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TITLE: Alkaline Phosphatase for the Prevention of Intestinal and Kidney Injury in a Piglet Model of Cardiopulmonary Bypass with Deep Hypothermic Circulatory Arrest

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| 14. ABSTRACT Purpose: To determine if alkaline phosphatase decreases intestinal and renal injury in a piglet model of cardiopulmonary bypass with DHCA, mediated in part through adenosine signaling pathways. Scope: Evaluate histologic (primary outcome), physiologic, and biomarker evidence of intestinal and kidney injury in this model with administration of escalating doses of bovine intestinal alkaline phosphatase or specific inhibitors of native alkaline phosphatase. Assess the role of downstream adenosine as a mediator of alkaline phosphatase effect. Major Findings: For the first reporting period, we had successfully established the model, demonstrating appropriate levels of physiologic disturbance (hemodynamic instability and lactic acidosis). Systemic interventions are nearly complete, at which time the initial analysis of the primary outcome will be performed for these groups. | | | | | | |
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1. Introduction

Cardiopulmonary bypass and deep hypothermic circulatory arrest are frequently required for the repair of complex congenital heart disease in neonates and infants. While use of these techniques is necessary for surgical repair, the associated ischemia-reperfusion injury to the intestines and kidneys can lead to substantial post-operative morbidity. The purpose of this project is to provide preliminary evaluation of the potential role of alkaline phosphatase for the prevention of intestinal and kidney injury after pediatric cardiopulmonary bypass with deep hypothermic circulatory arrest. In this model, we place 5-10kg infant pigs on cardiopulmonary bypass, cool them to 22 degrees C rectal temperature, stop blood flow for 75 minutes, rewarm using the bypass circuit, then separate from bypass for 4 hours prior to euthanasia. Injury from this basic model is being compared to systemic or intestinal treatment with bovine intestinal alkaline phosphatase as well as inhibition of native alkaline phosphatase. The primary outcomes are changes in acute intestinal and kidney injury histology scores; secondary outcomes include physiology changes and biomarkers of organ injury.

2. **Keywords:** Alkaline phosphatase, adenosine, cardiopulmonary bypass, deep hypothermic circulatory arrest, cardiac surgery, acute kidney injury, intestinal barrier function

3. Accomplishments

a. What were the major goals of the project?

- i. Protocol Development and Approval: 4 months
- ii. Initial Model Completion: 2 months
- iii. Testing Alkaline Phosphatase Interventions: 10 months
- iv. Mechanistic Assays (Adenosine receptor stimulation/blockade): 2.5 months
- v. Data Analysis, Abstracts, Publication: 5 months

b. What has been accomplished under these goals?

- i. Protocol Development and Approval: Complete. This task was delayed by ~5 months due to the need to transition to a piglet model from an adult rodent model (please see section 5a). We had IACUC approval for the rodent model originally, and while awaiting final funding approval we began working on the basic model development using internal funds. We quickly found that the variability of the surgery was too great in our hands and requested transition to the technically easier (and more scientifically applicable) infant pig model. The transition required initial approval by USAMRMC, resubmission to IACUC, and final approval by ACURO resulting in the initial delay. Following this transition, the timeline we have had a remarkably smooth experience with the project and encountered no other substantial delays.
- ii. Initial Model Completion: Complete. This task encompassed a total of 8 model development surgeries. These 8 animals allowed us to become proficient in the technical aspects of the surgery, build the experience of the animal lab team regarding intensive care of the piglets in the post-operative period, and assess the level of organ injury present in the basic model.
- iii. Testing Alkaline Phosphatase Interventions: Complete. This task encompassed a total of 43 surgeries to test the basic model/controls, three escalating doses of systemic bovine intestinal alkaline phosphatase infusion, systemic alkaline

- phosphatase blockade, intestinal alkaline phosphatase supplementation, and intestinal alkaline phosphatase blockade.
- iv. Mechanistic Assays: Complete. This task encompassed 6 additional surgeries to assess the potential role of adenosine in the mechanistic pathway of alkaline phosphatase, through either alkaline phosphatase infusion plus adenosine receptor blockade or alkaline phosphatase blockade with adenosine infusion.
 - v. Data analysis, Abstracts, Publication: Ongoing. The 18-month project period resulted in a very accelerated timeframe to both perform all of the surgeries and the specimen analysis, particularly with the transition to the large animal model as well as the need to move to an external blinded pathology expert to maintain blinding integrity (see section 5). Therefore, we are just beginning to complete sections of the analysis and production of abstracts. The progress to date can be divided into the following areas:

Model: To our knowledge, a model of peripheral cardiopulmonary bypass and deep hypothermic circulatory arrest without sternotomy has not been previously published so we have recently submitted an abstract to the American Heart Association Scientific Sessions detailing the technical and physiologic findings of the model (**Appendix 1**). Manuscript is currently in preparation. We are also preparing an abstract detailing differences in temperature monitoring techniques (esophageal vs rectal) and anticipate submitting this abstract to the Pediatric Cardiac Intensive Care Society meeting in November.

Systemic Alkaline Phosphatase Dosing: We have also recently submitted an abstract detailing the kinetics of our systemic bovine intestinal alkaline phosphatase infusion to the American Heart Association Scientific Sessions (**Appendix 2**). We found that low and medium dose infusions only marginally increased serum alkaline phosphatase activity, while high dose infusion more effectively increased this activity. We will therefore utilize the higher dosing in our studies. These data are combined in the abstract with the acute kidney injury data (see next).

Acute Kidney Injury (AKI): As stated in the previous section, our pilot data on acute kidney injury has also been submitted to the AHA in abstract form (**Appendix 2**). As a summary of our findings, moderate to severe AKI determined by blinded histology [a priori primary outcome] occurred in 50% of animals (20% with severe injury) and this rate was not decreased by low or moderate dose alkaline phosphatase infusion. However, the high dose alkaline infusion group demonstrated only a 20% rate of moderate injury and no cases of severe AKI. Despite the small subject numbers in this pilot study, mean histology score trended lower in the high dose group (0.4 vs 1.6; p=0.057). The manuscript detailing alkaline phosphatase dosing and AKI is currently in preparation. These data, along with our prior observational data in children,

will serve as the core of the preliminary data for an upcoming R01 submission in October, 2018.

Intestinal Injury: Having completed the kidney injury data, we have just begun to analyze the intestinal injury data. We expect blinded review of both the small intestine and colon (as well as liver and portal venous blood samples) to be completed over the next 4 months.

Other Analyses: While no other analyses were funded by the DOD, we did from an ethical standpoint seek to conform to published guidelines to maximize the scientific use of large animals undergoing research procedures. As part of this goal, we received funding from the American Heart Association to evaluate acute lung injury in these animals. These data have resulted in a recent oral abstract presentation at the Pediatric Academic Society Annual Meeting (May 2018-abstract included as **Appendix 3**). Manuscript preparation is currently underway. We also have collaborated with a group from the University of Colorado Department of Anesthesiology who study functional neurologic (hippocampal) injury in models of adult cardiac arrest. They were able to harvest the brains of our animals in a functionally preserved state and measure hippocampal activity in this model. These findings are currently being prepared as a manuscript

c. What opportunities for training and professional development has the project provided?

While this grant was not intended to be a career development grant, there have been multiple professional development opportunities to arise from this project. First and foremost, development of the first cardiac surgery-induced organ injury model on this campus opens multiple opportunities for ongoing study. As was previously described, this model will be used as the platform for an upcoming R01 application and we anticipate several more to come, especially since this cannulation technique would allow easy conversion of our bypass model to an extracorporeal membrane oxygenation model (ECMO) for study of longer term support of multi-organ failure. This model has also opened doors for collaboration with several prominent research groups on campus. We have previously described the collaboration with our pulmonary and neurologic injury groups. We are also now actively collaborating with the principal acute kidney injury group as well as a surgical group interested in developing nanoparticle-delivered therapy for acute lung injury and acute kidney injury.

d. How were the results disseminated to the communities of interest?

Our first two abstracts detailing the primary objectives of the project have been submitted to the AHA Scientific Sessions (November 2018). If accepted they will be presented at this major international conference and published in a supplemental edition of Circulation. We have also had an abstract on acute lung injury in this model presented as an oral presentation at the Pediatric Academic Society annual conference.

We anticipate multiple additional opportunities for presentation of this project over the coming 6-12 months.

e. What do you plan to do during the next reporting period to accomplish the goals?

While there are no further reporting periods in the grant, we anticipate substantial ongoing productivity from the project over the next 2 years. Ultimately we anticipate upwards of 10 abstracts and manuscripts to be produced from either the primary aims of the project (kidney and intestinal injury) or secondary analyses of injury to other organs (lung, brain, and liver).

4. Impact

a. What was the impact on the development of the principal discipline of the project?

The project has already made one impactful development, establishing drug dosing and preliminary efficacy data to support a larger study of alkaline phosphatase infusion to mitigate acute kidney injury after infant cardiac surgery. AKI in this population remains a substantial problem (over 50% incidence and a potentially large impact on post-operative morbidity/mortality) and there are currently no accepted therapies to reduce injury beyond cardiovascular support and reducing use of renal toxic medications.

b. What was the impact on other disciplines?

The impact on other disciplines is still early, but at minimum our findings on impaired hippocampal function in this model will lead to further study about functional neurology injury (as opposed to structural or cellular injury) in this patient population.

c. What was the impact on technology transfer?

We have filed a new PCT International Patent Application No. PCT/US2017/040737, and data from this project will be used to help support transition to the full patent in 6 months.

d. What was the impact on society beyond science and technology?

Nothing to report

5. Changes/Problems

a. Changes in approach and reasons for change

The primary change in approach for the study was the transition from a rodent model to the infant piglet model (reported in the prior interim report). This change occurred immediately following the project award and was approved by USAMRMC. The reason for the change was inconsistency in the ability to cannulate the rats for cardiopulmonary bypass, leading to unacceptable variation in the physiologic condition of the rats. Transition to the piglet model also had multiple benefits beyond greater consistency of surgical approach. We now have a true pediatric model and the piglet physiology more consistently mirrors human infant physiology leading to the potential for easier translation of our ultimate findings. The transition did result in a delay in model development as previously discussed, as we needed first overall approval from the sponsor, followed by approval of the full new protocol by the local regulatory agency as well as the Department of Defense. Model development thus did not begin until late January 2017; however, we were still able to complete the study as proposed with continued ongoing effort towards analysis and publication.

b. Actual or anticipated problems or delays and actions or plans to resolve them?

Other than the initial delay, problems with the protocol have been relatively minor:

- i. Donor blood: During model set up we realized that the donor blood for the bypass circuit contained multiple biomarkers of inflammation and injury that could affect our assessment of native production of these biomarkers by the experimental animal. Therefore, we have limited exposure to the donor blood to that needed to prime the pump (300ml in all cases) and use only blood from the circuit or crystalloid for volume resuscitation after separation from bypass. We also control for these biomarker changes by analyzing and reporting biomarker concentrations immediately following initiation of bypass.
- ii. Urine Sampling: Bladder catheterization proved to be much more challenging than anticipated, with ~70% success rate typically involving some urethral trauma (bleeding) that worsened with heparinization for bypass cannulation. This led to both physiologic instability for the piglet as well as blood contamination of the urine samples. As a best option available, we decided to forgo catheterization in the final model and instead perform direct bladder puncture at the time of euthanasia for collection of all pooled urine. This technique provides a non-contaminated sample for accurate analysis and a full sampling of all urine produced during the case. Negative impacts include primarily the inability to test differences in urine composition in pre versus post bypass samples.
- iii. Duration of Circulatory Arrest: We originally planned on a 60 minute deep hypothermic circulatory arrest period, although acknowledged in the original proposal that this may need to be extended up to 90 minutes if there was evidence of insufficient organ injury. We trialed 60 and 90 minutes with 60 producing too little injury and 90 minutes producing too much injury. Ultimately we settled on 75 minutes, which has produced physiology very similar to our children undergoing moderate to high risk surgery (elevated lactate, cardiovascular instability requiring inotropic support, and consistent acute kidney injury, intestinal mucosal injury, and acute lung injury at 4 hours post bypass). We have also adjusted the target rectal temperature from 18 degrees C to 22 degrees C in the final model. Originally we did not have access to esophageal temperature monitoring (standard of care in our operations in children) and were using rectal temperature monitoring. We became concerned that the large amount of stool in our piglets was insulating the rectal probe and underestimating the overall degree of cooling. We were able to borrow an esophageal probe to perform simultaneous recordings and indeed found that a rectal temperature of 22 degrees C best represented an esophageal temperature of ~18 degrees C.

- iv. Assessment of intestinal barrier function: After further calculations we decided that measurement of intestinal barrier function with FD-4 was difficult and very expensive to perform even in a subset of the larger animals (initially proposed for the rodent model). Instead we planned to perform lactulose/mannitol gavage to monitor lactulose to mannitol ratio in the blood and urine. However, given the uncertain effects on urine output of providing mannitol to a subset of the piglets, we ultimately opted to forego this analysis.
- v. Blinding: Initially we anticipated that a part of our original study team would be blinded to the intervention in order to allow blinded review of the primary outcomes (histology). However, we quickly realized that it was very difficult to blind study members participating in the surgery and that we needed all personnel available on the team to run the surgeries. Therefore, we recruited an expert clinical pathologist from Children’s Hospital Colorado, Dr. Amy Treece, to perform the blinded review. Since Dr. Treece was not receiving funding for her contribution, we had to make sure it fit into her academic time and therefore histology review was slower than originally anticipated. Ultimately, though, the end product of analysis was significantly better in Dr. Treece’s hands and she has agreed to continue to support the team in future analyses.

c. Changes that had a significant impact on expenditures

None

d. Significant changes in use or care of vertebrate animals

See prior sections.

6. Products

- a. Abstract: Experimental Model for Peripheral Cardiopulmonary Bypass with Deep Hypothermic Circulatory Arrest in Piglets. Submitted to AHA Scientific Sessions for November 2018 (**Appendix 1**)
- b. Abstract: Alkaline Phosphatase Infusion in Infant Piglet Model of Cardiopulmonary Bypass with Deep Hypothermic Circulatory Arrest: Kinetics and Effect on Kidney Injury. Submitted to AHA Scientific Sessions for November 2018 (**Appendix 2**)
- c. Abstract: Characterization of cardiopulmonary bypass associated acute lung injury in an infant piglet model. Oral Presentation--Pediatric Academic Society, May 2018 (**Appendix 3**)

7. Participants and Other Collaborating Organizations

- a. Jesse Davidson: No change
- b. Suzanne Osorio: No change
- c. James Jagers: No change
- d. Scott Lawson: No change
- e. Suhong Tong: No change
- f. Ludmilla Khailova: No change

8. Special Reporting Requirements

Nothing to report

9. Appendices

- a. Appendix 1: Abstract- Experimental Model for Peripheral Cardiopulmonary Bypass with Deep Hypothermic Circulatory Arrest in Piglets.
- b. Appendix 2: Alkaline Phosphatase Infusion in Infant Piglet Model of Cardiopulmonary Bypass with Deep Hypothermic Circulatory Arrest: Kinetics and Effect on Kidney Injury.
- c. Appendix 3: Characterization of cardiopulmonary bypass associated acute lung injury in an infant piglet model.

Experimental Model for Peripheral Cardiopulmonary Bypass with Deep Hypothermic Circulatory Arrest in Piglets

Suzanne Osorio Lujan, Ludmila Khailova, Justin Robison, James Jagers, Richard Ing, Scott Lawson, Jesse Davidson

Introduction:

Infant cardiac surgery is often performed with cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA). CPB cannulation is generally achieved centrally through a sternotomy, and cardioplegia is usually used to arrest the heart. Existing animal models, instrumental for the study of CPB and its impact on inflammatory processes and tissue insult, involve sternotomy and cardioplegia.

Objective:

To develop a CPB model with DHCA in infant pigs, avoiding sternotomy and cardioplegia.

Methods:

Twenty-nine SPF female piglets (8.33 ± 0.82 kg), separated into anesthesia controls ($n=7$), and intervention group (CPB with DHCA, $n=22$), were intubated and mechanically ventilated. Isoflurane anesthesia, analgesia, fluids and antibiotics were provided. Following femoral catheterization, ECG, temperature, hemodynamic and respiratory parameters were recorded. After heparin (700 UI/kg) administration (ACT > 400 s), CPB cannulation was performed through the right external jugular vein and right carotid artery (10F arterial and 14 F cannulas respectively). CPB was initiated, and animals were cooled to 22°C followed with 75 min of DHCA. Propofol was used during CPB and

DHCA. After DHCA, animals were rewarmed (36°C), separated from CPB and kept under isoflurane anesthesia for 4 hours with inotropic support. Control animals were placed under the same anesthetic and ventilatory regime, but no CPB or DHCA was performed.

Results:

CPB and DHCA all animals recovered spontaneous circulation and survived 4 hours of postoperative anesthesia. Identified significant hemodynamic and VIS differences between the control and intervention groups are shown on table1.

Table 1: Hemodynamic, lactate and VIS results at different time points

| | | Post intubation | Rewarming | 1 h post rewarming | 2 h post rewarming | 3 h post rewarming | Euthanasia |
|---------|---------|-------------------------|-------------|--------------------|--------------------|--------------------|--------------|
| HR | Control | 83 ±15 | NA | 87 ±16 | 91 ±16 | 85 ±14 | 83 ±13 |
| | CPB | 79 ±12 | NA | 132 ±19* | 128 ±22* | 126 ±22* | 124 ±22* |
| MBP | Control | 47 ±13 | NA | 53 ±11 | 46 ±3 | 46 ±4 | 48 ±11 |
| | CPB | 45 ±10 | NA | 56 ±7 | 59 ±7 | 49 ±7 | 51 ±7 |
| SBP | Control | 61 ±14 | NA | 70 ±12 | 63 ±5 | 62 ±6 | 63 ±13 |
| | CPB | 58 ±10 | NA | 71 ±8 | 77 ±8 | 76 ±10 | 68 ±10 |
| DBP | Control | 37 ±12 | NA | 41 ±9 | 35 ±3 | 34 ±2 | 37 ±9 |
| | CPB | 34 ±10 | NA | 43 ±8 | 45 ±8 | 43 ±7 | 37 ±6 |
| VIS | Control | NA | 0 | 0 | 0 | 0 | 0 |
| | CPB | NA | 4.37 ±6.64* | 11.54 ±3.55* | 11.51 ±4.29* | 11.05 ±4.55* | 11.69 ±1.23* |
| Lactate | Control | 1.60 ±0.93 | NA | NA | NA | NA | 0.59 ±0.11 |
| | CPB | 2.83 ±0.92 [†] | 5.67 ±1.55 | NA | NA | NA | 3.97 ±2.12* |

HR: heart rate; MBP: mean blood pressure; SBP: systemic blood pressure; DBP: diastolic blood pressure; VIS: Vasoactive-Inotropic Score; NA: non applicable. † Post cannulation lactate; *p< 0.05

Conclusions:

This model successfully recreated CPB and DHCA conditions without central CPB cannulation or cardioplegia. It avoids technical challenges of central cannulation complications related to the sternotomy, and is a far less painful and invasive surgery for the animal.

Alkaline Phosphatase Infusion in Infant Piglet Model of Cardiopulmonary Bypass with Deep Hypothermic Circulatory Arrest: Kinetics and Effect on Kidney Injury

Ludmila Khailova, Amy Treece, Justin Robinson, Danielle Soranno, James Jagers, Richard Ing, Scott Lawson, Suzanne Osorio Lujan, Jesse Davidson

Background:

Acute kidney injury (AKI) is a common complication of infant cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA), but therapeutic options are limited. Alkaline phosphatase (AP) infusion reduces AKI in sepsis through clearance of extracellular adenine nucleotides and endotoxin. AP has not been evaluated as a treatment for CPB-induced AKI.

Objective:

In a porcine model of infant CPB/DHCA-induced AKI:

- 1) Evaluate effect of escalating doses of AP infusion on serum AP activity
- 2) Assess the effects of AP infusion on development of AKI

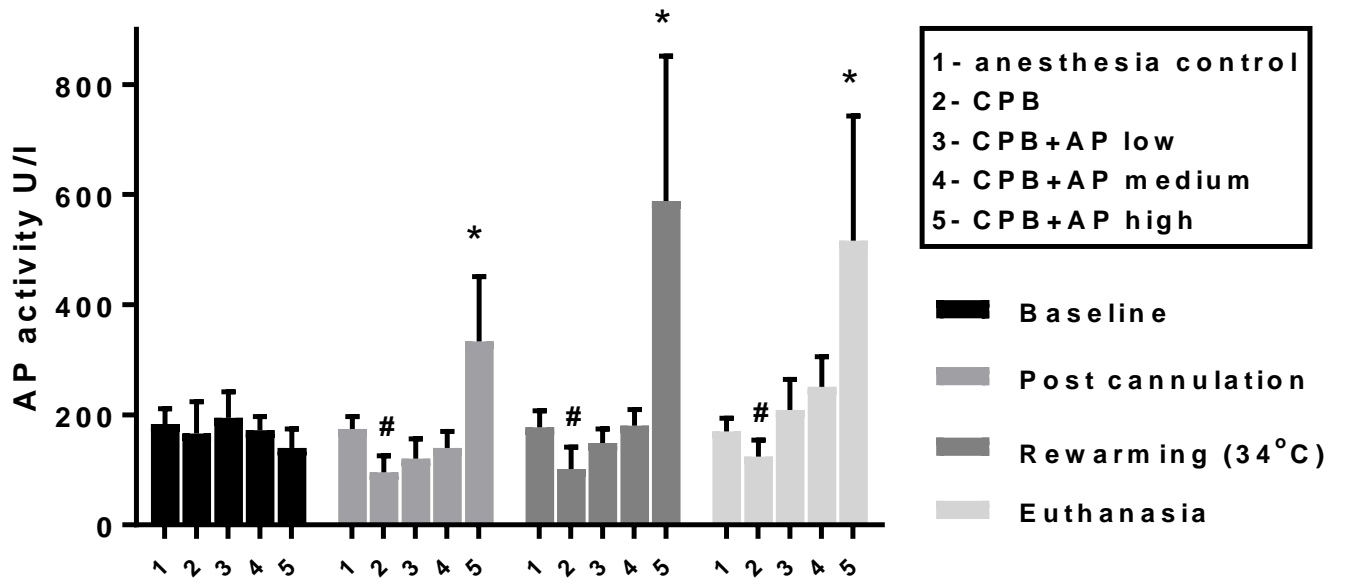
Methods:

Infant pigs (5-10kg) underwent peripheral CPB followed by 75 minutes of DHCA at 22°C. The piglets were then rewarmed, separated from CPB, and provided ICU care for 4h. Groups of 5 piglets received escalating doses of bovine intestinal AP (BiAP) (low: 1U/kg/h; medium: 5U/kg/h; high: 25U/kg/h). Anesthesia controls were mechanically ventilated for 7h. Blood samples were collected at induction, cannulation, rewarming, and euthanasia. Urine was obtained prior to euthanasia. Kidney tissue was collected for blinded histology scoring (primary outcome).

Results:

CPB animals (n=20) overall demonstrated higher kidney histology score (1.3 vs 0; p<0.01), lactate (3.76 vs 0.59; p<0.0001), serum NGAL (256.3 vs 118.1; p=0.0006), and urine NGAL/Cr ratio (0.72 vs 0.06; p<0.0001) at euthanasia compared to anesthesia controls (n=7). AP infusion increased AP activity only in the high dose group (Fig.1). Incidence of at least moderate histologic AKI was 20% in the high dose AP group (n=5) compared to 50% in the remaining CPB groups (n=15), with a trend towards lower mean histology scores in the high dose group (0.4 vs 1.6; p=0.057), with no significant difference between the histology scores of the high dose group and anesthesia controls (0.4 vs 0; p=0.37).

Conclusion: Continuous BiAP infusion at a dose of 25U/kg/h results in increased serum AP activity and may decrease early AKI in a model of infant CPB with DHCA.



*P<0.04 vs. anesthesia control,CPB,CPB+AP low

#P<0.02 vs. anesthesia control

CONTROL ID: 2901750

TITLE: Characterization of Cardiopulmonary Bypass Associated Acute Lung Injury in an Infant Piglet Model

ROLE TYPE: Abstract

CURRENT CATEGORY: Critical Care

CURRENT SUBCATEGORY: None

KEYWORDS: Regional Lung Injury, Cytokine, Deep hypothermic circulatory arrest.

AUTHORS (LAST NAME, FIRST NAME): Robison, Justin W.¹; Khailova, Ludmila³; Trejo Bittar, Humberto⁴; Tong, Suhong S.⁵; Vohwinkel, Christine³; Osorio Lujan, Suzanne M.²; Davidson, Jesse²

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TITLE: Characterization of Cardiopulmonary Bypass Associated Acute Lung Injury in an Infant Piglet Model

Background: Infants with congenital heart disease undergoing surgery with cardiopulmonary bypass (CPB)/ deep hypothermic circulatory arrest (DHCA) are known to develop acute lung injury (ALI). Development of diagnostic and therapeutic strategies for this condition is difficult in part due to lack of established large animal models. Similarities between pig and human lung make pigs great models for ALI. However, global and regional ALI have not been well characterized in infant piglets following CPB/DHCA.

Objective: 1. Characterize acute lung injury in a piglet model of CPB/DHCA. 2. Evaluate for regional differences of ALI in this model.

Design/Methods: Thirty-six infant piglets (5-10 kg) were intubated, placed supine, and cannulated for CPB. They underwent 75 minutes of DHCA and were then rewarmed, separated from CPB, and maintained on mechanical ventilation for 4 hours until necropsy. Serum sRAGE, PaO₂/FiO₂ ratio and lung compliance assessed overall lung injury. Regional lung injury was evaluated by gross assessment, wet/dry ratio, histologic ALI scoring, and tissue mRNA levels of IL-6, IL-8, and TNF α . Five piglets receiving only anesthesia served as controls.

Results: CPB/DHCA piglets demonstrated worse compliance, a greater increase in serum sRAGE from bypass initiation to rewarming, more IL-6 mRNA lower lobe expression and more global IL-8 mRNA expression (upper and lower lobe) compared to anesthesia-only controls (Table 1). The lower lobes also showed more gross injury than the upper lobes (P<0.0001). The lower lobes of the CPB and control groups had more IL-6 expression and increased wet/dry ratio compared to upper lobes (Table 2). Conversely, IL-8 expression was higher in the upper lobes compared to lower lobes with a similar trend in TNF α expression. Histology showed no difference in ALI score (upper vs lower lobe).

Conclusion(s): Piglets exposed to CPB/DHCA demonstrated worsened compliance, increased inflammation and potentially more epithelial injury but showed no difference in histologic injury score and physiologic oxygen exchange compared to controls. We further demonstrated regional differences in tissue cytokine production, wet/dry ratio and gross assessment. However, there were no regional differences in histologic injury score. The heterogeneity of ALI in our model requires further research to determine etiology and physiologic importance, but should be accounted for when describing ALI findings in experimental models of CPB/DHCA.

Content Type Expertise: Translational Research

Sabbath Conflict: No Conflict

APA SIG Comm Region: None of These

First Author Trainee?: Yes, Fellow in Training

AWARDS:

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Table 2

TABLE:

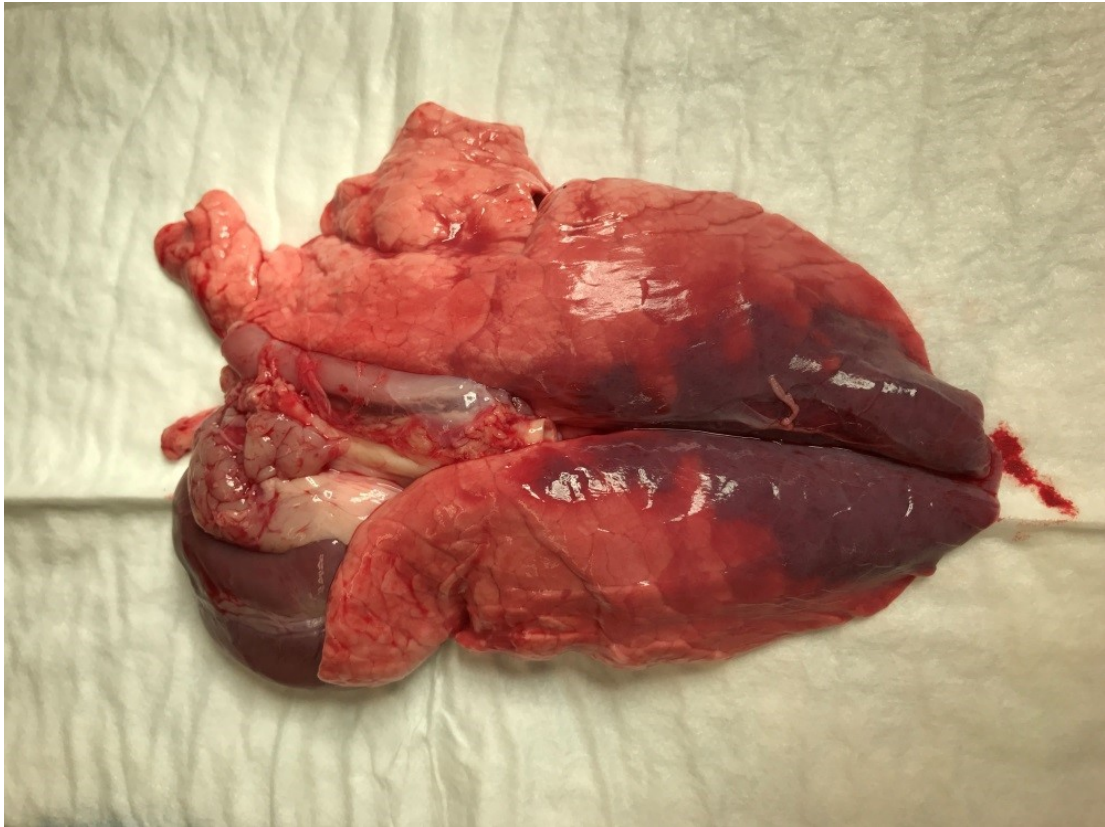
Note: The PDF table below is only an approximation of the HTML content and may not match formatting exactly.

Table 1

| Variable | Anesthesia Controls | Cardiopulmonary Bypass | P Value |
|---|-----------------------|------------------------|---------|
| Change in Compliance Vt/[(peak pressure- PEEP) X weight] Mean (SD) | -0.04 (0.05) | -0.13 (0.02) | 0.05 |
| Change in PaO ₂ /FiO ₂ Median (Range) | -50 (-6 to -141) | -37.5 (104 to -128) | 0.66 |
| Change in sRAGE ng/ml Median (range) | -0.02 (-0.21 to 0.13) | 0.26 (0.12 to 0.43) | 0.006 |
| IL-6 Upper Lobe Relative mRNA levels Median (range) | 0.8 (0.5 to 1.4) | 1.3 (0.29 to 14.7) | 0.2 |
| IL-6 Lower Lobe Relative mRNA levels Median (range) | 1.3 (0.3-39.6) | 3.1 (0.9 to 533) | 0.05 |
| TNFα Upper Lobe Relative mRNA levels Median (range) | 0.69 (0.42-2.1) | 1.1 (0.3-2.8) | 0.44 |
| TNFα Lower Lobe Relative mRNA levels Median (range) | 0.66 (0.41-1.8) | 0.96 (0.17-2.1) | 0.38 |
| IL-8 Upper Lobe Relative mRNA levels Median (range) | 1.53 (0.45-2.8) | 4.23 (0.39-15.1) | 0.04 |
| IL-8 Lower Lobe Relative mRNA levels Median (range) | 0.72 (0.26-1.5) | 2.01 (0.56-6.14) | 0.009 |

Table 2

| Variable | Upper Lobe | Lower Lobe | P Value |
|--|-------------------|-----------------|---------|
| IL-6 Relative mRNA Levels Median (range) | 1.26 (0.29-14.66) | 2.65 (0.33-533) | 0.0018 |
| IL-8 Relative mRNA Levels Mean (SD) | 4.59 (3.55) | 2.16 (1.5) | <0.0001 |
| TNF α Relative mRNA Levels Mean (SD) | 1.12 (0.61) | 0.98 (0.42) | 0.06 |
| ALI Right Lung Mean (SD) | 15.1 (7.9) | 14.6 (3.9) | 0.37 |
| Wet/Dry Ratio Mean (SD) | 3.64 (0.52) | 4.48 (0.69) | <0.0001 |



Dorsal view of piglet lungs status post cardiopulmonary bypass.

IMAGE CAPTION: Dorsal view of piglet lungs status post cardiopulmonary bypass.