Analyzing Treatments for Acute Respiratory Distress Syndrome in Pig Models

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Background

- Acute Respiratory Distress Syndrome (ARDS) is severe lung inflammation from injury or disease that causes fluid to leak into the lungs, making breathing progressively more difficult.
- Mechanical ventilation, a necessary step in maintaining patient blood oxygen levels during ARDS, is damaging to the lungs because it applies air pressure internally to inflate the lungs rather than allowing them to fill after diaphragm/intercostal/etc. muscle contractions increase thoracic volume.
- 100% O2 has also been shown to be more damaging than air ventilation due to its reactivity, but this becomes necessary to maintain arterial Po2 when too much of the patient's lung becomes physiologic dead space (can no longer facilitate blood-gas exchange).
- When an area of the lung is not effectively oxygenated (i.e. Po2 decreases), vasoconstriction of small arterioles prevents blood flow to this area, lessening hemorrhage in damaged areas, but also increasing dead space, decreasing perfusion and therefore oxygenation.
- Excess alveolar air pressure can cause capillary collapse. Small airway closure can also be a consequence of disease.
- Airway blockage (such as from fluid or mucus) can cause small airway collapse due to absorption atelectasis, further reducing lung volume.
- Blood flow typically increases linearly from the top to bottom of the lung due to hydrostatic pressure, and this difference is often exaggerated by injury. Therefore, patient positioning (supine vs. prone) is very important during mechanical ventilation to reduce ventilation-perfusion inequalities as much as possible and maximize gas exchange.
- Epinephrine is a treatment for ARDS. Its primary effect is increasing blood pressure, reintroducing blood flow to the areas of the lung with collapsed capillaries/vasoconstriction due to injury, as well as bronchodilation.
- Nitrous oxide gas is another ARDS treatment. NO is a vasodilator that will increase blood flow without raising blood pressure by relaxing smooth muscle.
- Alveolar edema can reduce lung compliance, reducing ventilation.
- Blocking pulmonary flow (such as through vasoconstriction) can decrease surfactant activity and reduce compliance, even hyperventilating neighboring units.
- HCl bronchoscopy in pig lungs has been shown to be an effective model of ARDS in humans, causing inflammation and edema.
- Modern 3D imaging allows for a model of injury throughout the lung while the pig is still alive.

Objectives

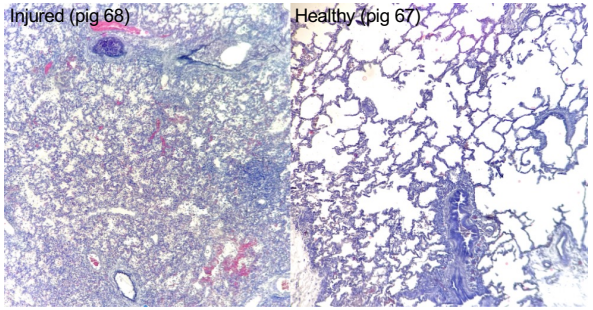
Our objective is to create a database of the effects of different treatment methods in our ARDS model to increase the body of knowledge and create more personalized treatment models for patients with different ARDS presentations to increase survival rates. We aim to study:

- Epinephrine
- Positioning during ventilation
- Ventilation injury in healthy pigs

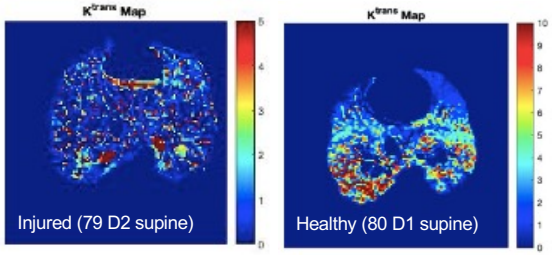
Methods

- 30-35kg pigs are sedated and intubated. Half receive injury from HCl introduction during bronchoscopy.
- After 6 hours (for injury to develop), all pigs are taken for imaging (D1).
- Approximately half receive epinephrine or NO gas during imaging.
- After a further 30 hours (36 in total), the same process is repeated (D2).
- The pigs are then put down and histology samples are collected for H&E staining in paraffin.

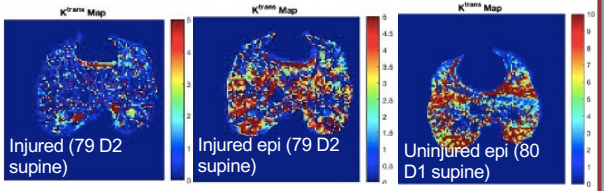
Results



H&E staining: The alveoli in the injured sample are completely collapsed/ filled with edema. The purple indicates nuclei, the pink is everything else (smooth muscle, cytoplasm, RBC, collagen, etc.). The edema does include blood, but it is primarily WBCs.

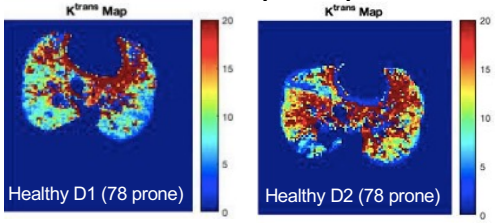


Injured vs Uninjured scan: The injured lungs have much less blood flow, whereas the healthy lungs have much more visible blood flow in a clear gradient increasing towards the bottom of the lung. This is because the injured regions have vasoconstriction as a response to low oxygenation. Note that the scale of the healthy lung is twice as high.

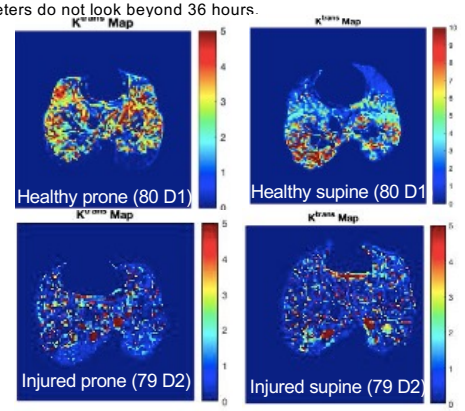


Epinephrine: The epinephrine reintroduces blood flow to non-perfused regions of the lung by raising blood pressure and reopening small arterioles. The effect looks the same between the healthy and injured lungs, although the uninjured lung still has higher perfusion (note scale).

Results (cont.)



Injury of Healthy Ventilated Lungs: Interestingly, the D2 lungs have more blood flow that the more recently ventilated healthy lungs. This is likely because the (comparatively slower) inflammation from just ventilation causes an initial increase in blood before vasoconstriction. Our study parameters do not look beyond 36 hours.



Effects of position on perfusion: Although position does affect blood flow, the effect is much less extreme in injured lungs using this metric.

Next Steps

- Continue collecting data.
- We are noticing a significant difference in degree of injury between male and female pigs due to hormonal differences (a difference that is also present in humans) so as the database develops, we can continue studying this disparity in greater detail.
- We are starting to implement bronchoalveolar lavage (saline solution pumped through airways to gather histological data while the pig is alive, allows for specific protein/cytokine identification) and are starting to see patterns, although it's too early to draw conclusions.
- We are also testing NO gas, although we do not have significant data to draw conclusions yet.

Acknowledgements

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