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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The goal of this research project was to develop *computationally-directed time-controlled adaptive ventilation* (CD-TCAV), which automatically adjusts expiratory duration (T_{low}) to reduce the injurious processes of cyclic recruitment / derecruitment (R/D). We hypothesize that a computational lung model may direct CD-TCAV settings for enhanced and personalized mechanical protection. To test this hypothesis, we simulated ARDS in a computational lung model using a random distribution of inflation-dependent surface tensions, to mimic the R/D associated with ARDS. Acinar recruitment within a subtree of the model decreased with increasing T_{low}, and was much more pronounced at lower inspiratory pressures. There were expiratory durations for which decreasing T_{low} offered no further benefit in terms of acinar recruitment. Estimates of global elastance of the subtree were highly correlated with the percentage of acinar derecruitment. We also modified a ZOLL EMV+® 731 transport ventilator to deliver a variant of CD-TCAV to a mechanical test load, with varying airway pressure levels as well as inspiratory and expiratory durations. We expect that the EMV+® 731 ventilator will be ready to deliver CD-TCAV in pigs with lung injury during the upcoming year. Preliminary results from these studies demonstrate that CD-TCAV will have a high likelihood of yielding a new, viable mode of ventilation for use in both military and civilian populations with ARDS.

15. SUBJECT TERMS
Acute Lung Injury, Time-controlled adaptive ventilation, acute respiratory distress syndrome, airway pressure release ventilation, combat related lung injury, computational model, ventilator-induced lung injury, mechanical ventilation

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1.0 INTRODUCTION

Severe trauma is a major problem in combat related casualties, which can progress into the acute respiratory distress syndrome (ARDS), especially for injured military personnel in austere, combat environments. Current ARDS treatment is supportive in the form of protective mechanical ventilation, typically using the ARDSnet protocol [1] which is designed to minimize ventilator induced lung injury (VILI). However, ARDS mortality has not been further reduced with this strategy [2]. Recent work has shown that regional lung strain is the primary mechanism driving progressive ARDS [3, 4]. We have previously demonstrated that alveoli change volume as a time-dependent, viscoelastic system, such that there is a time lag between the applied force (i.e., tidal volume) and alveolar recruitment. When this force is released (i.e., exhalation), there is a time lag before alveoli will collapse [5-7]. Thus the longer the time at inspiration the more alveoli will be recruited, and the shorter the expiration time the fewer alveoli will collapse. Our group has developed a "Time-Controlled Adaptive Ventilation" (TCAV) method, the set and adjust the airway pressure release ventilation (APRV) mode that we have shown to open and stabilize alveoli, and reduce regional lung strain, based on our knowledge of viscoelastic alveolar volume change [8, 9]. However, the ability to deliver TCAV reliably in the immediate post-trauma period, or during transport from the combat theater, is sorely lacking. **The objective of this project is to design candidate TCAV protocols for use in remote combat locations, as well as during pre-hospital transport, using sophisticated computational models of the injured lung with high anatomic and physiologic fidelity** [10, 11]. These protocols will be implemented on an existing military-grade transport ventilator, and validated in clinically relevant porcine models of ARDS. We hypothesize is that our computationally-directed TCAV method (CD-TCAV) will improve lung protective ventilation based on short-term physiologic indices of lung mechanics and gas exchange. More importantly our approach may have the ability to *personalize* ventilator settings based on the unique pathophysiology of individual patients, in contrast to the current standard of "one-size-fits-all" protocols. We anticipate that *these results will be directly translatable and testable in clinical trials*, thus guiding both therapy and technology development for future research in ARDS treatments and other forms of combat-related lung injury.

2.0 KEYWORDS

Acute lung injury
Acute respiratory distress syndrome
Airway pressure release ventilation
Combat-related lung injury
Computational model
Mechanical ventilation
Porcine
Time-controlled adaptive ventilation
Ventilator-induced lung injury

3.0 ACCOMPLISHMENTS

3.1 Goals of Project

Accomplishments in Year 1: Our **goal** for this project is to design computationally directed candidate TCAV protocols (CD-TCAV) for use in remote combat locations, as well as during prehospital transport, using sophisticated computational models of the injured lung with high anatomic and physiologic fidelity [10, 11]. These protocols will be implemented on an existing military-grade transport ventilator (ZOLL EMV+® 731 Series), and validated in clinically relevant porcine models of ARDS [12]. Once fully realized, our computational modeling approach may direct TCAV settings for improved lung protection. More importantly, our approach will have the potential to *personalize* ventilator settings based on the unique pathophysiology of individual patients, in contrast to the current standard of "one-size-fits-all" protocols. In addition, ventilator settings will be *adaptive* as the patient's lung gets better or worse. The Specific Aims our project are: 1) to design candidate TCAV protocols for the injured lung, using structurally explicit computational models of the porcine respiratory system; and 2) to implement computationally-directed TCAV (CD-TCAV) on a military-grade transport ventilator; and 3) to demonstrate that the CD-TCAV protocol will minimize VILI as compared to standard of care and protective (ARDSnet) protocols.

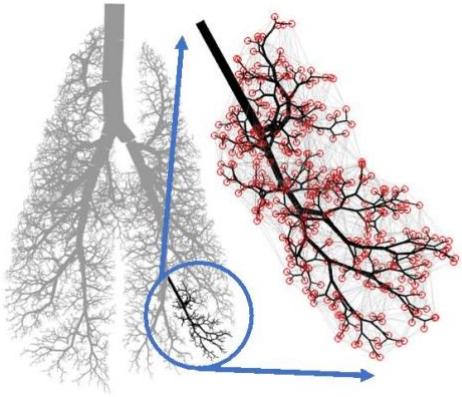

Figure 1: Left: Complete airway tree structure of the computational model used for the simulations of Specific Aim 1, generated from an X-ray CT scan of a porcine lung. Right: A small subset of airways illustrating parenchymal interconnectivity (gray) between neighboring acini (red).

3.2 Goal Accomplishments

During the first year of this award, we have made considerable progress with regard to our research plan, both in the development of a computational model of an injured porcine lung with high anatomic and physiologic fidelity, as well as in the implementation of airway pressure release ventilation (APRV) on the ZOLL 731 ventilator. This progress report details our accomplishments during the first year of our award, for each of the Specific Aims detailed below.

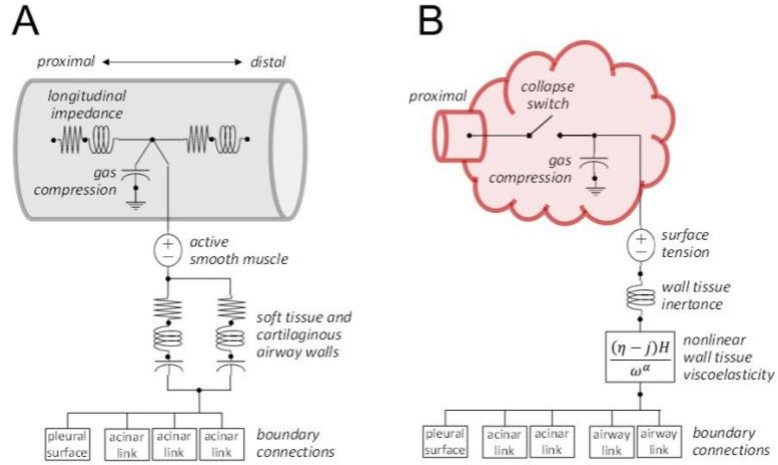

Figure 2: (A) Model of an individual airway segment. The model incorporates longitudinal resistive and inertial elements to account for pressure losses associated with gas flow, as well as flow losses within the segment due to gas compression and viscoelastic wall distention. (B) Model of an individual viscoelastic acinus, which is capable of time-dependent recruitment and derecruitment, as well as parenchymal strain-stiffening.

3.2.1 Specific Aim 1: Design candidate TCAV protocols for the injured lung, using structurally explicit computational models of the porcine respiratory system

With regard to the computational modeling and protocol development of Specific Aim 1, we have enhanced our existing computational model of a three-dimensional airway network to simulate the effects of airway pressure release ventilation (APRV), with varying pressure levels and durations of inspiration and exhalation. The model consisted of a subtree of peripheral airway segments and viscoelastic acini extracted from a three-dimensional porcine airway tree (**Figure 1**). We modeled each airway segment and acinus using nonlinear resistive, inertial, and elastic elements (**Figure 2**), with mechanisms for time-dependent recruitment and derecruitment of individual acini (**Figure 3**), as well as strain-stiffening. Parenchymal interdependence was simulated using viscoelastic elements connecting adjacent acini, with resistive and elastic components weighted according to spatial distance (**Figure 4**). Using this model, we simulated lung injury using a random distribution of inflation-dependent surface tensions, to mimic varying degrees of surfactant dysfunction typical of ARDS. Due to the high computational time required for these simulations (see below), we studied the dynamics of parenchymal recruitment within a subtree of the model, consisting of 755 airway segments and 378 acini. APRV was simulated for a duration of 60 cycles (i.e., breaths) within this subtree of the model, assuming inspiratory pressures (P_{high}) of 28 and 40 cm H_2O at the trachea, and exhalation durations (T_{low}) ranging from 0.2 to 1.5 seconds. The APRV cycles were obtained after a simulated recruitment maneuver to 45 cm H_2O for 30 seconds, and all data analyses were performed on the last five cycles of simulation. Example pressure profiles estimated at the trachea and at the root of the subtree are shown in **Figure 5**. As expected, overall acinar recruitment within the subtree was consistently high for P_{high} = 40 cm H_2O compared to P_{high} = 28 cm H_2O, regardless of T_{low} (**Figure 6A**). Moreover, lung recruitment decreased with increasing T_{low}, an effect that was much more pronounced for P_{high} = 28 cm H_2O. Interestingly for P_{high} = 28 cm H_2O, there were expiratory durations for which decreasing T_{low} offered no further benefit in terms of acinar recruitment (i.e., less than 0.4 seconds), and above which no further derecruitment occurred (i.e., about 1.1 seconds). Between T_{low} values of 0.4 and 1.1 seconds, there was a transition phase in recruitment. For P_{high} = 40 cm H_2O, this transition

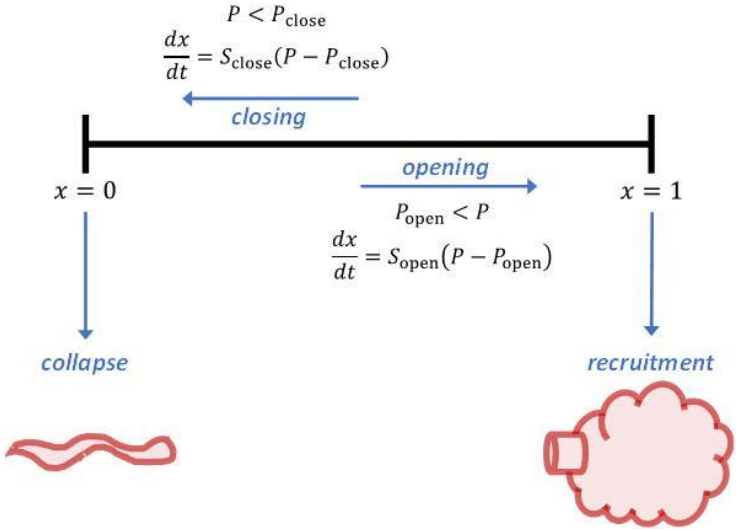

Figure 3: Time-dependent recruitment and derecruitment of an acinus, based a virtual trajectory variable $0 \leq x \leq 1$. During ventilation, x varies according to the distending pressure P relative to critical opening and closing pressures. Modified from Massa [12].

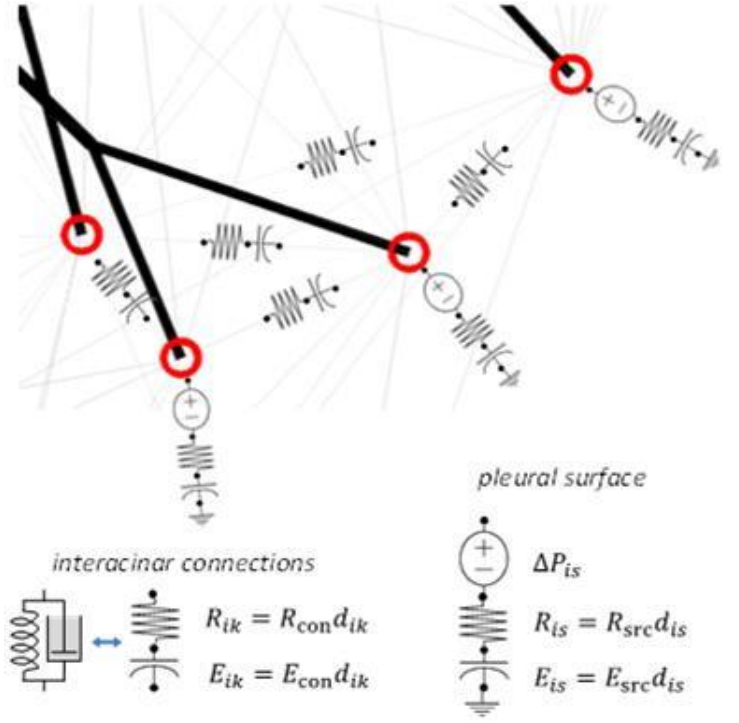

Figure 4: Example of viscoelastic inter-acinar connections and pleural surface boundaries, using resistive (R) and elastic (E) elements with weight based on acinar distance (d).

phase was less apparent, with continual derecruitment occurring as T_{low} increased. Corresponding estimates of global elastance (*E*) for the subtree, obtained from multiple linear regression of the flow and pressure waveforms at the root [13], are shown in **Figure 6B**. In general, these estimates of *E* paralleled the percentage of acinar recruitment, is indicated by their high degree of correlation (**Figure 7**).

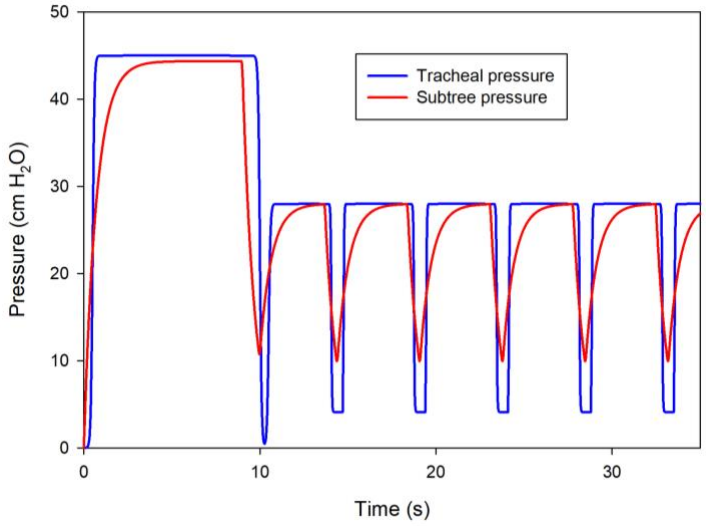

Figure 5: Example estimates of tracheal pressure and subtree root pressure for the computational porcine lung model. Simulations include a 10-second recruitment maneuver at 45 cm H_2O, followed by APRV with P_{high} = 28 cm H_2O and T_{low} = 1.0 seconds. Note that P_{low} at the trachea does not reach 0 cm H_2O, although P_{low} will be set on the ventilator to 0 cm H_2O at the location of the simulated ventilator.

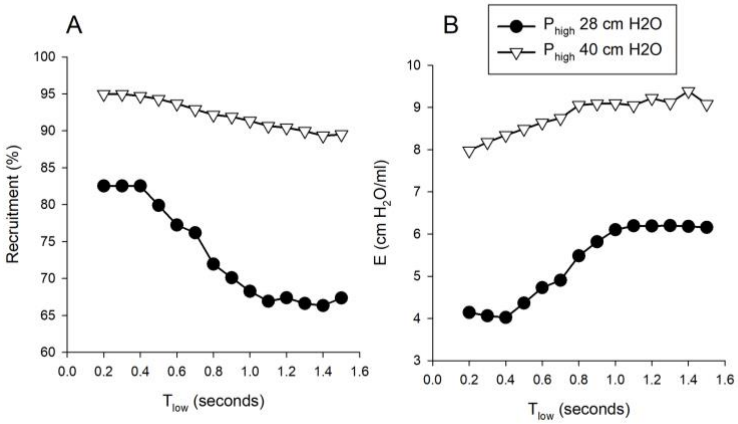

Figure 6: (A) Percentage of acinar recruitment and (B) global elastance (*E*) for the subtree vs. T_{low} for the computational porcine lung model during APRV. Simulations were obtained for P_{high} of 28 (black circles) and 40 (white inverted triangles) cm H_2O.

In addition to the above simulations, we conducted a re-analysis of regional expiratory time constants (**Figure 8**), based on dynamic X-ray CT images in pigs obtained using Dr. Kaczka's previous CDMRP award (W81XWH-16-1-0434). We discovered that mechanical time constants obtained from exhaled gas volumes at the airway opening underestimate regional aeration time constants obtained from dynamic 4D CT image registration (**Figure 8**). With lung injury, poorly aerated regions of the lung experience larger intratidal changes in aeration over shorter time scales compared to normally aerated regions. These dynamic 4D CT imaging data provide supporting evidence for the susceptibility of poorly aerated regions to VILI, and that short exhalation times during mechanical ventilation result in functional benefit for injured lungs. Such *in vivo* information on expiratory de-aeration time constants, especially with high anatomic resolution, have further enhanced our understanding of the process of derecruitment during exhalation. Moreover, these data provide a unique visual representation of how adjustments in T_{low} during APRV and TCAV may reduce the cyclic recruitment and derecruitment. Results from these CT images allow us to further improve the anatomic and physiologic fidelity of our computational model simulations. We also expect the results from these porcine lung images will be crucial for further development of candidate computationally-directed ventilator protocols.

In summary, these computational modeling simulations demonstrate a high potential for developing candidate ventilator protocols for the ZOLL 731 ventilator based on APRV and TCAV modalities. Ultimately, these unique modeling techniques developed from Specific Aim 1 will allow for the selection of subject-specific TCAV

waveforms, especially when eventually combined with the experimental evidence of Specific Aim 3, to justify physiologically-relevant emphasis on parenchymal strain vs. derecruitment to reduce the risk for VILI. More importantly, our model may be further extended to address important physiological and clinical problems regarding ventilator management in many other respiratory pathologies of pediatric and adult patients.

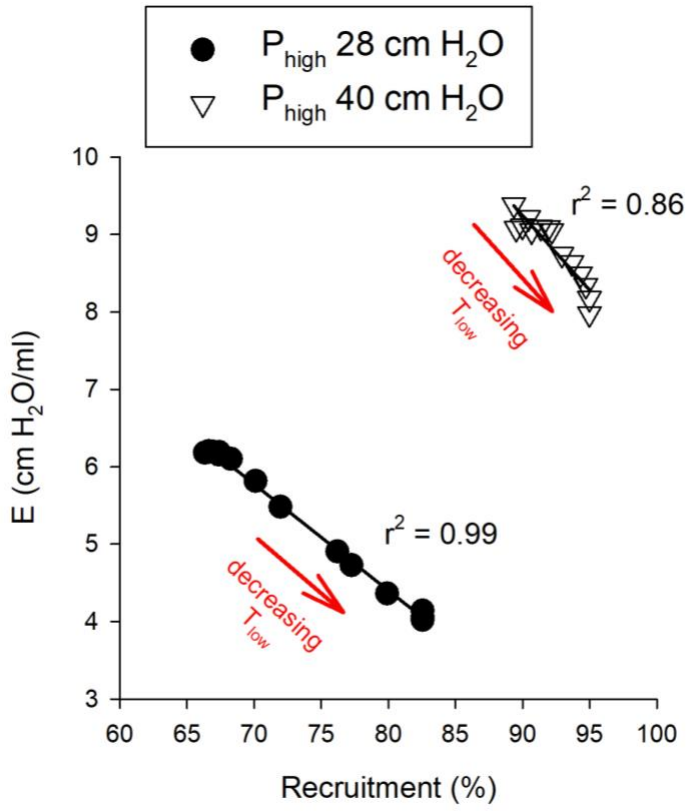

Figure 7: Correlations between global elastance (*E*) and percent acinar recruitment for the computational porcine lung model using the APRV mode, set and adjusted with the TCAV method. Simulations were obtained for P_{high} of 28 (black circles) and 40 (white inverted triangles) cm H_2O.

3.2.2 Specific Aim 2: Implement CD-TCAV on a military grade transport ventilator

In close collaboration with our corporate partners at ZOLL Medical Corporation, we have successfully implemented the airway pressure release ventilation (APRV) mode on the ZOLL 731 ventilator. This prototype device, with new firmware, is currently undergoing testing at the University of Iowa. Dr. Kaczka and his post-doctoral fellow Dr. Andrea Fonseca da Cruz have been using the modified ventilator to deliver APRV waveforms to a mechanical test load (**Figure 9**), with varying inspiratory and expiratory airway pressure levels (i.e., P_{high} and P_{low}, respectively), as well as the durations of inspiration and expiration (i.e., T_{high} and T_{low}, respectively). **Figure 10** shows example airway pressure, flow, and volume waveforms delivered by the ZOLL 731 ventilator to a mechanical test lung (Michigan Instruments, Grand Rapids, MI) with a resistance of 20 cm H_2O/L/s and compliance of 50 mL cm H_2O^{-1}. In addition to control by its firmware, the ventilator can also be controlled by a Matlab program (The Mathworks, Natick, MA), for programmable adjustments to T_{low} (i.e., the expiratory duration). We expect that this Matlab control will be interfaced with our computational modeling results, for the realization of a truly computationally-directed time controlled adaptive ventilation (CD-TCAV) mode. Additional *in vitro* testing of the ventilator, with varying resistive and compliant loads, is ongoing. We expect that the ZOLL 731 ventilator will be ready for our anticipated animal experiments at SUNY Upstate by March of 2022.

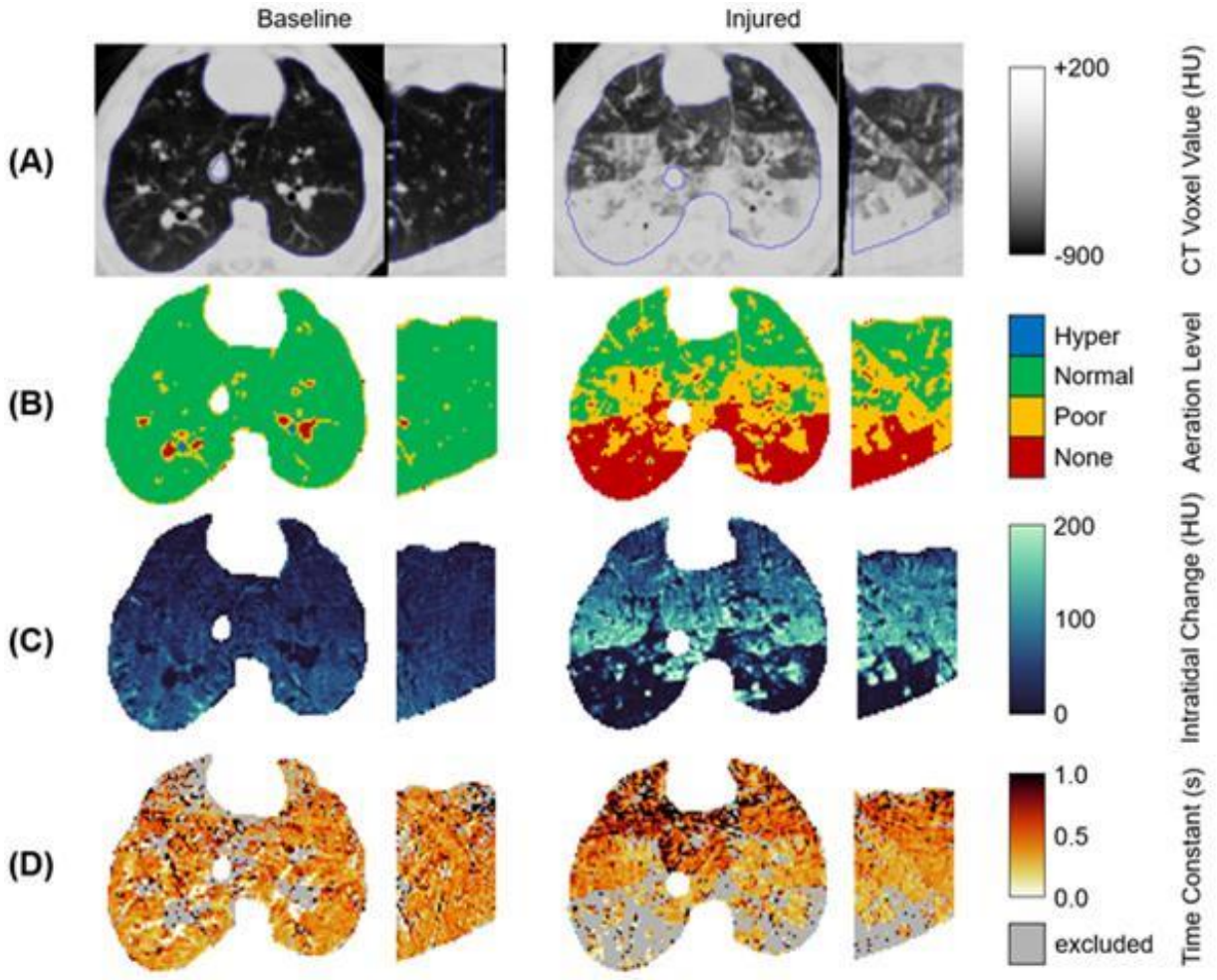

Figure 8: Example images from a porcine subject before and after lung injury. From top to bottom, rows show (A) the end-expiratory CT image with lung segmentation (blue line); (B) end-expiratory aeration level; (C) the intratidal density change given by the difference between end-inspiratory and end-expiratory densities; and (D) the regional density time constants. From Herrmann et al. (6)

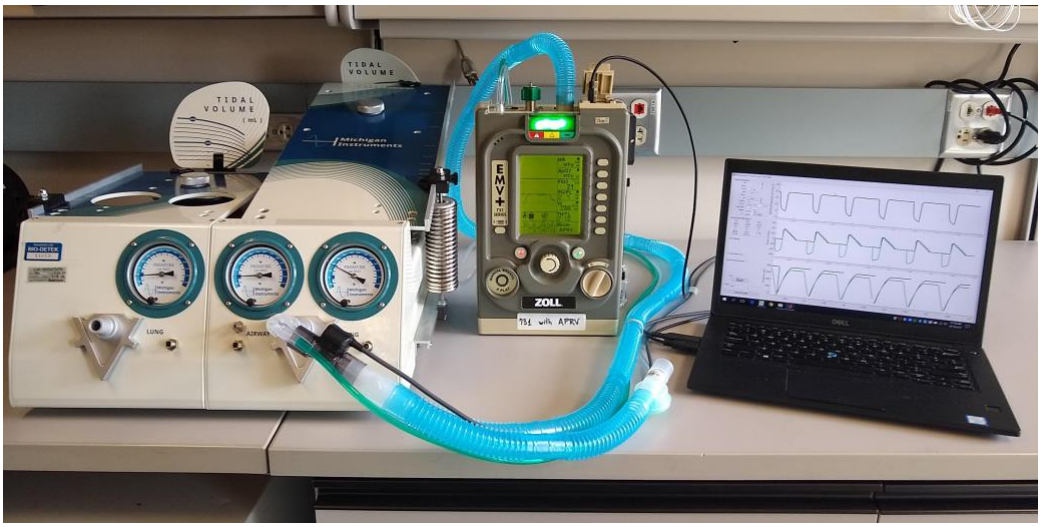

Figure 9: Photograph of the ZOLL EMV+® 731 Series ventilator with protype firmware, delivering an airway pressure release ventilation (APRV) waveform to a Michigan Instruments test lung.

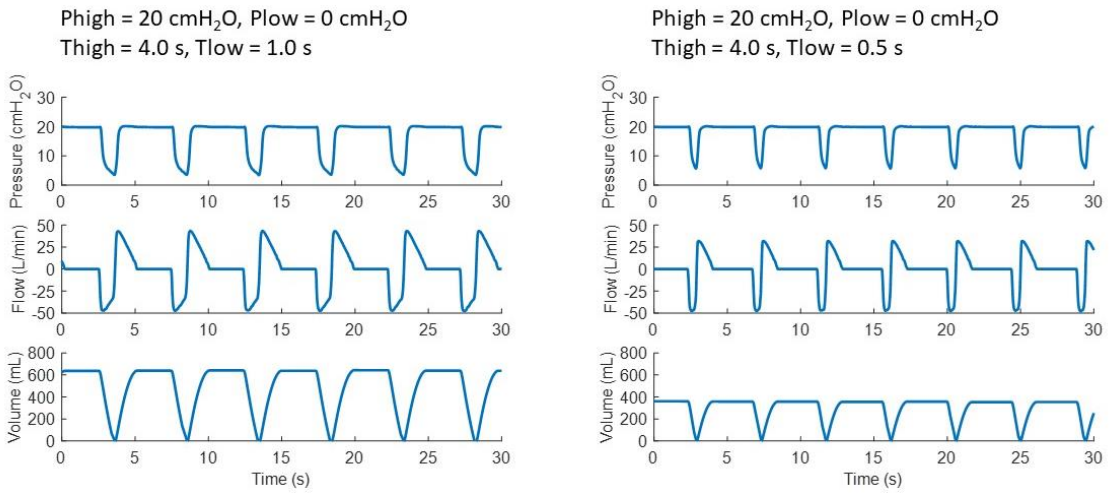

Figure 10: Example airway pressure, flow, and volume waveforms delivered to the Michigan Instruments test lung with resistance of 20 cm H_2O/L/s and compliance of 50 mL cm H_2O^{-1}.

3.2.3 Specific Aim 3: Demonstrate that the computationally-directed TCAV (CD-TCAV) protocol will minimize VILI as compared to standard of care and protective (ARDSnet) protocols

Accomplishments in Year 2:

In Year-2, Quarter-3 we began live animal experiments using the ZOLL ventilator that had been fitted to deliver the airway pressure release ventilation (APRV) mode with the settings and adjustment of the mode computationally directed (CD) using the time controlled adaptive ventilation (TCAV) method (CD-TCAV). To date we have completed nine (9) animals in each group (ARDSnet; Standard of Care; and CD-TVAV). **Figure 11** shows the Pressure/Time wave forms of a conventional mechanical breath (ARDSnet and Standard of Care) and of CD=TCAV.

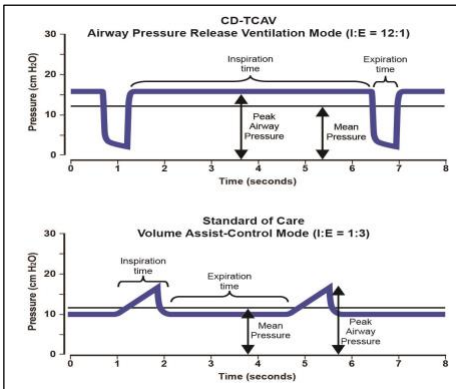

Figure 11. Pressure/Time wave forms for the Standard of Care and TCAV protocols. The major difference between the two protocols is that the TCAV protocol has a very Long Inspiration Time and very Short Expiratory Time, which will open and stabilize the lung based on our knowledge of the viscoelastic nature of alveolar recruitment-derecruitment. This base TCAV protocol will be computationally directed (CD-TCAV) to improve the efficiency of this strategy to open and stabilize the lung. The main difference between the Standard of Care Control and the ARDSnet groups will be in the Standard of Care group the Vt will be 10cc/kg and PEEP will remain at 5 cmH_2O throughout the study, regardless of oxygen saturation. The ARDSnet protocol would have the same I:E ratio as the Standard of Care protocol with a Vt of 6cc/kg with PEEP and FiO_2 adjusted in response to changes in oxygenation according to the ARMA protocol.[1] I:E = Inspiratory:Expiratory ratio.

Aim 3 Experimental Design & Methods: Yorkshire pigs were anesthetized and connected to a mechanical ventilator (ZOLL 731 EMV+ portable ventilator with CD-TCAV capabilities) and surgically prepared for hemodynamic monitoring. A PiCCO catheter placed in the right femoral artery was used for continuous measurement of cardiac parameters and pulmonary edema. A Swan Ganz catheter measured pulmonary artery (Ppa) and pulmonary artery wedge (Ppw) pressure measurements and mixed venous blood sampling for pulmonary shunt calculation. An esophageal balloon tipped catheter was placed into the distal esophagus to measure esophageal pressure (Pes), which was used to calculate transpulmonary pressure (Ptp). Dynamic changes in lung volume were made using Electrical Impedance Tomography (EIT). The following mediators will be measured to assess the following categories at the end of all experiments: 1) tumor necrosis factor (TNF), interleukin-1&6 (IL-1&6), apoptosis (capase-3), fibrogenesis (type III procollagen – PCIII), damage to alveolar Type I cells (RAGE), and of damage to the endothelium (VCAM-1). The right carotid artery was cannulated and used for arterial blood pressure monitoring and blood gas (ABG) measurements

Heterogeneous lung injury was induced by bronchoscopic Tween administration as previously described. Tween is a detergent that rapidly deactivates pulmonary surfactant causing an instantaneous acute lung injury. This lung injury is typical of ARDS since loss of surfactant function is a hallmark. Heterogenous lung injury with Tween will cause diffuse regional strain and inflammation. In addition, collapsed alveoli will become 'sticky' and open alveoli will become unstable such that it will take more time at the same pressure to open alveoli and less time at the same pressure to prevent them from collapsing. A 1% Tween-20 detergent solution (0.75 mL kg^{-1}) was instilled to target the dependent, diaphragmatic lung regions as previously described. In this novel heterogeneous injury model, we control the exact location of normal lung tissue (N_T) and acutely injured lung tissue (ALI_T) (i.e. the lung tissue that receives Tween). Using this model, we will be able to measure the impact of the test mechanical breath protocols on both N_T and ALI_T within the same animal.

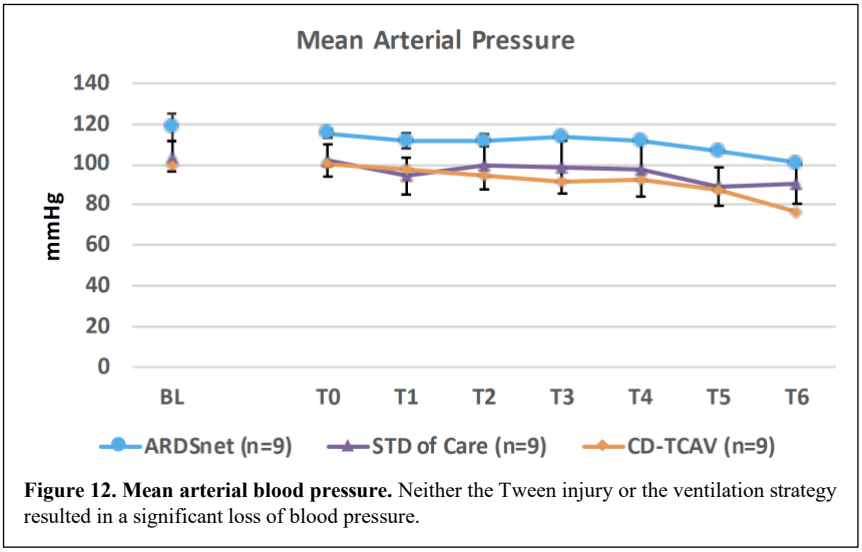

Figure 12. Mean arterial blood pressure. Neither the Tween injury or the ventilation strategy resulted in a significant loss of blood pressure.

After 6 hours of ventilation, the protocol was terminated, the animals euthanized, and necropsy performed. Bronchoalveolar lavage fluid (BALF) and lung tissue was collected and frozen, lung tissue was fixed in formalin for histopathology and edema was assessed by a lung tissue wet/dry weight ratio in both N_T and ALI_T. The BALF was spun and the supernatant snap frozen. The same measurements made on the plasma will be measured on the BALF at the end of all live animal experimentation.

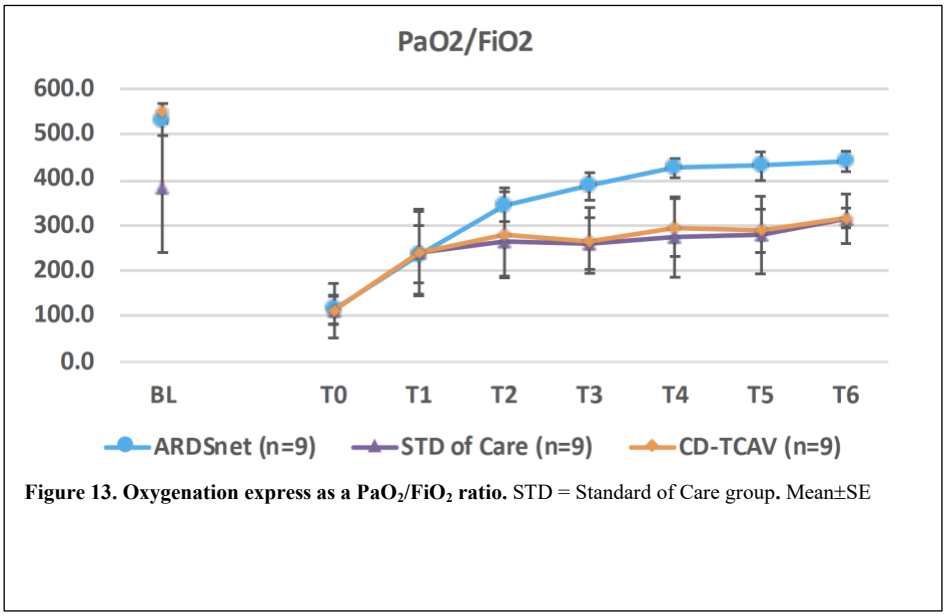

Figure 13. Oxygenation express as a PaO_2/FiO_2 ratio. STD = Standard of Care group. Mean±SE

Aim 3 Experimental Protocol: Following surgical instrumentation, baseline measurements, and Tween injury, animals were randomized into three groups: 1) **Standard of Care protocol (Group 1 - n=9)** Volume controlled ventilation with Vt 10 cc kg^{-1}, PEEP 5 cm H_2O, and FiO_2 adjusted to keep arterial saturation above 90%, 2) **ARDSnet protocol (Group 2 - n=9)** with Vt 6 cc kg^{-1}, and a sliding scale of PEEP and FiO_2 directed by changes in oxygenation and 3) **CD-TCAV protocol (Group 3 - n=9)** using the settings and adjustments suggested in Aim 1 with a Long Inspiration and very Short Expiratory phase. Basic Pressure/Time curves for both the Standard of Care and ARDSnet protocol using the Volume Assist-Control Mode and TCAV using the Airway Pressure Release Ventilation mode are shown in **Figure 11**. Adjustments in the TCAV protocol include the high pressure (P_{High}) set at 22 cmH_2O, the time at P_{High} (T_{High}) set at 4 seconds, the low pressure (P_{Low}) set at 0cmH_2O. The time at low pressure (T_{Low}), is set by the computational model described in Aim 1 and 2 above.

Results: Thus far we have conducted 14 pigs in total (3 Standard of Care, 6 ARDSnet and 5 CD-TCAV). All experiments went well and there no difference in mean arterial pressure between the groups (**Figure 12**). There was a trend for improved oxygenation (PaO_2/FiO_2 ratio) in the ARDSnet group although all 3-groups were above a PaO_2/FiO_2 of 300 so above the Mild ARDS cutoff value (**Figure 13**). It must be noted that this injury model only deactivates pulmonary surfactant so the lung will recover over time with reasonably protective mechanical ventilation. We felt this was a good model testing a transport ventilator for the warfighter with severe injuries but without full blown ARDS. CD-TCAV kept pulmonary edema (Wet/Dry weight ratio) low in both the normal tissue (black bar) and Tween injured tissues (grey Bar) whereas the ARDSnet group edema was elevated in the normal tissue and in the Standard of Care group edema was elevated in the Tween injured tissues (**Figure 14**). The gross appearance of the lungs of all three animals inflated to 25 cmH_2O were similar with only moderate areas of collapsed tissue and atelectasis (**Figue 15**). Using electrical image tomography (EIT) the regional ventilation delay (RVD) was measured, which provides a good estimate of tidal recruitment (**Figure 16**). Muders et al. showed that RVD inhomogeneity describes regional lung mechanic heterogeneity, which is caused primarily by different alveolar opening time constants.[14] Thus RVD is a surrogate for tidal recruitment. ARDSnet and Standard of Care ventilation trended to increase RVD from T3-T6 suggesting a temporal delay in the opening of some regions of the lung (**Figure 16**). In our heterogeneous lung injury model this would likely be the result of higher airway pressures needed to recruit the tissue with dysfunctional surfactant. The very brief Release Phase in the CD-TCAV group would not give sufficient time for these tissues to collapse during expiration and thus reducing tidal recruitment as measured by RVD.[15] This is evidenced by a lower RVD in the CD-TCAV group at T3-T6 (**Figure 16**). These data suggests that ARDSnet and Standard of Care ventilation may predispose the lung to a large volume of alveolar opening and collapse that could cause in severe atelectrauma-induced tissue damage if ventilated for a sufficiently long time. Lung histology and inflammatory mediators will be analyzed following the completion of live animal experiments.

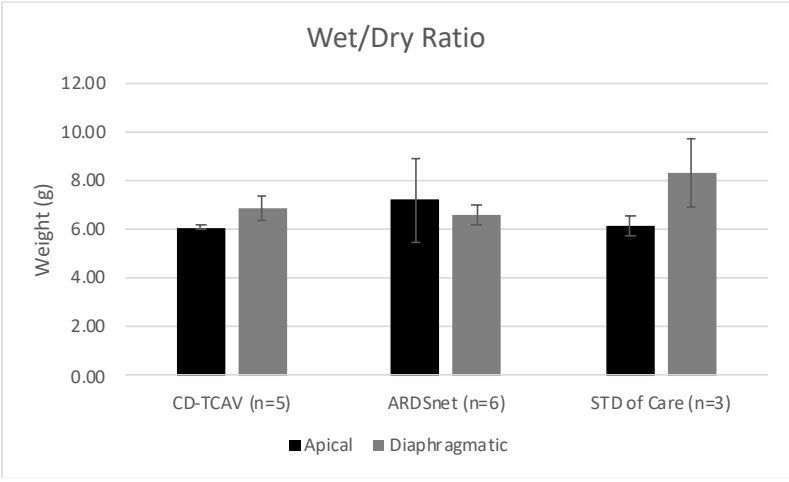

Figure 14. Pulmonary edema expresses as a lung tissue Wet/Dry weight ratio. Black Bars are Normal tissue and Grey Bars are Tween injured tissue. STD = Standard of Care group. Mean±SE

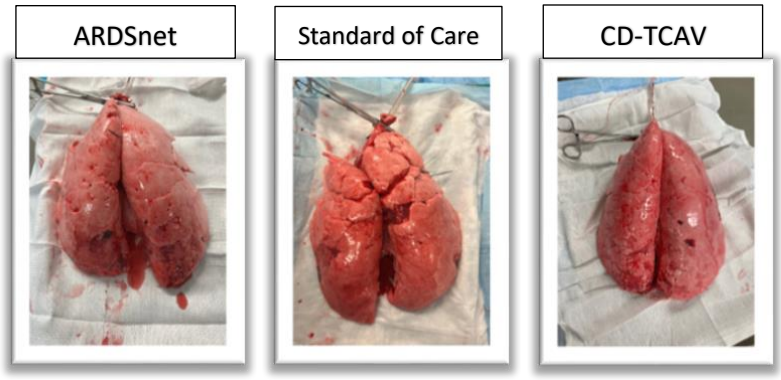

Figure 15. Representative gross lung photos from the three groups.

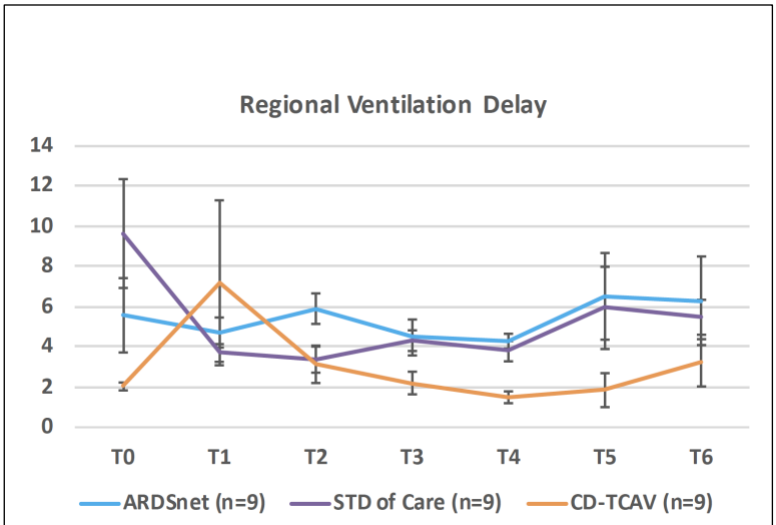

Figure 16. Electrical image tomograph (EIT) measurement of Regional Ventilation Delay (RVD). STD = Standard of Care group. Mean±SE

Summary: Problems with the computer directed calculation of T_{Low} was identified and corrected in the first year with further modification as described in our quarterly reports during the second year. Modifications to the computational model are detailed in Specific Aims 1 and 2 above. There were no problems conducting the live animal experiments. Using the modification of the computationally direct T_{Low} we have begin the fully randomized study in the near future. Molecular mediators and histologic analysis of lung tissue will be conducted following the end of the live animal experiments. We anticipate no major problems in the live animal experiments.

3.3 Opportunities for Training and Professional Development Andrea Fonseca da Cruz, PhD, is a post-doctoral fellow in the Department of Anesthesia at the University of Iowa, and has been working under the direct supervision of Dr. Kaczka on all computational modeling and ventilator-prototyping aspects of this project. Dr. Cruz has assisted with the development of our computational model, and has managed the model simulations and predictions. As a part of her research focus, she is also intimately involved with programming the ZOLL EMV+® 731 Series transport ventilator for the delivery of APRV / TCAV waveforms, with automated adjustments in P_{high} and T_{low}. With the support of this award, Dr. Cruz is the primary author of a manuscript detailing a technique to estimate tracheal pressure in intubated pigs, which will have tremendous utility for estimation of respiratory mechanics during our CD-TCAV animal protocol. Dr. Cruz dedicated 50% paid effort to this project in Year 1 and 25% in Year 2. During Year 1, Jacob Herrmann, PhD, was a post-doctoral fellow in the Roy J. Carver Department of Biomedical Engineering at the University of Iowa and has also been working under the supervision of Dr. Kaczka on the enhancement of the existing porcine computational model. He has also managed the analyses for the dynamic CT images in pigs, to determine the distribution of regional expiratory time constants during acute lung injury, to improve the predictions of derecruitment of the computational model. Dr. Herrmann was the primary author of a paper detailing this unique analysis [16]. Dr. Herrmann has started a new position as Assistant Professor in the Roy J. Carver Department of Biomedical Engineering is currently supported by that department and does not draw any paid effort from this award.

Harry Ramcharran, MD, is an Upstate Medical University surgical resident that is doing a Research Fellowship in the Nieman laboratory. Dr Ramcharran has just completed a NIH funded study (R01HL142702) investigating the role of lung overdistension versus dynamic strain as mechanisms of VILI using the same lung injury model that will be used in this study.[12] Dr. Ramcharran will be responsible for conducting the experiments using the APRV modified ZOLL EMV+® 731 ventilator under the direction of Drs. Kaczka and Nieman. Dr. Ramcharran recently published a paper using the identical lung injury model being used in this study (Ramcharran H. *J Appl Physiology*. 2022 doi: 10.1152/japplphysiol.00312.2022)

3.4 How were the results disseminated to the communities of interest?

Thus far, we have published one article in *Frontiers in Physiology* describing an image processing technique for estimating regional de-aeration during exhalation [16]. The audience for this journal consists mostly of organ-level physiologists and biomedical engineers. In addition, we have prepared another manuscript that describes a novel technique to estimate tracheal pressure in intubated pigs.. We had planned to present a poster at the 2021 Military Health System Research Symposium (MHSRS), although this meeting was cancelled due to the ongoing COVID-19 pandemic. We have also published a paper reviewing the functional pathophysiology of SARS-CoV-2 induced acute lung injury including the clinical implications. We recommend that the TCAV method should be used for COVID-19 acute lung injury and included a working protocol in the supplemental material. [Habashi NM. J Appl Physiol 2021;130:877]. In 2022 we were able to present three posters about this research project, two at American Thoracic Society (ATS) in San Francisco and one at the Military Health System Research Symposium (MHSRS) in Orlando.

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

We will continue to refine our computational model of the three-dimensional porcine lung, to simulate the effects of APRV and TCAV, with varying pressure levels and durations of inspiration and exhalation. We will continue to explore the various viscoelastic mechanisms by which the acini in the model are interconnected (**Figure 4**).

We are also exploring various arrangements of mechanical couplings among the acini in the model, including Voigt, Maxwell, Kelvin, and Jeffreys bodies. These interconnections have allowed us to simulate various patterns of acinar recruitment and derecruitment for healthy and injured lung (**Figure 17**). Finally, we will continue to refine our firmware development for the EMV+® 731 Series ventilator, and continue our *in vitro* testing of CD-TCAV in a mechanical test lung. We will finish the live animal experiment, analyze the inflammatory mediators, and histopathology and construct abstract and papers from these data.

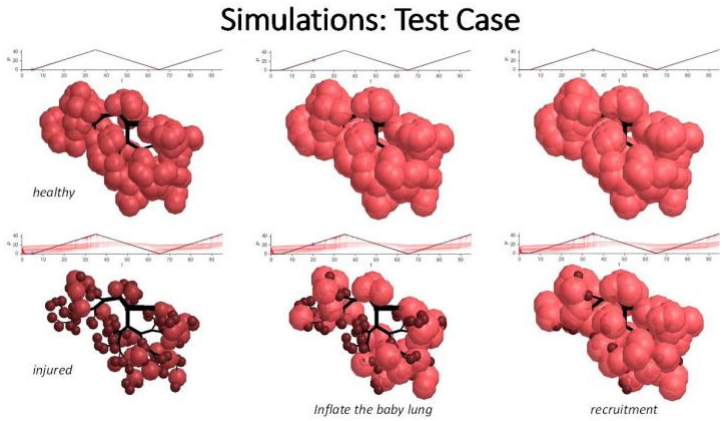

Figure 17: Recruitment and derecruitment patterns in a subtree of the porcine computational subtree under healthy and injured conditions, during quasi-static inflation from 0 to 45 cm H_2O.

4.0 IMPACT

4.1 What was the impact on the development of the principal discipline of the project?

The use of CD-TCAV is a promising and innovative approach to lung protective ventilation in ARDS and other forms of acute lung injury and respiratory failure. However, its use in patients still require considerable work to understand its application in pathophysiologies relevant to combat-related lung injury, especially in austere environments and far-forward locations. Heterogeneous overdistention and derecruitment of the injured lung has important implications for optimal ventilation protocols and treatment strategies. The novel computational modeling and *in vitro* experimental techniques detailed in this progress report address fundamental questions regarding the mechanism by which TCAV and APRV may reduce the risk for VILI compared to traditional lung protective ventilation protocols. *The immediate, short-term impact of this project is the development of a high-fidelity computational model that has tremendous potential to provide a mechanistic understanding of the factors associated with VILI.* Our work also provides a requisite, scientific basis for the eventual use of CD-TCAV in military environments, since our results will be easily translatable and testable in human clinical trials. CD-TCAV will have *long-term impact on guiding therapeutic and technological developments for future research in ARDS and other forms of combat-related lung injury*, with potential to significantly impact the morbidity and mortality.

4.2 What was the impact on other disciplines?

While our *in silico* work is still in its early stages, the computational techniques that we have developed for gas transport in the airway tree of the porcine lung may have applications for material transport in other biological branching networks, such as vascular, hepatobiliary, or botanical trees. There is a great deal of cross-talk between the lung and other organ systems. Protecting the acutely injured lung and minimizing progressive lung tissue damage will also reduce distant organ dysfunction [17]. The early use of CD-TCAV may benefit civilian trauma patients that need immediate mechanical ventilation. Also, maintaining CD-TCAV as the patient is being transported from the ICU to the operating room may improve outcomes. The ultimate goal is to have the most lung protective ventilation strategy. CD-TCAV is a novel form of protective mechanical ventilation that may be superior to the current protective ventilation strategies. We have found that the TCAV method rapidly stabilizes the acutely injured lung immediately protecting the lung from atelectrauma. Then, over an extended period of time (hours or days depending on the severity of lung injury) using a 'ratchet-like' action gradually reopens the collapsed tissue preventing both atelectrauma and volutrauma. We postulate that the addition of computationally directing TCAV (CD-TCAV) will make this method even more lung protective. If our hypothesis is correct CD-TCAV will be a paradigm shift in the way that patients with or at high risk of developing ARDS are ventilated and will significantly reduce ARDS-related incidence, morbidity, and mortality. We plan on pursuing our goals

investigating the mechanism of action that make TCAV so lung protective in *Peer Reviewed Medical Research Program*, Investigator-Initiated Research Award and Expansion Award next year.

4.3 What was the impact on technology transfer?

We have an active collaboration with our corporate partner, ZOLL Medical Corporation, who manufactures and sells the ZOLL EMV+® 731 Series portable ventilator that is used by the U.S. military, as well as other militaries and civilian prehospital and hospital-based users. For this project we are actively modifying the ventilator firmware, and take advantage of new hardware features that are currently being developed for DoD and commercial use, to provide the APRV modality using very specific settings from our CD-TCAV protocol. If successful, we will have a functioning portable ventilator that has been tested for safety and efficacy in a clinically applicable porcine model of ARDS. Given the potential benefit to both military and civilian patients, the data from this study, along with additional computational modeling and design history documentation, can then be used in an application to FDA for an Investigational Device Exemption (IDE). An IDE would allow us to study the performance of the system (ventilator with CD-TCAV software module) in a clinical trial of patients with trauma and acute illness. Data from the clinical trial could then be used to apply for device clearance and sale. ZOLL has always acted based on a commitment to developing solutions that enable our users to provide the best care possible. In parallel, ZOLL has ensured that these advancements meet the requirements necessary to support ill or injured warfighters and their care providers no matter the operating environment. ZOLL has more devices cleared and deployed in support of *en route* care and this work expands our collaboration and the prospect of new technology that evolves the standard of care.

4.4 What was the impact on society beyond science and technology?

ARDS and other forms of acute lung injury, whether in military or civilian settings, have major impact on public health in the United States, with an estimated 190,000 cases and 74,000 deaths annually. Significant reductions in mortality have been realized by the use of lung protective mechanical ventilation protocols, in which PEEP is used to recruit the lung and prevent repetitive end-expiratory opening and closing of airspaces, and smaller tidal volumes prevent end-inspiratory over-distension. Nonetheless, ARDS may still be exacerbated with inappropriate mechanical ventilation, resulting in a secondary VILI. CD-TCAV represents *a promising and innovative approach to lung protective ventilation*, although its use in patients will require considerably more work to understand its application in pathophysiologies relevant to ARDS and combat-related lung injury. Recent studies have shown that the combined ICU and post-hospital 2- year cost for an ARDS patient is $128,860. Also, Cely et al [18] demonstrated that the incidence of ARDS in a VA Medical Center is much higher than currently reported since many of these patients are not mechanically ventilated or in the ICU. Survivors of ARDS often have long-term cognitive and pulmonary disabilities that require additional medical resources and reduce their social productivity, further increasing healthcare costs. In the case of the combat patient, these chronic ailments would prevent them from returning to active duty. Our group has shown that the basic TCAV protocol preserves surfactant, reduces lung inflammation, and prevents proteinaceous edema from entering the alveoli despite massive fluid resuscitation [19-21]. Blocking this pathogenesis derails the subsequent disease progression and prevents the development of ARDS. *Personalizing* the basic TCAV protocol using computational model (CD-TCAV) will greatly improve the protective effect, further reducing the mortality associated with ARDS. In addition, the ability to apply the TCAV protocol very early, during transport from the scene of the accident, and then continuation of the protocol into the Emergency Department, the Operating Room, and finally the Intensive Care Unit (ICU), will offer the patient the best chance of never developing ARDS. Our TCAV protocol can also be used on patients with established ARDS, may be highly effective at opening and stabilizing the lung, and may minimize the risk for VILI and ARDS associated mortality. Accordingly, *our project seeks to provide a solid, scientific basis for the rational use of this CD-TCAV in critically ill patients*, by demonstrating that CD-TCAV reduces the potential for VILI in both computational and animal models of combat-related lung injury. However, TCAV may *have more far-reaching implications for critical care medicine*. For example, this modality may not be limited to a treatment solely for ARDS, but may be used in the management of other mechanically heterogeneous forms of acute respiratory failure requiring supportive mechanical ventilation, such as asthma, COPD, or pneumonia.

5.0 CHANGES / PROBLEMS

5.1 Changes in approach and reasons for change

We are actively exploring some alterations in our initial approach for developing a CD-TCAV protocol. The computational time for the model simulations of lung recruitment and overdistention remains a significant issue for our computationally-directed ventilator protocol. As stated in our previous progress reports from Quarters 1, 2, and 3, the structural complexity of our high-fidelity three-dimensional model requires several hours to simulate a few minutes worth of ventilation data on our current high-performance computing cluster at the University of Iowa. Indeed, the computational time for our simulations grows exponentially with the size of our airway tree. As detailed above, we continue to investigate other methodologies to perform within-breath adjustments, including simpler computational models that capture gross mechanical behavior of parenchymal recruitment and overdistention, albeit with substantial reductions in the degrees of freedom for the independent parameters. For example, estimates of global respiratory system elastance or the nonlinearity of elastance, may provide a very robust reflection of the overall degree of derecruitment or overdistention within the lung (**Figure 7**), and can be obtained with substantial reductions in computational overhead [13]. In addition, we are exploring more computationally efficient models of the porcine lung, for which the time-intensive dynamic processes of recruitment and derecruitment in the presence of mechanical tethering is limited to a "transitional" (or unstable) zone of the lung (**Figure 18**). The existence of such a transition zone is very consistent with our 4D CT imaging studies in pigs [16]. The live animal experiments are going well and we expect no changes or problems. No changes or problems are anticipated in the live animal experiments.

5.2 Actual or anticipated problems or delays and actions or plans to resolve them

The basic TCAV protocol has already been shown effective in reducing lung injury and mortality in both high-fidelity translational animal models of ARDS and in a statistical analysis on patients in the SICU [19-22]. It is also the primary ventilation strategy at the *R. Adam Cowley Shock/Trauma Center* of the University of Maryland. In the proposed application we seek to improve the basic TCAV protocol using computationally model. However, our model is based on the extensive database of Dr. Kaczka's whole-lung high resolution CT images, allowing these models to incorporate three-dimensional airway and vascular segments, as well as the heterogeneous parenchymal mechanics associated with ARDS. Our computational model is unique in its ability to replicate regional lung strain, with high anatomic and physiologic fidelity [10, 11]. We remain confident that our computational model predictions will identify the optimal combinations of airway pressures, flows, volumes, and application times necessary to open and stabilize the lung. In the unlikely event that computational modeling does not improve the efficacy of the basic TCAV protocol, we will identify the problem by analyzing the data from Specific Aim 3. After the possible errors are identified and used to further

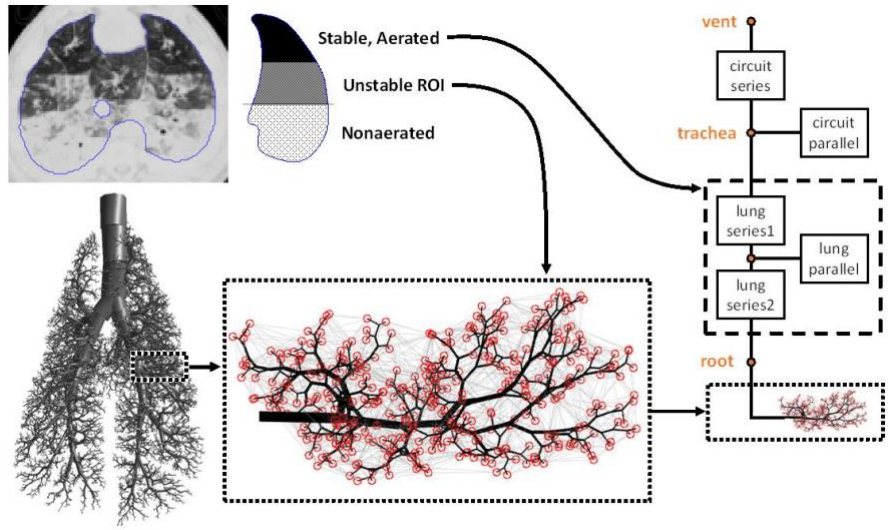

Figure 18: A more "computationally efficient" model for the porcine lung, which captures the gross mechanical features of a breathing circuit, endotracheal tube, and stable aerated regions, while still capturing the finer anatomic resolution of the "transitional" (or unstable) regions that undergo cyclic recruitment and derecruitment.

refine the computational model, another round of *in silico* simulations will be conducted, using this information and animal experiments with an alternative CD-TCAV protocol. We anticipate no problems in modifying the ZOLL EMV+® 731 Series ventilator to deliver the CD-TCAV protocol. The live animal experiments are on time and we plan on finishing the study, analyze the inflammatory mediators and histopathology and construct abstracts and paper used these data in 2023.

5.3 Changes that had a significant impact on expenditures

Nothing to report.

5.4 Significant changes in the use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

6.0 PRODUCTS

6.1 Journal Publications

Herrmann, J., Gerard, S.E., Shao, W., et al. (2021). "Effects of Lung Injury on Regional Aeration and Expiratory Time Constants: Insights From Four-Dimensional Computed Tomography Image Registration." *Front Physiol* **12**: 707119.

Beretta E, Romano F, Sancini G, Grotberg JB, Nieman GF, Miserocchi G. Pulmonary interstitial matrix and lung fluid balance from normal to the acutely injured lung. *Frontiers Physiol* 2021;112. doi: 10.3389/fphys.2021.781874

Habashi NM, Camporota L, Gatto LA, Nieman GF. "Functional pathophysiology of SARS-CoV-2-induced lung injury and clinical implications." *J Appl Physiol* 2021;130:877-891.

Beretta E, Romano F, Sancini G, Grotberg JB, Nieman GF, Miserocchi G. Pulmonary interstitial matrix and lung fluid balance from normal to the acutely injured lung. *Frontiers Physiol* 2021;112. doi: 10.3389/fphys.2021.781874

Nieman G, Kollisch-Singule M, Ramcharran H, Satalin J, Blair S, Gatto LA, Andrews P, Ghosh A, Kaczka DW, Gaver D, Bates J, Habashi N. Unshrinking the Baby Lung to Calm the VILI Vortex. *Crit Care*. 2022;26:242. doi.org/10.1186/s13054-022-04105-x

Ramcharran H, Bates JHT, Satalin J, Blair S, Andrews PL, Gaver, DP, Gatto LA, Wang G, Ghosh, AJ, Bobedee B, Vossler J, Habashi N, Daphtary N, Kollisch-Singule M, Nieman GF. The relative roles of time and pressure in ventilator-induced lung injury. *J Appl Physiol* 2022 DOI: 10.1152/japplphysiol.00312.2022

Herrmann J, Kollisch-Singule M, Satalin J, Nieman GF, Kaczka DW. Assessment of heterogeneity in lung structure and function during mechanical ventilation: A review of methodologies. *ASME J Medical Diagnostics*. 2022;5:040801

Cruz, A.F., Herrmann, J., Carvalho, C. R. R., Kaczka, D.W. A Comparison of Endotracheal Tube Compensation Techniques for the Measurement of Respiratory Mechanical Impedance. *J Clin Monit Comput* 2022 36(5):1461-1477. doi: 10.1007/s10877-021-00788-9.

6.2 Books or other non-periodical, one-time publications

Nothing to report

6.3 Other Publications, Conference Papers, and Presentations

Abstracts presented at the American Thoracic Society conference in May 2022:

Cruz, AF, Varghese F, Herrmann J, Harvey BP, Beck G, Lampe JW, Rodriquez D, Branson RD, Kaczka DW. Hemodynamic Effects of Positive End-Expiratory Pressure in Simulated Hemorrhagic Shock: Predictions Based on Computational Modeling.

Cruz AF, Herrmann J, Ramcharran H, Kollisch-Singule M, Tawhai M, Bates JHT, Nieman GF, Kaczka DW. Impact of Airway Pressure Release Ventilation and Acinar Interdependence on Lung Recruitment: A Computational Modeling Study.

Herrmann J, Gerard SE, Cruz AF, Akor EA, Reinhardt JM, Christensen GE, Hoffman EA, Kaczka DW. Nonlinear Intratidal Aeration During Multi-Frequency Ventilation Quantified Using 5DCT Imaging.

Abstract presented at the Military Health System Research Symposium (MHSRS) in Sep 2022

Cruz AF, Herrmann J, Ramcharran J, Kollisch-Singule M, Tawhai MH, Bates JHT, Nieman GF, Kaczka, DW. Sustained vs. Intratidal Recruitment in the Injured Lung During Airway Pressure Release Ventilation: A Computational Modeling Perspective

Upcoming Conferences:

6.4 Website or other Internet site

6.5 Technologies or techniques

Nothing to report

6.6 Inventions, patent applications and/or licenses

Nothing to report

6.7 Other Products

Nothing to Report

7.0 PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

7.1 What individuals have worked on the project?

Name:	David W. Kaczka, M.D., Ph.D.
Project Role:	Associate Professor, University of Iowa
Researcher Identifier (ORCID ID):	0000-0003-4378-5242
Nearest person month worked:	2.4 in Yr1, 1.8 in Yr 2
Contribution to Project:	Dr. Kaczka is directing the subcontract to the University of Iowa and directly supervising the work for Drs. Cruz and Herrmann in the development of the computational model in

	Specific Aim 1, as well as the programming the ZOLL EMV+® 731 Series transport ventilator for the delivery of APRV / TCAV waveforms in Specific Aim 2
Other Funding Support:	NIH, ZOLL Medical, Department of Defense

Name:	Andrea Fonseca da Cruz
Project Role:	Postdoctoral Fellow
Researcher Identifier (ORCID ID):	0000-0001-6969-1223
Nearest person month worked:	6 in Yr 1, 3 in Yr 2
Contribution to Project:	Dr Cruz is developing the computational model in Specific Aim 1, and is also intimately involved with programming the ZOLL EMV+® 731 Series transport ventilator for the delivery of APRV / TCAV waveforms
Other Funding Support:	ZOLL Medical Corporation, Department of Defense
Name:	Jacob Herrmann, Ph.D.
Project Role:	Postdoctoral Fellow
Researcher Identifier (ORCID ID):	0000-0001-5046-5592
Nearest person month worked:	1
Contribution to Project:	Dr Herrmann is developing the computational model in Specific Aim 1
Other Funding Support:	NIH
Name:	Gary Nieman
Project Role:	Principal Investigator
Researcher Identifier (ORCID ID):	0000-0002-4541-4472
Nearest person month worked:	1
Contribution to Project:	Analyzed the data generated by Drs. Kaczka, Cruz, and Herrmann for the development of the computational model in Specific Aim 1, as well as that generated by the ZOLL EMV+® 731 Series transport ventilator modified to deliver APRV / TCAV waveforms in Specific Aim 2
Other Funding Support:	NIH

7.2 Has there been a change in the active other support of the PI or key personnel since the last reporting period?

Dr Kaczka was awarded a FY20 PRMRP-Expansion Award: W81XWH-20-PRMRP-EA effective 01-Aug-2021 to 31-Jul-2024 for "Preclinical Evaluation of Multi-Frequency Oscillatory Ventilation in a Large Animal Model of Acute Respiratory Failure". This project has salary support for Dr. Kaczka and Dr. Cruz. This new project is fully independent of the current project.

7.3 What other organizations were involved as partners?

ZOLL Medical Corporation, Chelmsford, MA

8.0 SPECIAL REPORTING REQUIREMENTS

Nothing to report

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10.0 APPENDICES

N/A	6. **Herrmann J, Gerard SE, Shao W, Xin Y, Cereda M, Reinhardt JM, Christensen GE, Hoffman EA, and Kaczka DW**. Effects of Lung Injury on Regional Aeration and Expiratory Time Constants: Insights From Four-Dimensional Computed Tomography Image Registration. *Front Physiol* 12: 707119, 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8355819/
N/A	**Habashi NM, Camporota L, Gatto LA**. Effects of Lung Injury on Regional Aeration and Expiratory Time Constants: Insights From Four-Dimensional Computed Tomography Image Registration. *Front Physiol* 12: 707119, 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7984238/