CHEST Online Supplement

The Use of Inhaled Prostaglandins in Patients With ARDS

A Systematic Review and Meta-analysis

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The use of inhaled prostaglandins in patients with acute respiratory distress syndrome: a systematic review and meta-analysis

e-Appendix 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3, e-Appendix 3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3-4, e-Appendix 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5, e-Appendix 3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4-5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-8, Figure 2, Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-8, Figure 2, Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-8, e-Figure 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-9, Table 2, e-Figure 2, e-Table 2, e-Table 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title, Page, Acknowledgements

Page numbers provided consider the Abstract as Page 1.

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e-Appendix 2. MOOSE Checklist

	Reported on page	Comments
Reporting of background should include		
Problem definition	2	
Hypothesis statement	2-3	
Description of study outcomes	2	
Type of exposure or intervention used	2	
Type of study designs used	2-3, e-Appendix 3	
Study population	4, e-Appendix 3	
Reporting of search strategy should include		
Qualifications of searchers (eg librarians and investigators)	3, 4, e-Appendix 3	
Search strategy, including time period used in the synthesis and key words	3, 4, e-Appendix 3	
Effort to include all available studies, including contact with authors	3, 4, e-Appendix 3	
Databases and registries searched	3	
Search software used, name and version, including special features used (eg explosion)	e-Appendix 3	
Use of hand searching (eg reference lists of obtained articles)	3, 4, e-Appendix 3	
List of citations located and those excluded, including justification	e-Appendix 3, Figure 1	
Method of addressing articles published in languages other than English	e-Appendix 3	
Method of handling abstracts and unpublished studies	3, 4	
Description of any contact with authors	3	
Reporting of methods should include		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	4	
Rationale for the selection and coding of data	4	

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(eg sound clinical principles or convenience)		
Documentation of how data were classified and coded (eg multiple raters, blinding and interrater reliability)	4	
Assessment of confounding (eg comparability of cases and controls in studies where appropriate)	4, 5	
Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	4, 5	
Assessment of heterogeneity	5	
Description of statistical methods (eg complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	5, 6	
Provision of appropriate tables and graphics	Tables and Figures and eTables	
Reporting of results should include		
Graphic summarizing individual study estimates and overall estimate	Figure 2	
Table giving descriptive information for each study included	Table 1, e-Table 1	
Results of sensitivity testing (eg subgroup analysis)	Table 2	
Indication of statistical uncertainty of findings	7, 8	
Reporting of discussion should include		
Quantitative assessment of bias (eg publication bias)	10, Table 1	
Justification for exclusion (eg exclusion of non-English language citations)	11, 12	
Assessment of quality of included studies	10, Table 1	
Reporting of conclusions should include		
Consideration of alternative explanations for	10-12	

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observed results		
Generalization of the conclusions (eg appropriate for the data presented and within the domain of the literature review)	11, 12	
Guidelines for future research	13	
Disclosure of funding source	Title Page,Acknowledgements	

Page numbers provided consider the Abstract as Page 1.

e-Appendix 3

PROTOCOL: Search and identification of studies

The use of inhaled prostaglandins in patients with acute respiratory distress syndrome: a systematic review and meta-analysis

Patient/Problem: Mechanically ventilated patients with acute respiratory distress syndrome (ARDS) or acute lung injury (ALI)
Intervention: Inhaled epoprostenol or inhaled alprostadil
Comparison: Placebo or no intervention/usual care
Inhaled nitric oxide (iNO)
Outcome:
Main outcome measures of interest: oxygenation, pulmonary artery pressures, mortality, adverse effects (report qualitatively and combine *post hoc* if possible)

Clinical question: In mechanically ventilated patients with ARDS/ALI, does inhaled epoprostenol or inhaled alprostadil improve oxygenation or clinical outcome?
Is there any consistency in the data with respect to dosing, weaning, or evidence of rebound?

Inclusion Criteria	Exclusion Criteria
Any language or publication type, including case series/studies providing necessary data **Children and adults** **Invasive positive pressure ventilation during study period** **Outcomes of interest reported** **Crossover trials (e.g. with iNO) must report physiological effects and outcome data of prostaglandins transparently** **Must explicitly state the patient population is ALI or ARDS**	**Neonatal** **Non-human studies** **Paper = review, correspondence, or editorial** **Intravenous use of pulmonary vasodilators** **Epoprostenol or alprostadil for shock , RV failure, or reperfusion injury** **Pre- and post- intervention data not reported**

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Step 1 (Relevance Screen):
Search PubMed, EMBASE, CINAHL, and the Cochrane Library using the search strategy below.
BMF and NMM: Screen title and abstract of manuscripts resulting from electronic search.

Step 2:
Identify unpublished data

BMF: Manually screen reference lists of all review articles from relevance screen
BMF and SF: Search online for details of clinical trials registration (ClinicalTrials.gov)
BMF: Hand search abstracts from: SCCM, ESICM, ATS, CHEST, International Symposium on Intensive Care and Emergency Medicine, and Pharmacotherapy from 1999 to 2014
BMF and NMM: Manually screen reference lists of all articles to be potentially included from electronic and manual review of review articles
BMF: If unpublished data is found and clarification is needed, contact PI of that study

Step 3:
BMF, NMM, LS: Full review of the remaining manuscripts for agreement and final inclusion.

Step 4:
BMF, NMM, LS: Fill out data abstraction form for final studies included

Step 5: Transfer data from Data Abstraction Form to Tables

Step 6: Assess Table for potential for meta-analysis of the data
Rationale for inclusion of non-randomized studies:

1. There is a high likelihood that the existing body of literature does not contain a sufficient number of randomized trials to investigate the question of interest
2. Inclusion of non-randomized studies will allow an explicit evaluation of the strengths and weaknesses of the current literature
3. Non-randomized studies will allow some assessment of beneficial and harmful effects of inhaled prostaglandins
    a. Prospective interventional studies will allow an assessment of the influence of prostaglandins on physiology
    b. Inclusion of cohort studies will allow a better assessment of sustained physiologic benefit, as well as side effects and harm, as reported during using clinical dosing
4. To provide evidence for the undertaking of randomized trials

SEARCH STRATEGY:

24255157[uid]
Mechanically Ventilated
Acute lung Injury OR Acute Respiratory Distress Syndrome
PubMed
5/8/2014, 108 Results

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("Respiratory Distress Syndrome, Adult"[Mesh] OR "Acute Lung Injury"[Mesh] OR "Ventilator-Induced Lung Injury"[Mesh] OR "Shock Lung" OR "respiratory distress syndrome"[tiab] OR "adult respiratory distress" OR ARDS[tiab] OR "pulmonary distress syndrome"[tiab] OR RDS[tiab] OR "Acute Lung Injury"[tiab] OR "Acute Lung Injuries" OR Ventilator Induced Lung Injur*[tiab] OR VILI[tiab]) AND ("Epoprostenol"[Mesh] OR epoprostenol OR flolan OR pgi2 OR pgx OR prostacyclin OR "prostaglandin i 2" OR "prostaglandin I2" OR "prostaglandin x" OR "u 53217" OR epoprostanol[tiab]) AND ("Outcome Assessment Health Care "[Mesh] OR "Mortality"[Mesh] OR "mortality"[Subheading] OR "Survival"[Mesh] OR "Survival Analysis"[Mesh] OR "Quality of Life"[Mesh] OR "Pain Measurement"[Mesh] OR "Pain"[Mesh] OR "Health"[Mesh] OR "Health Status Indicators"[Mesh] OR "Health Status"[Mesh] OR outcome* OR respond* OR response* OR failure* OR mortality OR fatal* OR death OR dead OR deaths OR "passed away" OR demise* OR Recurren* OR progression OR progressed OR relaps* OR growth OR grew OR growing OR regress* OR surviv* OR nonsurviv* OR cure OR cures OR "quality of life" OR qol[tiab] OR HRQL[tiab] OR "life quality"[tiab] OR morbidit* OR adverse OR side effect* OR "side effects" OR event OR events OR nausea OR nauseous OR vomit* OR emesis OR comfort* OR pain OR painful OR painfree OR stress OR analges*) NOT (("Animals"[Mesh]) NOT ("Animals"[Mesh] AND "Humans"[Mesh]))

CINAHL
5/8/2014, 31 Results

(MH "Respiratory Distress Syndrome" OR MH "Respiratory Distress Syndrome, Acute" OR MH "Acute Lung Injury+" OR MH "Ventilator-Induced Lung Injury+" OR "Respiratory Distress Syndrome" OR "Acute Lung Injury" OR "Ventilator-Induced Lung Injury" OR "Shock Lung" OR "adult respiratory distress" OR "ARDS" OR "pulmonary distress syndrome" OR "RDS" OR "Acute Lung Injuries" OR "Ventilator Induced Lung Injury" OR "Ventilator Induced Lung Injuries" OR "VILI") AND (MH "Epoprostenol" OR epoprostenol OR flolan OR pgi2 OR pgx OR prostacyclin OR "prostaglandin i 2" OR "prostaglandin I2" OR "prostaglandin x" OR "u 53217" OR epoprostanol) AND (MH "Outcomes (Health Care)+" OR MH "Outcome Assessment" OR MH "Mortality+" OR MH "Survival" OR MH "Survival Analysis+" OR MH "Quality of Life+" OR MH "Pain+" OR MH "Pain Measurement" OR MH "Health+" OR MH "Health Status+" OR MH "Health Status Indicators" OR "Health Status" OR outcome* OR respond* OR response* OR failure* OR mortality OR fatal* OR death OR dead OR deaths OR "passed away" OR demise* OR Recurren* OR progression OR progressed OR relaps* OR growth OR grew OR growing OR regress* OR surviv* OR nonsurviv* OR cure OR cures OR "quality of life" OR qol OR HRQL OR "life quality" OR morbidit* OR adverse OR side effect* OR "side effects" OR event OR events OR nausea OR nauseous OR vomit* OR emesis OR comfort* OR pain OR painful OR painfree OR stress OR analges*)

Embase
5/8/2014, 269 Results

'respiratory distress syndrome'/de OR 'adult respiratory distress syndrome'/exp OR 'ventilator induced lung injury'/exp OR 'acute lung injury'/exp OR 'respiratory distress syndrome' OR 'ARDS' OR 'Shock Lung' OR 'ventilation induced lung injury' OR 'ventilator induced lung injury' OR 'ventilation induced lung injuries' OR 'ventilator induced lung injuries' OR VILI AND ('prostacyclin'/exp OR cycloprostin OR epoprostenol OR epoprostanol OR flolan OR pgi2 OR pgx OR 'prostacyclin' OR 'prostaglandin i 2' OR 'prostaglandin I2' OR 'prostaglandin x' OR 'u 53217' OR 'u 53217a' OR 'u53217' OR u53217a) AND ('outcome assessment'/exp OR 'mortality'/exp OR 'survival'/exp OR 'quality of life'/exp OR 'pain'/exp OR 'pain assessment'/exp OR 'health'/exp OR 'health status'/exp OR 'health status indicator'/exp OR outcome* OR respond* OR response* OR failure* OR mortality OR fatal* OR death OR dead OR deaths OR 'passed away' OR demise* OR Recurren* OR progression OR progressed OR relaps* OR growth OR grew OR growing OR regress* OR surviv* OR nonsurviv* OR cure OR cures OR 'quality of life' OR qol OR HRQL OR 'life quality' OR morbidit* OR adverse OR side

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effect* OR 'side effects' OR event OR events OR nausea OR nauseous OR vomit* OR emesis OR comfort* OR pain* OR stress OR analges*) NOT ([animals]/lim NOT [humans]/lim)

Scopus
5/8/2014, 51 Results

("Respiratory Distress Syndrome" OR "Acute Lung Injury" OR "Ventilator-Induced Lung Injury" OR "Shock Lung" OR "adult respiratory distress" OR ARDS OR "pulmonary distress syndrome" OR RDS OR "Acute Lung Injuries" OR Ventilator Induced Lung Injur* OR VILI) AND (epoprostenol OR flolan OR pgi2 OR pgx OR prostacyclin OR "prostaglandin i 2" OR "prostaglandin I2" OR "prostaglandin x" OR "u 53217" OR epoprostanol) AND ("Health Status" OR outcome* OR respond* OR response* OR failure* OR mortality OR fatal* OR death OR dead OR deaths OR "passed away" OR demise* OR Recurren* OR progression OR progressed OR relaps* OR growth OR grew OR growing OR regress* OR surviv* OR nonsurviv* OR cure OR cures OR "quality of life" OR qol OR HRQL OR "life quality" OR morbidit* OR adverse OR side effect* OR "side effects" OR event OR events OR nausea OR nauseous OR vomit* OR emesis OR comfort* OR pain OR painful OR painfree OR stress OR analges*)

The Cochrane Library
Cochrane Central Register of Controlled Trials: 5/8/2014, 9 Results
Cochrane Database of Systematic Reviews: 5/8/2014, 15 Results

#1 MeSH descriptor: [Respiratory Distress Syndrome, Adult] explode all trees 592
#2 MeSH descriptor: [Acute Lung Injury] explode all trees 112
#3 MeSH descriptor: [Ventilator-Induced Lung Injury] explode all trees 520
#4 #1 or #2 or #3 or "Respiratory Distress Syndrome" or "Acute Lung Injury" or "Ventilator-Induced Lung Injury" or "Shock Lung" or "adult respiratory distress" or ARDS or "pulmonary distress syndrome" or RDS or "Acute Lung Injuries" or Ventilator Induced Lung Injur* or VILI 3772
#5 MeSH descriptor: [Epoprostenol] explode all trees 472
#6 #5 or epoprostenol or flolan or pgi2 or pgx or prostacyclin or "prostaglandin i 2" or "prostaglandin I2" or "prostaglandin x" or "u 53217" or epoprostanol 1172
#7 MeSH descriptor: [Outcome Assessment (Health Care)] explode all trees 98934
#8 MeSH descriptor: [Mortality] explode all trees 10968
#9 MeSH descriptor: [Survival] explode all trees 130
#10 MeSH descriptor: [Survival Analysis] explode all trees 15518
#11 MeSH descriptor: [Quality of Life] explode all trees 14757
#12 MeSH descriptor: [Pain Measurement] explode all trees 14960
#13 MeSH descriptor: [Pain] explode all trees 32936
#14 MeSH descriptor: [Health] explode all trees 5818
#15 MeSH descriptor: [Health Status] explode all trees 5336
#16 MeSH descriptor: [Health Status Indicators] explode all trees 16074
#17 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or "Health Status" or outcome* or respond* or response* or failure* or mortality or fatal* or death or dead or deaths or "passed away" or demise* or Recurren* or progression or progressed or relaps* or growth or grew or growing or regress* or surviv* or nonsurviv* or cure or cures or "quality of life" or qol or HRQL or "life quality" or morbidit* or adverse or side effect* or "side effects" or event or events or nausea or nauseous or vomit* or emesis or comfort* or pain or painful or painfree or stress or analges* 502647
#18 #4 and #6 and #17 24

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ClinicalTrials.Gov
5/8/2014, 2 Results

Advanced Search…
Conditions: Respiratory Distress Syndrome OR Acute Lung Injury
Interventions: epoprostenol OR flolan OR prostacyclin

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e-Table 1 Study Results

Randomized Controlled Trials					
Author, Year	**Pre-intervention value**	**Post-intervention value**	***p***	**Dosing**	**Comments**
Dahlem, 2004	OI 10.0 (7.8-14.5) P_aO_2:F_iO_2 194 (120-219)	OI 7.4 (6.5-9.7) P_aO_2:F_iO_2 Not reported	0.001	Dose response protocol Range 10-50ng/kg/min	Significant improvement in OI at 30ng/kg/min
Siddiqui, 2013	P_aO_2:F_iO_2 148.4 (60.1)	P_aO_2:F_iO_2 161.5 (77.5)	0.21	20ug nebulized over 30 minutes	
Prospective, nonrandomized interventional studies					
Author, Year	**Pre-intervention value**	**Post-intervention value**	***p***	**Dosing**	
Walmrath, 1996	P_aO_2:F_iO_2 114 (11.9) P_aO_2 72.5 (3.2) mPAP 35.0 (2.2) PVR 228 (27.5)	P_aO_2:F_iO_2 135 (12.0) P_aO_2 88.0 (4.7) mPAP 31.9 (1.7) PVR 182 (17.0)	<0.001 <0.001 <0.05 <0.05	Titrated to maximal effect on oxygenation Mean 7.5 (2.5) ng/kg/min Range 1.5 to 34 ng/kg/min	No difference in outcomes between PGI_2 and iNO
van Heerden, 1996	P_aO_2 80.0 (14.3) mPAP Not reported	P_aO_2 122.3 (11.8) mPAP Reduced in all	0.06 NS	50 ng/kg/min	
Zwissler, 1996	P_aO_2 105 (10) mPAP 35.1 (2.0) PVR 225 (30.0)	P_aO_2 130 (12) mPAP 28.0 (1.5) PVR 190 (25.0)	<0.05 <0.05 <0.05	1, 10, then 25 ng/kg/min (each for 15 minutes)	No significant increase in P_aO_2 at 1 ng/kg/min
Putensen, 1998	P_aO_2 77 (3) mPAP 40.0 (2.0) PVR 156 (15.0)	P_aO_2 95 (4) mPAP 32.0 (2) PVR 100 (12.0)	<0.05 <0.05 <0.05	Titrated by 1ng/kg/min for maximal effect on P_aO_2 Mean 10(1) ng/kg/min Range 6-15 ng/kg/min	
van Heerden, 2000	P_aO_2:F_iO_2 187.2 (10) mPAP 29 (1)	P_aO_2:F_iO_2 202.2 (10) mPAP 28 (1)	<0.008 0.38	Titrated by 10ng/kg/min	No difference between doses of 10 and 50
Domenighetti, 2001	P_aO_2:F_iO_2 155 (15) P_aO_2 81 (3) mPAP 32 (1) PVR 177 (18)	P_aO_2:F_iO_2 157 (15) P_aO_2 82 (3) mPAP 29 (1) PVR 153 (18)	NS NS <0.05 <0.05	Titrated for optimal P_aO_2 Mean 34(9) ng/kg/min	Responders 8/15 0/6 patients with pulmonary ARDS responded Worsened

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				Range 2-40 ng/kg/min	oxygenation in pulmonary ARDS
Observational cohort studies					
Author, Year	**Pre-intervention value**	**Post-intervention value**	***p***	**Dosing**	**Comments**
Meyer, 1998	P_aO_2 60 (5) P_aO_2:F_iO_2 100 (5) mPAP 38 (4)	P_aO_2 90 (10) P_aO_2:F_iO_2 240 (30) mPAP 32 (2)	<0.05 <0.05 <0.1	Mean 41 (2) ug/h Range 20-80 ug/h	Weaning at intensivist discretion
Siobal, 2003	P_aO_2:F_iO_2 60 (11) S_pO_2 85.7 (7.7)	P_aO_2:F_iO_2 80 (17) S_pO_2 93.6 (3.3)	0.002 0.001	Mean 28(17) ng/kg/min Range 10-50ng/kg/min	Measurements taken within 2 hours of PGI_2 initiation
Rovira, 2004	P_aO_2:F_iO_2 152 (30)	P_aO_2:F_iO_2 203 (40)	<0.05	Not reported	
Camamo, 2005	PGI_2 P_aO_2:F_iO_2 66.7 (23) P_aO_2 62.9 (15.9) PGE_1 P_aO_2:F_iO_2 106.1 (53.4) P_aO_2 88.9 (38.7)	PGI_2 P_aO_2:F_iO_2 58.2 (22.4) P_aO_2 53.7 (17.4) PGE_1 P_aO_2:F_iO_2 123.5 (77.6) P_aO_2 78.1 (22.9)	 0.17 0.08 0.21 0.34	Start 17.4 (12.5) ng/kg/min Max 34.3 (13.2) ng/kg/min Start 15.8(7) ng/kg/min Max 28.3(14.2) ng/kg/min	No difference between the two drugs on MV duration, HLOS, ICU LOS
Raheem, 2009	P_aO_2:F_iO_2 57.7 (11.8)	P_aO_2:F_iO_2 105.7 (33.3)	Not reported	Not reported	No difference in oxygenation between doses ≤12.5 or ≥ 25
Ross, 2012	P_aO_2:F_iO_2 62.5 (24.4) P_aO_2 59.1 (6.9) S_pO_2 83.3 (8.9)	P_aO_2:F_iO_2 130.9 (38.6) P_aO_2 117.9 (32.8) S_pO_2 95.6 (4.1)	Not reported	Start 23.3 (18.3) ng/kg/min Max 39.9 (11.9) ng/kg/min	Dosed based on IBW
Dunkley, 2013	P_aO_2:F_iO_2 104.9 (48.5)	P_aO_2:F_iO_2 155.6 (94.6)	Not reported	Start 30 (10) ng/kg/min Max 50 ng/kg/min	10/16 patients with no titration
Pacheo, 2013	Survivors P_aO_2:F_iO_2 94.1 (34.5) Nonsurvivors P_aO_2:F_iO_2 81.7 (32.7)	Survivors P_aO_2:F_iO_2 254.3 (123.0) Nonsurvivors P_aO_2:F_iO_2 142.7 (102.2)	<0.05 <0.05	1st 24 hours Survivors 26.5 (10.3) ng/kg/min Nonsurvivors 34.9 (12.4) ng/kg/min End of therapy Survivors 13.3 (10.9) Nonsurvivors 32.6	No weaning occurred in nonsurvivors

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					(14.7)	
Torbic, 2013	P_aO_2:F_iO_2	110 (20)#	P_aO_2:F_iO_2	143.0 (36.2)	Not reported	Protocol: start at .05 ug/kg/min and decrease by .01 ug/kg/min every 1-2 hours as tolerated until off	
Singh, 2014	P_aO_2:F_iO_2	78.9 (30.2)	P_aO_2:F_iO_2	121.8 (71)	<0.0001	20ng/kg/min	Nonresponders 25.5%
Case studies and case series							
Author, Year	**Pre-intervention value**		**Post-intervention value**		***p***	**Dosing**	**Comments**
Walmrath, 1993	P_aO_2:F_iO_2 mPAP	119.5 (19.3) 40.3 (13.5)	P_aO_2:F_iO_2 mPAP	173.0 (17.7) 32.0 (3.8)	Not reported	17-50ng/kg/min	
Bein, 1994	P_aO_2 mPAP	79.4 49.0	P_aO_2 mPAP	150.5 38.0	Not reported	5 ng/kg/min	
Pappert, 1995	P_aO_2:F_iO_2	76.3 (2.5)	P_aO_2:F_iO_2	91.3 (17.6)	Not reported	2-20 ng/kg/min	
van Heerden, 1996	P_aO_2:F_iO_2	76.0	P_aO_2:F_iO_2	270.0	Not reported	20-50 ng/kg/min	Only reported oxygenation on 1 patient
van Heerden, 1997	P_aO_2	84.0	P_aO_2	110.0	Not reported	10-50 ng/kg/min	
Allan, 2010	P_aO_2:F_iO_2 P_aO_2	57.0 57.0	P_aO_2:F_iO_2 P_aO_2	200.0 147.0	Not reported	13 ng/kg/min	
McMillen, 2011	P_aO_2:F_iO_2	66.3 (8.5)	P_aO_2:F_iO_2	92.5 (45)	Not reported	20-40 ng/kg/min	

OI: oxygenation index; P_aO_2: partial pressure of arterial oxygen; F_iO_2: fraction of inspired oxygen; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; NS: not significant; PGI_2: epoprostenol; iNO: inhaled nitric oxide; ARDS: acute respiratory distress syndrome; PGE_1: alprostadil; S_pO_2: peripheral oxygen saturation; NS: non-significant; MV: mechanical ventilation; HLOS: hospital length of stay; ICU LOS: intensive care unit length of stay; IBW: ideal body weight
Estimated from figures

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e-Table 2. Adverse effects of inhaled prostaglandins

Author, Year	Adverse effects mentioned?	Details of reported side effects
Dahlem, 2004	Yes	No side effects reported No effect on systemic hemodynamics No bleeding complications
Siddiqui, 2013	Yes	None reported
Walmrath, 1996	Yes	No effect on systemic hemodynamics
Van Heerden, 1996	Yes	No effect on systemic hemodynamics
Zwissler, 1996	Yes	Hypotension, n= 1 (12.5%)
Putensen, 1998	Yes	No effect on systemic hemodynamics
van Heerden, 2000	Yes	No effect on systemic hemodynamics No effect on platelet aggregation (but wide variation) Dose response of 6-keto $PGF1_{\alpha}$
Domenighetti, 2001	Yes	No effect on systemic hemodynamics
Meyer, 1998	Yes	No effect on systemic hemodynamics
Siobal, 2003	Yes	Decrease in P_aO_2, n= 1 (9.1%)
Rovira, 2004	Yes	No “significant hemodynamic changes observed”
Camamo, 2005	No	
Raheem, 2009	No	
Ross, 2012	No (Obtained from author contact)	AKI, n=1 (8.3%) Bleeding, n=1 (8.3%) Hypotension, n=2 (16.7%) Thrombocytopenia, n=4 (33.3%)
Dunkley, 2013	Yes	Medication error, n= (25%) Hypotension, n= 3 (18.8%); tachycardia, n= 2 (12.5%); Hyperkalemia, n= 2 (12.5%); Hypokalemia, n= 1 (6.3%); thrombocytopenia, n= 2 (12.5%); anemia, n= 2 (12.5%); Increased LFTs, n= 2 (12.5%), AKI, n= 1 (6.3%)
Pacheo, 2013	No	
Torbic, 2013	Yes	PRBC transfusion and platelet transfusion in 25/52 and 10/52 respectively
Singh, 2014	Yes	Hypotension, n= 21 (21.4%) Tachycardia, n=11 (11.2%)
Walmrath, 1993	Yes	Hypotension, n= 1 (33.3%)
Bein, 1994	Yes	No effect on arterial pressure
Pappert, 1995	Yes	No effect on arterial pressure or cardiac output Decrease in P_aO_2, n= 1 (33.3%)
van Heerden, 1996	Yes	No evidence of systemic hypotension
van Heerden, 1997	Yes	Reduction in platelet aggregation Dose response of 6-keto $PGF1_{\alpha}$
Allan, 2010	No	
McMillen, 2011	Yes	Decrease in P_aO_2, n= 3 (75.0%)

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e-Table 3 Reported mortality in ARDS patients receiving inhaled prostaglandins

Outcome	Author, Year	N	Mortality, n (%)
Mortality*	Pappert, 1995	3	1 (33.3)
	Walmrath, 1996	16	7 (43.8)
	Zwissler, 1996	8	2 (25)
	van Heerden, 1997	1	1 (100)
	Meyer, 1998	15	6 (40)
	Putensen, 1998	10	3 (30)
	Domenighetti, 2001	15	7 (46.7)
	Siobal, 2011	11	7 (63.6)
	Dahlem, 2004	14	3 (21.4)
	Camamo, 2005	27	18 (66.7)
	Raheem, 2009	15	5 (33.3)
	Allan, 2010	1	0 (0%)
	McMillen, 2011	4	3 (75)
	Dunkley, 2013	16	9 (56.3)
	Pacheo, 2013	216	136 (63.0) hospital 148 (68.5) at 90
	Torbic, 2013	52 (32 with ARDS)	26 (50.0)
	Singh, 2014	98	49 (50.0)
Total	**17 studies**	**522**	**295 (56.5%)**

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