of carbon dioxide</td>
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<tr>
<td>F₁O₂</td>
<td>fraction of inspired oxygen</td>
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<tr>
<td>CCI</td>
<td>Charlson Comorbidity Index</td>
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<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
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<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
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<tr>
<td>AIDS</td>
<td>acquired immuno deficiency syndrome</td>
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<td>PSM</td>
<td>propensity score matching</td>
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**Declarations**

**Ethics approval and consent to participate:**
Ethical approval for the current study was provided by the ethics committee (no. 492/20) of the University Hospital of Bonn, Germany, and the need for informed consent was waived.

**Consent for publication:**

Not applicable.

**Availability of data and materials:**

The clinical datasets generated and/or analyzed during the current study are not publicly available due to the local data protection law but are available from the corresponding author on reasonable request.

**Competing interests:**

Stefan Muenster, M.D. is currently a member of the scientific advisory board that advises Air Liquide in the use of inhaled nitric oxide in adult patients undergoing cardiac surgery. All the other authors have no conflicts of interest to declare.

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**Authors Contributions:** All authors meet the ICMJE recommendations regarding authorship.

S.M., J.N., J-C.S., H.E., S.K., C.P., S.F.E made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

S.M., J.N., J-C.S., H.E., S.K., C.P., S.F.E drafted the work or revised it critically for important intellectual content; AND

All authors gave final approval of the version to be published; AND

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**References**


**Figures**
Figure 1

Inclusion process for the selected patient cohort. ECMO extracorporeal membrane oxygenation, VV venovenous, VA venoarterial, iNO inhaled nitric oxide, PSM propensity score matching. The observation period is from 2015 to 2021.
Figure 2

A Treatment summary of iNO therapy. B Duration of iNO treatment. C Mean PAP before and during iNO treatment in patients with ARDS under VV ECMO defined as iNO responders (decrease in mPAP during treatment ≥ 6 mmHg). D Mean PAP before and during iNO treatment in patients with ARDS under VV ECMO defined as iNO nonresponders (decrease in mPAP during treatment < 6 mmHg). Differences in mPAP were compared using the paired t-test with statistical significance at $p<0.01$. ppm parts per million, iNO inhaled nitric oxide, mPAP mean pulmonary artery pressure.
Figure 3

A Kaplan–Meier estimates of survival. Differences in survival were compared using the stratified log-rank test. iNO inhaled nitric oxide. B Subgroup analysis of the survival rates of inhaled nitric oxide responders and nonresponders.
Figure 4

Cox proportional hazards analysis using the time point of iNO administration as the independent variable and in-hospital mortality as the dependent variable revealed that iNO during VV ECMO increased the risk of mortality. *iNO* inhaled nitric oxide, *ECMO* extracorporeal membrane oxygenation.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- graphabstract.png
- TableS1.docx