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Title: Surfactant Depletion Combined with Injurious Ventilation Results in A Reproducible Model of the Acute Respiratory Distress Syndrome (ARDS)

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Author Questionnaire

1. **Microscopy**: Does your protocol require the use of a dissecting or stereomicroscope for performing a complex dissection, microinjection technique, or something similar? **No**

2. **Software:** Does the part of your protocol being filmed include step-by-step descriptions of software usage? **No**

3. **Interview statements:** Considering the COVID-19-imposed mask-wearing and social distancing recommendations, which interview statement filming option is the most appropriate for your group? **Please select one**.

   ☒ Interview Statements are read by JoVE's voiceover talent.

4. **Filming location:** Will the filming need to take place in multiple locations? **No**

Current Protocol Length

Number of Steps: 15
Number of Shots: 29

Introduction

1. Introductory Interview Statements

Videographer: VO talent will read the introduction and conclusion statements, so you don't need to film those.

VO talent: Please record the introduction and conclusion statements.

1.1. The combination of surfactant washout with injurious ventilation reduces the recruitability of the lung injury as compared to models with exclusive surfactant washout.

1.1.1. *4.2.1 and 5.2.1*

1.2. The model is reproducible and does not require additional techniques. Furthermore, a two-hit model closely mimics the realistic clinical situation.

1.2.1. *3.1.2*

1.3. The low recruitability of this model supports the experimental investigation of new ventilation strategies, paving the way for the translation of experimental lung research into clinical practice.

1.3.1. *5.3.1 and 4.3.1*

Introduction of Demonstrator on Camera

1.4. The procedure will be demonstrated by Dr. Taher and Dr. Russ, who are anesthesiologists as well as research fellows in our laboratory for applied physiology in anesthesia and intensive care medicine.

1.4.1. The named demonstrator(s) looks up from workbench or desk or microscope and acknowledges the camera.

Ethics Title Card

1.5. Procedures involving animal subjects have been approved by the federal authorities for animal research in Berlin, Germany.

Protocol

2. The Mechanical Ventilation

2.1. To begin, set the mechanical ventilation parameters as described in the text manuscript and target an end-expiratory partial pressure of carbon dioxide of 35 to 40 millimeters of mercury and an oxygen saturation above 95% **[1]**.

2.1.1. WIDE: Establishing shot of talent inputting setting for ventilator.

2.2. Use a continuous intravenous infusion of thiopentone and fentanyl to maintain the anesthesia and administer a muscle relaxant if required **[1-TXT]**.

2.2.1. Drug being infused in pigs from pipes **TEXT: Thiopentone (20 mg/kg/h), fentanyl (7 µg/kg/h)**

2.3. Cannulate the external jugular vein with a central venous catheter and insert the introducer sheath of the pulmonary arterial catheter into the same vein **[1].** Then, cannulate the femoral artery for invasive blood pressure monitoring **[2].**

2.3.1. Talent inserting central venous catheter and introducer sheath in the vein.

NOTE: No clapperboard – Clip 5

2.3.2. Talent cannulating the femoral artery.

2.4. Calibrate the transducers against the atmosphere, which is zero millimeters of mercury and 200 millimeters of mercury for the arterial line and 50 millimeters of mercury for the central venous line **[1]**, and start monitoring by connecting them to the arterial catheter and the central venous line **[2]**.

2.4.1. Talent calibrating the pressure transducer.

2.4.2. Talent connecting the transducers to the arterial catheter and the central venous line.

3. Introduction of the Pulmonary Artery Catheter

3.1. Connect the pulmonary artery catheter to the pressure transducer system **[1]** and calibrate the transducer against the atmosphere and 100 millimeters of mercury **[2]**. Then, introduce the pulmonary artery catheter through the introducer sheath with a deflated balloon for 10 to 15 centimeters, depending on the sheath length **[3]**.

3.1.1. Talent connecting the transducer to PAC

3.1.2. and calibrating it.

3.1.3. Talent introducing the PAC.

NOTE: New shot was added and labeled as 3.1.2

3.2. Once the balloon has left the sheath, inflate it **[1]** and advance the pulmonary artery catheter further **[2]** while monitoring the pressure **[3].**

3.2.1. Talent inflating the balloon.

3.2.2. Talent advancing the PAC.

3.2.3. Pressure wave on the monitor.

NOTE: Shot 3.2.1 and 3.2.2 were filmed in one take.

3.3. Push the pulmonary artery catheter forward when the right atrium, the right ventricle, and the pulmonary artery pressure waves appear on the monitor and stop when the pulmonary capillary wedge pressure wave is seen **[1]**. Then, record the pulmonary capillary wedge pressure at end-expiration **[2]** and deflate the balloon **[3]**.

3.3.1. Talent pushing the PAC with monitor in the view.

3.3.2. Talent recording PCWP.

3.3.3. Talent deflating the balloon.

3.4. Calculate the pressure parameters described in the text manuscript and record the required respiratory settings and measurements to complete the data set **[1].**

3.4.1. Talent recording the parameters.

4. Surfactant Depletion

4.1. Ventilate the animal with a fraction of inspired oxygen of 1 **[1]**, then disconnect the animal from the ventilator **[2]**. *Videographer: This step is important!*

4.1.1. Talent ventilating the animal.

4.1.2. Talent disconnecting the ventilator.

4.2. Fill the lungs with pre-warmed saline using a funnel connected to the endotracheal tube. Stop if the mean arterial pressure decreases below 50 millimeters of mercury **[1-TXT]**. Drain the lavage fluid by lowering the funnel to the ground level **[2]** and monitor the wave [3]. *Videographer: This step is important!*

4.2.1. Talent filling the lungs with pre-warmed saline. **TEXT: Saline-35 mL/kg**

4.2.2. Talent draining the lavage.

4.2.3. Wave Monitor

NOTE: new shot was added in step 4.2.

4.3. Reconnect the animal to the ventilator for oxygenation and wait until the animal recuperates, then repeat lavages until the Horowitz index decreases below 100 millimeters of mercury for at least 5 minutes at a fraction of inspired oxygen of 1 and a

positive end-expiratory pressure above 5 millibar **[1].** *Videographer: This step is important!*

4.3.1. Talent reconnecting the ventilator.

NOTE: No clapperboard – Takes 27-28

4.4. Take an arterial blood gas sample after 5 minutes following each lavage **[1]**.

4.4.1. Talent taking the gas samples.

5. Injurious Ventilation with High Tidal Volume/Low PEEP (High Tv/low PEEP)

5.1. Keep the fraction of inspired oxygen at 1 and set the ventilator on the volume guaranteed, pressure-controlled ventilation mode **[1]**. Increase the alarm threshold for peak inspiratory pressure to 60 millibar **[2]**. *Videographer: This step is important!*

5.1.1. Talent setting the ventilator to pressure-controlled ventilation mode.

5.1.2. Talent increasing the alarm threshold.

NOTE: From 5.2.1 till 5.3.2 were filmed in one take

5.2. Lower the respiratory rate and set the inspiration to expiration ratio **[1-TXT]**, then increase the tidal volume slowly up to 17 milliliters per kilogram bodyweight over at least 2 minutes. Do not increase the tidal volume further if an inspiratory pressure of 60 millibar is reached **[2]**. *Videographer: This step is difficult and important!*

5.2.1. Talent lowering the respiratory rate and setting the I:E ratio. **TEXT: Respiratory rate: 12/min ; I:E ratio: 1:1.5**

5.2.2. Talent increasing the tidal volume.

5.3. Reduce the positive end-expiratory pressure to 2 millibar **[1]** and ventilate the animal for up to 2 hours **[2]**. *Videographer: This step is important!*

5.3.1. Talent setting the ventilation parameters for high tidal volume/low PEEP.

5.3.2. Animal on ventilator.

Results

6. Results: Effects of the Injurious Ventilation on the Lungs

6.1. The Horowitz index decreased during the surfactant washout in all animals **[1]** but the recruitment maneuver resulted in a notable increase in oxygenation after the surfactant washout **[2]**.

6.1.1. LAB MEDIA: Figure 3

6.1.2. LAB MEDIA: Figure 3A *Video Editor: Please emphasize [■] dots at the first RM point on the x-axis in the graph.*

6.2. The 2-hour injurious ventilation diminished lung recruitability with respect to gas exchange **[1]** and the mean arterial pressure **[2]**.

6.2.1. LAB MEDIA: Figure 3A

6.2.2. LAB MEDIA: Table 1 *Video Editor: Please emphasize the mPAP raw of Table 1.*

6.3. The gas exchange parameters were improved with high tidal volumes due to the cyclic recruitment while mean arterial pressure was elevated due to high intrathoracic pressures and hypercapnia **[1]**.

6.3.1. LAB MEDIA: Figure 3B

6.4. Computer tomographic imaging of the lungs showed extensive atelectasis of the dependent areas of the lung during the ventilation with a positive end-expiratory pressure of 6 millibar **[1]**, which resolved largely when the ventilation was escalated to a positive end-expiratory pressure of 15 millibar **[2].**

6.4.1. LAB MEDIA: Figure 4 *Video Editor: Please emphasize "#" in the bottom image of PEEP 6 mbar image column.*

6.4.2. LAB MEDIA: Figure 4 *Video Editor: Please emphasize "Red arrows" in the bottom image of PEEP 15 mbar image column.*

6.5. However, the substantial ubiquitous ground glass opacities did not resolve **[1]**.

6.5.1. LAB MEDIA: Figure 4 *Video Editor: Please emphasize "*" all images.*

6.6. The alveolar opacities observed with a positive end-expiratory pressure of 15 millibar indicated structural damage of the lungs **[1]**. They were also observed in the post-mortem examination of the lungs **[2]**.

6.6.1. LAB MEDIA: Figure 4 *Video editor: Please emphasize "+" mark in the first image of PEEP 15 mbar image column.*

6.6.2. LAB MEDIA: Figure 5 *Video editor: Please emphasize "+" mark in the right image of the figure.*

Conclusion

7. Conclusion Interview Statements

7.1. When attempting this protocol, it is important to adjust the duration of injurious ventilation because structural lung damage cannot be recruited and an animal might die prematurely if the injury is too extensive.

7.1.1. *5.3.1-5.3.2*

7.2. The combination of surfactant depletion and injurious ventilation supports the investigation of therapies resulting in a fast recruitment of atelectatic lung regions, such as ventilation modes with high ventilatory pressures.

7.2.1. *5.1.2 and 5.2.2*