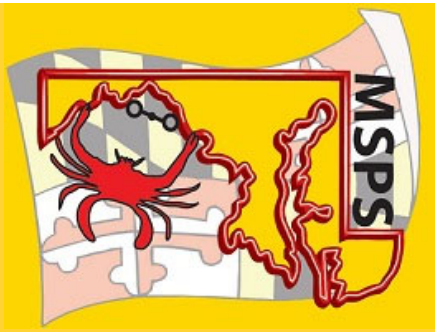
MAVES
Mid-Atlantic VAD and ECMO Symposium



Welcome to the 12th Annual MAVES

3 May 2020

MAVES
Mid-Atlantic VAD and ECMO Symposium

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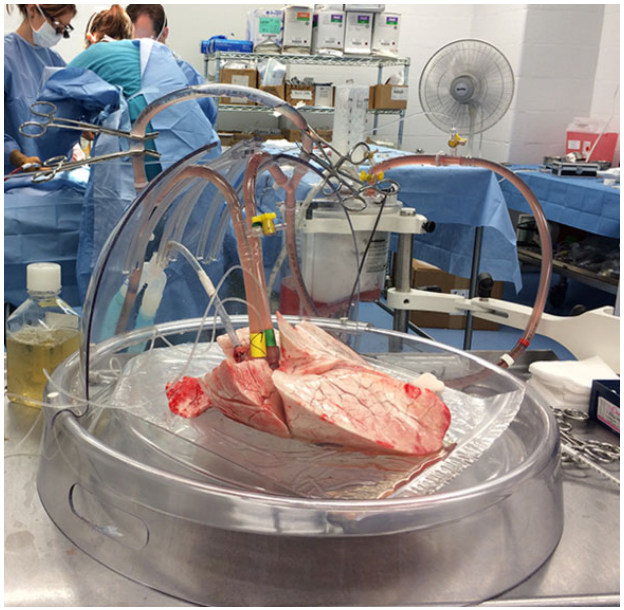
- We have no financial disclosures

EVLP and IVLP

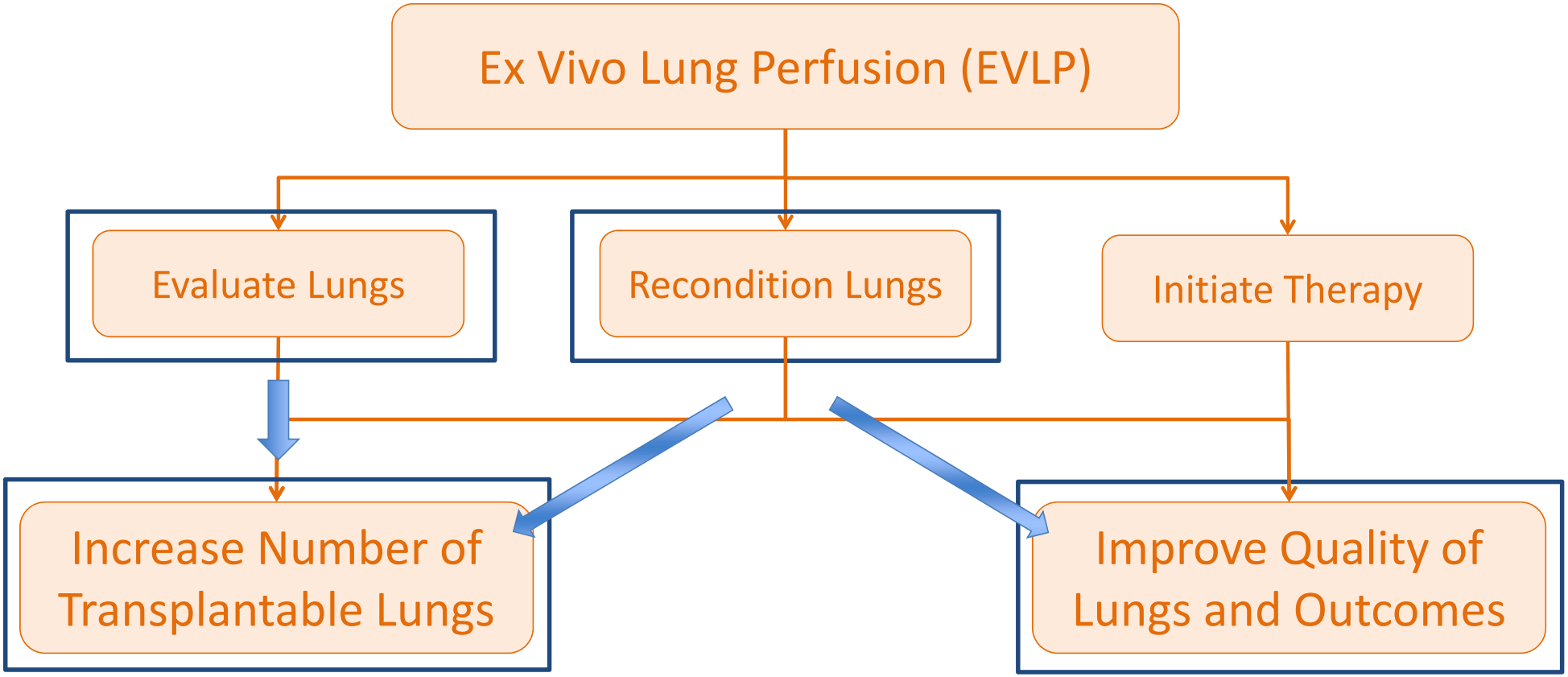
- **EVLP**
  - Donation after cardiac death (DCD) donors
  - Rehabilitate marginal donor lungs
- **Mechanism**
  - Limits hydrostatic edema
  - Balances oncotic forces
  - Attenuates inflammatory response
  - Improved pulmonary function
- **IVLP**
  - Directed chemotherapy phase II clinical trial
  - Can attenuate sepsis-induced ARDS in porcine model



Ongoing Challenges in Lung Transplant

- Primary Graft Dysfunction
  - Complicating up to 25% of transplants
- Donor shortage/low utilization
  - 15-20% of lungs from multi-organ donors transplanted
- Potential solutions?
  - Extended criteria donors
  - Donation after cardiac death (DCD) donors
  - **Ex Vivo Lung Perfusion (EVLP)**

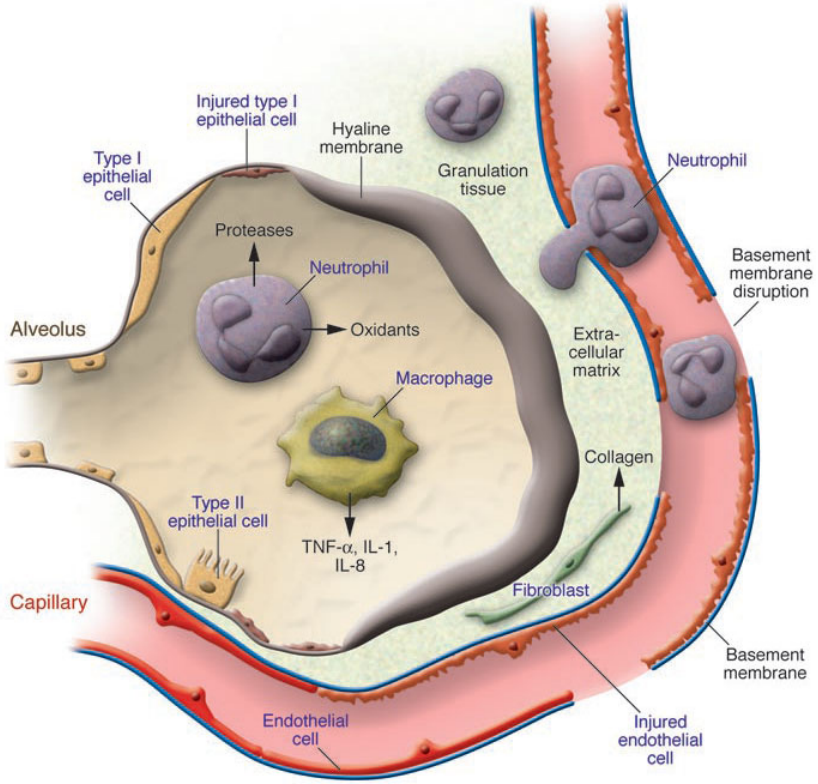
EVLP – Framework

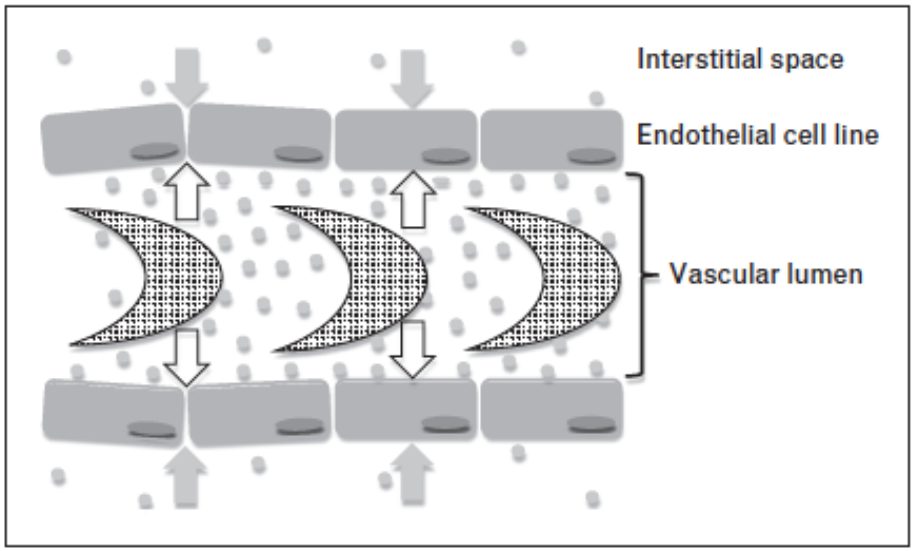


EVLP Protocols

	Toronto	Lund	OCS
Perfusion			
Target Flow	40% Cardiac Output	100% Cardiac Output	2-2.5L/min
Start of Evaluation	37	37	37

Experimental Rationale



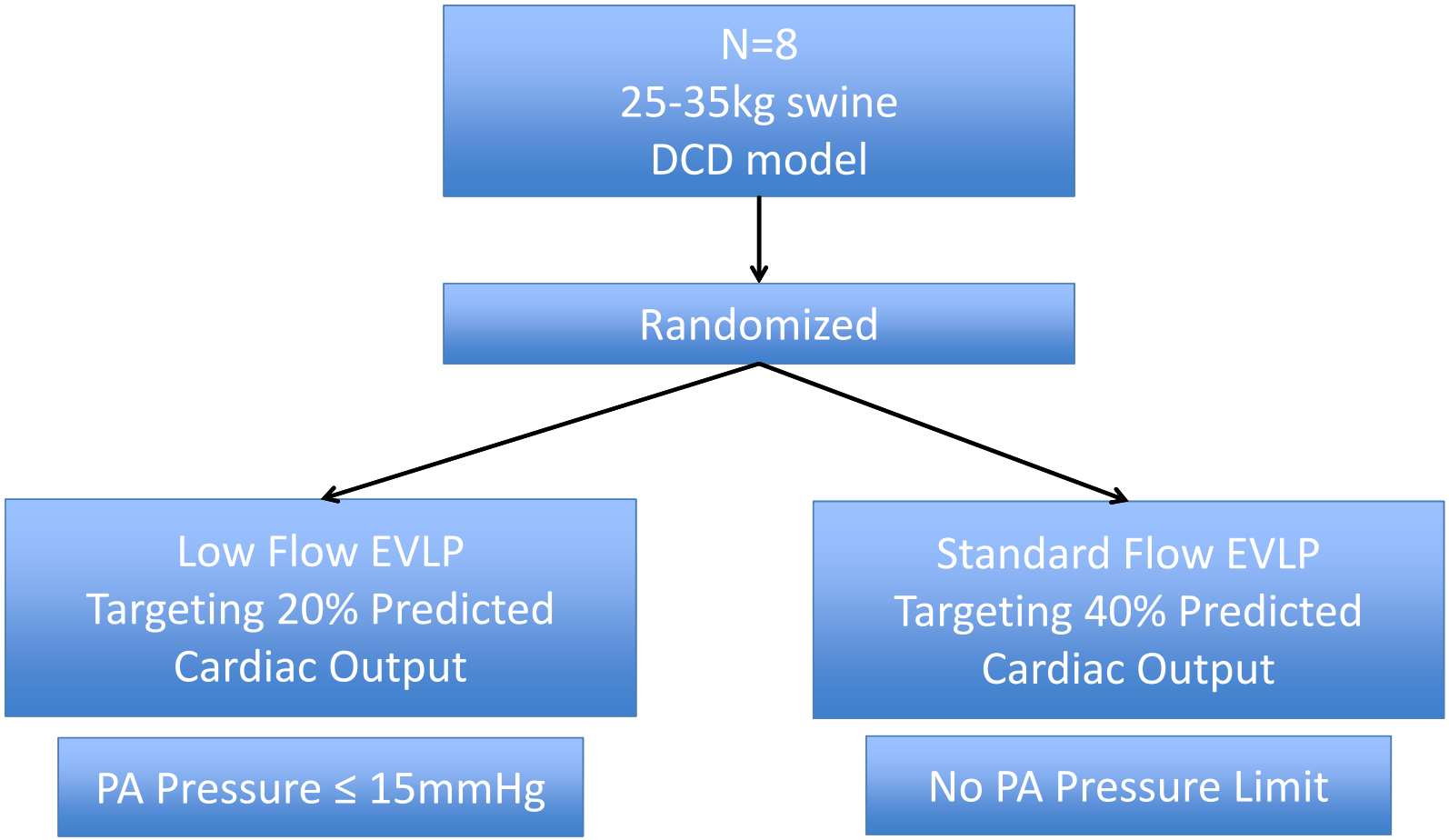


- Limit inflammation and shear stress to protect the endothelium
- Improve the balance between hydrostatic and oncotic forces to limit edema

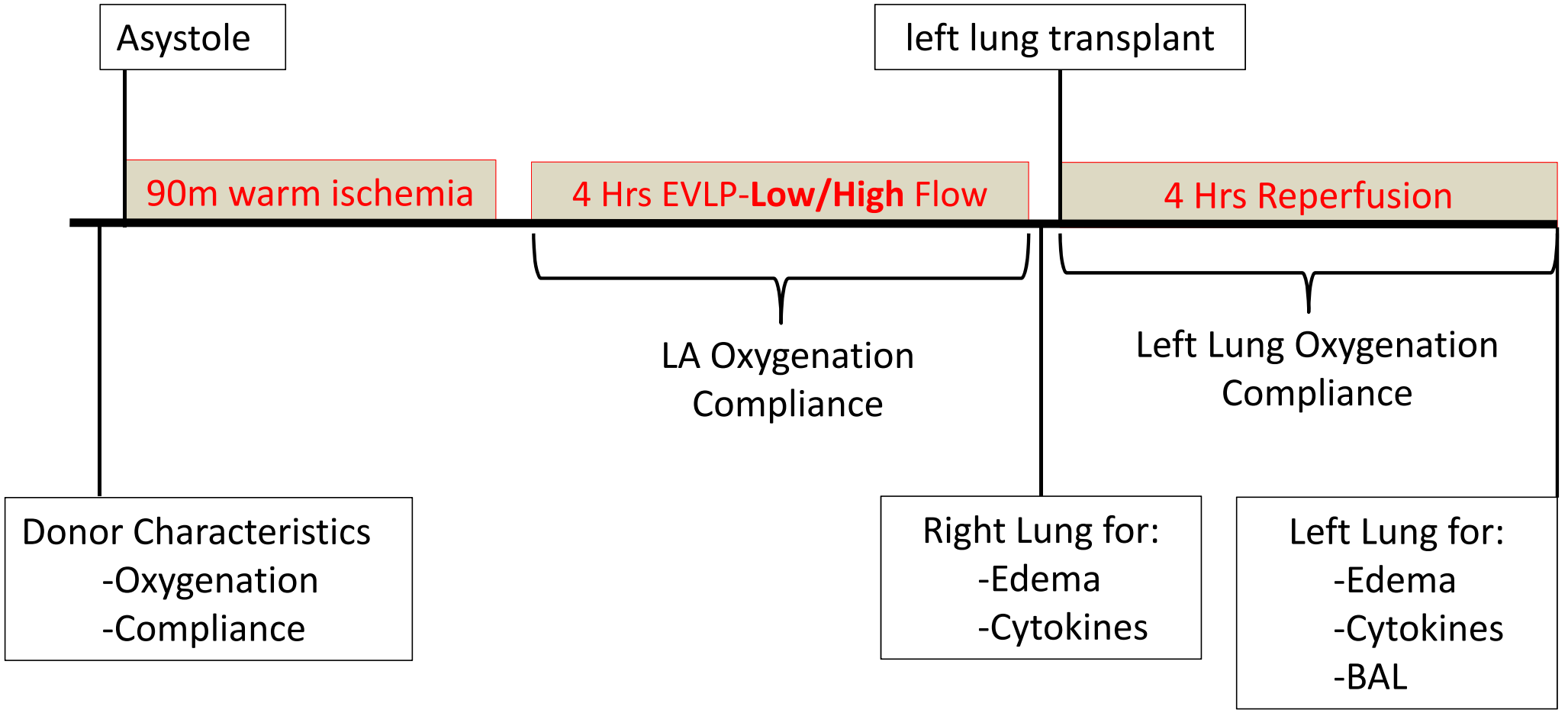
Hypothesis

EVLP utilizing lower flow perfusion would result in improved lung function compared to standard perfusion targets.

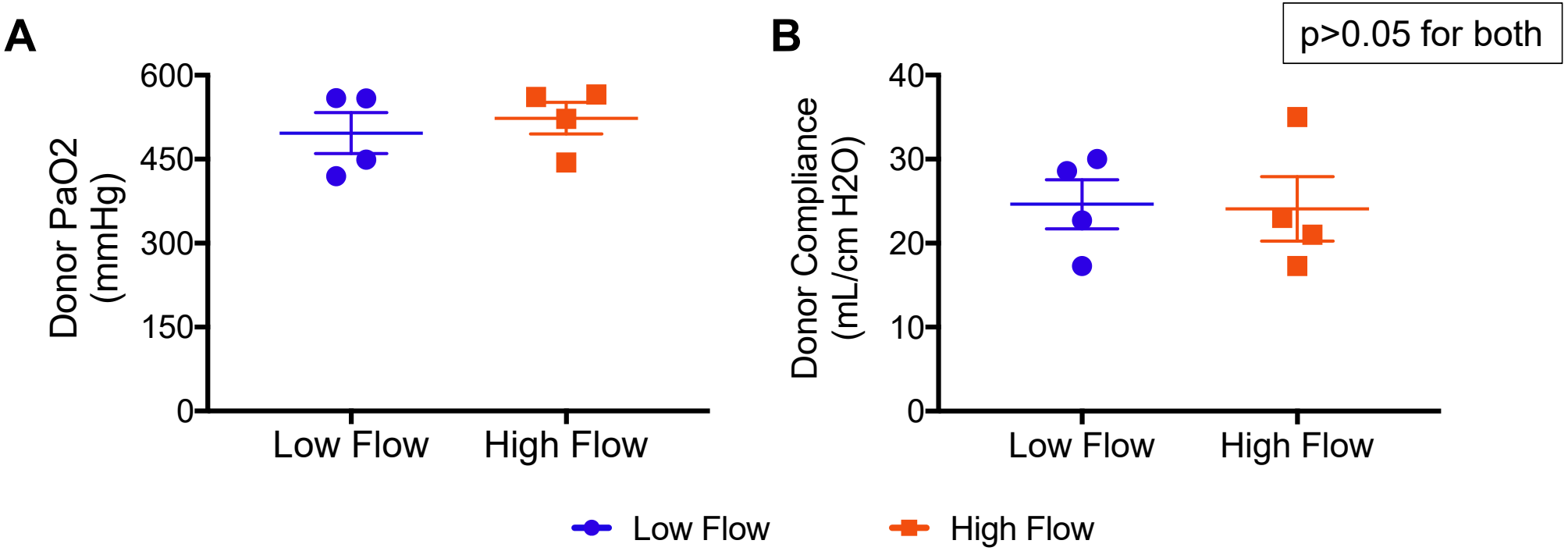
Methods – Study Groups



Methods – Experimental Overview

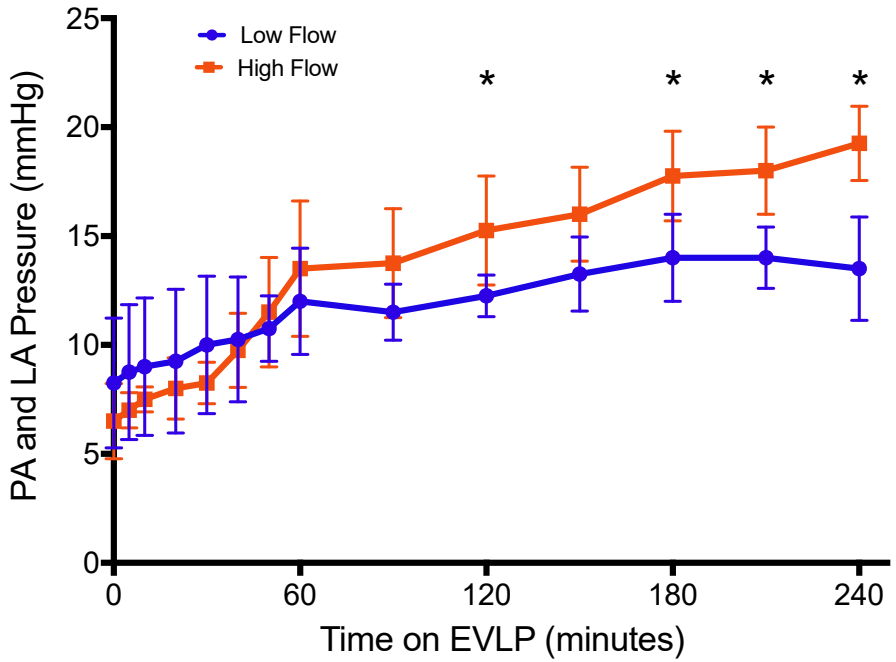


Donor Characteristics



- No difference in donor oxygenation or compliance

EVLP Pulmonary Artery Pressure

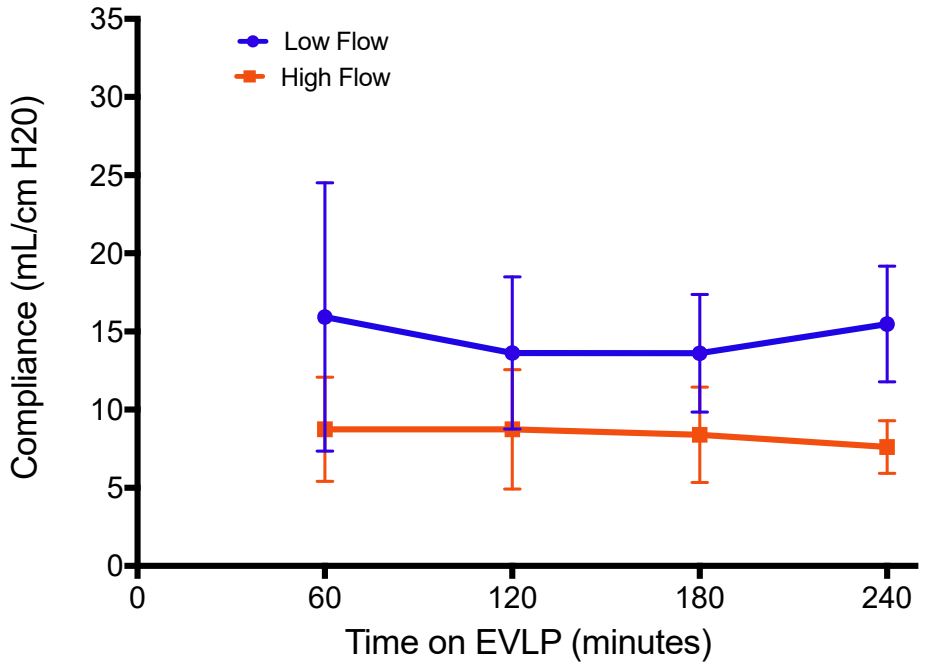


* Indicates p<0.05

- PA pressures higher in High Flow beyond 2 hours of EVLP

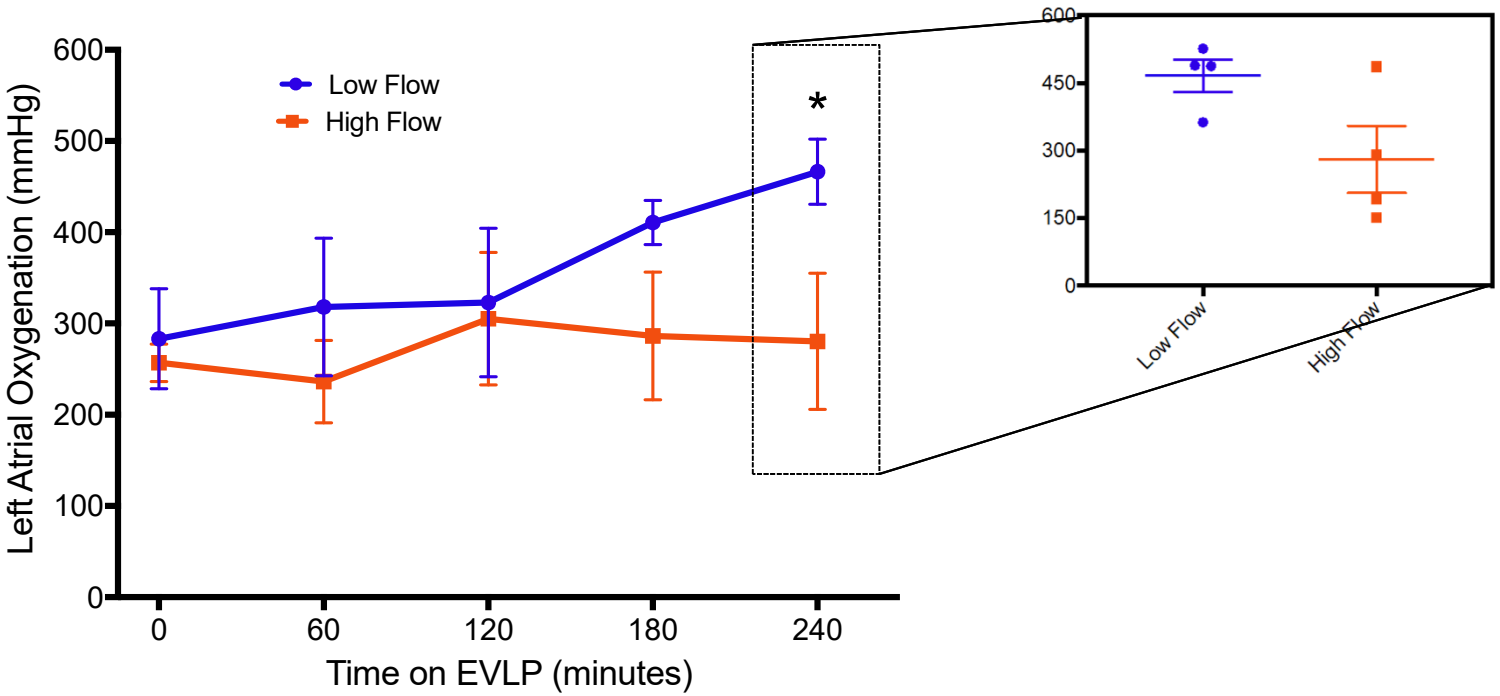
EVLP Compliance

p>0.05 for all



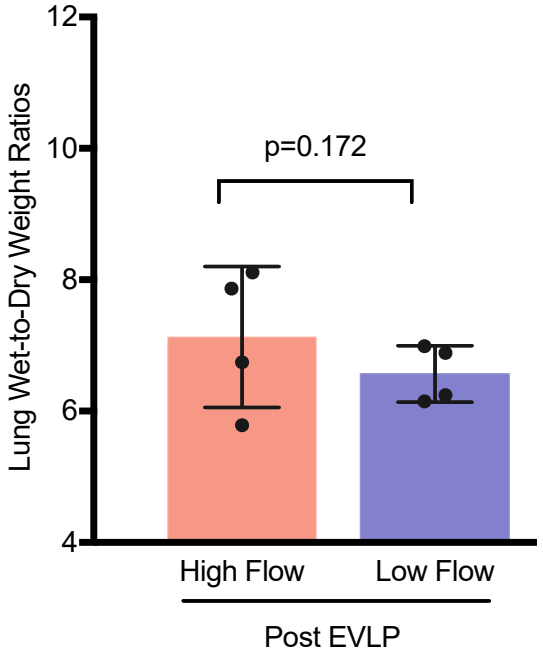
- No difference in compliance between groups during EVLP

EVLP Oxygenation



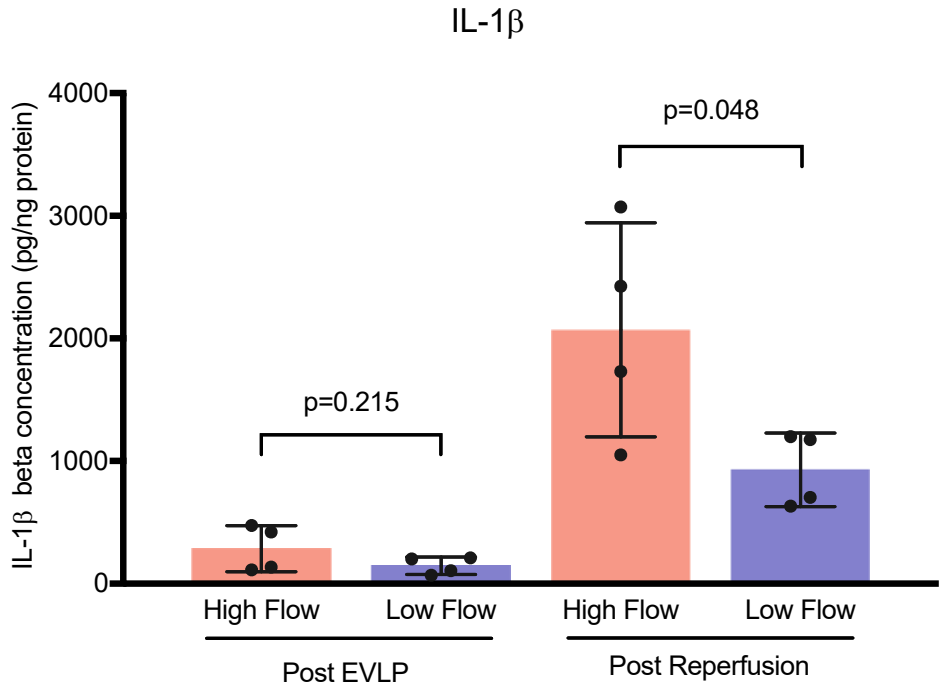
- Better oxygenation at the end of EVLP in Low Flow treated lungs

Reduced Pulmonary Edema



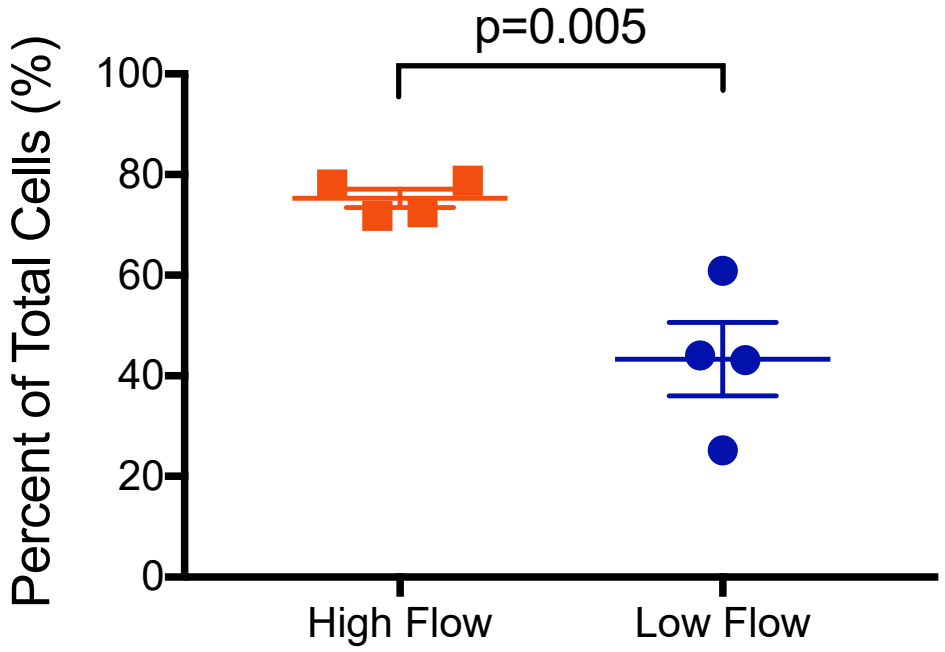
- Similar tissue edema after ex vivo lung perfusion
- Decreased tissue edema after transplant and 4 hours of reperfusion

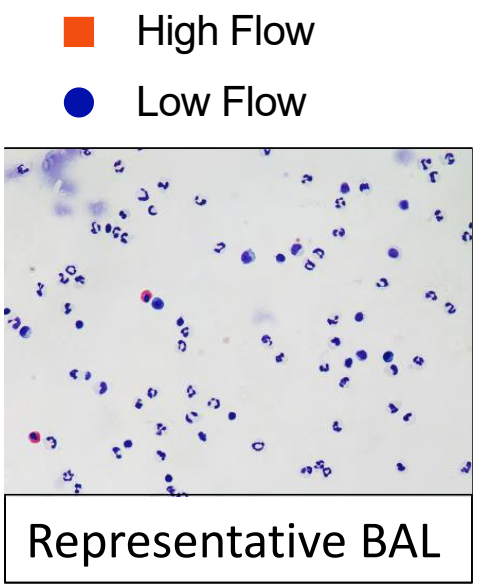
Pro-Inflammatory Cytokine IL-1β



- Attenuation of IL-1β in post-transplant lung tissue in Low Flow
- IL-1β key in neutrophil adhesion and initiation of lung inflammation

Differential Counts of BAL





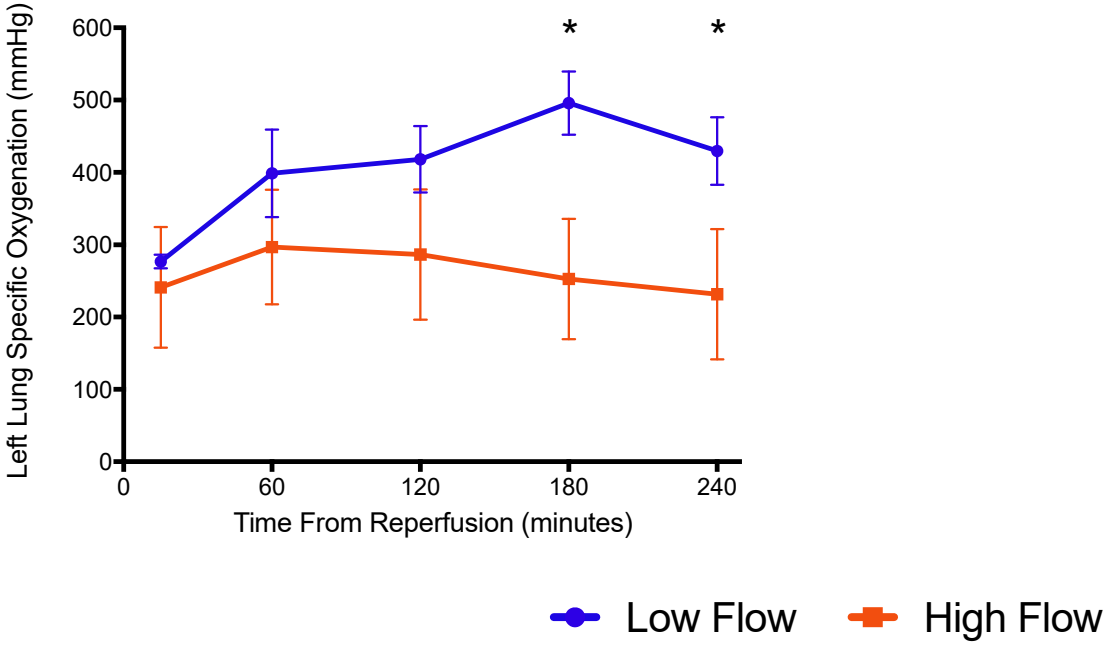
Representative BAL

- More neutrophil infiltration into alveolar space in High Flow
- Alveolar capillary barrier breakdown and acute inflammation

Post-Reperfusion Graft Function

* Indicates p<0.05

A



- Oxygenation improves after transplant in Low Flow
- Compliance better early after transplant and persists

Summary – Low Flow EVLP Rehabilitates

- Improvement in post-transplant lung function
  - Graft oxygenation (430 vs. 232 mmHg)
  - Lung compliance (21.1 vs. 10.3 ml/cm H_2O)
- Involves attenuation of inflammation and endothelial preservation
  - IL-1β reduced (927 vs. 2070 pg/ng protein)
  - Less edema accumulation (wtd: 7.1 vs. 8.8)
  - Fewer alveolar neutrophils (43.3% vs. 75.3%)

Conclusions

1. Low Flow EVLP improves post-transplant graft function.

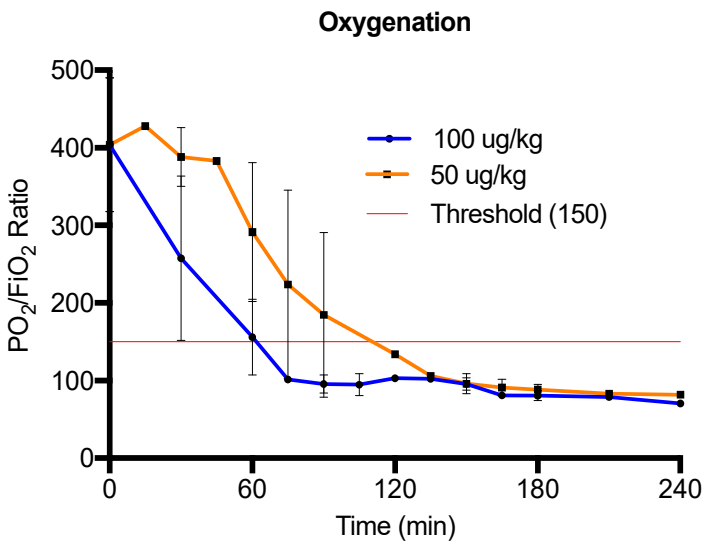
2. Lower perfusion flows attenuate post-transplant inflammation and edema compared to standard EVLP flows.

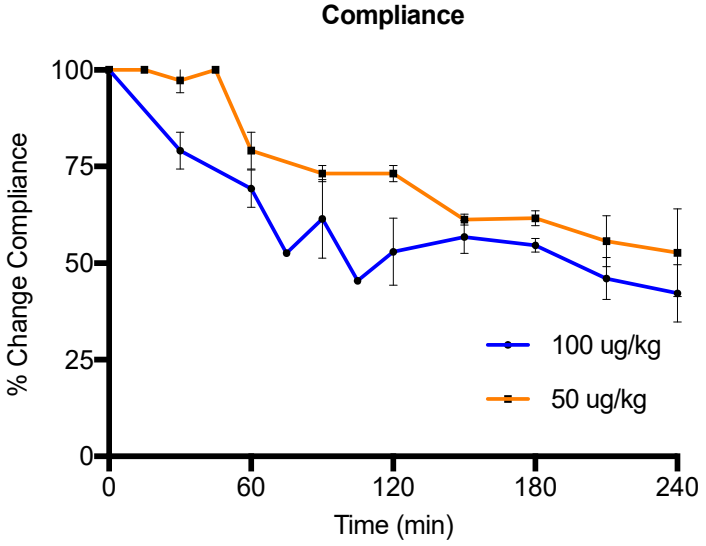
3. Low Flow EVLP should be used as the basis for lung rehabilitation protocols and may be key to expanding the use of EVLP.

EVLP for ARDS?

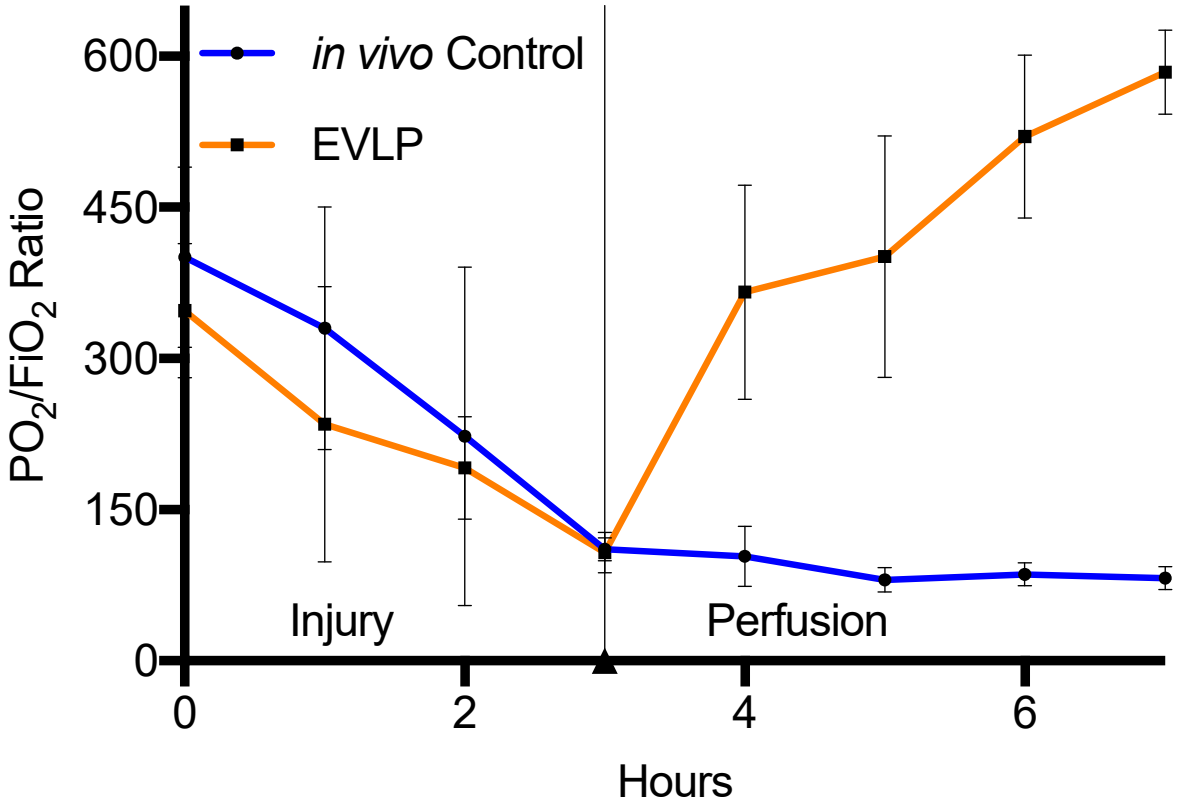
- LPS injection
- HCL down airway
- Colon perforation

Injury Model

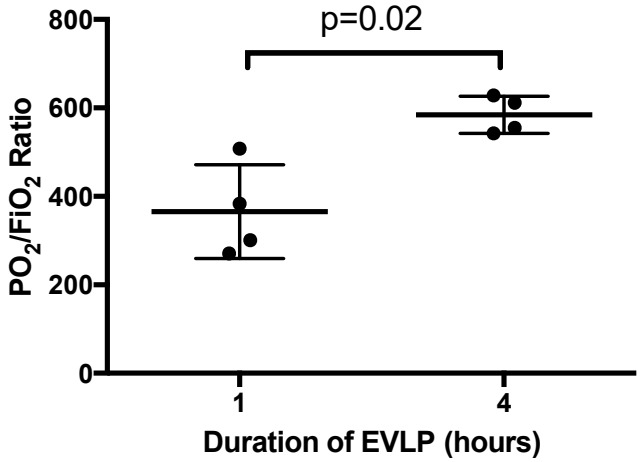


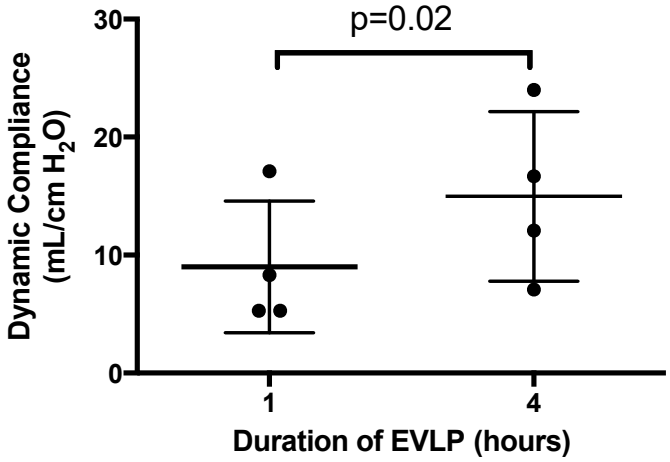


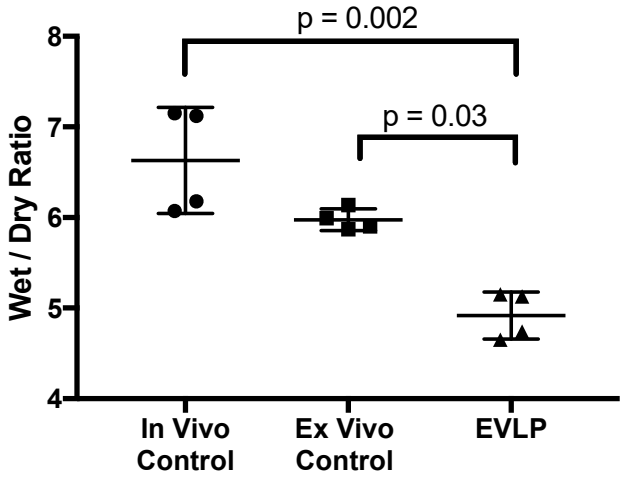
Superior Oxygenation

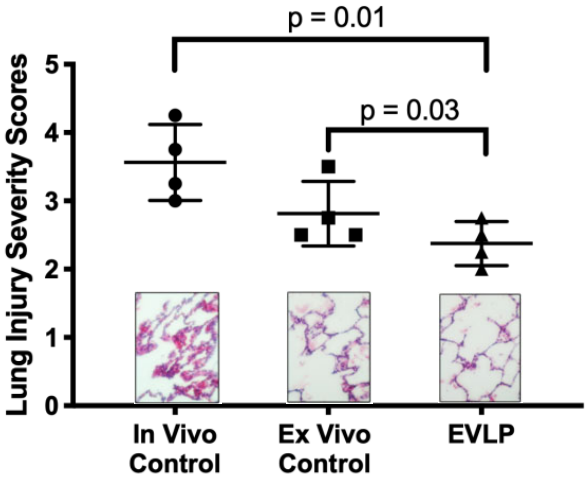


Rehabilitation on EVLP







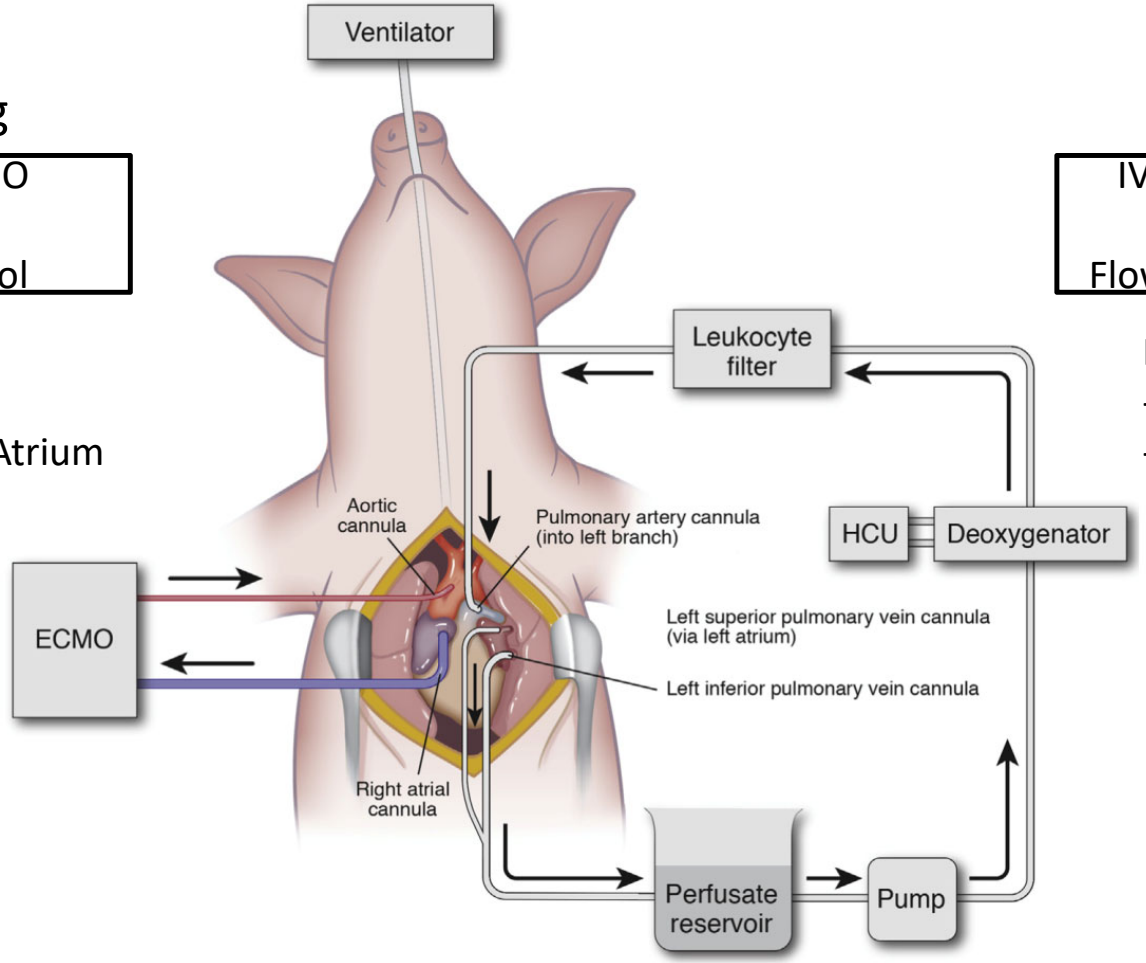


In Vivo Lung Perfusion

Right Lung

Systemic/ECMO Circulation
Internal Control

ECMO Circulation
- Inflow: Aorta
- Outflow: Right Atrium

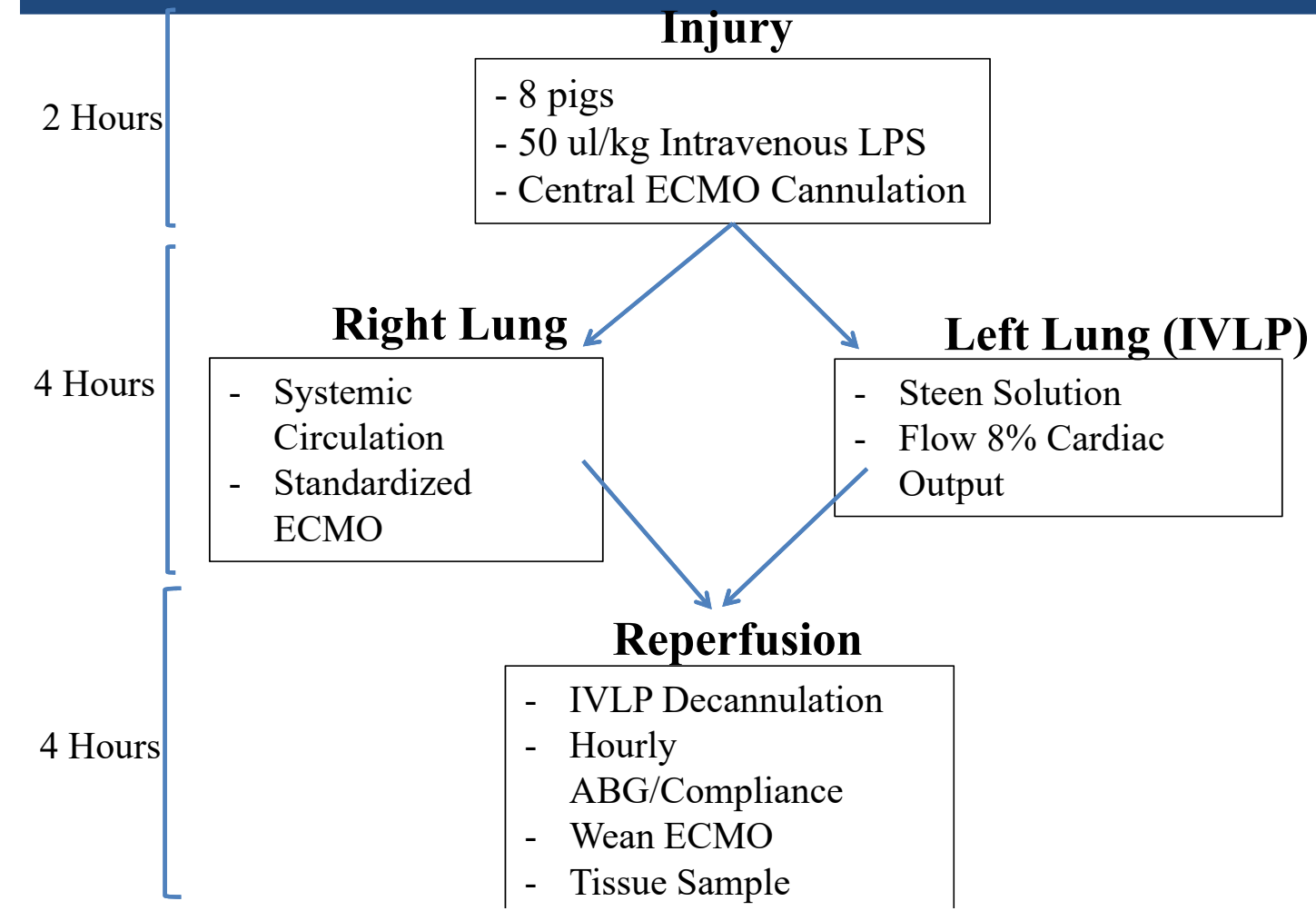


Left Lung

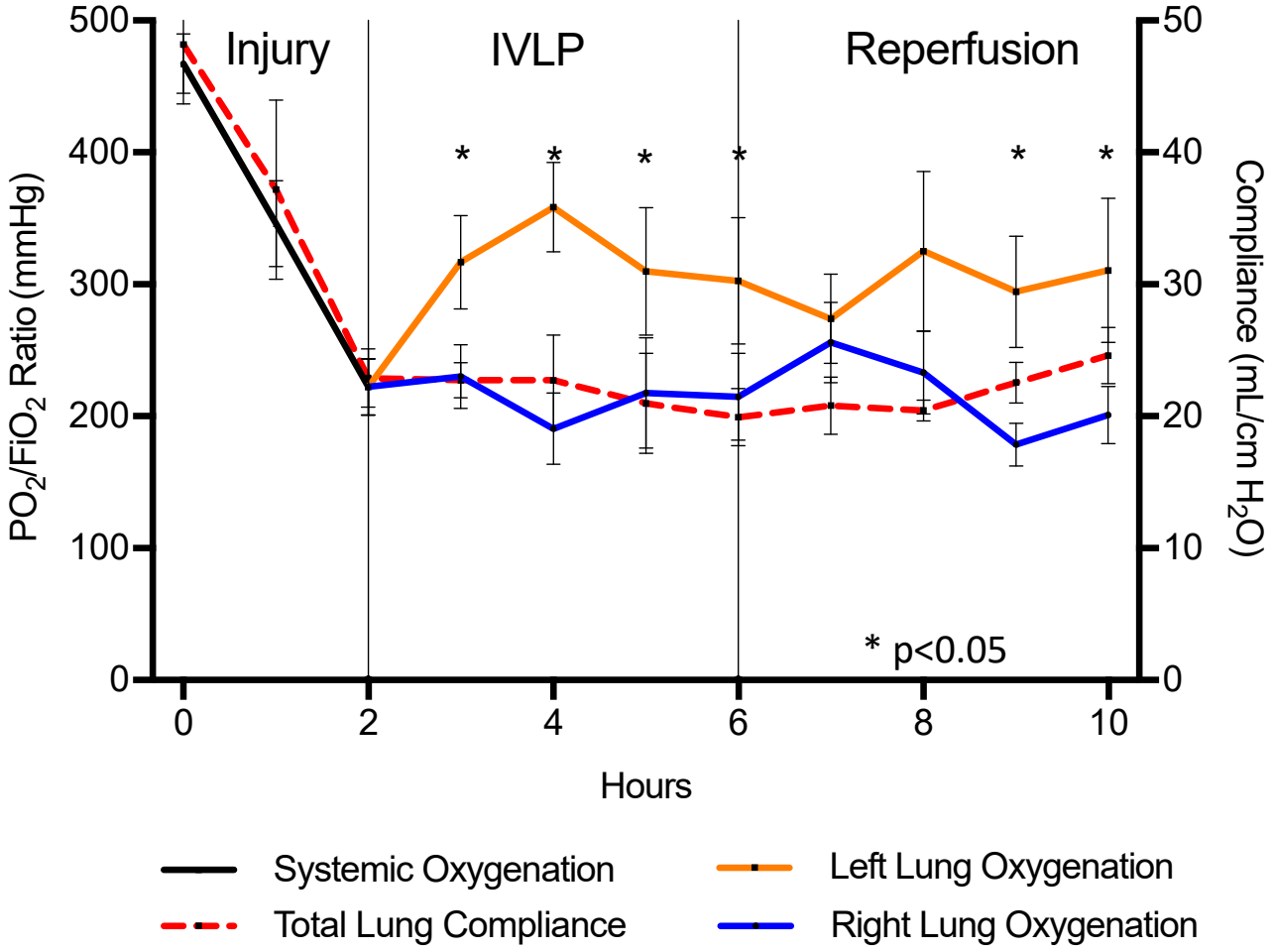
IVLP Circulation with Steen
Flow 8% Cardiac Output

IVLP Circulation
- Inflow: Left PA
- Outflow: Sup & Inf Pulmonary Vein

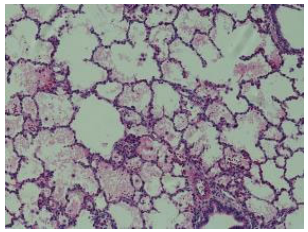
Methods


2 Hours
4 Hours
4 Hours
Injury
- 8 pigs
- 50 ul/kg Intravenous LPS
- Central ECMO Cannulation
Right Lung
- Systemic Circulation
- Standardized ECMO
Left Lung (IVLP)
- Steen Solution
- Flow 8% Cardiac Output
Reperfusion
- IVLP Decannulation
- Hourly ABG/Compliance
- Wean ECMO
- Tissue Sample

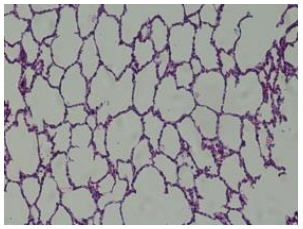
Superior Function



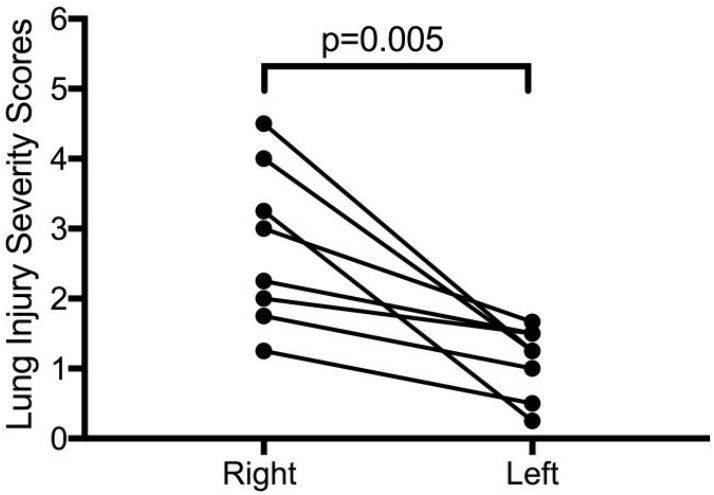
Reduced Histologic Injury / Edema

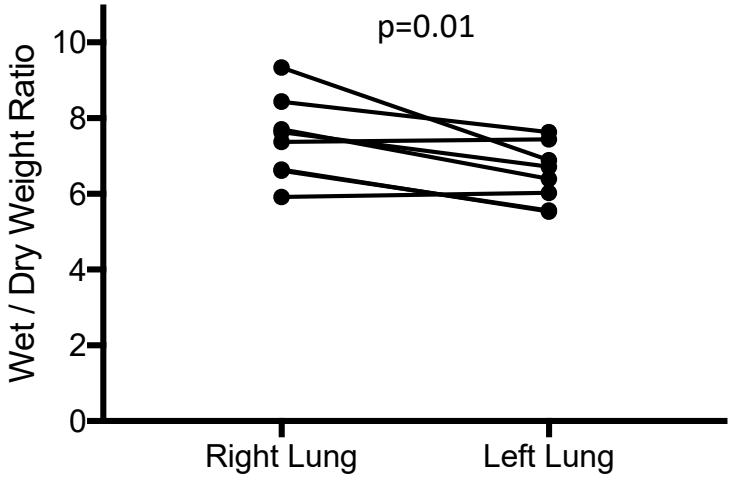


Right Lung

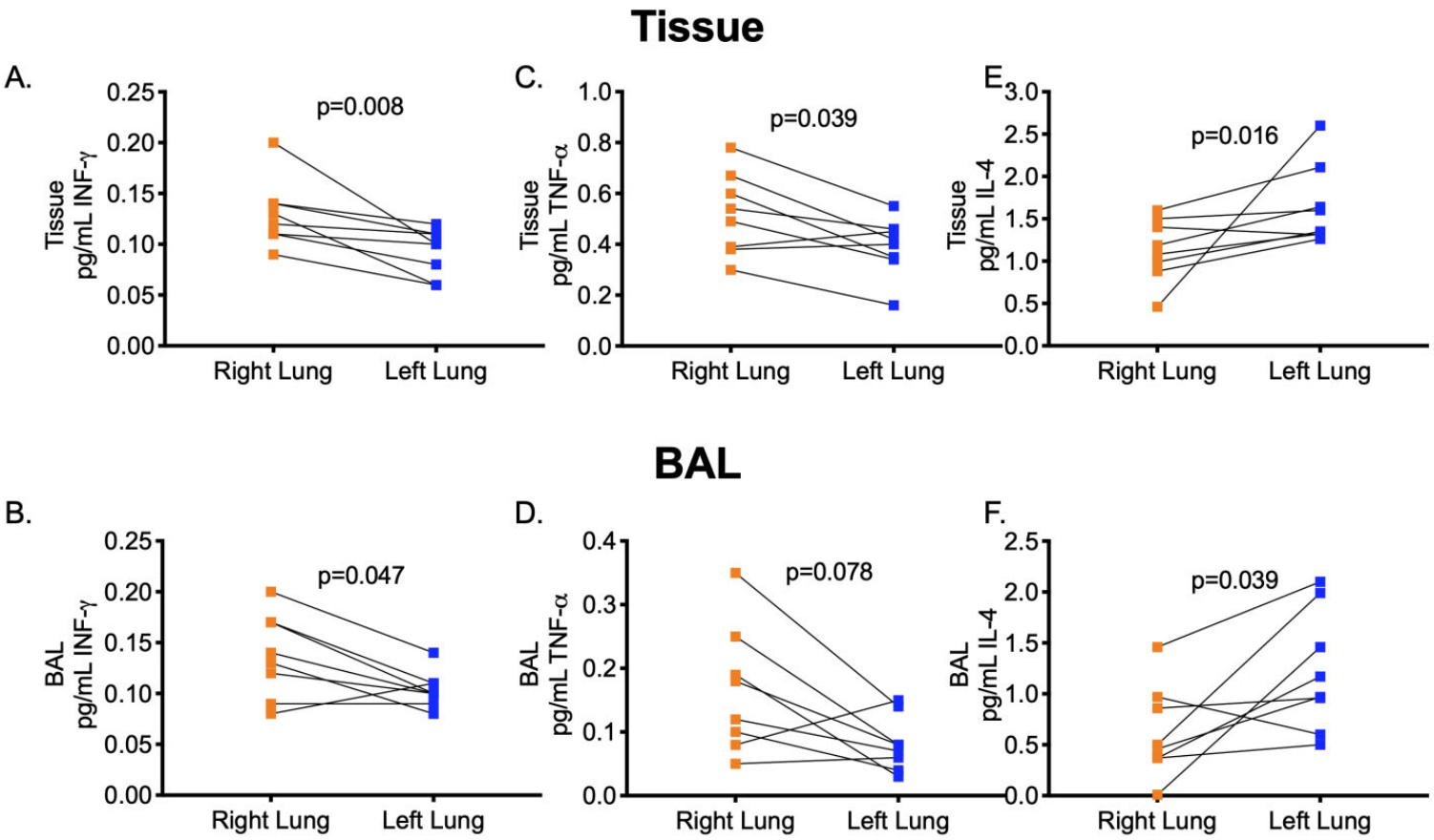


Left Lung

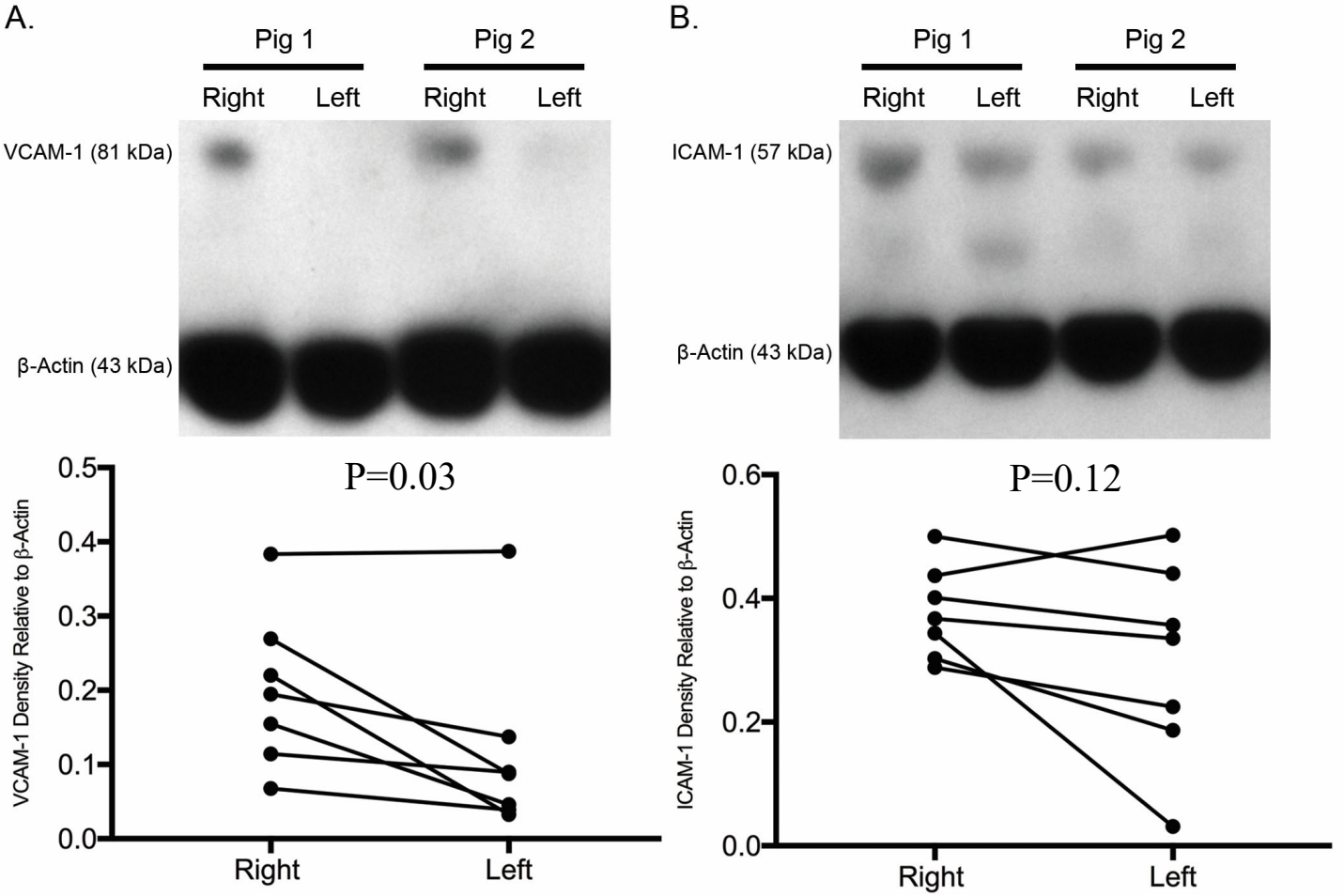




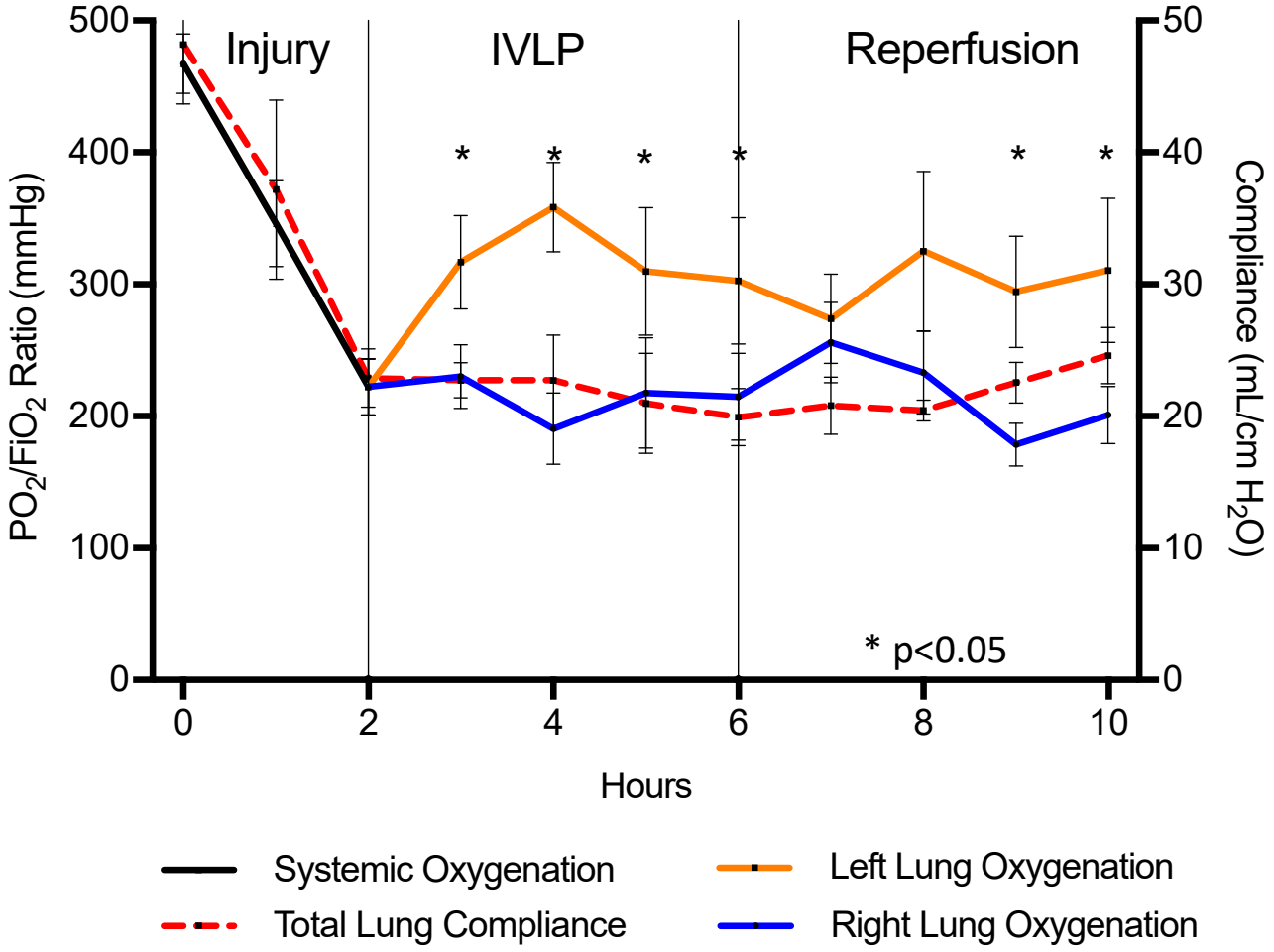
Cytokines


Tissue
A.
Tissue pg/mL INF-γ
0.25
0.20
0.15
0.10
0.05
0.00
p=0.008
Right Lung
Left Lung
C.
Tissue pg/mL TNF-α
1.0
0.8
0.6
0.4
0.2
0.0
p=0.039
Right Lung
Left Lung
E.
Tissue pg/mL IL-4
3.0
2.5
2.0
1.5
1.0
0.5
0.0
p=0.016
Right Lung
Left Lung
BAL
B.
BAL pg/mL INF-γ
0.25
0.20
0.15
0.10
0.05
0.00
p=0.047
Right Lung
Left Lung
D.
BAL pg/mL TNF-α
0.4
0.3
0.2
0.1
0.0
p=0.078
Right Lung
Left Lung
F.
BAL pg/mL IL-4
2.5
2.0
1.5
1.0
0.5
0.0
p=0.039
Right Lung
Left Lung

Adhesion Molecules



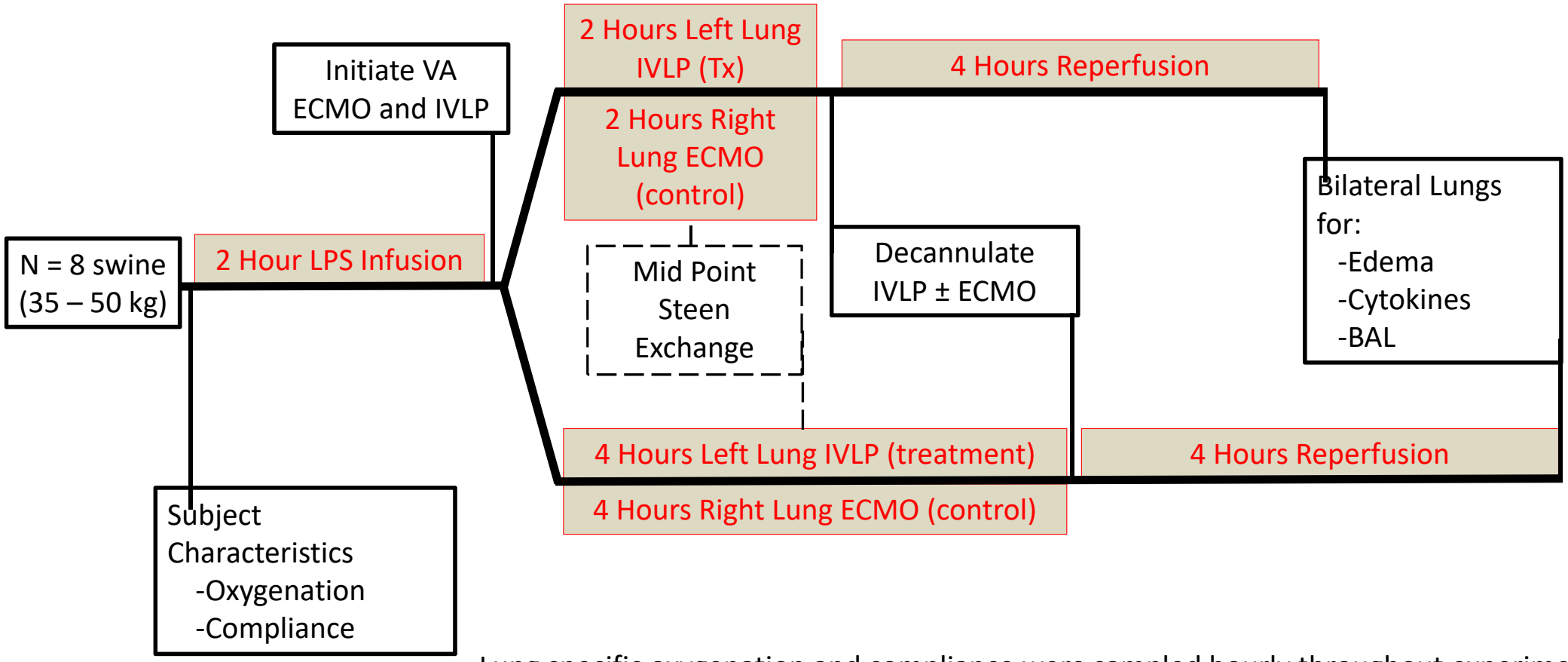
Superior Function



Hypothesis

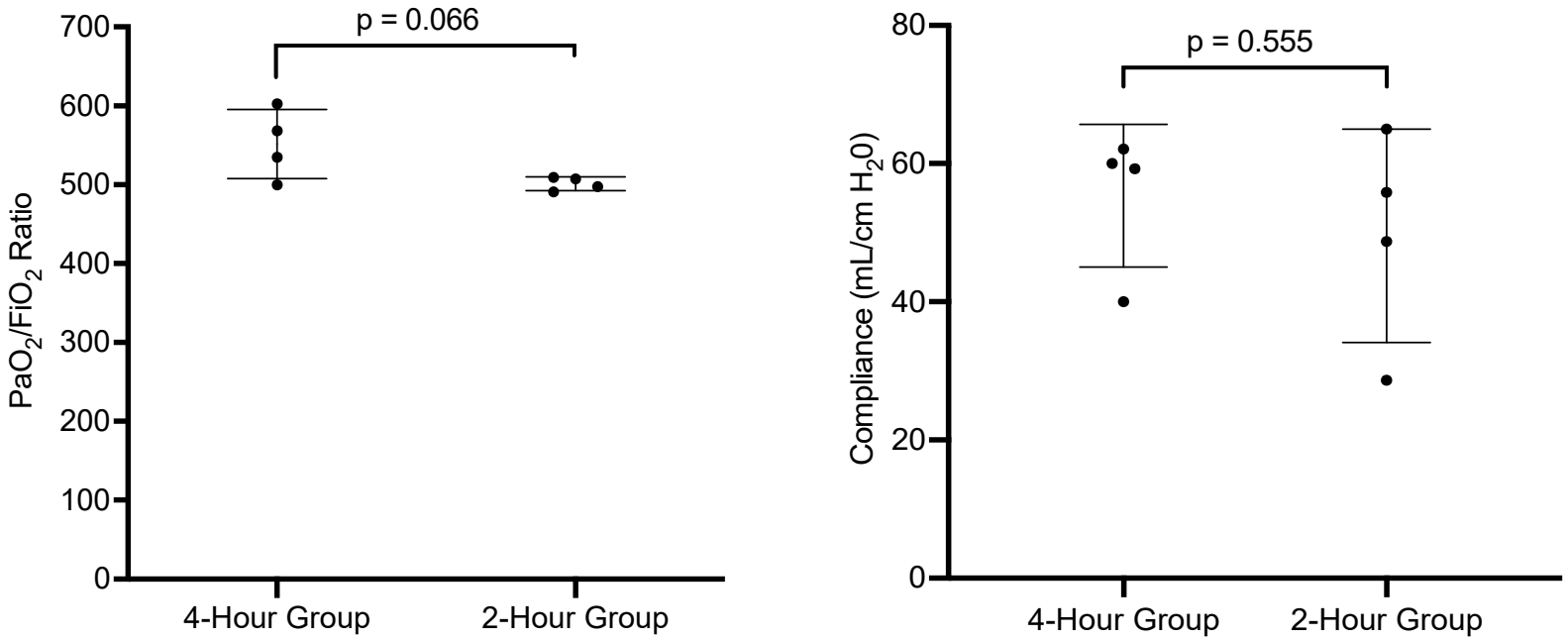
Treatment with 2-hours of IVLP would result in non-inferior lung rehabilitation when compared to 4 hours of treatment.

Methods – Experimental Overview



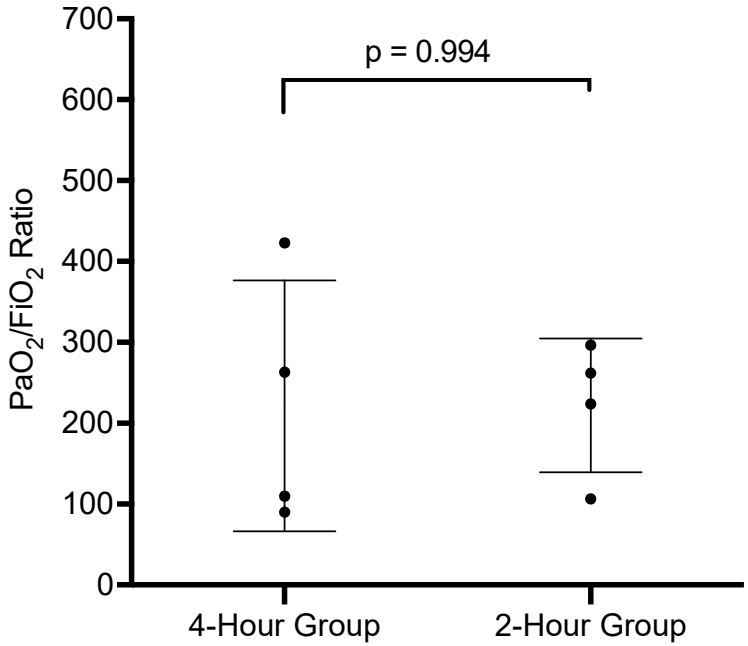
Lung specific oxygenation and compliance were sampled hourly throughout experimen

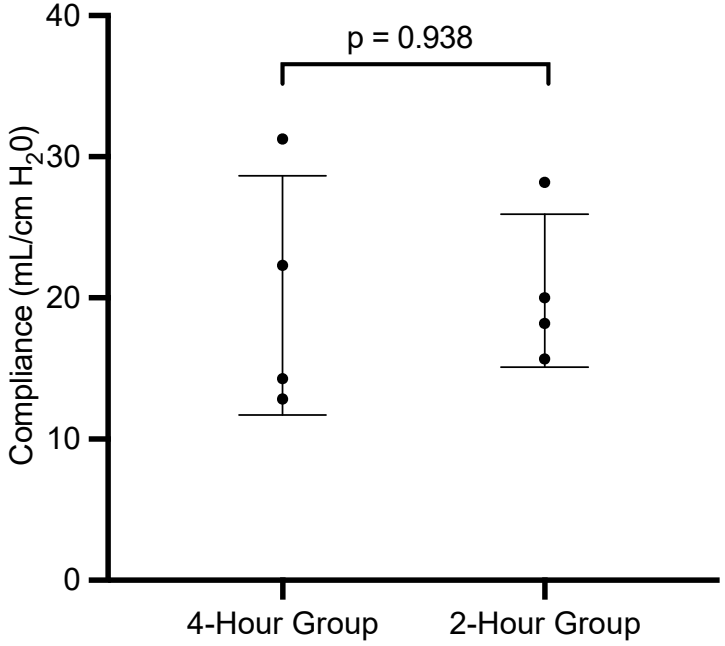
Baseline Characteristics



- No significant difference in baseline oxygenation and compliance

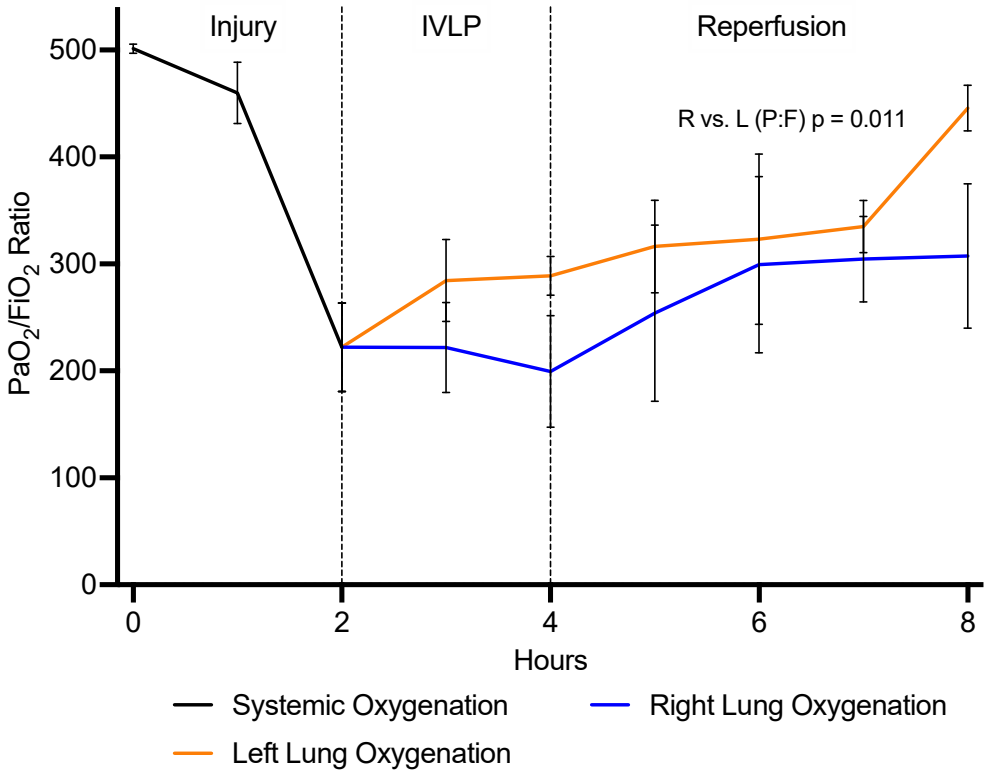
Injury Severity





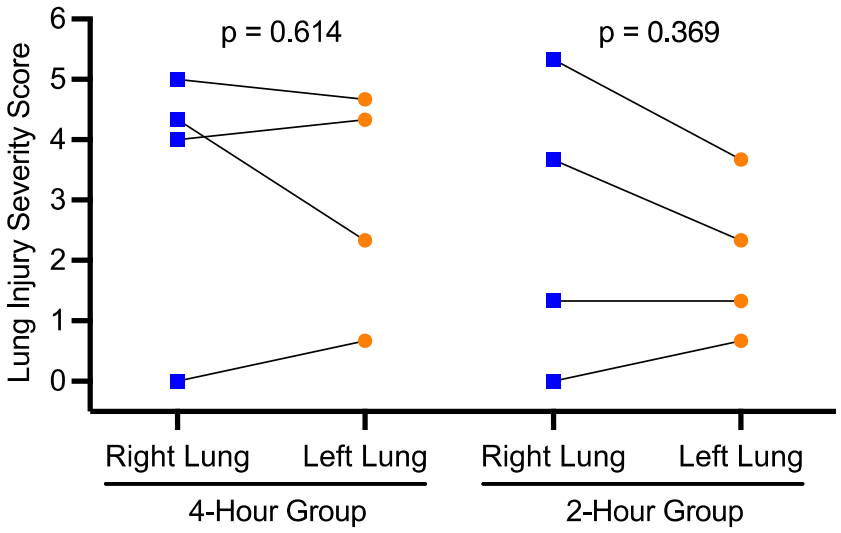
- No significant difference in post-LPS oxygenation and compliance

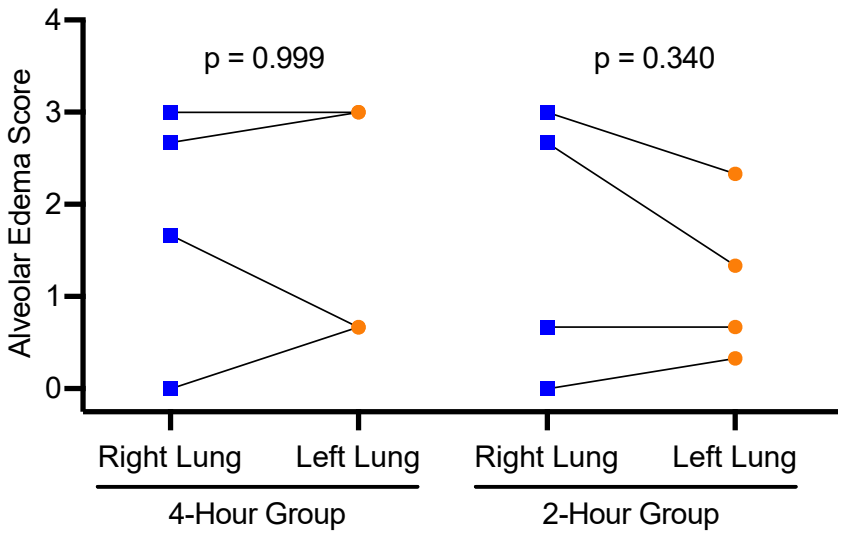
2-Hour Group Oxygenation



- Treated left lung performed significantly better in 2-Hour Group
- 332.2 ± 58.94 vs. 264.4 ± 46.53
- 75% (3/4) Decannulated from ECMO

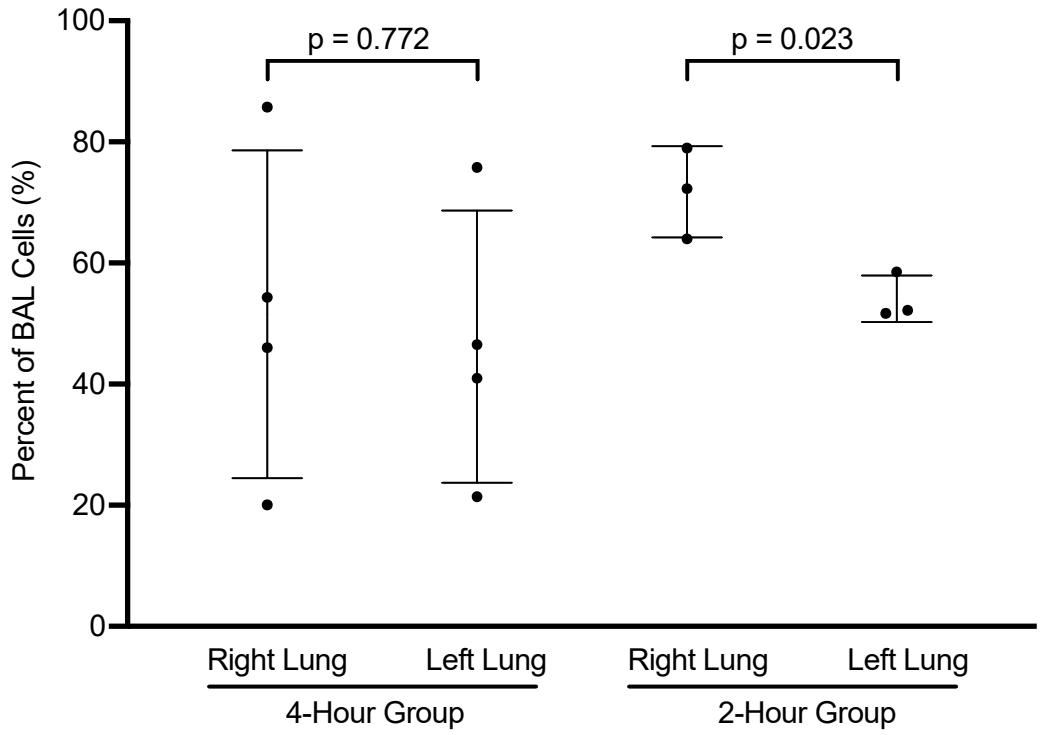
Histologic Changes





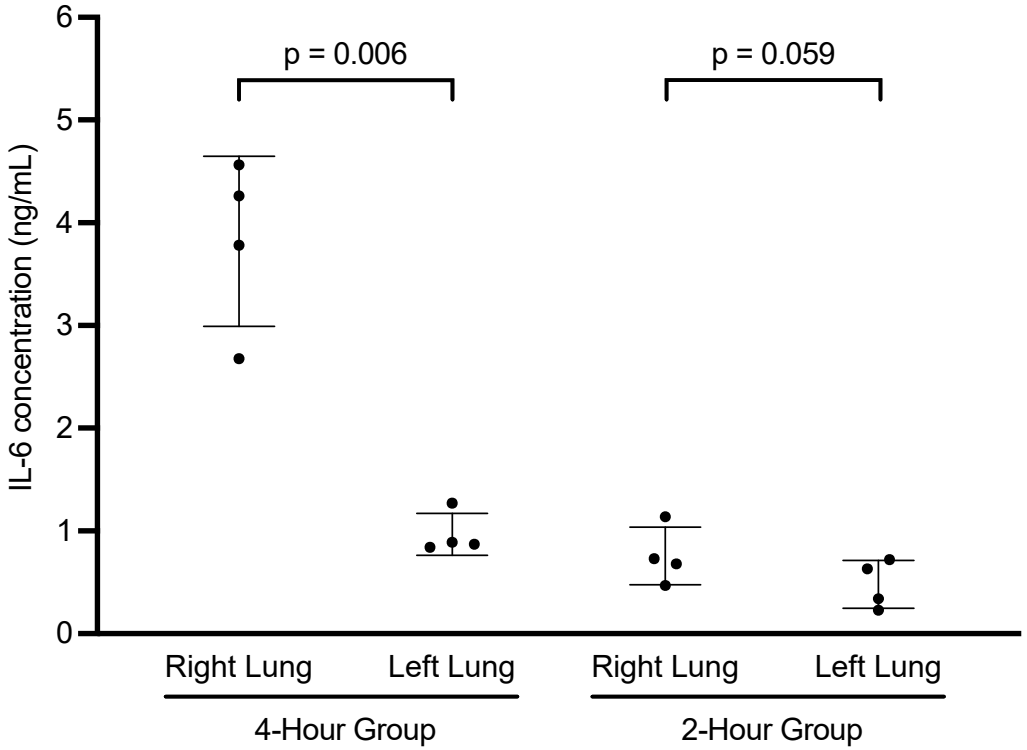
- Lung Injury Severity trended lower for the treated lungs in the 2-Hour Group
- Edema score trended lower for the treated lungs in the 2-Hour Group

Differential Counts of BAL



- Significantly less neutrophil infiltration into the treated lung of the 2-Hour Group
- 2-Hour Group
  - 54.11% ± 3.83 vs. 71.75% ± 7.52
- 4-Hour Group
  - 46.19% ± 22.48 vs. 51.52% ± 27.07

IL-6 Concentration in BAL



- Decreased IL-6 expression in treated lungs of 4-Hour Group.
- 2-Hour Group:
  - 0.480 ± 0.233 ng/mL (left lung) vs. 0.755 ± 0.280 ng/mL (right lung)
- 4-Hour Group:
  - 0.968 ± 0.203 ng/mL (left lung) vs. 3.820 ± 0.828 ng/mL (right lung)

Future?

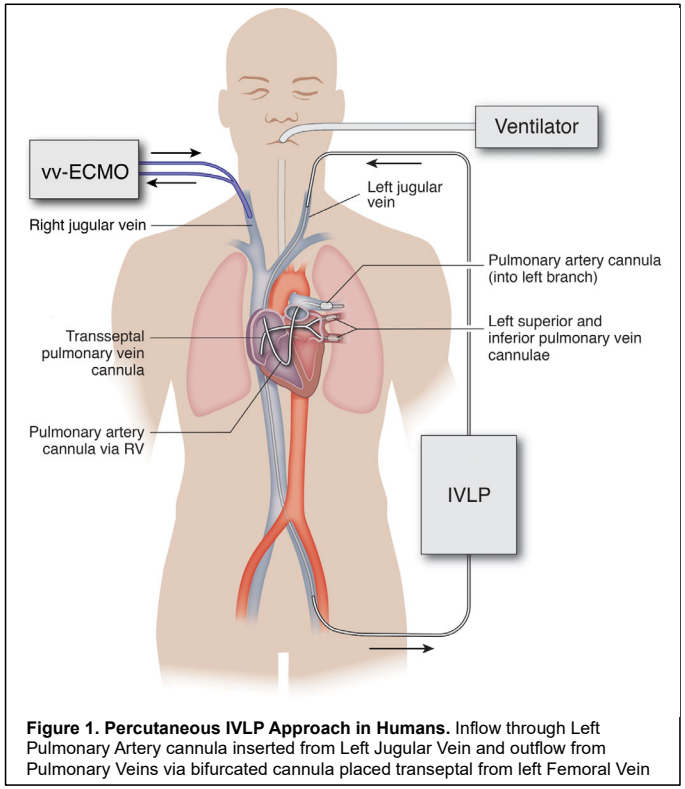


Figure 1. Percutaneous IVLP Approach in Humans. Inflow through Left Pulmonary Artery cannula inserted from Left Jugular Vein and outflow from Pulmonary Veins via bifurcated cannula placed transeptal from left Femoral Vein

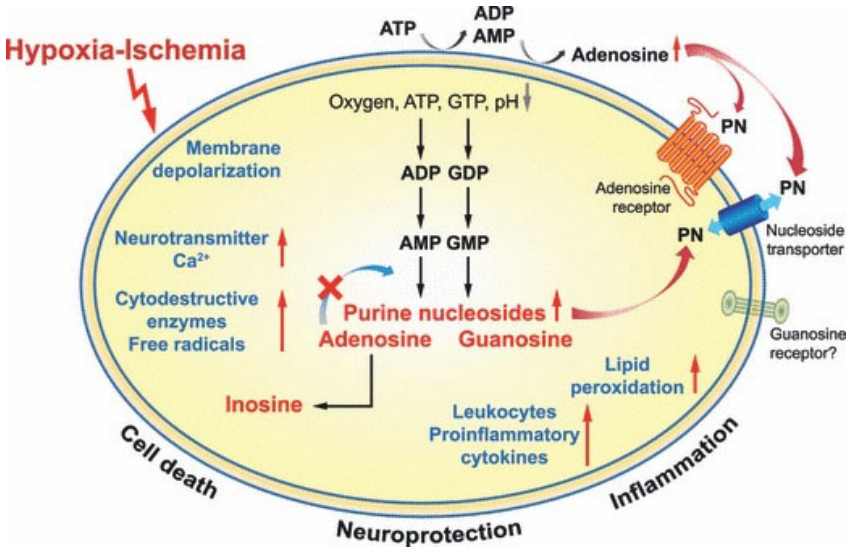
Extracorporeal Cardiopulmonary Resuscitation (ECPR)

- Benefits of ECPR
  - Improved survival and neurologic function
  - Oxygenated blood to vital organs
  - Additional time to treat reversible causes of cardiac arrest

- Does not address damage caused by no-flow and low-flow periods

Post cardiac arrest syndrome

- Comprised of:
  - Myocardial damage
  - Cerebral inflammation
  - Global tissue damage



- Due to Ischemia-reperfusion injury

- Attenuated by Adenosine 2A receptor activation

Hypothesis

Adenosine 2A receptor activation will improve survival and decrease the overall burden of injury in cardiac arrest treated with ECPR.

Methods

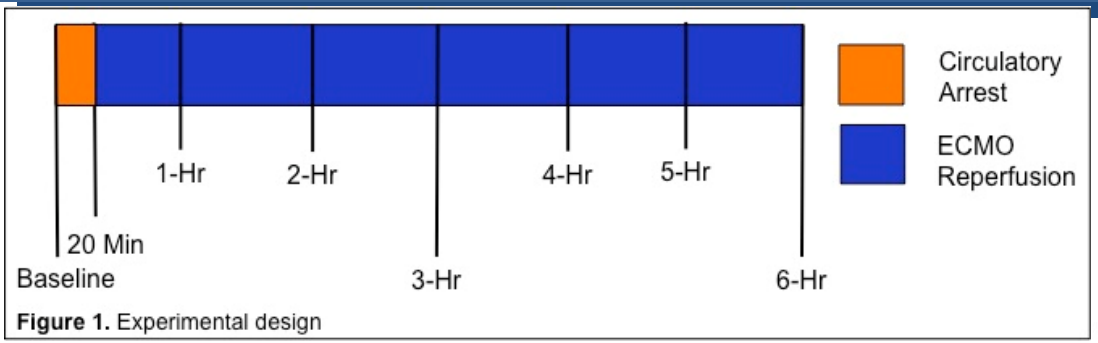
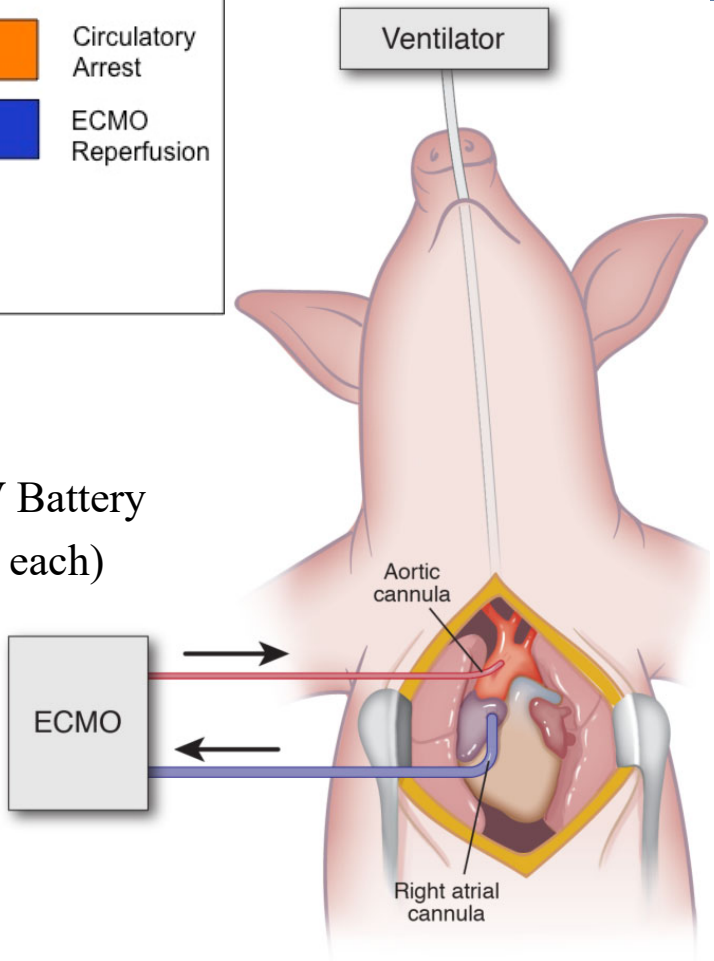
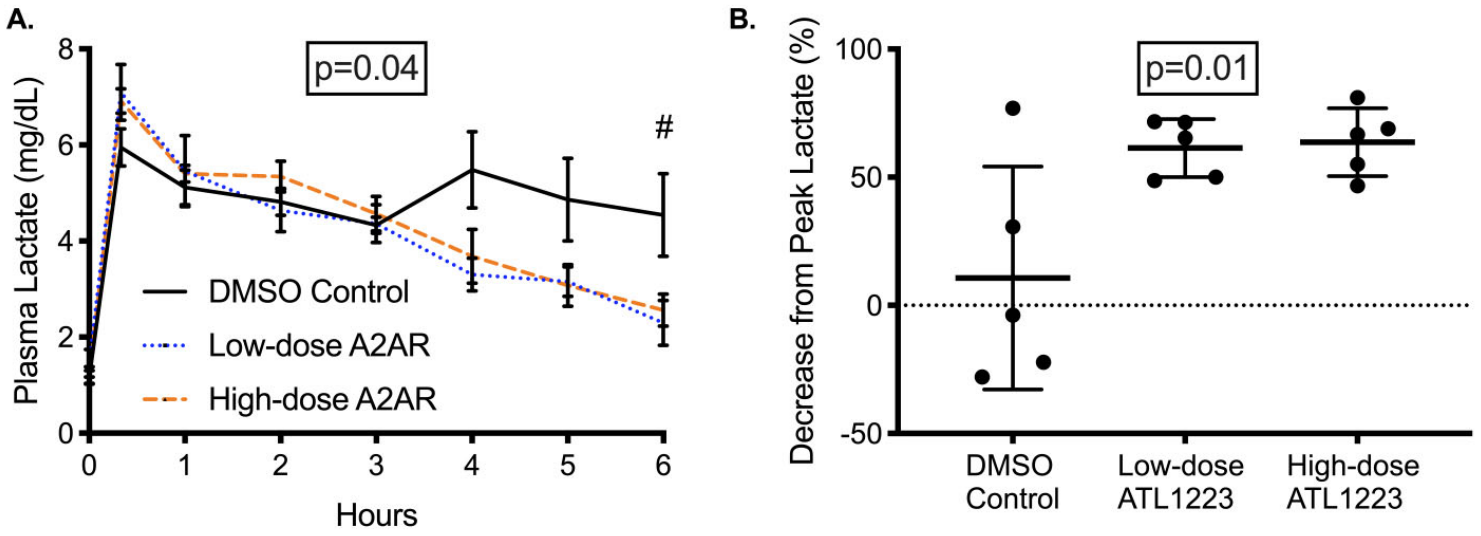


Figure 1. Experimental design

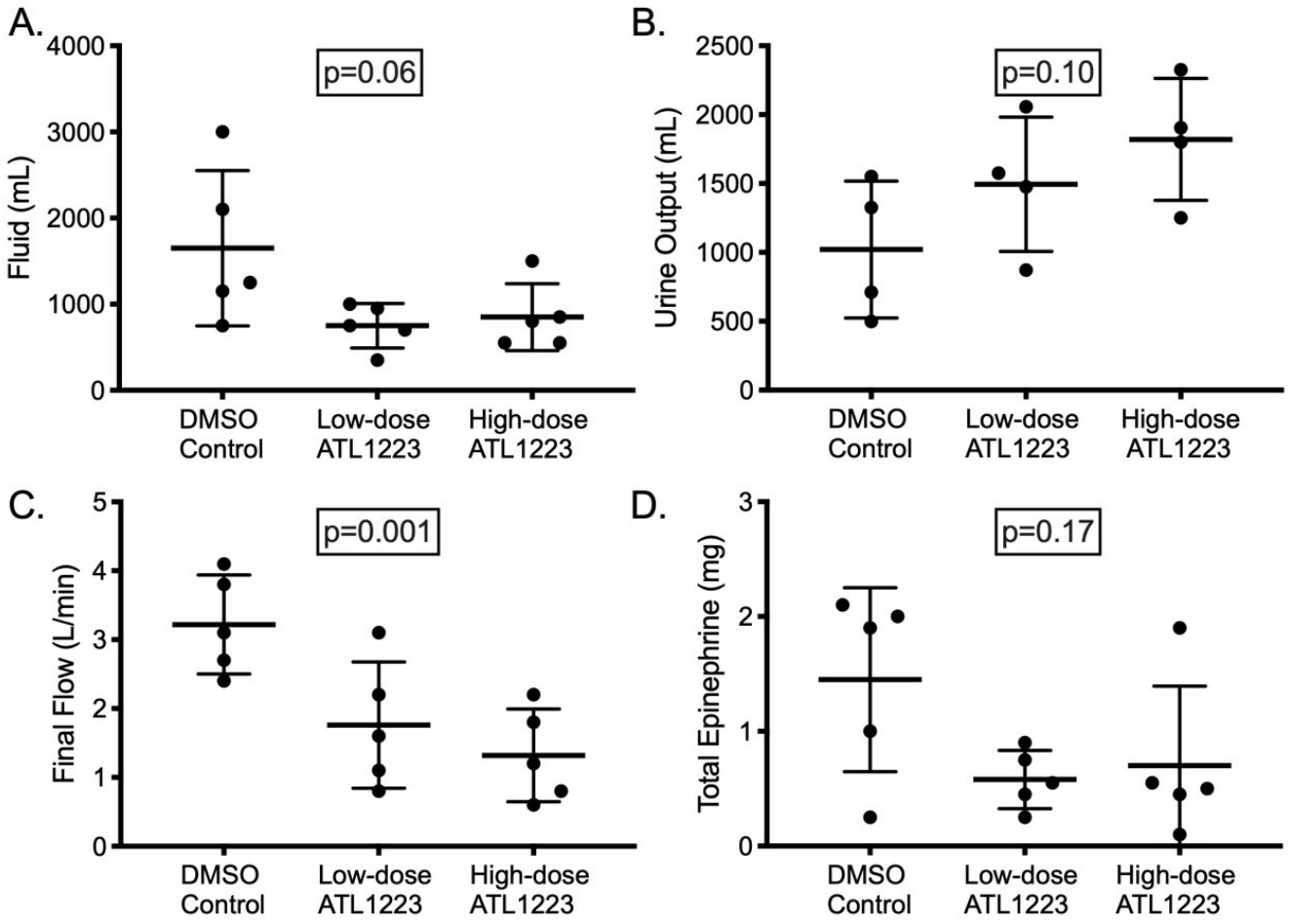
- Sternotomy (n=15 pigs)
- Electric Ventricular Fibrillation Arrest: 9V Battery
- Randomized on Induction of ECMO (n=5 each)
  - Vehicle Control
  - Low Dose ATL1223 (0.3ng/kg/min)
  - High Dose ATL1223 (0.6ng/kg/min)



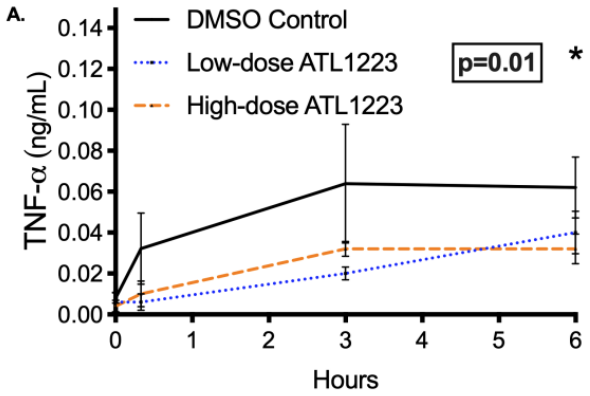
Systemic Injury

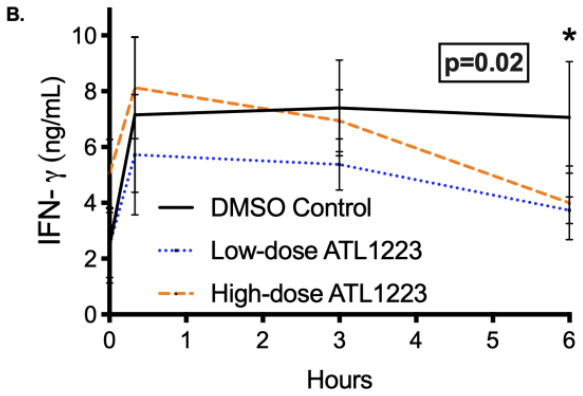


Fluid and Hemodynamics

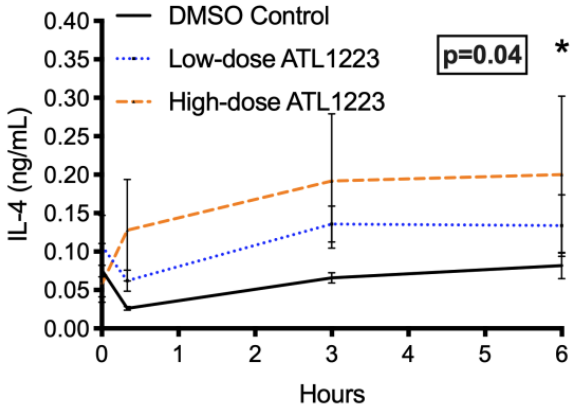


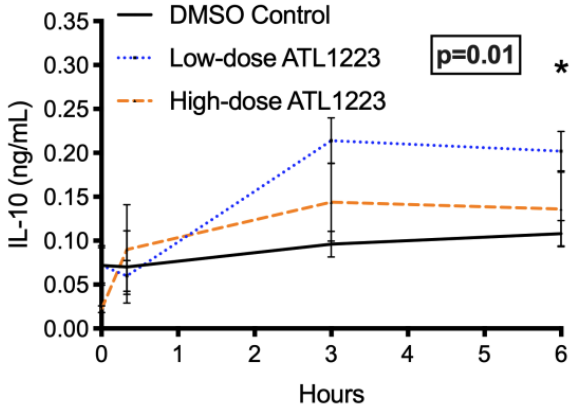
Proinflamatory Cytokines



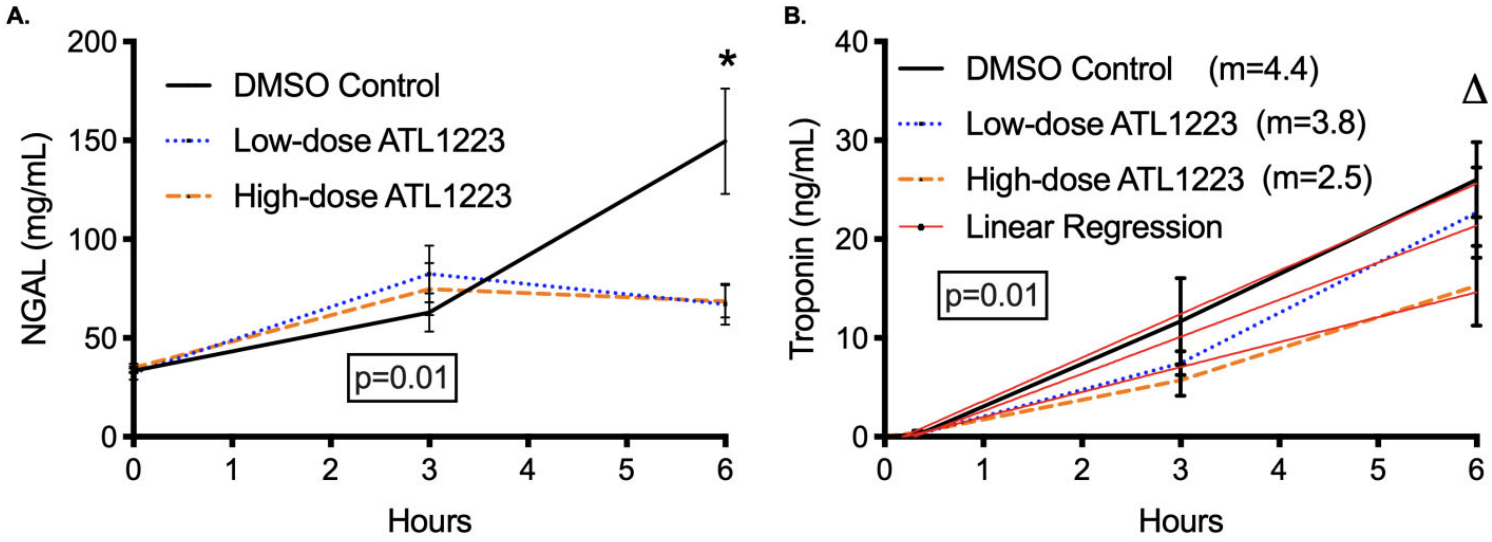


Anti-inflamatory Cytokines





Organ Injury



24 hour survival model

- Build upon the 6 hour study
- See if Adenosine 2A receptor agonist given during ECPR has a lasting effect
- Try an Adenosine 2A receptor approved by the FDA for human use

Methods

- Porcine model of fibrillatory arrest and ECPR
- Double-blind experimental design

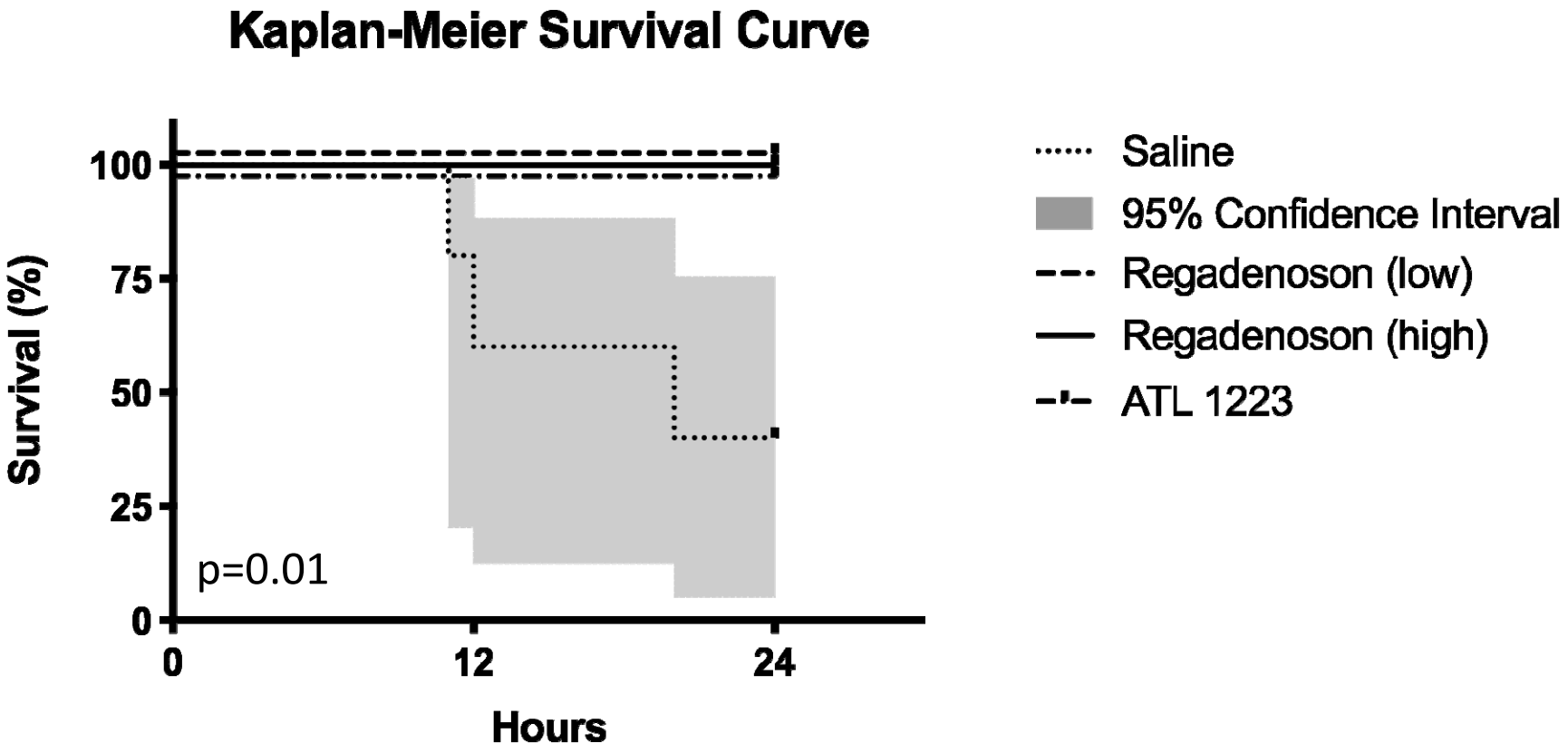
Randomization

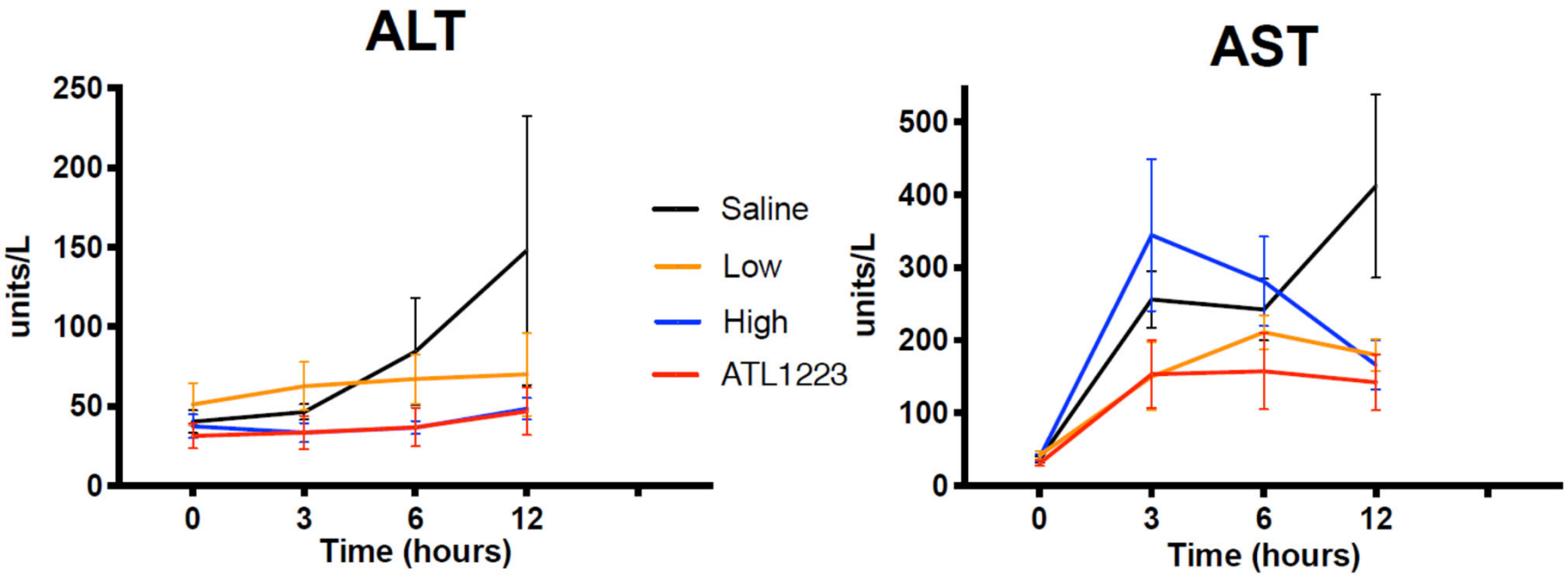
- Saline control (5mL/hour)
- ATL1223 (0.6 ng/kg/min)
- Low dose Regadenoson (0.144 mcg/kg/hour)
- High dose Regadenoson (14.4 mcg/kg/hour)

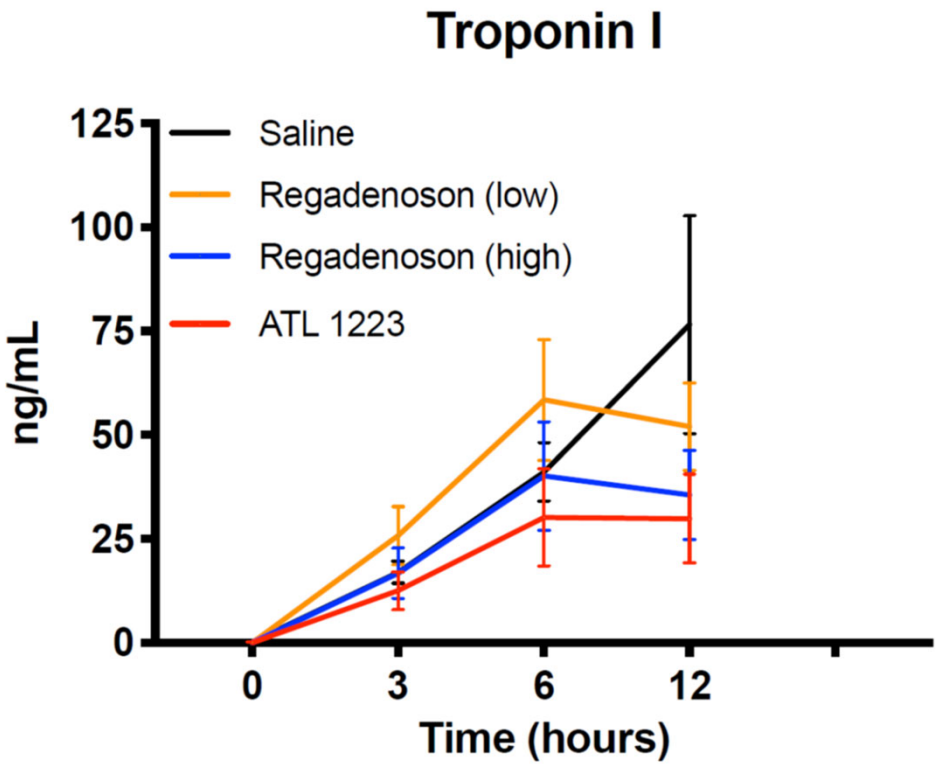
Results

- 20 swine included in the experiment
  - n=5 per group
- All were defibrillated into sinus rhythm after 30 minutes and weaned from ECMO at 6 hours
- Neurologic function was demonstrated in all animals

Survival


Kaplan-Meier Survival Curve
Survival (%)
100
75
50
25
0
0
12
24
Hours
p=0.01
Saline
95% Confidence Interval
Regadenoson (low)
Regadenoson (high)
ATL 1223


ALT
250
200
150
100
50
0
units/L
0
3
6
12
Time (hours)
Saline
Low
High
ATL1223
AST
500
400
300
200
100
0
units/L
0
3
6
12
Time (hours)


Troponin I
125
100
75
50
25
0
ng/mL
Saline
Regadenoson (low)
Regadenoson (high)
ATL 1223
0
3
6
12
Time (hours)

Conclusions

- Selective Adenosine 2A receptor activation improves survival after cardiac arrest treated with ECPR

- Clinical use of Adenosine 2A receptor agonists could decrease the considerable morbidity and mortality associated with post cardiac arrest syndrome

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