NITRIC OXIDE/EPOPROSTENOL – OVERVIEW AND EVIDENCE

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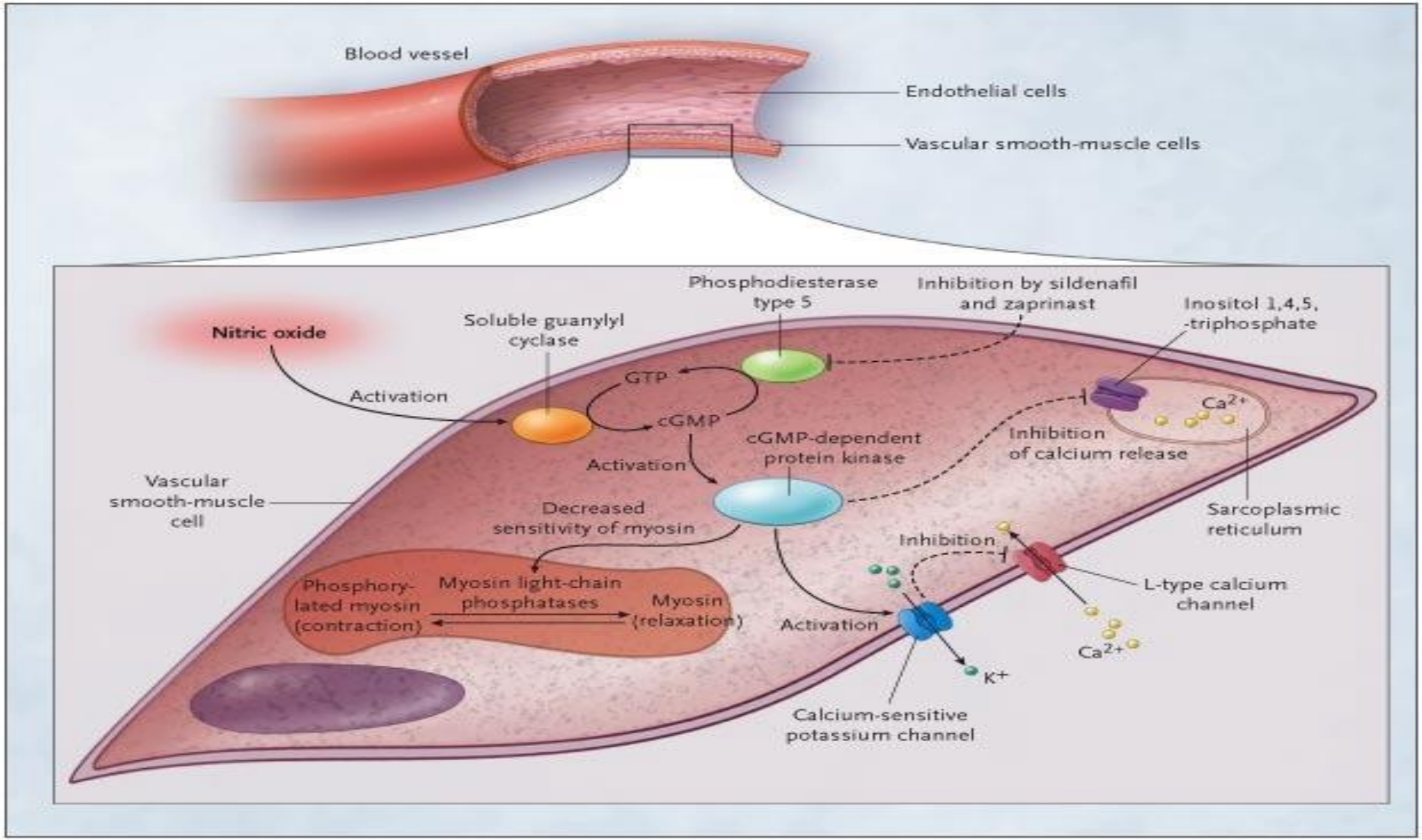
- No disclosures

OBJECTIVES

Describe	Describe the mechanism of action for inhaled nitric oxide and inhaled prostacyclin to better understand potential uses
Discuss	Discuss the use of these therapies in different disease states
Review	Review the evidence of these therapies in the disease states

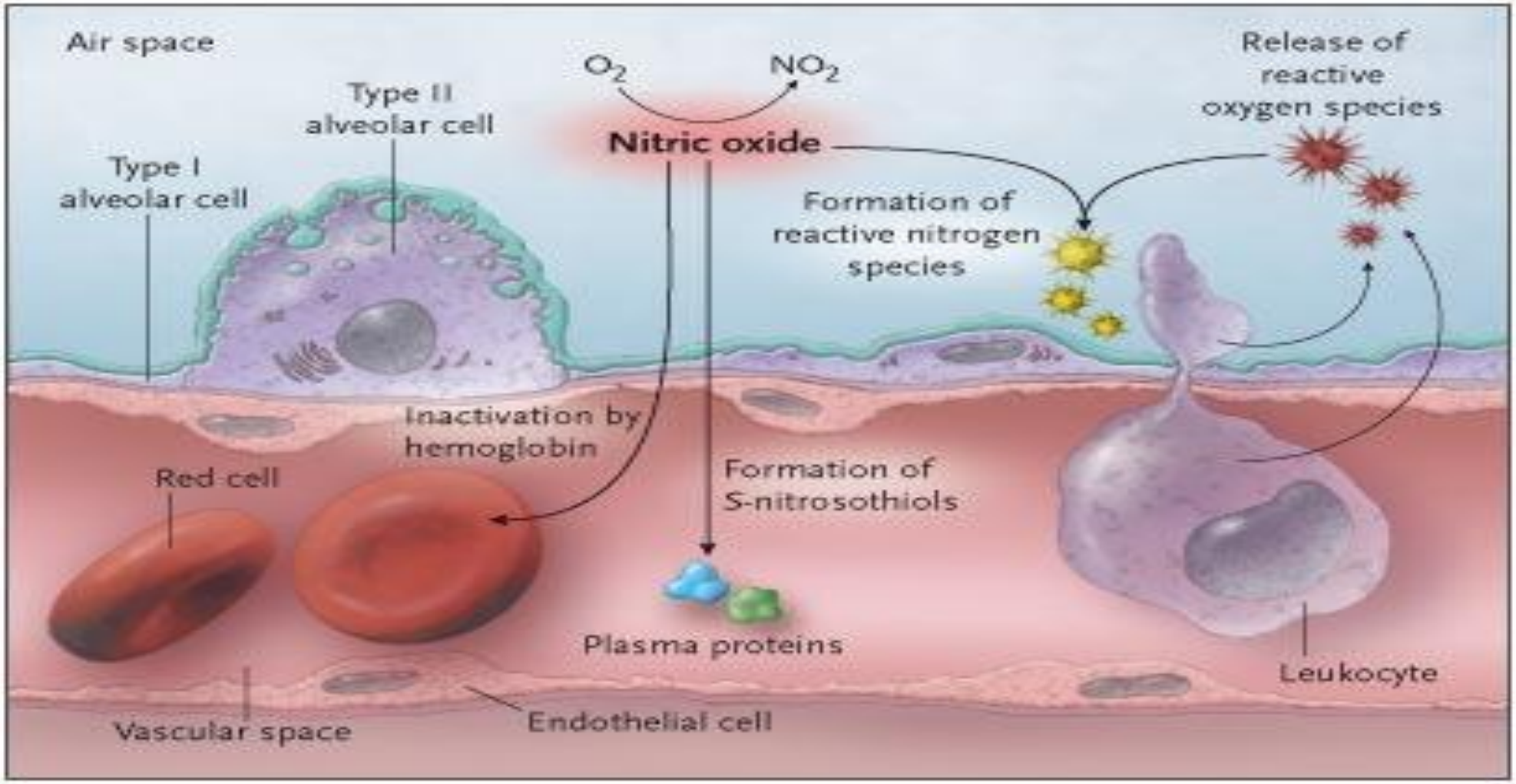
THE SCIENCE AND BACKGROUND

- Nitric oxide is similar biologically to endothelium-derived relaxing factor which is involved with modulation of vascular tone by forming cyclic guanosine 3',5'-monophosphate (cGMP) which leads to vascular smooth muscle relaxation.
- Endogenous nitric oxide is then formed by L-arginine and nitric oxide synthase
- Has both systemic and pulmonary pressor responses
- 1991, inhaled nitric oxide was first shown to be a selective pulmonary vasodilator in those with pulm hypertension
- 1993, first used as therapy for ARDS as it was shown to decrease pulmonary vascular resistance without affecting blood pressure and improved oxygenation by redistributing the pulm blood flow to ventilated parts of the lung


Blood vessel
Endothelial cells
Vascular smooth-muscle cells
Nitric oxide
Soluble guanylyl cyclase
Phosphodiesterase type 5
Inhibition by sildenafil and zaprinast
Inositol 1,4,5, -triphosphate
Activation
GTP
cGMP
Activation
cGMP-dependent protein kinase
Inhibition of calcium release
Ca2+
Vascular smooth-muscle cell
Decreased sensitivity of myosin
Sarcoplasmic reticulum
Inhibition
L-type calcium channel
Phosphory-lated myosin (contraction)
Myosin light-chain phosphatases
Myosin (relaxation)
Activation
Ca2+
K+
Calcium-sensitive potassium channel

NITRIC OXIDE

- Gas that is colorless and odorless. Generally poorly reactive with biological molecules except for free radicals and some amino acids
- When inhaled with higher concentrations of oxygen, it forms nitrogen dioxide.
- When dissolved in airway-lining fluid, it may react with reactive oxygen species (like superoxide) to form a reactive nitrogen species. This is a powerful oxidant which can then decompose to nitrogen dioxide and hydroxyl radicals
- Potentially cytotoxic and can be a measure of oxidative stress


Air space
O_2
NO_2
Type II alveolar cell
Nitric oxide
Release of reactive oxygen species
Type I alveolar cell
Formation of reactive nitrogen species
Inactivation by hemoglobin
Red cell
Formation of S-nitrosothiols
Plasma proteins
Leukocyte
Vascular space
Endothelial cell

NITRIC OXIDE

- Forms methemoglobin and nitrate when reacting with oxyhemoglobin which is in the pulmonary circulation
- Most of the methemoglobin is reduced to ferrous hemoglobin and is excreted as nitrate in the urine within 48 hours
- Many proteins will react reversibly with nitric oxide to form S-nitrosothiols and these are vasodilators and will inhibit platelet aggregation.
- Since NO is rapidly inactivated when it binds to hemoglobin in the pulmonary capillaries, systemic effects are not seen and this is also why the half-life is a few seconds

EFFECTS ON THE CARDIOVASCULAR SYSTEM

- Inhaled NO relaxes pulmonary vessels and this leads to decreased pulmonary vascular resistance, decreased pulmonary arterial pressure and reduces right ventricular afterload. Leads to an overall increase in the pulmonary blood flow
- It is selective to the pulmonary circulation due to the very fast inactivation of nitric oxide by hemoglobin.
- Initially studies compared NO with intravenous pulmonary vasodilator. It was found that IV epoprostenol worsened oxygenation due to increased hypoxic pulmonary vasoconstriction
- The inhaled NO works because the vasculature affected by NO are well ventilated parts of the lung and led to improved ventilator-perfusion mismatch

PHYSIOLOGICAL EFFECTS

- Reduced PVR as mentioned
- Improved ventilation-perfusion mismatch with better vasodilation of the alveoli that are ventilated better
- Reduce right-to-left shunt by dropping pressure in right atrium. If PFO is present, then shunt may close entirely. Also reduces shunt due to the reduction in PVR
- Important to identify shunts as it is possible they may respond adversely to recruitment maneuvers as this will increase blood flow through the shunt

EVALUATING FOR SHUNT

https://youtu.be/sYM1HYFpyXA

FACTORS THAT AFFECT NO IN THE CV SYSTEM

- In patients with septic shock, in addition to ARDS, there can be induction of nitric oxide synthase produced in the body, as well as the vasoconstrictor endothelin-1. This will reduce the affects of inhaled NO and you will not have as much improvement in oxygenation

- If ventilation-perfusion mismatch and pulmonary vasoconstriction are high and this is why the patient has decreased oxygenation, then inhaled NO will have a greater affect

- While studies are conflicting, there is some evidence that the venous system is affected more than the arterial system.

REBOUND

- Rapid withdrawal of inhaled NO can lead to a significant rebound in pulmonary hypertension and hypoxia, depending on the cause of decreased oxygenation
- Reason for this is that when inhaled NO is used, it will reduce the nitric oxide synthase activity described earlier and increase endothelin-1, when basically inactivates the endogenous nitric oxide synthase.
- If you withdraw inhaled NO, there can be a rebound of increased nitric oxide synthase that is produced.
- This is all in theory, but in practice this is rarely seen, although sometimes it is difficult to quickly get off the last 1-2 ppm likely related to this phenomenon.

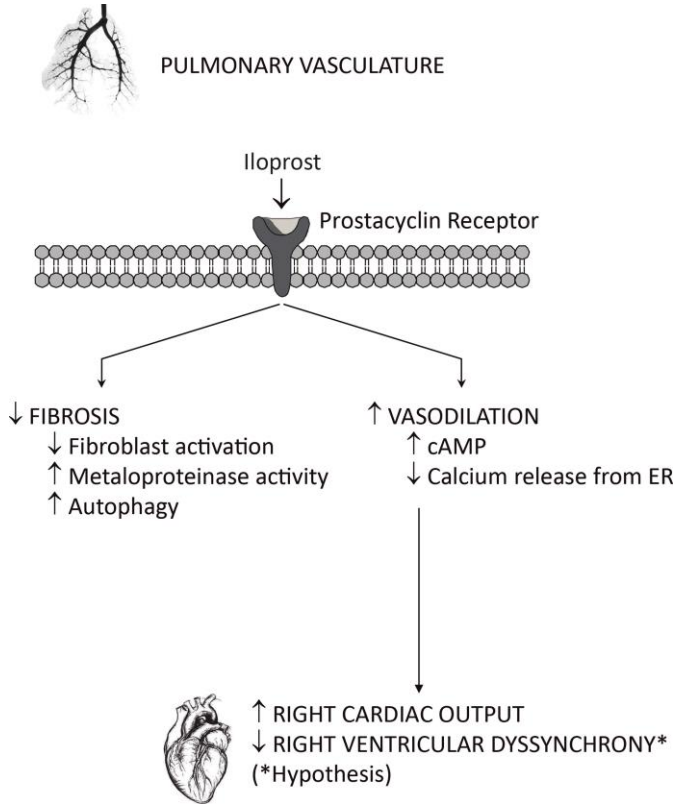
OTHER EFFECTS

- Inhibits platelet aggregation – may have role in reducing pulmonary artery pressures and platelet aggregation in pulmonary embolism. No clear evidence that it causes increased bleeding
- Possible that inhaled NO can lead to increased surfactant production, but unclear
- Dose-dependent effect on bronchoconstriction, so may be beneficial in asthma

EPOPROSTENOL

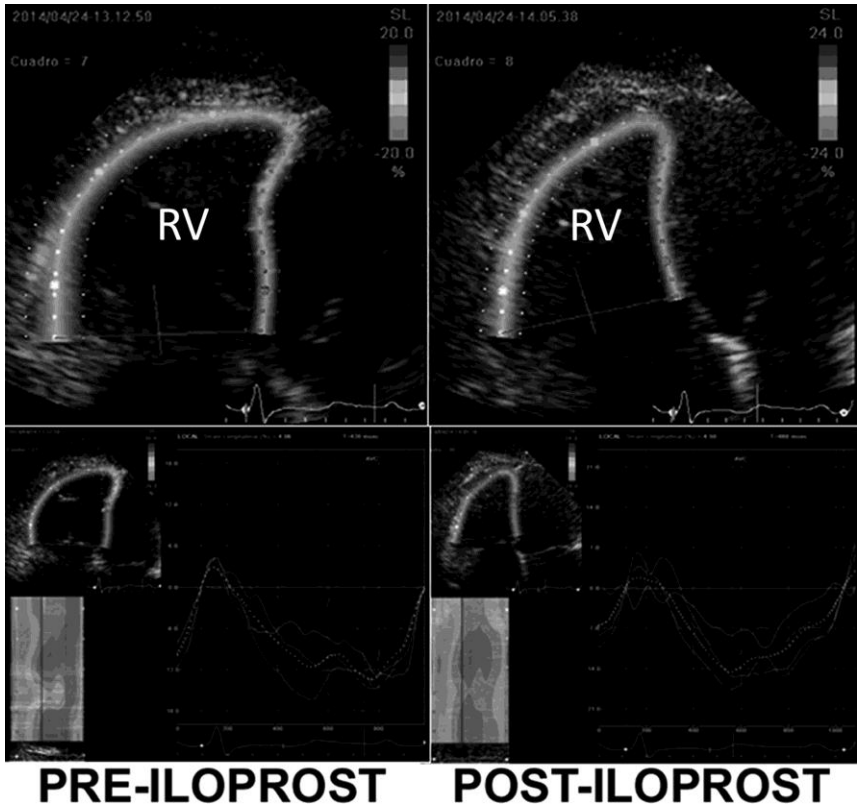
- Prostacyclins are also known to have significant vasodilation properties
- IV administration is not selective and will lead to systemic effects such as hypotension, and as stated earlier, has been shown to decrease oxygenation
- Inhaled prostacyclins, such as epoprostenol, are selective for the pulmonary system, so systemic effects are not seen
- Epo interacts with the prostaglandin I receptor, which is expressed on blood vessels, leukocytes and platelets.
- Stimulation of this receptor incudes more cAMP which leads to smooth muscle relaxation

Acute effect of iloprost inhalation on right atrial function and ventricular dyssynchrony in patients with pulmonary artery hypertension



Echocardiography, Volume: 34, Issue: 1, Pages: 53-60, First published: 14 October 2016, DOI: (10.1111/echo.13401)

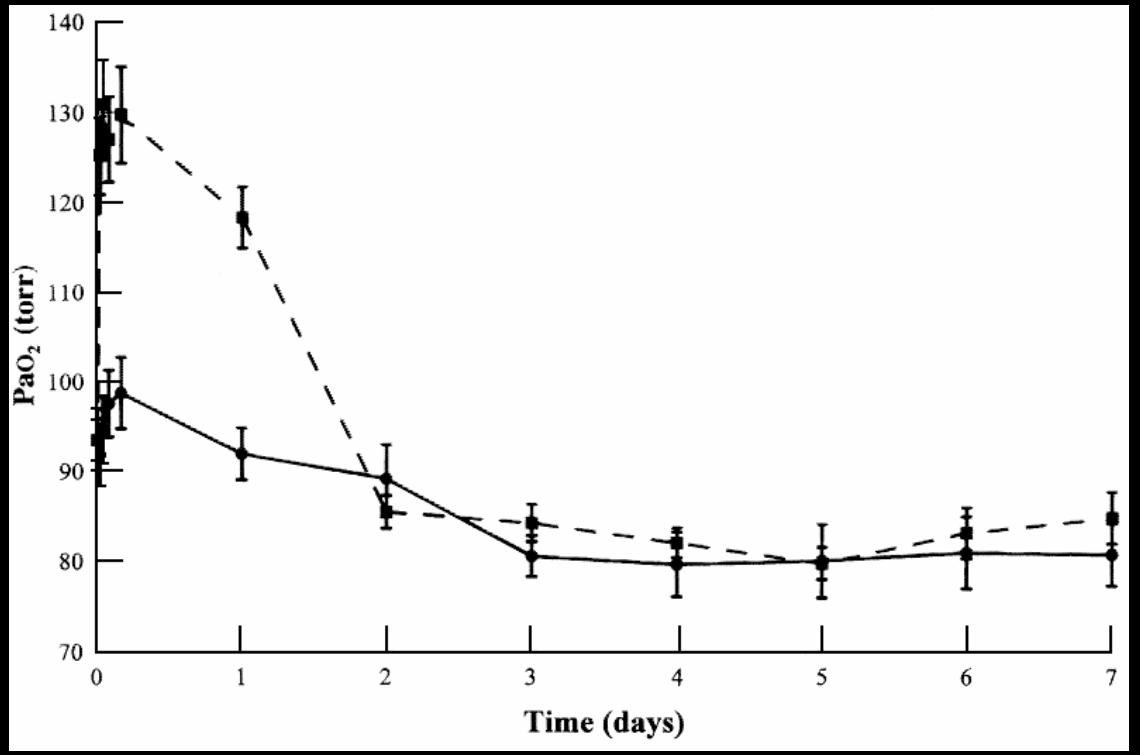
Acute effect of iloprost inhalation on right atrial function and ventricular dyssynchrony in patients with pulmonary artery hypertension



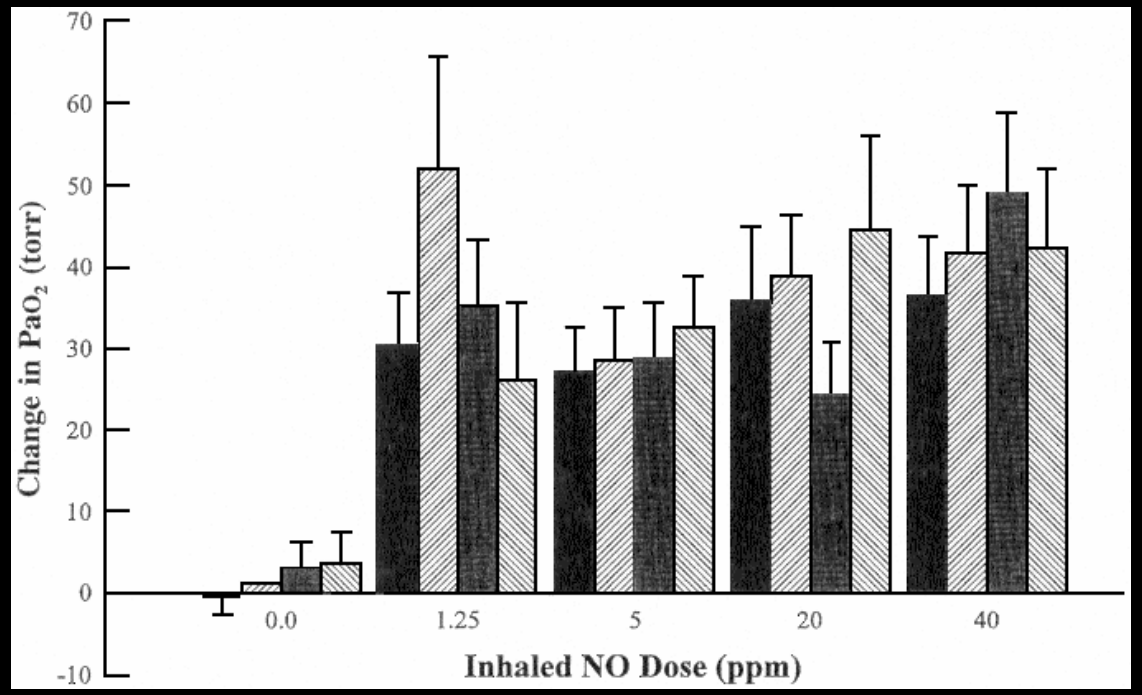
Echocardiography, Volume: 34, Issue: 1, Pages: 53-60, First published: 14 October 2016, DOI: (10.1111/echo.13401)

ARDS

- 177 patients over 14-month period
- Evaluated improvement in oxygenation as well as mortality both on and off mechanical ventilation
- Dashed line was NO group



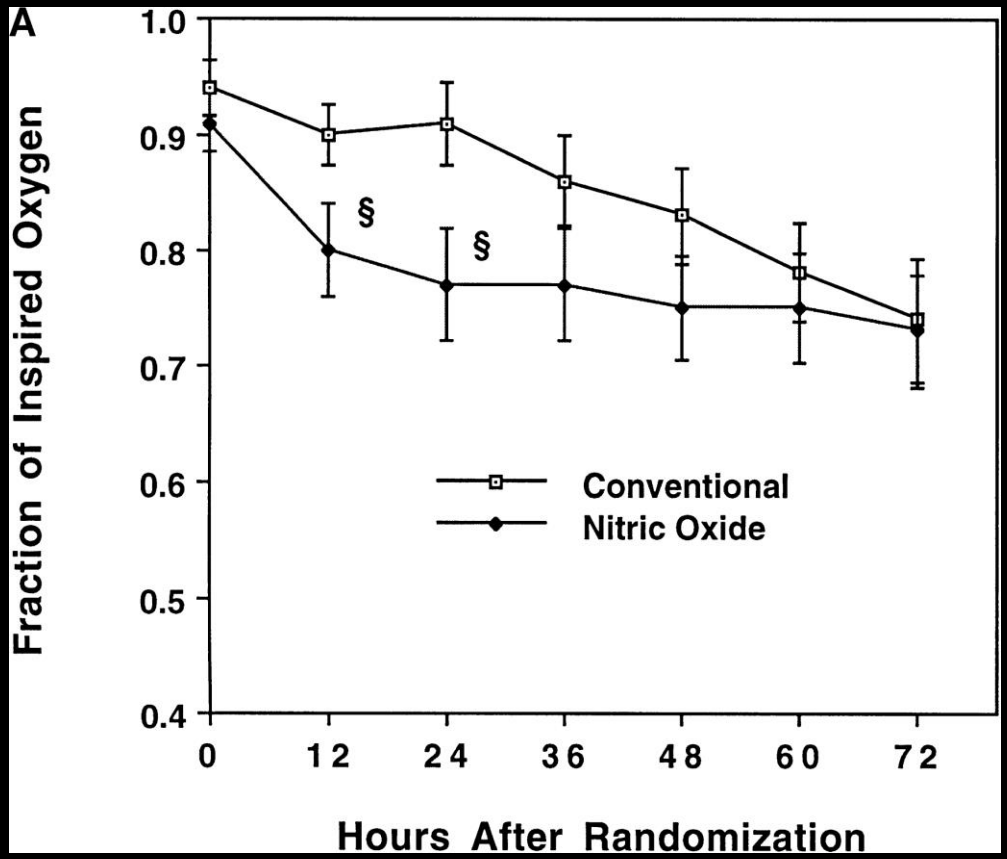
ARDS



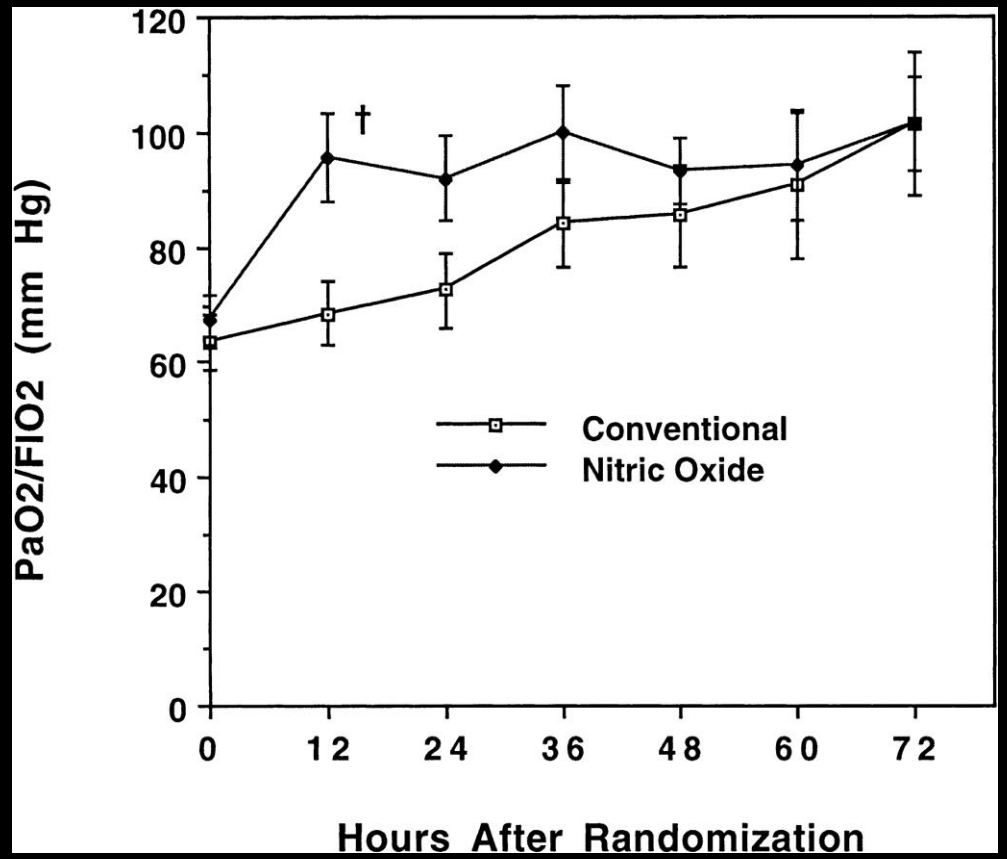
- Demonstrated that oxygenation did improve with NO, and it occurred rapidly, but did not have a sustained effect
- No change in mortality
- Number of days alive was also not different

SECOND ARDS STUDY

- Randomized, controlled trial comparing conventional therapy to inhaled NO
- 40 patients from one hospital
- Evaluated improvement in oxygenation and reduction in FiO2 requirements

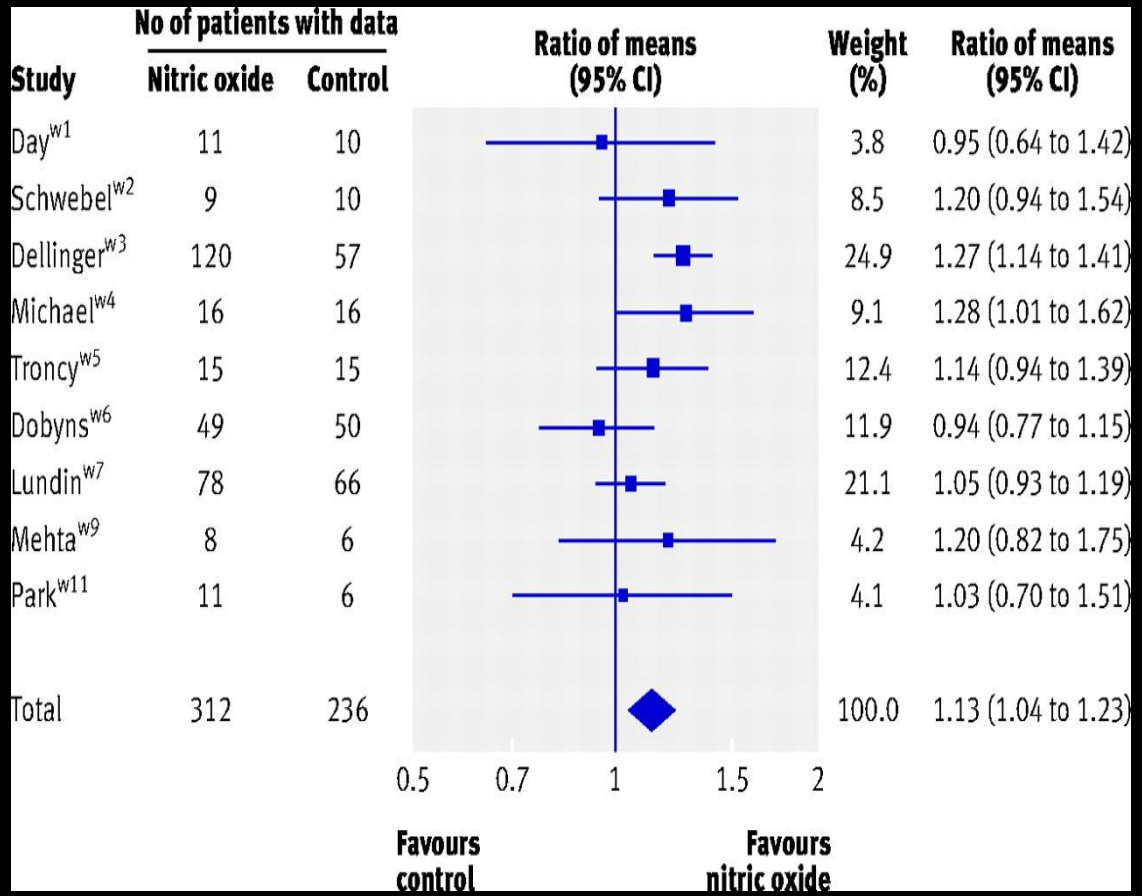


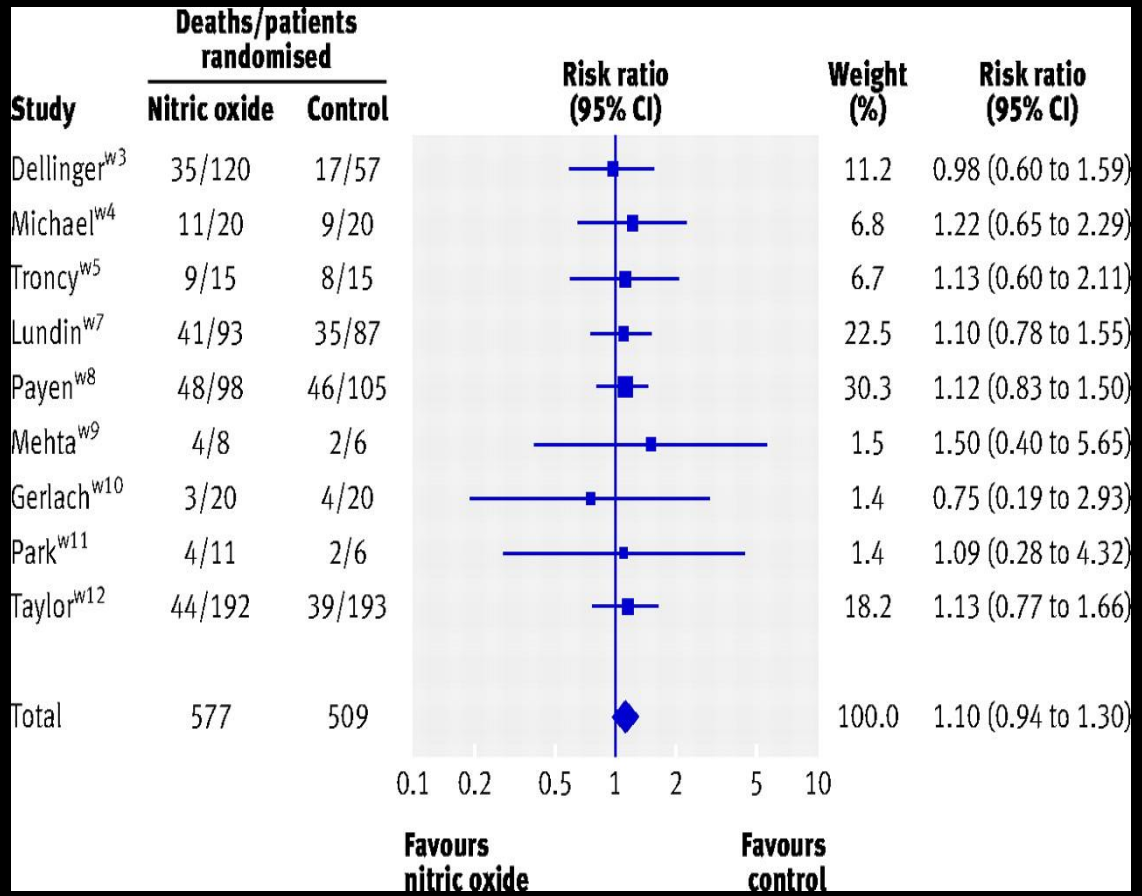
SECOND ARDS STUDY



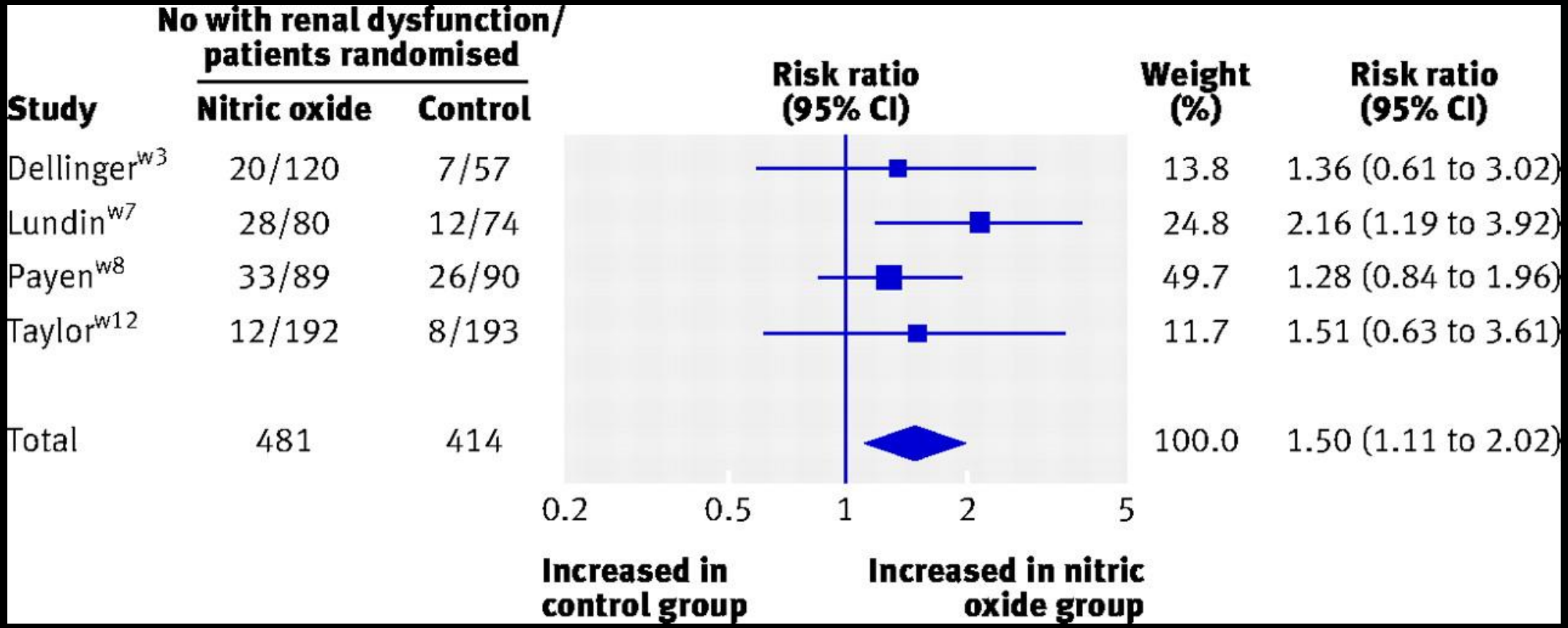
- No significant change in PaO2/FiO2 ratio
- No significant improvement in oxygenation overall, although NO group did increase faster
- No appreciable difference in ability to wean FiO2

BMJ META-ANALYSIS





UNEXPECTED FINDING IN META-ANALYSIS



EPOPROSTENOL IN ARDS

- There are no placebo controlled trials or even large trials looking at inhaled epoprostenol in ARDS
- Several case series demonstrate some improvement in oxygenation, but it was minimal
- No studies looking at mortality

EPO VS NO IN ARDS

- Retrospective study
- 105 patients with ARDS by usual defined definition who received either iNO or EPO for at least 1 hour were included
- Could not have received combined inhaled therapy and had to be intubated when it was initiated
- Dosing did not appear to be well controlled
- Found that inhaled epoprostenol was noninferior to iNO for ventilator-free days
- No major differences in secondary outcomes

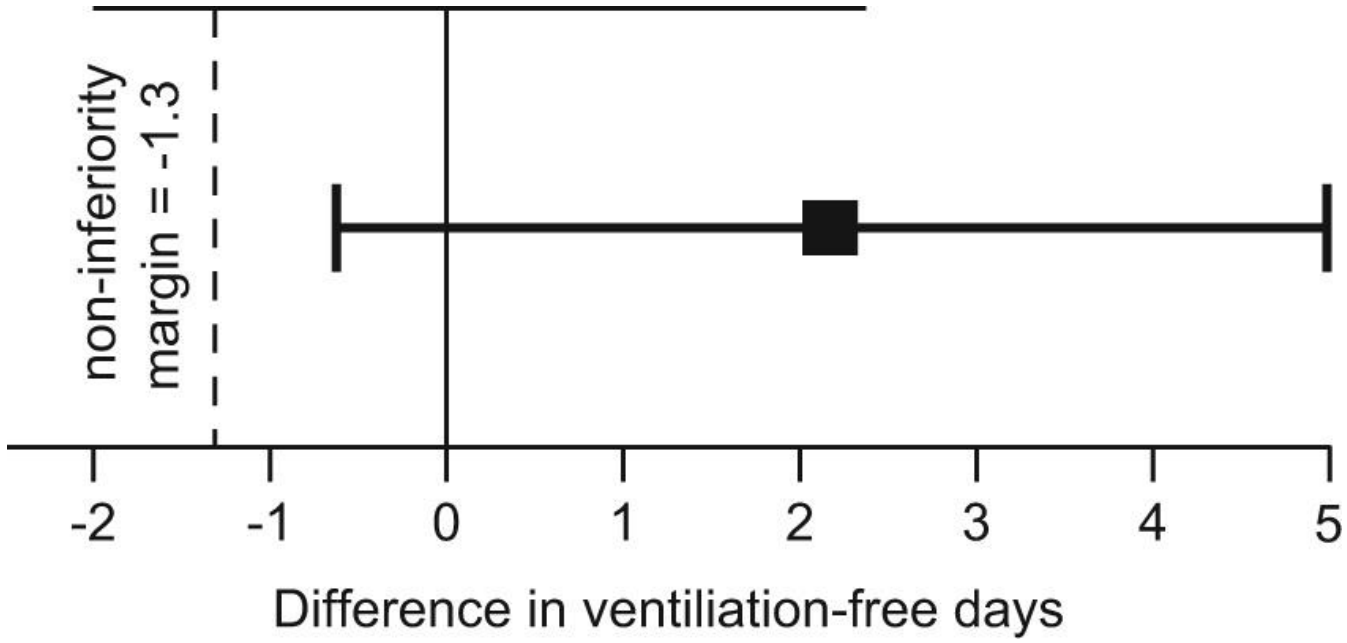


Figure 2. Forest plot depicting difference in ventilation-free days (VFDs) between inhaled epoprostenol and inhaled nitric oxide. Mean difference in VFDs between inhaled epoprostenol and inhaled nitric oxide was 2.16 days (95% confidence interval = −0.61 to 4.9 days).

Table 4. Secondary Endpoints[a].

Outcome	iEPO (N = 47)	iNO (N = 47)	*P*
Day 28 ICU free days	3.13	1.28	0.14
Death at discharge	34 (72)	36 (77)	0.64
Change in PaO_2/FiO_2 ratio from baseline			
1 hour	18 (1 to 85)	9 (−9 to 31)	0.20
6 hours	7.8 (−23 to 55)	21 (−1.8 to 47)	0.23
12 hours	21 (−11 to 73)	26 (2 to 66)	0.44

Abbreviations: iEPO, inhaled epoprostenol; iNO, inhaled nitric oxide; ICU, intensive care unit; IQR, interquartile range.
[a]Data presented as n (%) or median (IQR).

Table 4. Secondary Endpointsa.

Table 5. Safety Endpoints[a].

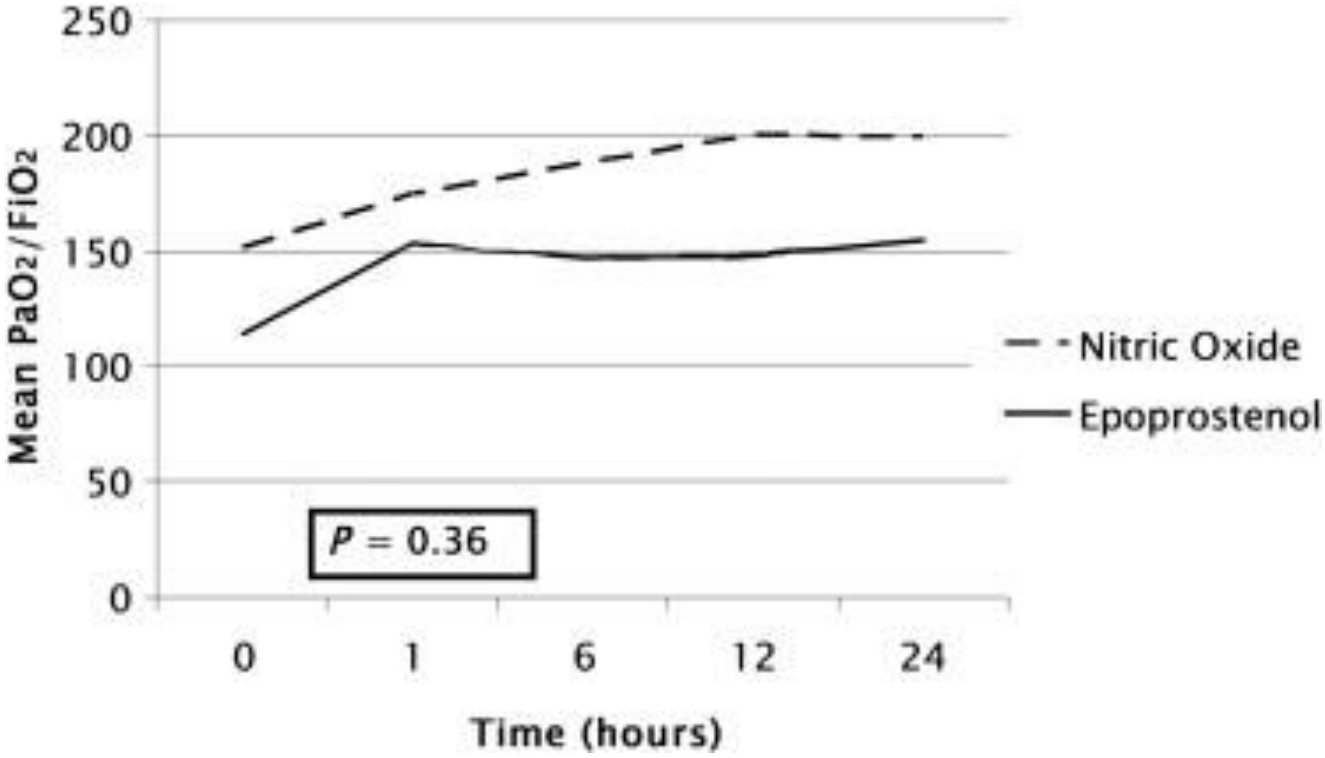
Outcome	iEPO (N = 47)	iNO (N = 47)	*P*
Rebound hypoxemia	2 (4.3)	2 (4.3)	1.00
Thrombocytopenia[b]	10 (21)	8 (17)	0.60
Significant bleeding	8 (17)	8 (17)	1.00
Methemoglobinemia	0	0	N/A
Renal dysfunction[c]	6 (12.8)	10 (21)	0.27
Hemodynamic instability[d]			
1 hour	26 (55)	31 (66)	0.29
6 hours	26 (55)	28 (60)	0.68
12 hours	25 (53)	26 (55)	0.84

Abbreviations: iEPO, inhaled epoprostenol; iNO, inhaled nitric oxide.
[a]Data presented as n (%).
[b]Thrombocytopenia defined as platelets <50 000/μL.
[c]Renal dysfunction defined as new-onset need for renal replacement therapy.
[d]Hemodynamic instability defined as new-onset hypotension.

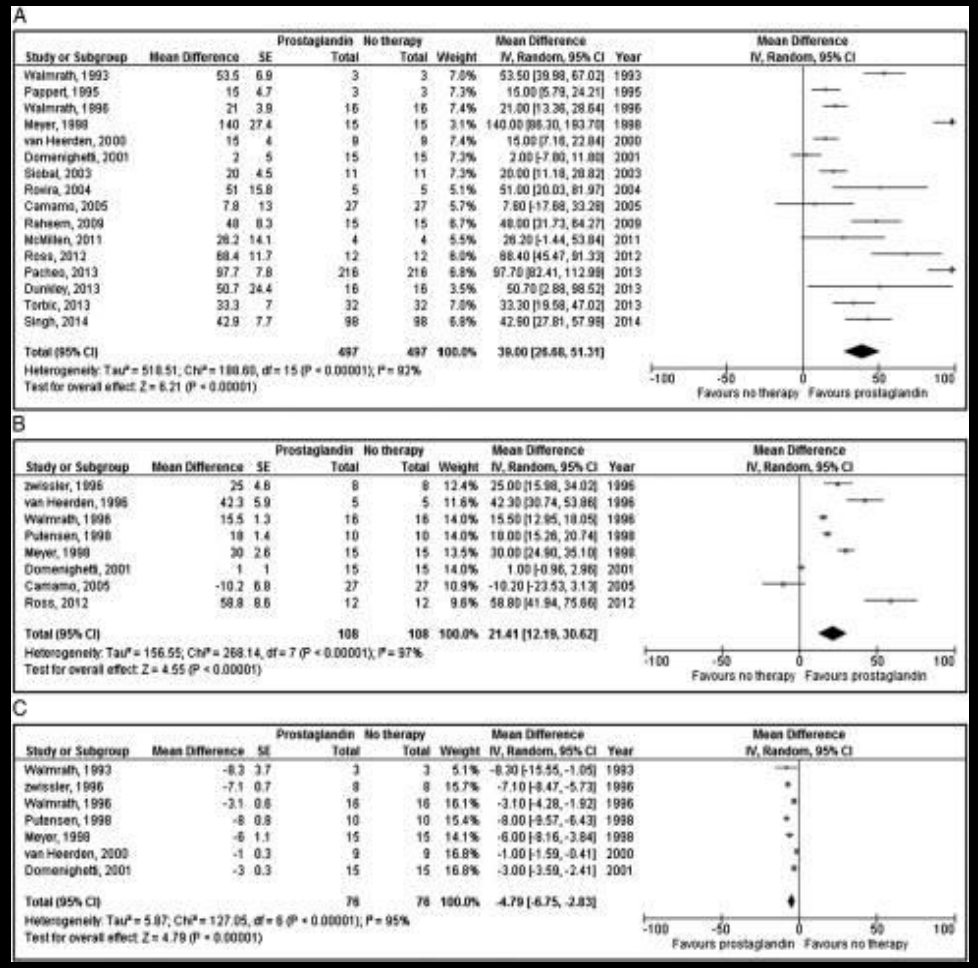
Table 5. Safety Endpointsa.

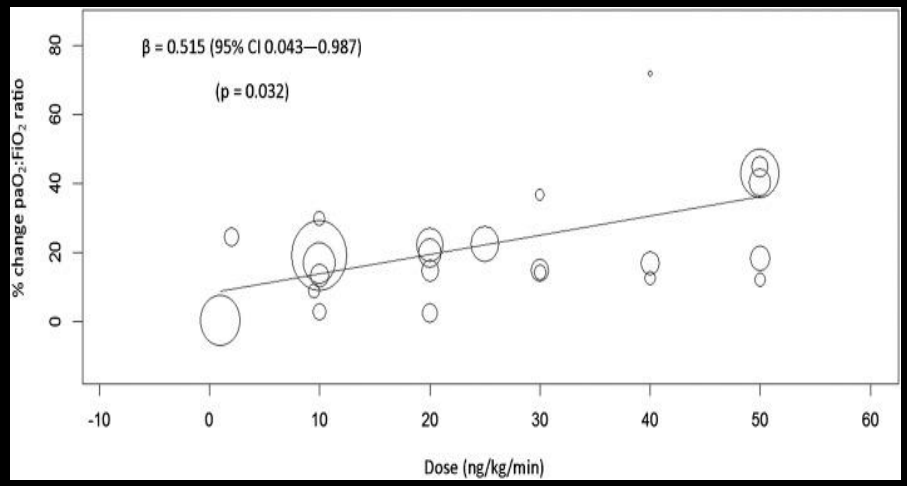
EPO VS NO FOR HYPOXEMIA

- 105 mechanically ventilated patients with half on epo and half on NO
- Most for ARDS
- No difference in change of PaO2/FiO2, duration of therapy, time on mechanical ventilation, ICU or hospital length of stay, or mortality
- NO 4.5-17 times more expensive
- J Crit Care (2013); 28,5



META-ANALYSIS OF EPO IN ARDS





SUMMARY OF FINDINGS

Studies show that increased use of inhaled prostaglandins over the past decade in ARDS

Did see improvement in PaO_2 and PaO_2/FiO_2, but unable to really state a cause and effect relationship based on how most of the studies were done. Most had no control group.

No reduction in mortality, in fact, mortality rate was higher in the studies of patients where inhaled prostaglandins were used – maybe this worsens mortality, but that is also unclear

SUMMARY FOR ARDS

- In some cases, improve oxygenation, likely more benefit in the population with RV dysfunction due to reduction in pulm hypertension
- No mortality benefit
- But are we surprised? And should we care? Most ARDS patients die from multi-organ failure, not hypoxemia. So maybe improvement in oxygenation is enough initially
- Most studies not powered to detect small changes in mortality
- These inhaled vasodilators of the pulmonary system are bridges and support, not a treatment for the pathology of the disease. Similar to ECMO, but ECMO has received increasing support

WHEN TO USE IN ARDS

- NOT routinely
- Transiently stabilize when failing to respond to other therapies, maybe just after intubation until proned or transitioned to ECMO
- MAYBE Those with a PFO
- MAYBE Those with echo evidence of RV dysfunction
- Hypoxemia refractory to other therapy – little downside except cost for NO

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Review Article

Inhaled Nitric Oxide (iNO) and Inhaled Epoprostenol ($iPGI_2$) Use in Cardiothoracic Surgical Patients: Is there Sufficient Evidence for Evidence-Based Recommendations?

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Key Words: Inhaled Nitric Oxide; inhaled prostacyclin; epoprostenol; pulmonary artery hypertension; right ventricular failure; heart transplant; lung transplant; left ventricular assist device

INHALED NITRIC OXIDE (iNO) and inhaled epoprostenol or prostacyclin I_2 ($iPGI_2$) are used widely to treat pulmonary hypertension, right ventricular failure, and hypoxemia in cardiac surgical patients.[1–6] The widespread use of inhaled pulmonary vasodilators in this patient population can be justified by the well-established and often immediately observable physiologic actions of these agents, the high-stakes nature of the operations that these agents are being used for, the seriousness of the conditions they are used to treat, and the lack of therapeutic alternatives with proven efficacy. These factors have contributed to institution- and physician-specific practice patterns on the use and choice of iNO or $iPGI_2$ that have become well established over time. However, economic pressures to contain increasing pharmacy costs are forcing hospitals and physicians to scrutinize the routine administration of iNO and $iPGI_2$, because these agents are expensive and the published evidence supporting the clinical efficacy of these agents on patient outcomes remains controversial. Furthermore, the cost differential between using iNO and different formulations of $iPGI_2$ can be substantial (Table 1). In the cost-benefit analysis, it is important to determine if these agents provide clinical efficacy, whether iNO offers advantages to justify its added cost, whether these 2 agents are interchangeable, or whether less expensive substitutes are clinically equivalent. Finally, there are potential adverse effects associated with the use of these selective pulmonary vasodilators that include precipitating pulmonary edema, contributing to surgical bleeding, contributing to systemic hypotension, causing methemoglobinemia, as well as delivery system malfunction causing acute hypoxemia or right heart failure.

The purpose of this review is to address the cost-benefit and risk-benefit considerations on the clinical use of iNO and $iPGI_2$ in cardiac surgical patients based on the available evidence in the medical literature. Establishing and implementing clinical guidelines on the appropriate clinical indications for iNO and $iPGI_2$, contraindications to the administration of iNO or $iPGI_2$, the comparative advantages of iNO versus $iPGI_2$, and the use of less expensive formulations of $iPGI_2$ have already demonstrated that they can have a marked impact on clinical practices and pharmacy expenses. Identifying the knowledge gaps that exist in the medical literature on the clinical efficacy of iNO and $iPGI_2$ in cardiac surgical patients also may serve to guide future clinical investigations.

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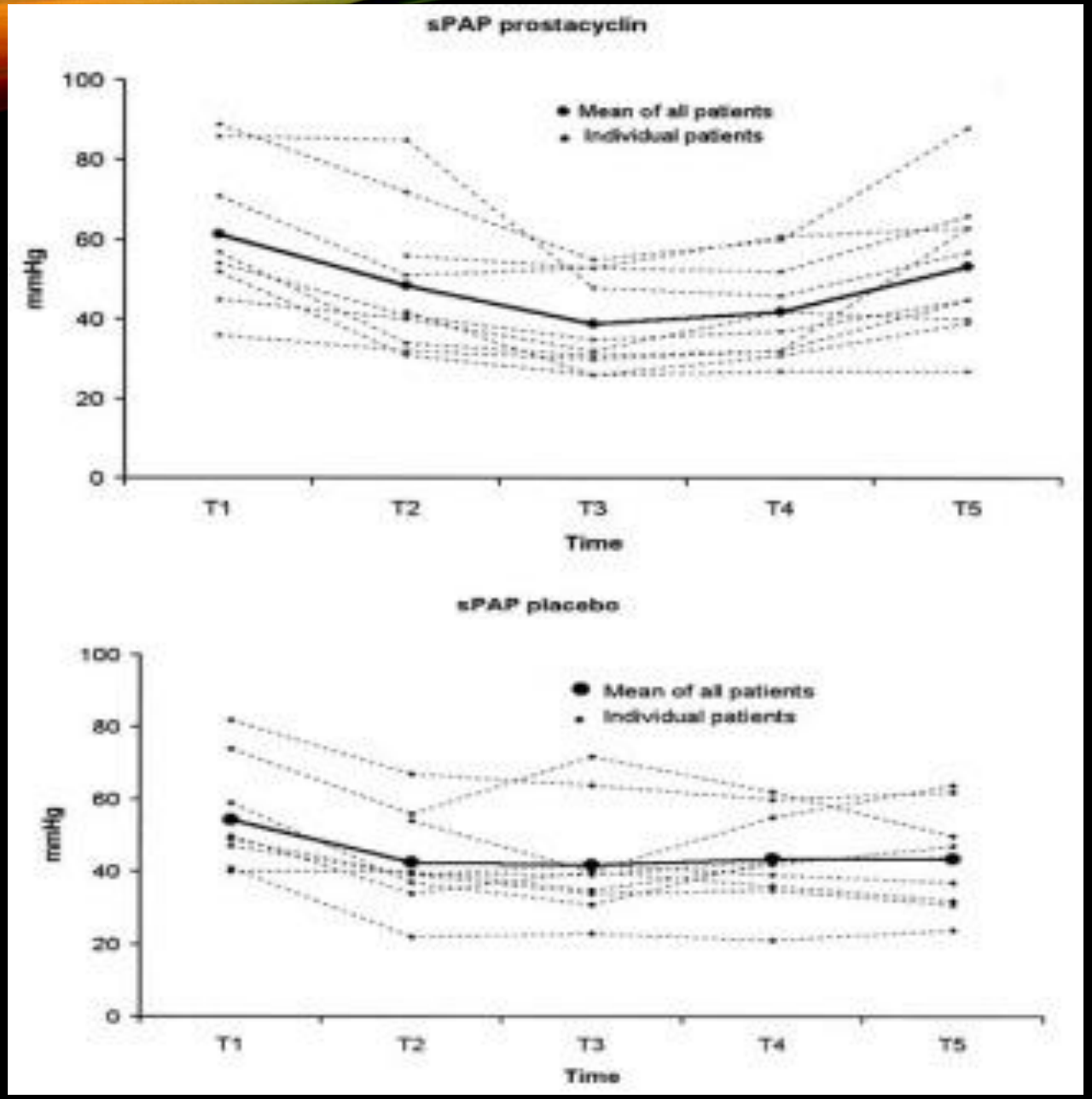
CARDIAC SURGERY WITH PULM HYPERTENSION

- 20 patients with pulmonary hypertension defined as systolic PAP of greater than 30 or mean PAP of greater than 25 randomized to inhaled epoprostenol (60 mcg) vs placebo. Double-blinded study.
- Started just after induction and prior to incision
- Epoprostenol significantly reduced right ventricular stroke work and systolic PAP and the effective was greater with higher pulmonary artery pressures
- No effect on LV function, oxygenation, platelet aggregation or blood loss

- Hache et al. Journal of Thoracic and cardiovascular surgery. 125(3)


sPAP prostacyclin
100
80
60
40
20
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mmHg
Mean of all patients
Individual patients
T1
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Time
sPAP placebo
100
80
60
40
20
0
mmHg
Mean of all patients
Individual patients
T1
T2
T3
T4
T5
Time

MVR USING EPO VS NO VS CONTROL

- 58 patients randomized and double-blinded to either iEPO, iNO or control
- Considered to have pulm hypertension if sPAP greater than 45 or mPAP greater than 25
- Given after induction of anesthesia and no anesthetic gas was used
- mPAP and PVR decreased in both compared to control and maintained
- Improved right ventricular ejection fraction
- Increased cardiac indices, easier weaning from CPB, reduced time of intubation, and less inotropes and pressors compared to control

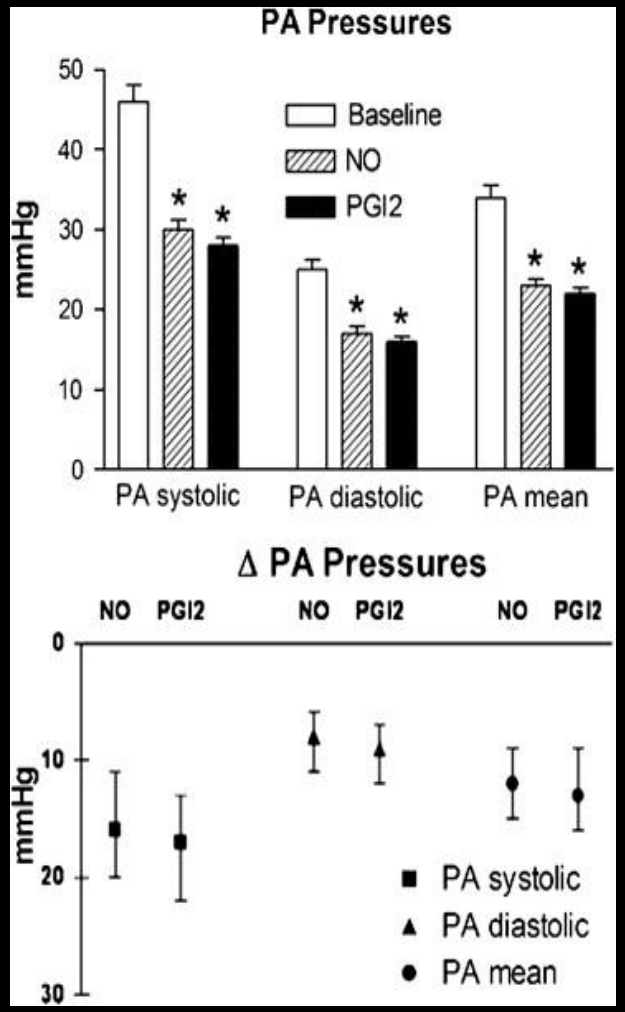
- Khalil et al. Journal of cardiovascular medicine. 7(2)

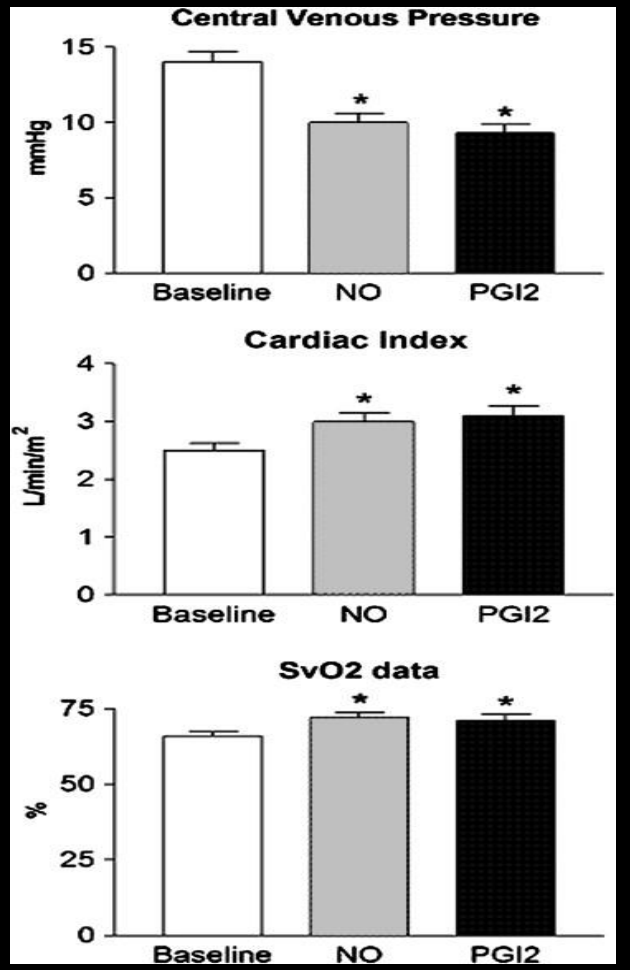
CROSSOVER IN TRANSPLANT

- 25 patients undergoing heart or lung transplant surgery
- Started on either inhaled nitric oxide or inhaled epoprostenol and then at 6 hours crossover to the other agent was used
- The crossover agent was used for 30 minutes and then went back to the original agent
- Duration of treatment and weaning not protocolized
- Several limitations to this study

- Khan et al. Journal of Thoracic and Cardiovascular Surgery. 138(6).

CROSSOVER STUDY





CROSSOVER STUDY

Both agents reduced pulmonary artery pressure and CVP

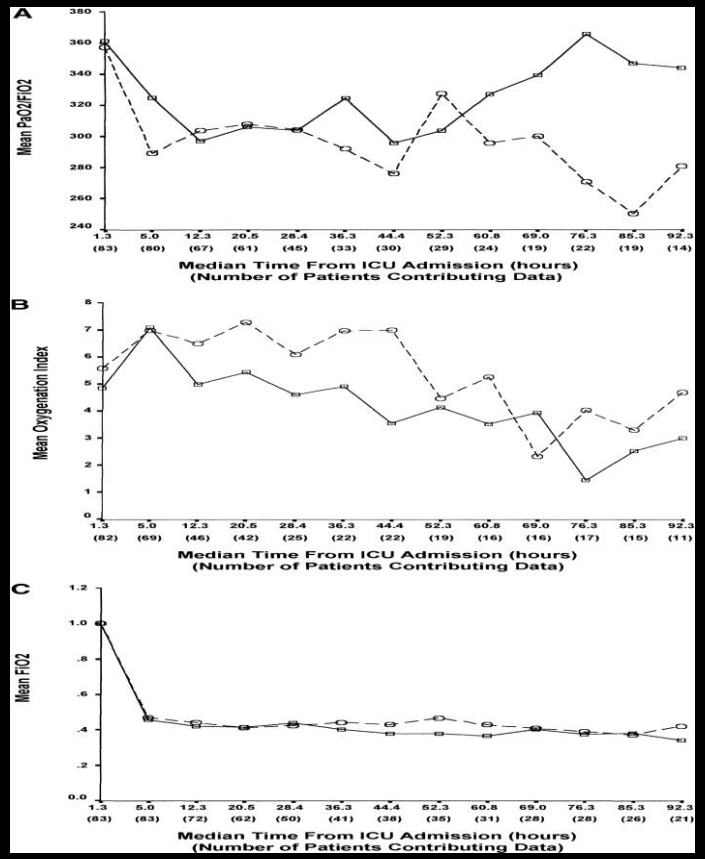
Both improved cardiac index and mixed venous oxygen saturation

After crossover, there was no significant differences between the two agents in any of the above findings

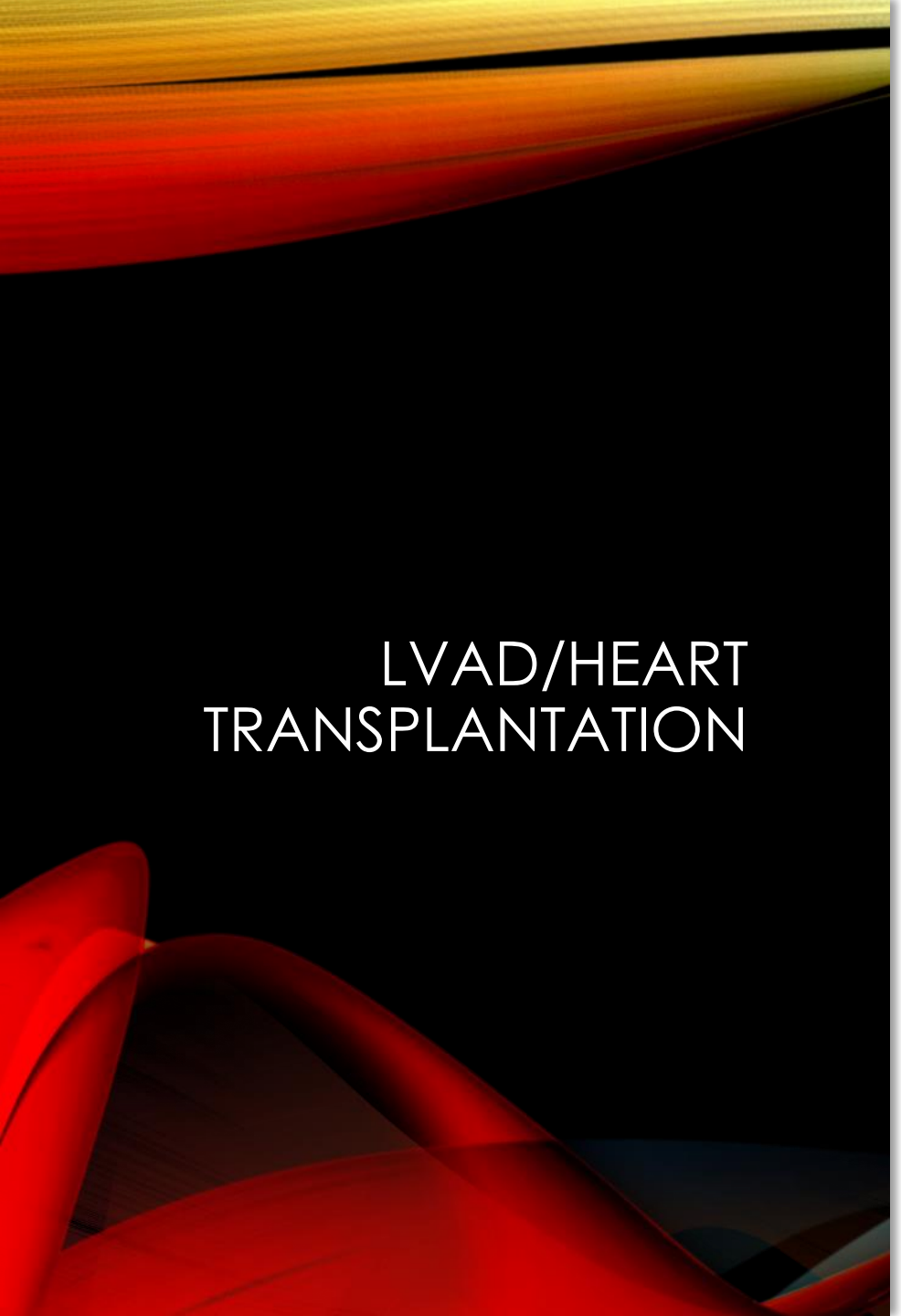
No systemic affects and no complications

Confirming that iEPO may be safe alternative to iNO

LUNG TRANSPLANTATION



- 84 transplant patients, began 10 min after reperfusion and for at least 6 hours – randomized, placebo-controlled
- No benefit in oxygenation, time to extubation or 30-day mortality rate
- Some evidence in this population that combining iNO and epo may have additive effect



LVAD/HEART TRANSPLANTATION

LV and RV function differently with LV using torsional and rotational forces and the RV using peristaltic contractions (somewhat like the GI system)

RV is dependent on low pressures of the pulm vascular bed, so the output is comparable to the LV with using much lower myocardial energy. The LV also contributes to RV function through the shared ventricle.

Due to all of this, the RV is more sensitive to increased afterload from pulmonary hypertension and this can cause fast RV decompensation

RV failure after LVAD ranges from 9-44% and for heart transplant around 45%

EVIDENCE FOR NO AFTER HEART TRANSPLANT

- One prospective trial evaluated NO VS EPO immediately after coming off bypass. PVR in NO group decreased significantly but then remained unchanged for the next 6 hours. PVR in the epo group only decreased 10% immediately, but then gradually decreased further over the next 6 hours
- So overall the results were similar for reduction of PVR. Weaning from bypass was successful for all in NO group, but failed in 17% of epo group
- Another trial looked at 16 transplant patients with elevated PA pressures. Given iNO 20 ppm prior to wean from bypass and compared to 16 others not in iNO. There was no difference in survival, but only 1 developed RVF in the iNO group and 6 in the control

EVIDENCE FOR NO AFTER LVAD

- 3 prospective trials confirmed that iNO reduced PVR in this population
- 11 patients with elevated PVR with older LVAD devices either iNO 20 ppm or inhaled nitrogen placebo. iNO group had decreased mPAP and improvement in LVAD flow with one requiring RV support after rapid wean of iNO
- 150 patients with elevated PVR either iNO of 40 ppm or nitrogen placebo started just before bypass wean and continued for 48 hours or until extubation. Trends toward decreased RVF and less required RV support devices, but 45% crossed over from placebo to treatment group so no firm conclusions could be made

EVIDENCE FOR EPO AFTER HEART TRANSPLANT

One pharmacodynamic dose-response study confirmed dose-dependent decrease in PVR

Another crossover study compared iNO to inhaled epo as initial treatment, with cross over to other agent at 6 hours.

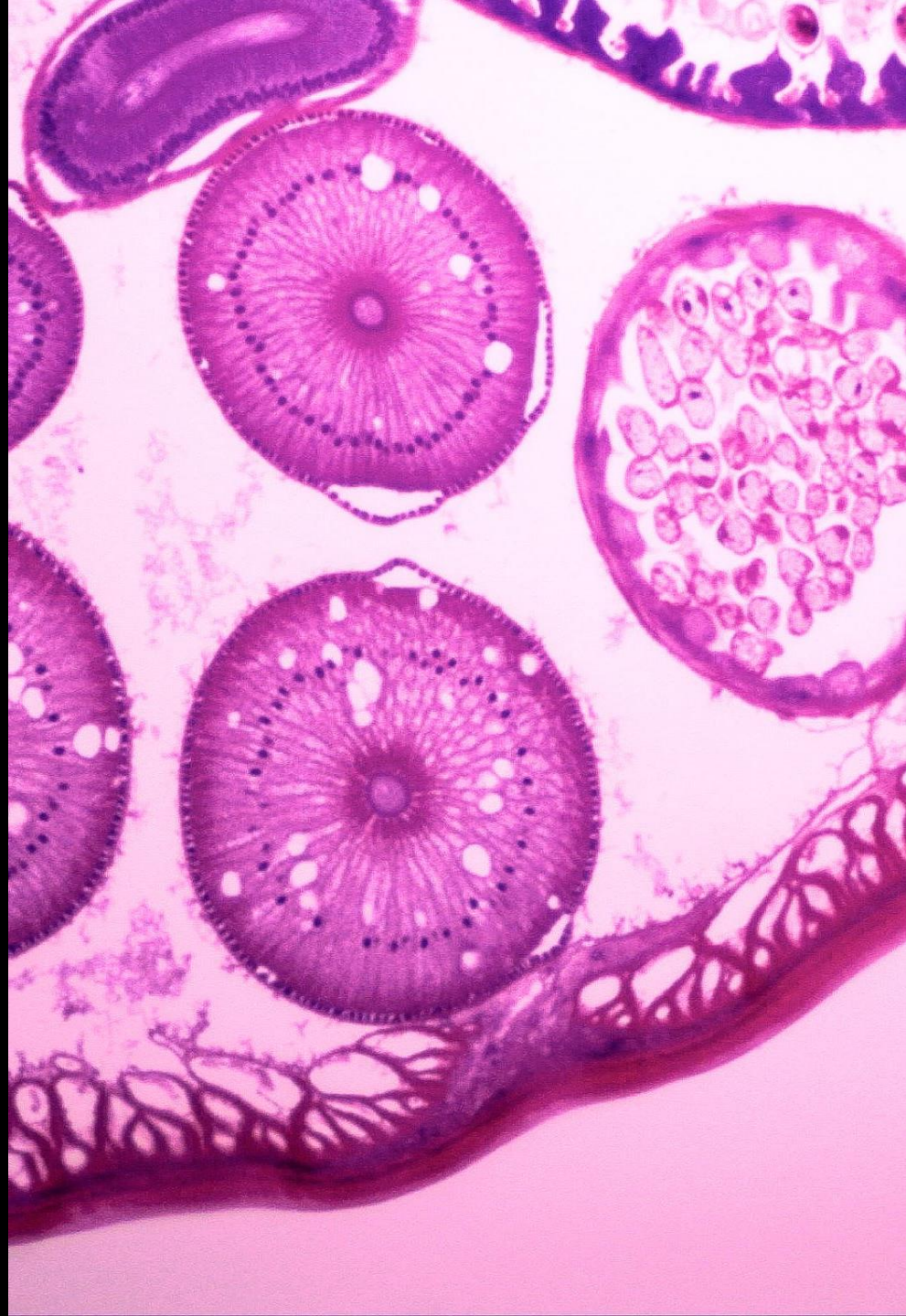
No difference in mPAP

Improvement in CVP, CI and mixed venous oxygen saturation were similar

Note this study was in both heart and lung transplant patients

EVIDENCE FOR EPO AFTER LVAD

- Minimal evidence, mostly case reports
- One study did look at if differences where iEPO was started after induction of anesthesia versus after weaning from bypass in LVAD patients
- Found that timing of initiation did not matter and that both led to lower postoperative pulmonary artery pressures
- However, earlier initiation was associated with higher blood loss – there is evidence for platelet aggregation as mentioned previously



RV MI OR DYSFUNCTION

- Some has been discussed already
- No randomized controlled trials specific to RV myocardial infarction as this is rare and difficult to enroll in trials
- NO in STEMI has been shown to be safe and a trend in improved outcomes
- Cardiac output improved in RVMI
- Many case reports in cardiogenic shock with RV failure with both NO and epoprostenol and successful improvements without systemic effects

SUMMARY OF EVIDENCE IN CARDIAC SURGERY

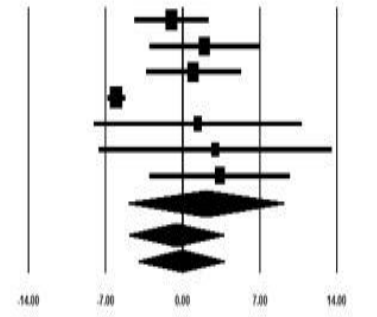
- Both iEPO and iNO reduce pulmonary artery pressures and lead to improvement in right ventricular function and cardiac output
- Has been shown independently with both agents in small studies
- Despite these improvements, there is no data showing that it reduces mortality or morbidity
- Most of the data showing reduced vasopressors and inotropes, reduced time on CPB, reduced intubation time were all in small studies that were never reproduced
- Overall can only say that these agents appear equivalent in what they do, but unclear if there is any outcome benefit to their use

POST-OPERATIVE PULMONARY HYPERTENSION

- Pulmonary hypertension has been identified as a prognostic factor for increased morbidity and mortality after several different types of surgical interventions, so it is presumed that pulmonary vasodilators would improve outcomes
- Meta-analysis comparting NO to inhaled prostacyclin
- No difference in improvement in mPAP or PVR between the two groups. No difference in outcomes
- Subgroup analysis showed decrease in mPAP greater in inhaled prostacyclin group as far as speed, but overall lower in NO group but not significant
- Most studies did not have a control group and only 7 studies out of 832 were eligible (RCT's)

(A) Mean pulmonary arterial pressure

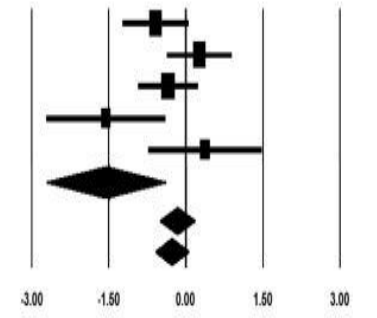
Study name	Pediatric/Adult	Difference in mean change	Lower limit	Upper limit	Z-Value	P-Value	Relative Weight
Fattouch (2005) [20]	Adult	-1.00	-4.33	2.33	-0.588	0.557	17.71
Fattouch (2006) [21]	Adult	2.00	-3.00	7.00	0.784	0.433	15.23
Winterhalter (2008) [25]	Adult	1.00	-3.29	5.29	0.457	0.647	16.32
Khan (2009) [22]	Adult	-6.00	-6.79	-5.21	-14.892	0.000	20.21
Loukanov (2011) [24]	Pediatric	1.40	-8.05	10.85	0.290	0.772	9.23
Kirbas (2012) [23]	Pediatric	3.00	-7.57	13.57	0.556	0.578	8.11
Abe (2017) [19]	Adult	3.40	-2.95	9.75	1.049	0.294	13.18
Pooled effect (Pediatric)		**2.11**	**-4.94**	**9.16**	**0.587**	**0.557**	
Pooled effect (Adult)		**-0.57**	**-4.87**	**3.73**	**-0.259**	**0.796**	
Pooled effect (Total)		**-0.10**	**-3.98**	**3.78**	**-0.051**	**0.959**	



Heterogeneity test:
Pediatric: Q = 0.049, df = 1, P =0.825, I-square = 0%
Adult: Q = 33.06, df = 4, P <.001, I-square = 87.90%
Total: Q = 37.245, df = 6, P <.001, I-square = 83.89%

(B) Pulmonary vascular resistance

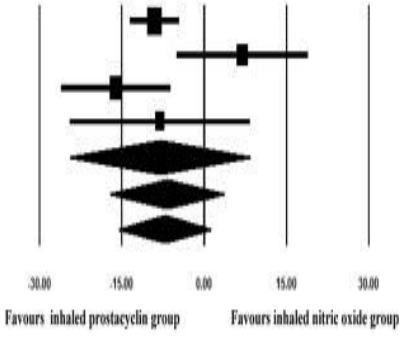
Study name	Pediatric/Adult	Std. Diff. in mean change	Lower limit	Upper limit	Z-Value	P-Value	Relative Weight
Fattouch (2005) [20]	Adult	-0.58	-1.22	0.05	-1.795	0.073	23.00
Fattouch (2006) [21]	Adult	0.27	-0.36	0.89	0.843	0.399	23.23
Winterhalter (2008) [25]	Adult	-0.34	-0.92	0.24	-1.142	0.253	23.99
Loukanov (2011) [24]	Pediatric	-1.55	-2.71	-0.40	-2.630	0.009	14.51
Abe (2017) [19]	Adult	0.37	-0.73	1.47	0.667	0.505	15.28
Pooled effect (Pediatric)		**-1.55**	**-2.71**	**-0.40**	**NA**	**NA**	
Pooled effect (Adult)		**-0.16**	**-0.50**	**0.17**	**-0.952**	**0.341**	
Pooled effect (Total)		**-0.27**	**-0.60**	**0.05**	**-1.649**	**0.099**	



Heterogeneity test:
Pediatric: not assessed
Adult: Q = 4.777, df = 3, P = 0.189, I-square = 37.20%
Total: Q = 12.566, df = 4, P =.014, I-square = 68.17%

(A) Heart rate

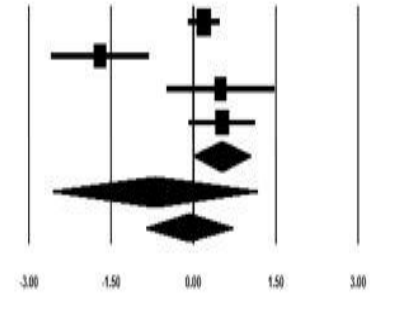
Study name	Pediatric/Adult	Difference in mean change	Lower limit	Upper limit	Z-Value	P-Value	Relative Weight
Fattouch (2005) [20]	Adult	-9.00	-13.47	-4.53	-3.95	<0.001	36.363
Fattouch (2006) [21]	Adult	7.00	-4.98	18.98	1.15	0.252	22.060
Winterhalter (2008) [25]	Adult	-16.00	-25.90	-6.10	-3.17	0.002	25.794
Kirbas (2012) [23]	Pediatric	-8.00	-24.38	8.38	-0.96	0.339	15.784
Pooled effect (Pediatric)		**-8.00**	**-24.38**	**8.38**	**NA**	**NA**	
Pooled effect (Adult)		**-6.77**	**-17.09**	**3.56**	**-1.28**	**0.199**	
Pooled effect (Total)		**-7.12**	**-15.44**	**1.21**	**-1.68**	**0.094**	



Heterogeneity test:
Pediatric: not assessed
Adult: Q = 8.68, df = 2, P = .013, I-square = 76.96%
Total: Q = 8.682, df = 3, P =.034, I-square = 65.45%

(B) Cardiac output

Study name	Pediatric/Adult	Difference in mean change	Lower limit	Upper limit	Z-Value	P-Value	Relative Weight
Fattouch (2005) [20]	Adult	0.20	-0.09	0.49	1.37	0.170	30.105
Winterhalter (2008) [25]	Adult	-1.70	-2.59	-0.81	-3.76	<0.001	22.412
Loukanov (2011) [24]	Pediatric	0.50	-0.48	1.48	1.00	0.320	21.003
Kirbas (2012) [23]	Pediatric	0.53	-0.07	1.13	1.73	0.084	26.480
Pooled effect (Pediatric)		**0.52**	**0.01**	**1.04**	**1.99**	**0.046**	
Pooled effect (Adult)		**-0.70**	**-2.56**	**1.16**	**-0.74**	**0.459**	
Pooled effect (Total)		**-0.08**	**-0.86**	**0.71**	**-0.19**	**0.851**	



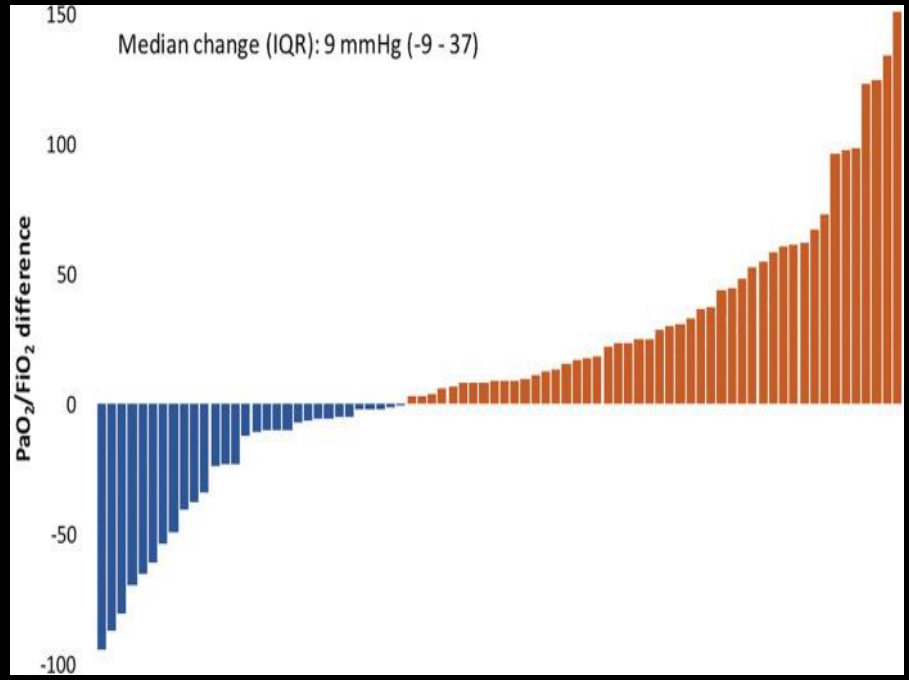
Heterogeneity test:
Pediatric: Q = 0.003, df = 1, P = 0.959, I-square = 0%
Adult: Q = 16.005, df = 1, P <.001, I-square = 93.75%
Total: Q = 18.859, df = 3, P =<.001, I-square = 84.09%

COMBINATION THERAPY

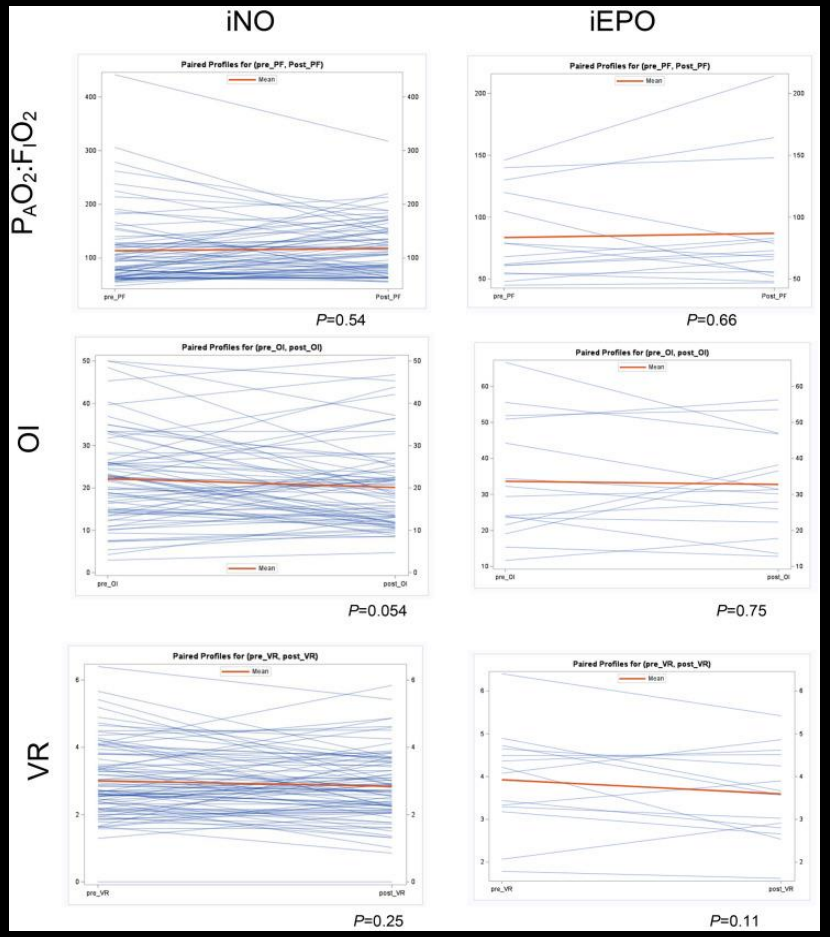
- There is limited data on combination of NO and EPO in the posteroperative pulmonary hypertension realm
- Some evidence that combination of agents in cardiac surgery and lung transplant, but it is retrospective data and there is not enough data to say this conclusively
- Adding inhaled NO to those already being treated with epo for chronic pulm hypertension did see benefit
- Chen, S. et al. Annals of Medicine. 2020. 53(3-4).

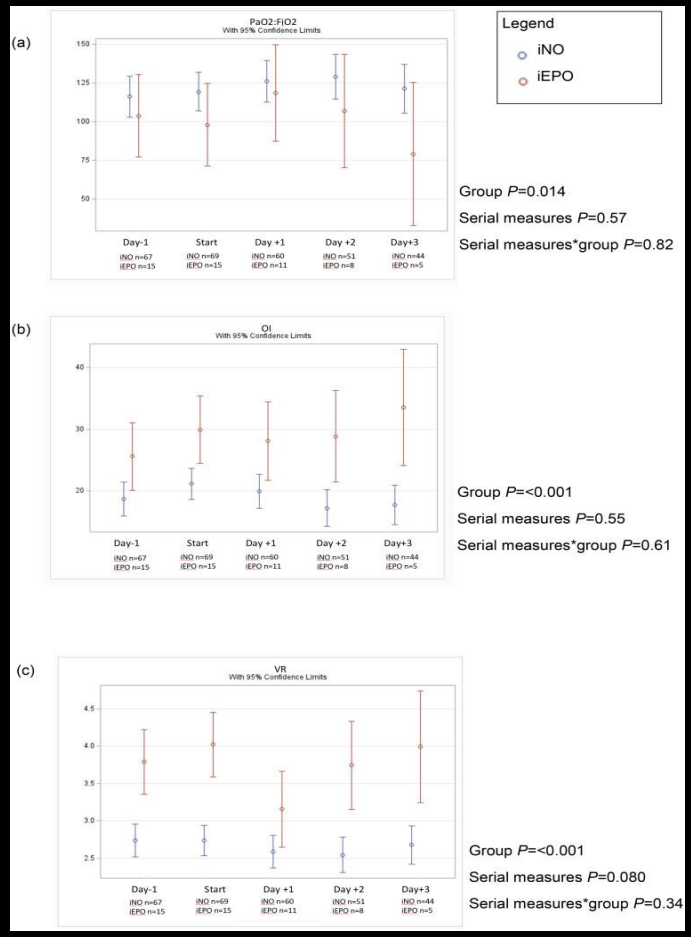
EPO IN COVID-19

- Retrospective study involving 2 tertiary care centers – dosing started at 50 nongrams/kg of ideal body weight per minute.
- Evaluated change in PaO2/FiO2 ratio
- 50 percent had a clinically significant improvement
- Those who were proned and started with lower PaO2/Fio2 benefited most, so may be best for sicker patients – potential rescue therapy



EPO/NO IN COVID-19





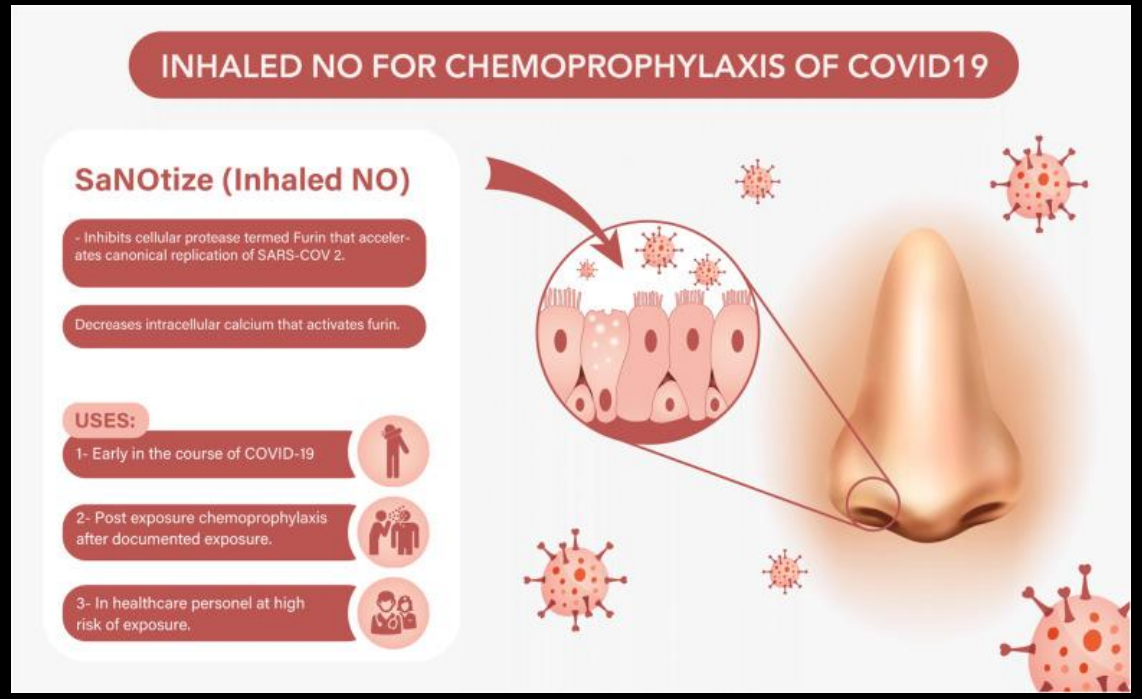
EPO/NO IN COVID19

- 69 patients in the iNO group and 15 in the inhaled iEPO group
- No significant change in PaO2/FiO2, oxygenation index or Ventilatory ratio
- Significant dropout was seen in both groups due to death and overall EPO worse than iNO. No significant changes over a 5 day period.
- No evaluation of mortality

NO IN COVID-19

- Mostly case reports, correspondence and letters to the editor with a few research trials mixed in
- Some did show improvement in PaO2/FiO2 likely due to decreased PVR and increase pulm flow. Others showed no improvement in oxygenation. One study of 272 patients showed initial improvement over the first 12 hours, then subsequent increase in oxygen requirements with no overall benefit, but did increase cost and length of stay
- Trends toward decreased use and time on mechanical ventilation, but unclear if cause and effect. No outcome studies
- No real conclusion can be made from these studies

POTENTIAL FOR PROPHYLACTIC ROLE IN COVID-19?



- Inhibits furin which is required for viral replication in the nose of COVID-19
- May decrease viral load and reduce risk of symptomatic infection
- No clear studies

INOPE TRIAL

- Most patients with submassive PE die from right ventricular failure and a big contributing factor is pulmonary vasoconstriction
- Why potentially useful in PE? Reduction in PVR, improving ventilation-perfusion mismatch, anti-platelet effect
- 76 patients randomized to placebo vs iNO at 50 ppm
- Endpoints were unusual for a study – Primary endpoint needed normal RV function on echo and troponin less than 14. Secondary need both BNP less than 90 and a Borg dyspnea score less than or equal to 2.
- Why unusual? BNP and troponin are not measures of only RV function, they also relate the LV and troponin may no improve right away. The endpoints also combine composites that don't make sense – an echo and a lab test?
- RV function analysis on echo is already a composite and should have been used alone

INOPE TRIAL

- More patients in the iNO group met the primary endpoint, but not statistically significant
- Fewer patients, but still more with iNO met the secondary endpoint, but not statistically significant
- Looking at echo data only – Higher chance of normal RV after 24 hours in iNO group and that was significant. iNO group saw improvement over time of RV function, while placebo group had no change in RV function
- No adverse events
- Potential role for bailout of crashing PE patient or stabilization of submassive PE as a bridge to definitive therapy like clot extraction
- Kline et al. Nitric Oxide. 2019. 84:60-68

MONITORING AND SAFETY

- NO can be given via face mask or nasal cannula, although recommendation is via ventilator and use other modalities if not intubated
- Up to 40 ppm rarely should cause methemoglobinemia
- Environmental concentrations should not exceed 25 ppm over 8 hours, so as long as room is well ventilated, should be fine
- Inhaled EPO can be given via bipap or high-flow nasal cannula effectively. Most start at 50 ng/kg/min and then slowly reduce
- Both are effective via the ventilator
- For NO evaluate for methemoglobinemia, but this is rare at most doses used

CASES