Acute Respiratory Distress Syndrome (ARDS):
Developing a Better Diagnostic Tool

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OUTLINE
1. Present an ARDS case study.
2. Review ARDS prevalence, causes, disease progression, and current diagnosis criteria.
3. Describe the approach we are using to develop a better tool for diagnosing ARDS.

ARDS Case Study
- 80 year old male admitted to the ER with:
  - Shortness of breath, rapid breathing rate, and low blood oxygen saturation.
  - Diagnosed with ARDS, and admitted to the ICU.
  - Placed on mechanical ventilation to improve blood oxygenation.
  - Blood oxygenation improved within the first 24 hours, but worsened by the second day.
  - Day 4: kidneys failed.
  - Patient died later that day.

Less than a week from ER admission to death!
What caused the ARDS in this patient?

- 7 weeks prior to admission to ICU, the patient was diagnosed with cancer (lymphoma).
  - Lung CT scan was normal at the time of cancer diagnosis.
- Received 2 doses of chemotherapeutic drugs with low risk for lung injury in most patients.
- Drugs caused lung injury and ARDS, which in turn caused death from multi-organ failure.

Could a better diagnostic tool have changed the outcome for this patient?

Review ARDS prevalence, causes, disease progression, and current diagnosis criteria.

ARDS: Prevalence, Mortality, and Healthcare Costs

- A devastating lung disease.
- One of the most frequent causes of admission to Medical ICUs.
- Severe ARDS:
  - Accounts for 10-15% of ICU admissions.
  - Occurs in ~200,000 patients in the US per year.
  - Carries a mortality rate of ~40%.
  - Accounts for 75,000 deaths, 3.6 million hospital days, and $5 billions in healthcare costs in the U.S. alone per year.
- Lack of clinical means for early diagnosis.
- Lack of effective therapies.

- The long-term goal of my research is to address these critical clinical needs.
### Clinical Causes of ARDS

**Direct Injury to the Lung**
- **Common:** Pneumonia

**Less common:**
- Inhalation injury
- Pulmonary contusion
- Fat emboli
- Near drowning

**Indirect Injury to the Lung**
- **Common:**
  - Sepsis
  - Severe trauma

**Less common:**
- Multiple blood transfusions
- Severe burns
- Head injury
- Drug overdose

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### Gas Exchange in a Normal Lung: “Tight” Air-Blood Barrier

- **Alveolus**
- **Air**
- **O₂/CO₂**
- **Capillary**
  - "Thin and tight" Air-Blood Barrier

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### ARDS: “Leaky” Air-Blood Barrier

- **Alveolus**
- **Air**
- **Fluid (edema)**
- **O₂/CO₂**
  - "Leaky" air-blood barrier

- **Edema**
- **Low blood oxygenation**
- **Multi-organ failure**
- **Death**
  - Recovery

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Biochemical Changes Precede Structural Changes

Early

- Inflammation
- Increase in oxidants production
- "Leaky" air-blood barrier

ARDS: Lung edema, shortness of breath, rapid breathing, low blood oxygenation.

Current diagnosis

Late

- Multi-organ failure and death

Describe the approach we are using to develop a better tool for diagnosing ARDS.

Rat Model of Human ARDS

- ARDS induced by exposing rats to 100% oxygen ($O_2$)

High oxygen chamber

Early Biochemical Changes in the Progression of ARDS

Glutathione (GSH): Important cellular antioxidant

![Graph showing cumulative mortality (%) over hours of exposure to 100% O2]

Inflammation, oxidants

GSH

cell

GSH

cell

Hours of Exposure to 100% O2

Cumm ulative Mortality (%)

0 20 40 60 80 100

GSH

Early phase

Single-Photon Emission Computed Tomography (SPECT) Imaging

- Clinical functional imaging modality.
- Requires the delivery of a biomarker (compound labelled with a gamma-emitting radioisotope) into a patient.
- Detection of the accumulation of the biomarker in the lungs using a gamma camera.

99mTc-hexamethylpropyleneamine (HMPAO)

- Clinical SPECT biomarker.
- Biomarker of tissue glutathione (GSH) content.
- When 99mTc-HMPAO enters the cells, it interacts with GSH and gets stuck within the cells.
- The more GSH present within the lung cells, the more lung uptake of 99mTc-HMPAO, and the brighter the image.
**Lung Uptake of 99mTc-HMPAO Increases Early in the Progression of ARDS**

**Second Rat Model of Human ARDS**
- Intra-tracheal instillation of endotoxin (bacteria, LPS).
- Rats experience ARDS like injury (mild) after 24 hrs, but fully recover within 7 days.

**Could early detection of ARDS have changed the outcome for the patient in the case study?**
- SPECT scan with 99mTc-HMPAO after the first dose of chemotherapy could have revealed early lung injury.
  - Assess the risk-to-benefit of the cancer treatment.
  - Use different drugs.
  - Take precautionary measures to reduce the risk of severe ARDS development.
SUMMARY

- ARDS is a devastating lung disease with a high mortality rate, in part due to the lack of a clinical tool for early diagnosis.
- Current diagnosis is based on late changes in disease progression.
- Cellular biochemical changes that occur early in the progression of ARDS can be used for early diagnosis of ARDS using clinical SPECT imaging.
- The lung uptake of the SPECT biomarker $^{99m}$Tc-HMPAO increases early in the progression of ARDS, and tracks ARDS progression and regression.
- Early diagnosis of ARDS using SPECT imaging can enhance the efficacy of existing therapies, reduce the severity and healthcare costs of ARDS, and improve outcomes.

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