The Use of Inhaled Prostaglandins in Patients With ARDS
A Systematic Review and Meta-analysis

Brian M. Fuller, MD, MSCI; Nicholas M. Mohr, MD; Lee Skrupky, PharmD, BCPS; Susan Fowler, MLIS; Marin H. Kollef, MD, FCCP; and Christopher R. Carpenter, MD

OBJECTIVE: This study aimed to determine whether inhaled prostaglandins are associated with improvement in pulmonary physiology or mortality in patients with ARDS and assess adverse effects.

METHODS: The following data sources were used: PubMed, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, reference lists, conference proceedings, and ClinicalTrials.gov. Studies selected included randomized controlled trials and nonrandomized studies. For data extraction, two reviewers independently screened titles and abstracts for eligibility. With regard to data synthesis, 25 studies (two RCTs) published over 21 years (1993-2014) were included. The PROSPERO registration number was CRD42014013180.

RESULTS: One randomized controlled trial showed no difference in the change in mean PaO₂ to FIO₂ ratio when comparing inhaled alprostadil to placebo: 141.2 (95% CI, 120.8-161.5) to 161.5 (95% CI, 134.6-188.3) vs 163.4 (95% CI, 140.8-186.0) to 186.8 (95% CI, 162.9-210.7), P = .21. Meta-analysis of the remaining studies demonstrated that inhaled prostaglandins were associated with improvement in PaO₂ to FIO₂ ratio (16 studies; 39.0% higher; 95% CI, 26.7%-51.3%), and PaO₂ (eight studies; 21.4% higher; 95% CI, 12.2%-30.6%), and a decrease in pulmonary artery pressure (−4.8 mm Hg; 95% CI, −6.8 mm Hg to −2.8 mm Hg). Risk of bias and heterogeneity were high. Meta-regression found no association with publication year (P = .862), baseline oxygenation (P = .106), and ARDS etiology (P = .816) with the treatment effect. Hypotension occurred in 17.4% of patients in observational studies.

CONCLUSIONS: In ARDS, inhaled prostaglandins improve oxygenation and decrease pulmonary artery pressures and may be associated with harm. Data are limited both in terms of methodologic quality and demonstration of clinical benefit. The use of inhaled prostaglandins in ARDS needs further study.

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In terms of mortality and survivor morbidity, ARDS exacts a significant toll on patients and the health-care system.\(^1\) Shunt physiology drives hypoxemia; pulmonary hypertension is common and may have adverse prognostic significance.\(^2,3\) The use of inhaled pulmonary vasodilators, which could improve oxygenation by preferentially improving perfusion to well-ventilated lung regions and reduce pulmonary pressures, therefore, has physiologic rationale. Inhaled nitric oxide (iNO) continues to be used for a significant minority of patients with ARDS.\(^6,7\) While shown to improve oxygenation, meta-analyses of randomized trials demonstrate no mortality benefit with iNO, and an association with harm.\(^8,9\) It is unknown whether other inhaled pulmonary vasodilators are associated with similar physiologic or clinical outcomes.

The inhaled prostaglandins epoprostenol (prostacyclin E\(_1\) [PGE\(_1\)]; Flolan) and alprostadil (prostaglandin E\(_2\) [PGI\(_2\)]; Prostin VR) promote pulmonary vasodilation via a cyclic adenosine monophosphate-mediated decrease in intracellular calcium.\(^10\) They also have antiinflammatory and antiplatelet aggregation properties, providing further potential mechanistic benefit in ARDS.\(^10-15\) One observational study demonstrated the use of inhaled epoprostenol in 22% of patients with severe ARDS treated with extracorporeal support.\(^16\) A systematic review that included only one randomized controlled trial (RCT) of 14 pediatric patients concluded that enough evidence did not exist to support or refute the use of inhaled epoprostenol in ARDS.\(^17\) However, other clinical studies have been completed since this review was published. As such, it is unknown whether the use of inhaled prostaglandins in ARDS provides any benefit.

Therefore, the objectives of this study were to perform a systematic review of the literature, including RCTs and observational studies, to determine whether the inhaled prostaglandins epoprostenol and alprostadil are associated with an improvement in pulmonary physiology (eg, oxygenation, pulmonary artery pressures) or mortality in postneonatal children and adults with ARDS.

An assessment of the adverse effects associated with this therapy was also an aim of interest. Based on the existing data regarding iNO, the primary hypothesis was that the use of inhaled prostaglandins would be associated with an improvement in oxygenation and pulmonary artery pressures, but would not confer any mortality benefit.

Materials and Methods

This systematic review was designed, conducted, and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (e-Appendix 1) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) (e-Appendix 2) guidelines.\(^18,19\) It was registered with PROSPERO (registration number CRD42014013180). Ethical approval from the Human Research Protection Office at the principal investigator’s institution was not required.

Search and Identification of Studies

A written protocol (e-Appendix 3) that was finalized prior to beginning the search was followed. The timeline was from 1976 (discovery of PGI\(_2\)) through 2014, and searched PubMed, EMBASE, Cumulative Index of Nursing and Allied Health Literature (CINAHL), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews. Searches were completed in May 2014. A trained medical librarian (S. F.) experienced in systematic reviews assisted in designing the search strategy and in conducting the electronic search. Two authors (B. M. F. and N. M. M.) also manually screened reference lists of articles selected for inclusion to identify additional studies. To identify potential unpublished data, B. M. F. also (1) searched abstracts from

Institutes of Health National Center for Advancing Translational Sciences.

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Assessment of Study Quality

The quality of clinical trials selected for inclusion was assessed by using the Cochrane Collaboration Tool for assessing the risk of bias in clinical trials. High quality was defined as a grade of “A” in at least three of the four methodology domains. For studies of observational design, quality was assessed with the Newcastle-Ottawa Scale, assigning a maximum of nine points. Five or fewer points indicated a high risk of bias.

Assessment of Publication Bias

A graphic display (funnel plot) of the size of the treatment effect against the precision of the trial was used to evaluate for potential publication bias.

Data Analysis

During the conduct of the systematic review, a scoping review of the literature revealed a lack of controls from which to compare mortality or adverse events. Therefore, the decision was made to assess physiologic end points as the primary outcomes, including oxygenation parameters (Pao2/Fio2 ratio and Pao2), and mean pulmonary artery pressure (mPAP). Secondary outcomes included mortality and adverse effects.

Meta-analysis: Review Manager (RevMan, Version 5.1; The Nordic Cochrane Centre, The Cochrane Collaboration) was used to conduct the meta-analysis. A generic inverse variance, random effects model was used. Continuous data are reported as mean difference (measure of absolute change). Overall effect estimates were generated using a Z test and presented as mean differences (measures of absolute change). A P value of ≤ .05 was considered statistically significant. The decision to combine the data on epoprostenol and alprostadil was made a priori. The decision to not combine evidence from randomized trials and nonrandomized studies was also made a priori, as per expert recommendation. Stratified subgroup analyses were performed, as were sensitivity analyses, which excluded the study with the largest mean difference in Pao2/Fio2 ratio and the largest number of patients.

Heterogeneity between studies was assessed using the F statistic, with suggested thresholds for low (25%-49%), moderate (50%-74%), and high (≥ 75%) values. During the systematic review, it was evident that the secondary outcomes (mortality and adverse effects) could not be assessed quantitatively. A post hoc decision was, therefore, made to report overall mortality and reported adverse effects in a descriptive, qualitative fashion. A post hoc decision to use a x2 test to compare differences in the rate of hypotension between the observational cohort studies (longer exposure to inhaled prostaglandins) and the prospective studies (very brief exposure to inhaled prostaglandins) was also made.

Meta-Regression: The I2 statistic indicated significant heterogeneity among the entire collection of data. Subgroup analysis and meta-regression were performed to explain some of the heterogeneous effect sizes between studies. Possible sources of heterogeneity tested included baseline oxygenation, pulmonary vasodilator dosing, source of ARDS (pulmonary vs nonpulmonary), and study year. A linear meta-regression model weighted to reflect the variance of the individual studies was used to model the data. OpenMeta [Analyst] (Center for Evidence-Based Medicine, Brown School of Public Health) was used for regression with continuous covariates.

Results

Search and Selection

The comprehensive search yielded a total of 380 potentially relevant publications. Details regarding the search, study selection, and reason for exclusion are shown in Figure 1.

Inclusion

After the relevance search, a complete manuscript review was performed on the remaining 47 articles. Twenty-five studies were included in the final analysis.

Study Characteristics and Outcomes Reporting

The characteristics of the included studies are shown in Tables 1 and 2. Two studies were RCTs, six were prospective, nonrandomized interventional studies, 10 were observational studies, and seven were case series. The total number of patients across studies was 606 (n = 497 epoprostenol, n = 109 alprostadil, median 11 patients per study).

The RCTs were rated as high quality by the Cochrane Collaboration Tool for assessing the risk of bias in clinical trials. On the nine-point Newcastle-Ottawa Scale, the median risk of bias score was 5, indicating a high risk of bias. The main risk of bias was selection bias (eg, lack of a nonexposed cohort) and information bias (eg, lack of description in outcome assessment).

Figure 1 – Search, inclusion, and exclusion flow diagram.
### TABLE 1  
Study Characteristics of Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>N</th>
<th>Therapy</th>
<th>Duration of Therapy</th>
<th>Timing of Therapy</th>
<th>High-Quality RCT?</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dahlem et al 2004</td>
<td>14</td>
<td>PGI₂</td>
<td>~125 min ICU day 3</td>
<td>Yes</td>
<td>OI</td>
<td>Hemodynamics, LVEDP</td>
<td>Crossover with normal saline placebo</td>
<td></td>
</tr>
<tr>
<td>Siddiqui et al 2013</td>
<td>67</td>
<td>PGE₁</td>
<td>30 min Within 24 h</td>
<td>Yes</td>
<td>Diastolic dysfunction, PaO₂:FIO₂</td>
<td>Double-blind, with normal saline placebo control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continuous data are presented as mean (SD) unless otherwise noted. LVEDP = left ventricular end-diastolic pressure; PGE₁ = alprostadil; PGI₂ = epoprostenol; RCT = randomized controlled trial.

- Timing of therapy reported variably across studies and is referenced either to onset of ARDS, respiratory failure, or ICU day.
- As assessed by the Cochrane Collaboration Tool for assessing risk of bias in clinical trials. Four domains were assessed: random sequence generation, concealment of allocation, blinding, and selective outcome reporting. High quality was defined as a grade of “A” in at least three-fourths of the methodology domains. To explain, for trials where blinding is not feasible at the point of intervention, a grade of “A” would be assigned if the investigator collecting the primary outcome was blinded to the treatment allocation.
- Some outcomes were not explicitly stated or defined in the manuscript as primary or secondary outcomes, but reported as such in the table.

The primary outcome was physiologic in 24 of 25 studies (oxygenation, pulmonary artery pressures) and clinical (length of stay, mortality) in four (e-Table 1).
**TABLE 2**  | Study Characteristics of Nonrandomized Studies

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>N</th>
<th>Therapy</th>
<th>Duration of Therapy</th>
<th>Timing of Therapy</th>
<th>Risk of Bias (NOS Score)</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, nonrandomized interventional studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walrmrath et al[3]/1996</td>
<td>16</td>
<td>PGI₂</td>
<td>&lt;70 min</td>
<td>1-4 d</td>
<td>High (5)</td>
<td>PaO₂, FIO₂, Pao₂, shunt</td>
<td>mPAP, PVR</td>
<td>Crossover study with iNO</td>
</tr>
<tr>
<td>Van Heerden et al[3]/1996</td>
<td>5</td>
<td>PGI₂</td>
<td>30 min</td>
<td>Not reported</td>
<td>High (4)</td>
<td>Pao₂, mPAP</td>
<td>None stated</td>
<td>Crossover study with iNO</td>
</tr>
<tr>
<td>Zwissler et al[3]/1996</td>
<td>8</td>
<td>PGI₂</td>
<td>45 min</td>
<td>10.3 d</td>
<td>High (5)</td>
<td>Pao₂, mPAP, PVR, shunt</td>
<td>Establish dose-response curve and optimal safe dose</td>
<td></td>
</tr>
<tr>
<td>Putensen et al[3]/1998</td>
<td>10</td>
<td>PGE₁</td>
<td>100 min</td>
<td>16 (1)</td>
<td>High (5)</td>
<td>Pao₂</td>
<td>mPAP, PVR, RVEF</td>
<td>Crossover with iNO and IV PGE₁</td>
</tr>
<tr>
<td>van Heerden et al[3]/2000</td>
<td>9</td>
<td>PGI₂</td>
<td>150 min</td>
<td>5.8 d</td>
<td>High (5)</td>
<td>Pao₂, FIO₂, A-a gradient</td>
<td>6-keto PGF1α, platelet aggregation</td>
<td></td>
</tr>
<tr>
<td>Domenighetti et al[3]/2001</td>
<td>15</td>
<td>PGI₂</td>
<td>75 min</td>
<td>32 (2) h</td>
<td>High (5)</td>
<td>Pao₂, FIO₂, Pao₂</td>
<td>mPAP, PVR</td>
<td>Examined difference between pulmonary and nonpulmonary ARDS</td>
</tr>
<tr>
<td>Observational cohort studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meyer et al[3]/1998</td>
<td>15</td>
<td>PGE₁</td>
<td>103 (17) h, range 1-7 d</td>
<td>42 (8) h</td>
<td>High (5)</td>
<td>Pao₂, Pao₂, FIO₂</td>
<td>None stated</td>
<td></td>
</tr>
<tr>
<td>Siobal et al[3]/2003</td>
<td>11</td>
<td>PGI₂</td>
<td>Mean 41 h, range 9-116 h</td>
<td>3.9 (3.4) d</td>
<td>High (5)</td>
<td>Pao₂, FIO₂, SPO₂</td>
<td>None stated</td>
<td></td>
</tr>
<tr>
<td>Rovira et al[3]/2004</td>
<td>5</td>
<td>PGI₂</td>
<td>1-3 d</td>
<td>1-2 d</td>
<td>High (4)</td>
<td>Pao₂, FIO₂</td>
<td>None stated</td>
<td>Abstract only</td>
</tr>
<tr>
<td>Camamo et al[3]/2005</td>
<td>27</td>
<td>PGI₂ (n = 10), PGE₁ (n = 17)</td>
<td>5.9 (7.6) d, 4.6 (3.1) d</td>
<td>Not reported</td>
<td>High (4)</td>
<td>Pao₂, FIO₂, Pao₂</td>
<td>Differences between the two drugs on clinical outcomes</td>
<td></td>
</tr>
<tr>
<td>Raheem[4]/2009</td>
<td>15</td>
<td>PGI₂</td>
<td>23 (1-46) h</td>
<td>Not reported</td>
<td>High (4)</td>
<td>Pao₂, FIO₂</td>
<td>None stated</td>
<td>Abstract only</td>
</tr>
</tbody>
</table>

*Continued*
<table>
<thead>
<tr>
<th>Study/Year</th>
<th>N</th>
<th>Therapy</th>
<th>Duration of Therapy</th>
<th>Timing of Therapy</th>
<th>Risk of Bias (NOS Score)</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ross et al /2012</td>
<td>12</td>
<td>PGI₂</td>
<td>4.2 (2.5) d, range 1-9 d</td>
<td>Not reported</td>
<td>High (4)</td>
<td>Pao₂:Fio₂, SpO₂, A-a gradient</td>
<td>Not stated</td>
<td>Abstract only Compared with iNO</td>
</tr>
<tr>
<td>Dunkley et al /2013</td>
<td>16</td>
<td>PGI₂</td>
<td>4.8 (6.0) d</td>
<td>Not reported</td>
<td>High (3)</td>
<td>Pao₂:Fio₂ at 4 h, medication errors</td>
<td>Dose response, therapy duration, adverse events, mortality</td>
<td>...</td>
</tr>
<tr>
<td>Pacheo et al /2014</td>
<td>216</td>
<td>PGI₂</td>
<td>Survivors 118.5 (85.1) h; nonsurvivors 99.1 (108.7) h</td>
<td>Survivors 55.2 (76.8) h; nonsurvivors 69.6 (93.8) h</td>
<td>Low (7)</td>
<td>Hospital mortality, 90-d mortality</td>
<td>Not stated</td>
<td>...</td>
</tr>
<tr>
<td>Torbic et al /2013</td>
<td>32</td>
<td>PGI₂</td>
<td>3.2 (2.6) d</td>
<td>Not reported</td>
<td>Low (6)</td>
<td>Pao₂:Fio₂ at 1 h</td>
<td>ICU LOS, HLOS, Duration of therapy, MV duration, adverse events, cost</td>
<td>Compared PGI₂ to iNO</td>
</tr>
<tr>
<td>Singh et al /2014</td>
<td>98</td>
<td>PGI₂</td>
<td>Not reported</td>
<td>Not reported</td>
<td>High (5)</td>
<td>Pao₂:Fio₂</td>
<td>Not stated</td>
<td>Abstract only</td>
</tr>
</tbody>
</table>

**TABLE 2 (continued)**

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>N</th>
<th>Therapy</th>
<th>Duration of Therapy</th>
<th>Timing of Therapy</th>
<th>Risk of Bias (NOS Score)</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walmrath et al /1993</td>
<td>3</td>
<td>PGI₂</td>
<td>~90 min</td>
<td>2-3 d</td>
<td>N/A</td>
<td>Pao₂:Fio₂, mPAP</td>
<td>Shunt</td>
<td>...</td>
</tr>
<tr>
<td>Bein et al /1994</td>
<td>1</td>
<td>PGI₂</td>
<td>30 min</td>
<td>Not reported</td>
<td>N/A</td>
<td>Pao₂, mPAP</td>
<td>Not stated</td>
<td>...</td>
</tr>
<tr>
<td>Pappert et al /1995</td>
<td>3</td>
<td>PGI₂</td>
<td>Not reported</td>
<td>Day 15-55</td>
<td>N/A</td>
<td>Pao₂:Fio₂</td>
<td>Not stated</td>
<td>Studied children</td>
</tr>
<tr>
<td>van Heerden et al /1996</td>
<td>2</td>
<td>PGI₂</td>
<td>~48 h</td>
<td>Not reported</td>
<td>N/A</td>
<td>Pao₂:Fio₂</td>
<td>Not stated</td>
<td>...</td>
</tr>
<tr>
<td>van Heerden et al /1997</td>
<td>1</td>
<td>PGI₂</td>
<td>~5 d</td>
<td>Not reported</td>
<td>N/A</td>
<td>Pao₂</td>
<td>6-keto PGF₁α, platelet aggregation</td>
<td>...</td>
</tr>
<tr>
<td>Allan et al /2010</td>
<td>1</td>
<td>PGI₂</td>
<td>~31 h</td>
<td>~1.5 d</td>
<td>N/A</td>
<td>Pao₂:Fio₂, Pao₂</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>McMillen et al /2011</td>
<td>4</td>
<td>PGI₂</td>
<td>72.5 (58.8-99.8) h</td>
<td>Day 1-8</td>
<td>N/A</td>
<td>Pao₂:Fio₂</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Continuous data are presented as mean (SD) unless otherwise noted. A-a = alveolar-arterial oxygenation; HLOS = hospital length of stay; iNO = inhaled nitric oxide; LOS = length of stay; mPAP = mean pulmonary artery pressure; MV = mechanical ventilation; N/A = not applicable; NOS = Newcastle-Ottawa Scale; OI = oxygenation index [(Fio₂ x mean airway pressure)/Pao₂]; PGF₁α = prostaglandin F₁α; PVR = pulmonary vascular resistance; RVEF = right ventricular ejection fraction; SpO₂ = peripheral oxygen saturation. See Table 1 legend for expansion of other abbreviations.

aTiming of therapy reported variably across studies and is referenced either to onset of ARDS, respiratory failure, or ICU day.

bAs assessed by the Newcastle-Ottawa Quality Assessment Scale.

cSome outcomes were not explicitly stated or defined in the manuscript as primary or secondary outcomes, but reported as such in the table.
**Table 3**  Stratified Summary Values for Meta-analyses

<table>
<thead>
<tr>
<th>Stratification</th>
<th>No. of Studies (Patients), Meta-analysis</th>
<th>Mean Difference [95% CI]</th>
<th>P Value</th>
<th>I² %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All datasets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Pao_2$: $Fio_2$</td>
<td>16 (497)</td>
<td>39.00 [26.68, 51.31]</td>
<td>&lt;.0001</td>
<td>92</td>
</tr>
<tr>
<td>mPAP</td>
<td>7 (76)</td>
<td>-4.79 [-6.75, -2.83]</td>
<td>&lt;.0001</td>
<td>95</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Pao_2$: $Fio_2$</td>
<td>15 (465)</td>
<td>35.68 [23.67, 47.69]</td>
<td>&lt;.0001</td>
<td>92</td>
</tr>
<tr>
<td>$Pao_2$</td>
<td>6 (66)</td>
<td>20.72 [9.15, 32.29]</td>
<td>.004</td>
<td>97</td>
</tr>
<tr>
<td>mPAP</td>
<td>5 (51)</td>
<td>-3.75 [-5.71, -1.78]</td>
<td>&lt;.0001</td>
<td>95</td>
</tr>
<tr>
<td>Alprostadil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Pao_2$: $Fio_2$</td>
<td>2 (32)</td>
<td>77.45 [-42.67, 197.57]</td>
<td>.21</td>
<td>92</td>
</tr>
<tr>
<td>$Pao_2$</td>
<td>3 (42)</td>
<td>16.79 [4.27, 29.32]</td>
<td>.009</td>
<td>92</td>
</tr>
<tr>
<td>mPAP</td>
<td>2 (25)</td>
<td>-7.14 [-9.08, -5.20]</td>
<td>&lt;.0001</td>
<td>54</td>
</tr>
<tr>
<td>Prospective, interventional studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Pao_2$: $Fio_2$</td>
<td>3 (40)</td>
<td>13.07 [2.78, 23.35]</td>
<td>.01</td>
<td>78</td>
</tr>
<tr>
<td>$Pao_2$</td>
<td>5 (54)</td>
<td>19.17 [9.26, 29.07]</td>
<td>.0002</td>
<td>98</td>
</tr>
<tr>
<td>mPAP</td>
<td>5 (58)</td>
<td>-4.35 [-6.52, -2.19]</td>
<td>&lt;.0001</td>
<td>97</td>
</tr>
<tr>
<td>Cohort studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Pao_2$: $Fio_2$</td>
<td>13 (457)</td>
<td>46.91 [31.33, 62.49]</td>
<td>&lt;.0001</td>
<td>91</td>
</tr>
<tr>
<td>$Pao_2$</td>
<td>3 (54)</td>
<td>25.89 [-5.23, 57.01]</td>
<td>.10</td>
<td>96</td>
</tr>
<tr>
<td>mPAP</td>
<td>2 (18)</td>
<td>-6.19 [-8.25, -4.12]</td>
<td>&lt;.0001</td>
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<tr>
<td>Publication y, 1993-2000</td>
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<tr>
<td>$Pao_2$: $Fio_2$</td>
<td>6 (50)</td>
<td>32.30 [17.12, 47.47]</td>
<td>&lt;.0001</td>
<td>89</td>
</tr>
<tr>
<td>$Pao_2$</td>
<td>5 (54)</td>
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<td>&lt;.0001</td>
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</tr>
<tr>
<td>mPAP</td>
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<td>Publication y, 2001-2014</td>
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<tr>
<td>$Pao_2$: $Fio_2$</td>
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</tr>
<tr>
<td>$Pao_2$</td>
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<td>.31</td>
<td>96</td>
</tr>
<tr>
<td>mPAP</td>
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<tr>
<td>High risk of bias</td>
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</tr>
<tr>
<td>$Pao_2$: $Fio_2$</td>
<td>11 (239)</td>
<td>33.73 [21.64, 45.83]</td>
<td>&lt;.0001</td>
<td>87</td>
</tr>
<tr>
<td>mPAP</td>
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<td>-4.60 [-6.61, -2.59]</td>
<td>&lt;.0001</td>
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<tr>
<td>Low risk of bias</td>
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<tr>
<td>$Pao_2$: $Fio_2$</td>
<td>2 (248)</td>
<td>65.41 [2.30, 128.52]</td>
<td>.04</td>
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<td>$Pao_2$</td>
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<tr>
<td>Exclusion of case series</td>
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<tr>
<td>$Pao_2$: $Fio_2$</td>
<td>13 (487)</td>
<td>41.16 [26.60, 55.73]</td>
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<td>6 (73)</td>
<td>-4.60 [-6.61, -2.59]</td>
<td>&lt;.0001</td>
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</table>

See Table 2 legend for expansion of abbreviations.
studies were more homogeneous with respect to size (n = 5-16 patients) and duration of intervention (very brief exposure to inhaled prostacyclins). The subgroup analyses are presented in Table 3. A similar effect on physiology was seen in the subgroup analyses. After exclusion of the study with the largest mean difference in \( \text{Pa}_2 : \text{Fi}_2 \) ratio, analysis demonstrated that inhaled prostaglandins were associated with improved \( \text{Pa}_2 \) to \( \text{Fi}_2 \) ratio (15 studies, 482 patients, 964 measurements; 35.7% higher, 95% CI, 23.7%-47.7%). A similar result was obtained when excluding the study with the largest number of patients (15 studies, 281 patients, 562 measurements; 33.0% higher, 95% CI, 23.2%-42.9%).

**Meta-regression:** Linear meta-regression was used to assess the impact of continuous covariates on treatment effect. Year of publication (\( P = .862 \)), baseline \( \text{Pa}_2 \) to \( \text{Fi}_2 \) ratio (\( P = .106 \)), and proportion of nonpulmonary ARDS (\( P = .816 \)) were not associated with the treatment effect. A dose-response relationship was tested among studies that reported data separately for cohorts with a defined dose, and higher doses of inhaled prostaglandins increased \( \text{Pa}_2 \) to \( \text{Fi}_2 \) ratio linearly (Fig 4).

**Adverse effects**

Adverse events were variably reported overall. Twenty studies mentioned adverse events, or a lack of adverse

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**Figure 2** – A-C: Effect of inhaled prostaglandins on \( \text{Pa}_2 \) to \( \text{Fi}_2 \) ratio (A), \( \text{Pa}_2 \) (B), and mean pulmonary artery pressure (C). These parameters were assessed in a before-after fashion with respect to prostaglandin therapy. Therefore, the term “Total” refers to the number of measurements taken, which is exactly double the number of total patients in each study. df = degrees of freedom.
effects (eg, “no effect on blood pressure”), somewhere in the manuscript (e-Table 2). Eleven studies reported no effect on systemic hemodynamics, while five studies reported hypotension, ranging from an incidence of 12.5% to 33.3%. There was a statistically significant difference in the rate of hypotension between the prospective studies vs the observational studies, 0.69% (1 of 144) vs 27 of 155 (17.4%) ($P < .001$). Three studies reported thrombocytopenia, anemia, or transfusion requirement.

**Mortality**

Mortality was reported in 17 of 25 studies (e-Table 3). Due to lack of controls, an investigation into an association of inhaled prostaglandin with mortality could not be ascertained. The overall reported mortality in patients with ARDS receiving inhaled prostaglandins was 295 of 522 (56.5%).

**Discussion**

In patients with ARDS, the traditional inhaled pulmonary vasodilator of choice has been iNO, with little data on inhaled prostaglandins. This systematic review and meta-analysis was, therefore, undertaken to assess outcomes associated with inhaled prostaglandins. The first finding is that inhaled prostaglandins appear to be used with some frequency in ARDS. This is demonstrated by the 25 publications included in the analysis, as well as the discovery of several other studies not meeting the inclusion criteria. The data would also suggest that use is increasing in frequency, as approximately 75% of the patients were from studies published in the last 3 years. This is an interesting phenomenon when put into context of other findings in this analysis: (1) a lack of clinical outcome data demonstrating benefit, (2) overall low quality for the
majority of data, and (3) significant heterogeneity in the data that does exist.

Only one study, to our knowledge, reported a clinical outcome as a primary analysis of interest. The two RCTs that exist had very brief exposure to study drug and did not study patient-centered outcomes. Furthermore, one RCT included only children, a potentially unique population with respect to ARDS incidence, outcome, and response to therapy.63,64 The majority of observational studies were low quality. This suggests a lack of transparency and significant potential for bias in the published literature. Heterogeneity was demonstrated not only statistically, but also in a clinical overview of the reported data with respect to dosing, duration of exposure, and timing of therapy.

Aggregate meta-analysis and stratified subgroup analyses show improved oxygenation in ARDS. Similar results have been demonstrated with iNO, yet there is a lack of correlation between changes in oxygenation and outcome benefit in ARDS.8,9,65,66 Furthermore, the majority of studies measured oxygenation changes in a before-after fashion, suggesting that the oxygenation benefit should be interpreted with caution. Without a placebo, it is impossible to assess whether oxygenation benefit was secondary to the use of inhaled prostaglandins. Consistency across data suggests this, but in a dose-finding study of iNO, 24% of the placebo group had an increase in PaO₂ of ≥20%.67 Similar placebo effects were seen in one RCT included in this review.43 Furthermore, some of the cohort studies specifically excluded patients whose oxygenation did not respond to therapy, and although averaged measures of oxygenation were found to improve for the group overall, multiple studies report that a significant percentage of patients were nonresponders.34-36,39,44 So, it is possible that inhaled prostaglandins confer no oxygenation benefit, and these results reflect improved oxygenation secondary to a change in FiO₂ or other concomitant therapies that were not reported (eg, prone positioning, positive end-expiratory pressure setting).

Descriptive analysis of cohort studies suggests that patients dosed with inhaled prostaglandins experience adverse events that are serious and fairly common. Specifically, hypotension was reported in 17.4% of patients in the cohort studies. This is in contrast to the prospective interventional studies, which reported adverse events with less frequency. This may be secondary to the difference in drug exposure between the two study types, as the treatment duration in the cohort studies was significantly longer. There is biologic plausibility, as a prostaglandin metabolite, of 6-keto PGF₁α, has been measured in the systemic circulation and demonstrates that the effect of inhaled prostaglandins is not isolated to the lung.50 The lack of a control group in these studies also makes it difficult to conclude that the reported adverse events were related to inhaled prostaglandin therapy. Little data were provided on other ARDS treatments, such as adherence to lung-protective ventilation, and selective reporting of adverse events was common. However, the reported rate of hypotension in the cohort studies suggests that inhaled prostaglandins may be associated with possible harm and raises concern about prolonged exposure in the routine setting of ARDS treatment.

iNO does not reduce mortality in patients with ARDS.9 Inasmuch as inhaled prostaglandins may have a similar effect on hypoxemia and pulmonary hypertension as iNO, if the only effect of inhaled prostaglandins is on this physiology, then it is unlikely that they will improve long-term clinical outcome either. However, there is also biologic plausibility that a potential effect of inhaled prostaglandins could be derived from their antithrombotic and antiinflammatory properties.10-13 This may be more impactful as far as meaningful clinical outcome is concerned, but needs to be studied further. Reported ARDS mortality rate was 56.5% in patients treated with inhaled prostaglandins. While no inference on causation can be drawn, with this mortality rate exceeding that in reported ARDS literature, it is unclear that any benefit is derived.

There are important limitations in this systematic review. Due to a lack of RCTs, unpublished and nonrandomized studies were included in the analysis.68,69 This decision has several implications. By including nonrandomized trials, biases in the primary data are likely to be greater.20 An attempt to control for this was done by systematically grading each study for bias and reporting these results transparently. Nonrandomized trials often lead to increased heterogeneity, which was demonstrated in a clinical overview of the data reported, as well as statistically. Stratified subgroup meta-analyses were conducted in an attempt to control for this, and these gave similar results as the aggregate data. Meta-regression analysis was also performed. Confounding is also an issue with nonrandomized studies. It is possible that clinicians dosed patients with ARDS with inhaled prostaglandins based on a higher likelihood of clinical response or survival (ie, confounding by indication). A mortality rate of 56.5% speaks against this. On the
other hand, it is also possible that clinicians chose to
dose patients with the most severe ARDS with inhaled
prostaglandins, and the high mortality rate is a reflec-
tion of ARDS severity and a lower chance of survival. It
is also possible that the search did not uncover all of the
published literature in this domain, as nonrandomized
studies are indexed poorly and have a lack of study reg-
istries. The search was exhaustive, rigorous, and repro-
ducible, giving confidence that the largest amount of
data on this topic to date was uncovered. Finally, while
ARDS was an explicit inclusion criterion for this sys-
tematic review, not every individual study stated how
ARDS was defined. An assumption would be that con-
sensus definitional criteria for ARDS were used, but
without an explicit statement to this fact in each publi-
cation, we are unsure. 76,77 It is recognized that these lim-
itations make drawing conclusions on the use of inhaled
prostaglandins for ARDS difficult. It, therefore, must be
emphasized that due to the paucity of quality data, this
analysis cannot discern whether there is truly any ben-
efit or harm. However, this analysis provides an explicit
evaluation of the strengths and weaknesses of the cur-
rent literature to date, and by demonstrating a signal in
the data for both benefit (ie, physiologic effects) and
harm (ie, rate of hypotension), evidence for the need for
randomized trials in this area has been provided.

Conclusions
The data regarding the use of inhaled prostaglandins
for ARDS are limited both in terms of methodologic
quality and demonstration of clinical benefit. Meta-analysis
demonstrates that inhaled prostaglandins improve
oxygenation and decrease pulmonary artery pressures
and may be associated with adverse events. The use of
inhaled prostaglandins in ARDS is in need of further
study.

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and contributed to its design, obtained research funding, supervised the conduct of the study,
screened studies for inclusion in the analysis, and managed, analyzed, and interpreted
data; N. M. M. and L. S. contributed to the design of the study, screened studies for
inclusion in the analysis, and analyzed and interpreted data; S. F. contributed to the design
of the search strategy, conducted the electronic search, and analyzed and interpreted data;
M. H. K. contributed to the design of the study, as well as data analysis and interpretation;
C. R. C. contributed to the design of the study, analyzed and interpreted data, and
provided methodologic oversight; and all authors contributed to the drafting of the
manuscript, revision of the manuscript, and approval of the final version.

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Additional information: The e-Appendices
and e-Tables can be found in the Supplemental
Materials section of the online article.

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