AFRL-RH-WP-TR-2022-0083

AUTOMATED ASSESSMENT OF PULMONARY MECHANICS & FLUID RESPONSIVENESS

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SEPTEMBER 2022
Final Report

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AFRL-RH-WP-TR-2022-0083 HAS BEEN REVIEWED AND IS APPROVED FOR PUBLICATION IN ACCORDANCE WITH ASSIGNED DISTRIBUTION STATEMENT.

LEHMAN.JAMES.B.1074588715 Digitally signed by LEHMAN.JAMES.B.1074588715 Date: 2022.12.29 15:31:11 -05'00'

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE (*DD-MM-YY*)	2. REPORT TYPE	3. DATES COVERED (*From - To*)
26-09-22	Final Report	08/22/2019 - 8/21/2022

4. TITLE AND SUBTITLE
Automated Assessment of Pulmonary Mechanics & Fluid Responsiveness

5a. CONTRACT NUMBER
FA86550-15-2-6605

5b. GRANT NUMBER
FA8650-19-2-6G32

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER
15-002

5e. TASK NUMBER

5f. WORK UNIT NUMBER
Legacy

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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Cincinnati, OH 45221-0222

8. PERFORMING ORGANIZATION REPORT NUMBER
17-091

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

**Air Force Materiel Command
Air Force Research Laboratory
711th Human Performance Wing
Airman Systems Directorate
Airman Biosciences Division
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10. SPONSORING/MONITORING AGENCY ACRONYM(S)
711 HPW/RHBA

11. SPONSORING/MONITORING AGENCY REPORT NUMBER(S)
AFRL-RH-WP-TR-2022-0083

12. DISTRIBUTION/AVAILABILITY STATEMENT Distribution A. Approved for Public Release.

13. SUPPLEMENTARY NOTES: AFRL-2022-5553, cleared on 20 December 2022

14. ABSTRACT: Acute lung injury (ALI) and hypovolemia due to hemorrhage, burns and other injuries are not uncommon in critical care. Hypovolemia is primarily treated with intravenous fluid. ALI is treated by increasing oxygen, positive end expiratory pressure (PEEP) and positive pressure ventilation. Unfortunately, PEEP reduces blood flow to the heart, which can result in excessive fluid needs and edema. Optimization of therapeutic endpoints for hypovolemia in ALI has been the subject of several investigations. We hypothesized that a novel ventilation maneuver, called a pressure volume loop (PVloop – also termed PVcurve) would optimize PEEP and identify how much fluid is needed. Anesthetized swine underwent hemorrhage and resuscitation with and without ALI. Catheters were placed for blood sampling, pressure monitoring, mean arterial pressure (MAP), cardiac output (CO) and fluid infusions. Specific variables collected included central venous pressure (CVP), pulmonary artery occlusive pressure (PAOP), heart rate (HR), pulse pressure CO and MAP every 10 min. ALI was induced to achieve a partial pressure of arterial oxygen (PaO2) to fractional inspired oxygen (FiO2) or PaO2/FiO2 <150. Hypovolemia was induced by a rapid hemorrhage followed by fluid resuscitation to achieve PAOP of 5, 10, 15 and 20 mmHg. Pilot studies showed that a PV loop could best be achieved using inspiratory pressure 20 cm H_2O above PEEP. Data demonstrated that PVloop could be used to assess iv fluid needs after ALI + single hemorrhage. We then compared swine undergoing a rapid hemorrhage followed by slower hemorrhage and fluid resuscitation as a model of *en route* care. Two fluid resuscitation strategies were compared. The test group used a PV loop and pulse pressure to determine fluid needs. The control group used pulse pressure variability to administer fluid. No differences in resuscitation endpoints or oxygenation were observed. While the PVloop could indicate fluid responsiveness in varying levels of resuscitation, the use of this technique was not superior to pulse pressure variability in this model. We also observed, in this model, that the PVloop challenge in early stages of resuscitation resulted in larger decreases in blood pressure.

15. SUBJECT TERMS: Closed Loop Control, Acute Lung Injury, hypovolemia, Autonomy

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT:	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON (Monitor)
a. REPORT	b. ABSTRACT	c. THIS PAGE	SAR	26	James Lehman
Unclassified	Unclassified	Unclassified			19b. TELEPHONE NUMBER (*Include Area Code*) N/A

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PREFACE:

The research effort involved a collaboration between the University of Cincinnati (UC) and the University of Texas Medical Branch (UTMB). The study involved large pre-clinical model research that was accomplished at the University of Texas Medical Branch. The research protocols were reviewed and approved by the University of Texas Medical Branch, Institutional Animal Care and Use Committee as well as the Air Force Medical Readiness Agency, Research Oversight and Compliance Department.

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1.0. SUMMARY

Introduction
Acute lung injury (ALI) and hypovolemia are common following traumatic injury. These injuries are prevalent on the battlefield. ALI is often more insidious and can evolve over several days. Concomitant injuries occur with frequency example (e.g.), chest-trauma or other trauma as well as severe burn injury with inhalation injury and result in fluid loss and lung injury. Trauma, in general, induces a systemic inflammatory response syndrome that can precipitate and worsens ALI. The primary treatment for vascular volume losses is intravenous fluid therapy. ALI is treated by increasing the concentration of functional inspired oxygen (FiO_2) and the positive end expiratory pressure (PEEP). Optimization of therapeutic endpoints for hypovolemia in patients with lung injury has been the subject of several reviews, investigations, and clinical trials Some newer ventilators optimize PEEP using a tool called pressure volume (PV) loop. Since the PV loop maneuver reduces venous return, we hypothesized that a novel ventilation challenge would optimize PEEP and identify how much fluid is needed.

Methods: We studied Swine 20-40 kilograms (kg) that underwent hemorrhage and resuscitation with and without ALI (control and ALI, respectively) for acute anesthetized studies. Catheters are placed in the femoral arteries and veins for blood sampling, pressure monitoring and fluid infusions, respectively. A pulmonary artery catheter will be placed to measure pulmonary blood pressures and cardiac output (CO). ALI was induced over 60-90 minutes (min) by using saline lavage and mechanical ventilation to achieve a partial pressure of oxygen (PaO2)/FiO2 less than (<) 150. Hypovolemia was induced by initial hemorrhage 10 milliliter per kilogram (mL/kg) over 30 min. Thereafter, either directed fluid resuscitation occurred or a slow continuous hemorrhage (0.5 mL/kg per min) was begun plus fluid resuscitation. Specific variables collected included central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), CO, mean arterial pressure (MAP), heart rate (HR), pulse pressure and pulse pressure variability (PPV). A PV loop was done to examine its effect on fluid and oxygenation needs.

Results: Our pilot studies showed that a PV loop could best be achieved using a modest inspiratory pressure of 20 centimeters of water (cm H_2O) above PEEP. Data from fluid responsiveness demonstrated that ALI and hemorrhage could be simultaneously achieved using a PV loop to assess volume needs. Finally, we compared two groups in which a PV curve algorithm was used to optimize fluid needs and oxygenation vs standard of care fluid resuscitation using PPV. We found no differences in resuscitation endpoints or oxygenation.

Conclusion: While we found that the PV loop can be utilized in both lung injury and sham states to indicate fluid responsiveness, the use of this technique in moderate to severe hemorrhage was not reliable. The aggressiveness of the PV curve maneuver often resulted in loss of the pulse oximetry signal, defeating any analysis of the changes. Less provocative techniques are being studied.

2.0. BACKGROUND:

ALI and hypovolemia are common in trauma and critical care. Co-injuries occur in chest-trauma or other trauma as well as severe burn injury with inhalation injury and result in fluid loss and lung injury. ALI isoften more insidious evolving over several hours and days. Trauma induces a systemic inflammatory response syndromethat can precipitate and worsen ALI. The primary treatment for vascular volume losses is intravenous fluid therapy.

Unfortunately, treating ALI with secondary vascular volume losses can be paradoxical, in which too little fluid resuscitation (hypovolemia) worsens systemic oxygen delivery and excessive volume (hypervolemia) contributes tofurther lung injury. ALI is treated by increasing the percent of FiO2 and PEEP, as well as positive supportive ventilation to achieve and maintain normoxemia. Early recognition of pulmonary dysfunctions and initiation of life saving interventions (LSI's) are critical for survival. Strategies aimed at achieving the right balance between adequate FiO2 and PEEP as well as approaches to limit ventilator induced lung injury have been shown to improve clinical outcomes.

There has been an overall evolution in guiding and optimizing the LSI of fluid therapy. Clinicians have moved away fromusing formula-based fluid resuscitation treatment plans and are choosing patient-specific fluid treatment plans such as goal directed therapy (GDT) endpoints that integrate dynamic variables from heart–lung interactions. The use of endpoints is increasingly being used to identify patients in need of fluid therapy or fluid responsiveness. Indices such as pulse pressure variability (PPV) or stroke volume variability (SVV) provide information about preload or venous return. The difference or variability over a mechanical breath cycle provides the clinician information regarding the likelihood that a fluid bolus will increase stroke volume. Since intrathoracic pressure compresses the vena cava, during hypovolemia,these indices become exaggerated [very high]. The rate and amplitude of increasing inspiratory pressure could be considered a provocative challenge in determining circulating vascular volume entering the heart (preload). The ideal endpoint for fluid resuscitation continues to be explored as these indices do not prevent hypervolemia.

PV curves or loops are used to optimize the amount of PEEP needed to maintain oxygenation. We assert that a PV loop maneuver also provides diagnostic assessment of venous return, since during inflation, increased intrathoracic pressure compresses the vena cava and reduces stroke volume. Modern ventilators on the market automatically generate PV curves based on pressure, flow and time.

Significance

The ideal endpoint for fluid resuscitation continues to be explored. Additionally, there remains to be an effective endpoint to determine when not to give fluid e.g., preventing hypervolemia. This is primarily due to limitations in using these surrogates to assess vascular volume, as previous studies have shown that only 40-70 percent (%) of critically ill patients show significant increases in stroke volume and cardiac output after fluid therapy. Together, this information outlines the importance for indices that can serve as a seamless means to best optimize fluid therapy in sicker patients.

Optimizing lung function

The PV curves or loops can be set to optimize the amount of PEEP needed to maintain oxygenation. Intrathoracic pressure increases during the lung inflation part of the PV curve which compresses the vena cava and reduces stroke volume, but there would be no regular breaths occurring and thus no PPV occurs. The proper metric here is simply the change in PP from the bottom to the top of the PV curve, which is what we use to guide fluid therapy in the test group. Modern ventilators can automatically generate optimal PV curves and displays by inputting a set of parameters. One such ventilator, Hamilton Intellivent (Hamilton Medical, Bonaduz Switzerland), can initiate a PV curve by selecting the option under the "PV tools". Specifically, the user can set the pressure via flow and time both during inspiration and expiration, which provides guidance in optimizing PEEP and oxygenation based on the type of lung injury, e.g., acute respiratory distress syndrome (ARDS), chronic hypercapnia, brain injury. The user can set limits, rate, and the progressing pressure steps. Figure 1 shows a PV curve produced by the Hamilton S1ventilator.

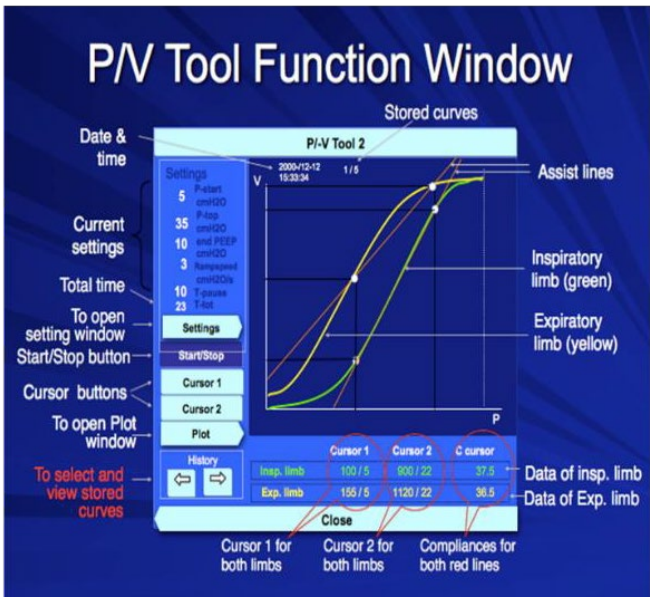

Figure 1. PV curve demonstrating the lower inflection point (beginning of alveolar recruitment) and upper inflection point (beginning of alveolar overdistention)

A PV curve can be created using a slow rise in pressure or volume. For pulmonary mechanical measures, a slow pressure rise helps eliminate changes due to airway resistance. A pressure rise to test cardiopulmonary performance could use a faster pressure rise.

PV curve to optimize PEEP and assess preload

We hypothesized that generating a PV curve not only can be used to determine optimal PEEP, but also used diagnostically to rapidly assess effectiveness circulating vascular volume and therapeutically to guide fluid therapy. The PV curve will provide a critical pathway to treat patients in need of fluid therapy with and without lung injury of when and when not to administer fluid. Further, the programmability would represent a decision support feature for optimizing lung function and preload. A key feature that we will test in this proposal would

allow clinicians to use this "autonomous switch" as a provocative challenge to seamlessly determine fluid responsiveness. The proposed use will initially be a decision support feature and, if positive, will move towards closed-loop autonomous control integration.

Impact

We hope to define a better fluid therapy protocol for ALI. These data will provide validation of the test or treatment-protocol, and may allow us to develop an even more effective decision support table linking a fluid recommendation basedon delta PP. In addition, these data will provide insight into an alternative, non-invasive approach that can be used to determine fluid necessity.

Our hypothesis was that periodic PV curve generation cannot only optimize PEEP, but also be used diagnostically, to rapidly assess circulating vascular volume and therapeutically, to guide fluid therapy.

Our work is summarized by three Aims or objectives.

Aim 1: Pilot testing to determine relationship of PV curves with and without ALI and hemorrhage

Aim 2: Develop decision support fluid tables using PV curves to optimize cardiopulmonary function after injury

Aim 3: Preclinical study that compares fluid and oxygenation optimization using PV curves versus standard of care
(SOC).

Previous Critical Work Specific For This Project

Our groups at UC and UTMB have been exploring autonomous critical care therapies for past 15+ years. Specifically, closed loop control (CLC) and decision support for treating oxygenation deficits using PEEP and FiO2 as well as fluid deficits by using CLC fluid and decision support tools have shown that these interventions improve efficacy and efficiency. Moreover, it appears that activation of the algorithm (that automates treatment) has diagnostic capabilities, e.g., the more active the algorithm, the more likely the patient is sicker. Towards this end, we have integrated software and hardware to develop prototypes for these types of conditions. There is limited work looking at how different systems interact with each other, e.g., how to optimize oxygenation in face of hypovolemia and its treatment.

3.0. METHODS

Overview of hardware, software and connectivity: We tested closed loop control devices for ventilators and fluid delivery systems. In particular, we have been using the Hamilton S1 to compare closed loop control of PEEP and FiO2 to optimize oxygenation. In other Department of Defense (DoD) contracts, we have integrated a decision support system that connects to the Hamilton S1 called smart oxygenation system (SOS). The SOS development was highlighted in the Joint Program Committee JPC6 combat casualty care Congressionally Directed Medical Research Program (CDMRP) –

http://cdmrp.army.mil/dmrdp/research_highlights/16kinsky_highlight. In brief, the communication protocol driver is written in Java and uses an RS232 serial port connection to communicate with the Hamilton S1 data output and Powerlab system for hemodynamic variables.

System architecture: The graphs will be produced in Java using a graph library called JFreeChart. The program adds the data values every 2 seconds to the graphs which are automatically updated and rendered. The architecture of the system sets up a main thread of execution for the user interface and then starts a separate thread of execution for each driver. This multi-threaded design allows for communication to happen asynchronously from the user interface. Therefore, the interface does not hinder the communication and vice versa. To facilitate communication between the threads, the architecture defines a named data "channel" for each signal. As the data is received from the devices it is written to the appropriate data channel. The user interface then graphs the data being read from the data channel providing a robust system for multiple drivers to work independently of each other as well as graphing.

Activation of PV tool function: For pulmonary optimization, the PVcurve was plotted and the optimal PEEP (lower inflection point) displayed (this is already initiated and part of the Hamilton software). As noted, we have similarly demonstrated connectivity using the Panasonic Toughbook prototype with our Powerlab system [multichannel amplifier that incorporates both digital and analog transduced signals]. The Powerlab system displays and stores variables up to 1000 Hertz (Hz). One limitation we recognized during the initial pilot studies was that multi-breath cycles that normally incorporate pulse pressure variability could not be used as the PV loop resulted in a single challenge. Thus, we incorporated change in PP from the intra-arterial signal as a primary tool to investigate 'circulatory volume'. Therefore, during each activation of PV tool function, temporal hemodynamic and cardiopulmonary indices were produced. **Decision support coding and displays were based on threshold values the cardiopulmonary indices for a specific duration [time] (Figure 2).** Each became apparent in all three aims.

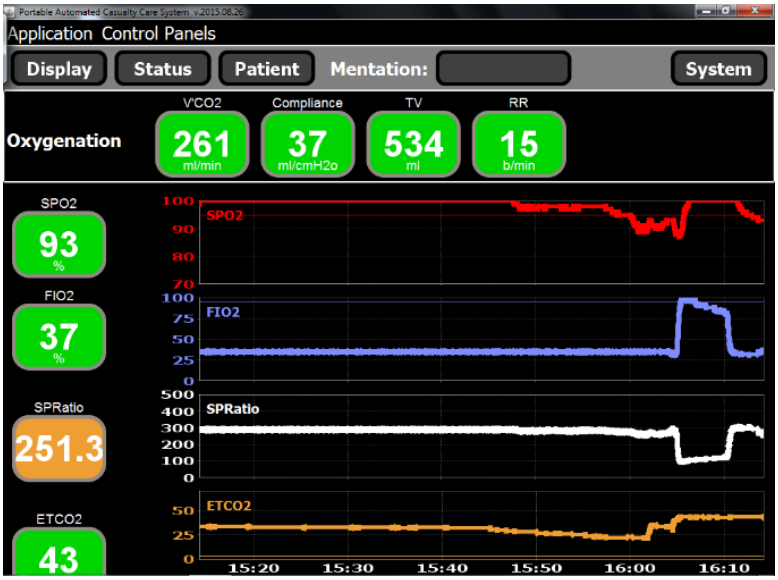

Figure 2. Decision support platform for incorporating cardiopulmonary indices

Experimental Animal preparation and protocol (Figure 3)**:** Swine (20-40 kg) were fasted overnight before the experiment. On the day of the study, animals were medicated with an intramuscular injection of ketamine, telazol, and xylazine. Each pig was then placed in prone position and received oxygen by facemask. A small peripheral intravenous line (PIV) was placed in an ear vein followed by 1.5 mg/kg propofol bolus to induce general anesthesia. The pigs were endotracheally intubated, mechanically ventilated and the anesthesia was maintained with a propofol infusion of 100-300 micrograms per kilograms per minute (mcg/kg/min) in oxygen for the surgical preparation. During the surgical preparation, the initial ventilation settings were: FiO_2 of 0.4, tidal volume of 8-12 mL/kg and a respiratory rate of 12 breaths/minute. Ventilation was adjusted to maintain an end-tidal (ET) carbon dioxide (CO_2) ($ETCO_2$) of 35-40 millimeter of mercury (mmHg) measured by a mainstream capnometer (Capnostream™ 20, Oridion, Massachusetts, USA). Each animal was instrumented bilaterally with catheters in the femoral arteries and veins for blood sampling, pressure monitoring and fluid infusions, respectively. An introducer sheath with a pulmonary artery catheter was placed through the jugular vein into the pulmonary artery monitor (Vigileo™, Edwards Lifesciences, Irvine CA, U.S.A.) to measure CO**.** A catheter was placed via the right carotid artery to produce the hemorrhage.

Pre-injury baseline [Trial (T) minus (-) 30]: Once the animal preparation was complete, an additional 30 min was added on to ensure stabilization before recording baseline. The animal was then placed in adaptive support ventilation (ASV) mode [Hamilton S1], which auto-adjusts ventilation based on work of breathing and $ETCO_2$.

ALI was induced by surfactant washout followed by barotrauma, a technique described by Luecke et al.. Our clinical criterion for ALI was based on a PaO_2/FIO_2 (P/F) ratio < 150.

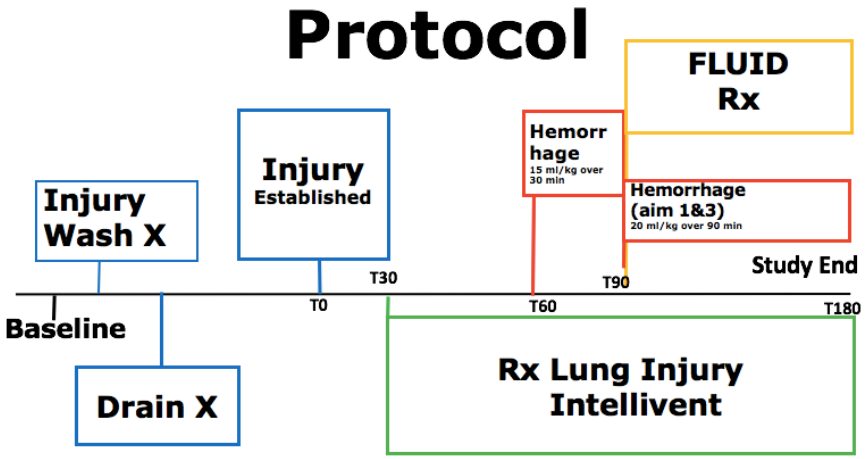

Figure 3. Generalize protocol for animal studies for optimizing cardiopulmonary indices

The ALI is an evolving injury and takes at least 30 min (T30) to perform the lavage and one hour to begin oxygenation deficits (P/F < 150). The onset of lung injury was defined as time point zero (T0) – see figure 3. From stabilization 30 min after injury (T30) to the end of the study at

180 min (T180), swine were treated using ASV Intellivent with automated PEEP/FIO_2.
Hemorrhage: Hemorrhage was performed using a Masterflex controlled pump connected to a catheter in the carotid artery. Blood was removed into a collection bag (containing 2000 units of heparin) and weighed on a scale (each gram =0.95 mL). The initial hemorrhage was followed by slower continuous bleed. The initial bleed rate was 0.5 mL/kg/min for 30 min or 15 mL/kg from 60 to 90 min (T60 –T90). Then, at 90 min, a slow continuous bleed of 0.25 mL/kg/min commenced and continued until end of the study (T180). The additional amount of blood removed over this duration represented 20 mL/kg over 90 min. Fluid resuscitation began at T90 and continued through T180 (study end). This model simulates an ongoing *en route* care casualty in which bleeding occurs from occult sites. At T180, final fluid and other data was recorded. Then, euthanasia was achieved by injecting propofol, ketamine, and 20 mL of a supersaturated solution containing 35% Potassium Chloride (KCl).

The experimental animal preparation were similar to all Aims, specifically with regards to lung injury and hemorrhage. Important differences are noted in each specific aim section.

Measurements: Cardiovascular: Heart rate Electrocardiogram (ECG), HR, MAP, systolic blood pressure (SBP), PPV, PP, flow data [bleed rate and fluid rate], urinary output, total fluid in, CVP, pulmonary artery pressure (PAP) occlusion pressure (PAOP), Cardiac output, saturation of oxygen using plethysmography (SpO_2), $ETCO_2$, and myocardial oxygen consumption (MvO_2) were all collected at 1000 Hz and stored electronically in our Powerlab system. Pulmonary: Ventilatory parameters including, PEEP, FIO_2, SpO_2, production of CO_2per minute (VCO_2), compliance, resistance, peak pressure, plateau pressure, tidal volume, respiratory rate and minute ventilation were automatically collected and stored in a separate computer that is time stamped for the Hamilton S1 ventilator. All data were additionally collected on paper records at designated time points. Fluid balance data including Fluid in, blood removal and urinary output were also recorded. Blood analytes (blood gas and chemistry) were recorded similarly.
Aim 1: Pilot testing to determine relationship of PV curves with and without ALI and hemorrhage

Study groups and protocol. Swine underwent a hemorrhage protocol as described above in concurrence to a lung injury or no lung injury protocol. To accomplish this, a total of six subjects [n=6] were examined, three [n=3] exposed to a lung injury protocol and three [n=3] exposed to the no lung injury protocol. In the no lung injury protocol, there was a 60 min waiting time after instrumentation. Specific interventions in this pilot aim determined the most favorable PV curve using PV tools, with the appreciation that the impact of lung injury may result in more than one PV curve function. All animals were placed in Intellivent ASV mode with automated PEEP/FIO_2. Once in the PV tool menu (figure 4 – top), the user had the ability to set the starting pressure, ramp speed and pause [time] as well as starting and ending PEEP. By adjusting the end pressure and ramp speed, inspiratory and expiratory curves are displayed (figure 4 – bottom). The slope depicted by the inspiratory and expiratory limb provides an opening pressure and closing pressure, respectively. Thus, optimal PEEP can be inferred from the Pressure-Volume line. The PV curve was performed at baseline, after lung injury, after initial hemorrhage, and every 10 min during resuscitation.

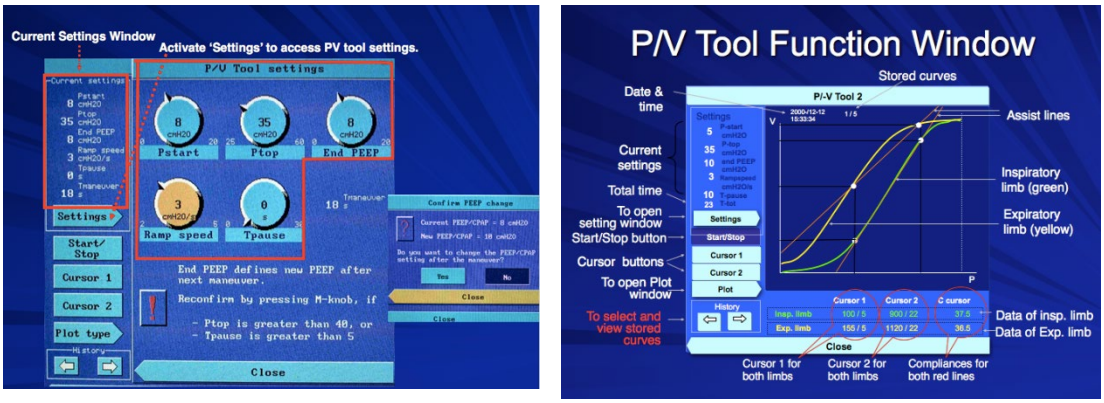

Figure 4. PV tool menu to set targets [top] & [bottom] display showing curves that provide slope characteristics for PEEP optimization

In order to determine the most favorable PV tool function, we tested two different PV tool settings. The differences in settings included ramp speed and pause time. Starting and ending pressures remained the same. For example, PV-1 induced a 5 cm H_2O ramp speed with a 5 second pause. PV-2 induced a 3 cm H_2O ramp speed with a zero second pause. For pulmonary optimization, the optimal PEEP was averaged and recorded and then re-established on the ventilator in ASV mode for each time period. For these pilot data, fluid was automatically titrated using CLC based on a proportional–integral–derivative controller (PID) algorithm using blood pressure. The CLC fluid algorithm was weighted for lower extremes versus higher extremes, i.e., "soft landing", which means that larger volumes of fluid were administered at lower blood pressures and fluid is reduced or eliminated once target BP (Target BP will be set at 90 mmHg to potential induce hypervolemia) was achieved. All fluid initially administered was lactated Ringer's. However, if hemoglobin [Hgb] fell below 5 grams per deciliter (g/dL), whole blood was administered (blood that was removed via hemorrhage).

Specific measurements: After each activation from PV tools, variable measurements were obtained. Key cardiovascular variables relied on changes in stroke volume (Gold-Standard) determined by thermodilution.

Aim 2: Develop new indices to optimize cardiopulmonary function after injury

This aim identified differences in fluid responsiveness of cardiopulmonary indices during hemorrhage and resuscitation when lung injury was present or absent. Further, we hypothesize that the PV tool function will induce a more significant and sustained provocative challenge than current methods. Specifically, we anticipate exaggerated variability of cardiopulmonary indices during hypovolemia and fluid responsiveness (for example pleth variability index (PVI) greater than (>) 25%) and that as euvolemia is restored, these indices will show reduced variability. Additionally, during hypervolemia, we anticipated that indices will demonstrate an absence of variability after fluid administration. Finally, we developed a decision support table (to be used

in Aim 3) that provides a specific fluid recommendation. We used pre vs. post cardiopulmonary indices after PV tool function along with corresponding stroke volume change and volume change using PAOP for resuscitation.

To accomplish this aim, swine [n=12] were instrumented and prepared, as above. We induced either ALI [n=6] or no lung injury [n=6], which were both followed by hemorrhage and fluid resuscitation and over-resuscitation, e.g., hypervolemia. Thus, only a single hemorrhage was induced (figure 3). This allowed us, regardless of lung injury, to explore how the PV tool function can be used to assess cardiopulmonary indices during euvolemia, hypovolemia and hypervolemia. Our initial baseline for both sets of swine included "normal state", defined as euvolemia with normal lung function. We then induced lung injury, as described previously and below, or no lung injury. Then we induced hemorrhage followed by progressive fluid resuscitation to induce hypervolemia. In brief, at end of hemorrhage and after measurements, intravenous fluid (in both groups) was infused to attain a step-wise increase in PAOP at 5 mmHg, 10 mmHg, 15 mmHg and 20 mmHg. Fluid alternated between 5% Albumin or Blood (from the removal) to maintain viscosity. Fluid responsiveness was determined based on stroke volume, e.g., when stroke volume no longer increases greater than 15%, this was identified as a non-responder. We have previously demonstrated, in swine with normal lung function, that fluid non-responsiveness occurs at a PAOP between 10-15 mmHg. The PV tool function was initiated at the following time points: Baseline T0, T30 (after injury or sham lung injury but before ASV activation), T60 (before hemorrhage), T90 (after hemorrhage) and at every resuscitation stage to achieve a PAOP (5,10,15 and 20 mmHg). Immediately after each PV tool function, the optimal PEEP was recorded and incorporated on the ventilator and all measurements and calculated will be recorded as described.

Data analysis: will specifically compare PPV and PVI/ heart lung interaction/index (HLI) versus stroke volume change. One aspect that became apparent was that during the PV loop, PPV and other dynamic cardiopulmonary indices, could not be assessed as there was no "breath cycle". We decided to observe the change in pulse pressure using an automated tool on our power lab. This provided new indices to observe the pre vs post challenge of the PV curve. Since we knew the specific volume removed during hypovolemia, and corresponding volume [colloid and blood stay inside the circulation] we could then compare PP changes with each volume shift as well as PAOP. Functionally, this was also done by observing the change in stroke volume. This provided an output decision table [simplified] for Aim 3 studies:

PP change > X_1% – give 250 mL/70 kg reassess – PV curve – X1 = 10-15
PP change > X_2% – give 500 mL/70 kg reassess – PV curve – X2 = 16-20
PP change > X_3% – give 1000 mL/70 kg reassess – PV curve– X3 = >20

Aim #3: Compare SOC versus decision support: optimizing cardiopulmonary function using PV curves.

This aim compared two groups of swine induced with lung injury followed by a series of hemorrhages and resuscitation, which allowed us to utilize identical methodology from Aim 1 pilot with lung injury.

Two groups of swine were compared. A MAP of < 70 mmHg triggered a response for each

group. We used crystalloid fluid [Lactated Ringers] for intravenous (IV) resuscitation as crystalloid fluid is most common and can exaggerate edema if used unwisely.

Group 1 – SOC [n=6], after lung injury, oxygenation and ventilation was achieved using the Hamilton S1 Intellivent's ASV with PEEP and FIO_2 based on ARDSnet protocol. This will be followed by an initial and then slow continuous hemorrhage. Fluid resuscitation was guided by PPV every 10 min.

PP > 10% - give 250 mL/70 kg reassess every 10 min
Rate of fluid is 25 mL/70 kg per min
PPV > 13% – give 500 mL/70 kg reassess every 10 min
Rate of fluid is 50 mL/70 kg per min
PPV > 20% - give 1000 mL/70 kg reassess every 10 min
Rate of fluid is 100 mL/70 kg per min

Group 2 – Decision support [n=6], after lung injury, ventilation and oxygenation parameters was guided by the S1 ventilator. However, PEEP was potentially reset based on PV optimal curves each time the PV tools function is initiated. After the onset of continuous hemorrhage, PV tools were performed every 10 min to assess volume responsiveness and fluid needs. We used the decision table above (Aim 2) to administer specific volume.

PP change > X_1% – give 250 mL/70 kg reassess – PV curve – X1 = 10-15
PP change > X_2% – give 500 mL/70 kg reassess – PV curve – X2 = 16-20
PP change > X_3% – give 1000 mL/70 kg reassess – PV curve– X3 = >20

4.0. RESULTS:

The prototype components developed (figure 5) during these studies include the Hamilton ventilator [allows for optimizing PEEP and PV curve for fluid responsiveness (upper left), A monitor that provided arterial pressure [beat-to-beat as well as pulse pressure changes and pulse pressure variability] upper right, a fluid pump [masterflex capable of delivering 100 milliliter per min (mL/min) fluid] and decision support computer with embedded algorithm. In brief, data during the PV curve provides a hemodynamic response to blood pressure, which is relayed into the decision support algorithm. Based on the response, a set fluid challenge is initiated, which in turn provides feedback to hemodynamics and potentially oxygenation.

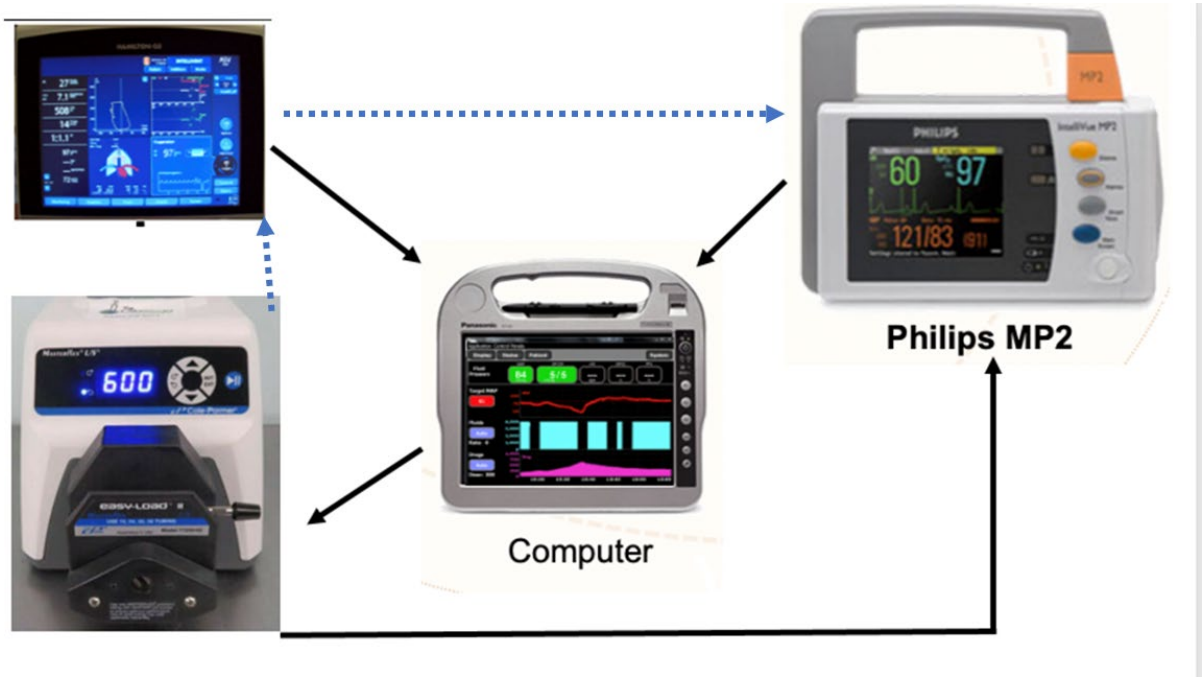

Figure 5. Current prototypes developed

Aim 1 key results:

Our goal in this aim was to provide detail and develop specific tools for the rate, peak pressure and timing for performing PV curves. Towards that end, we found that excessive peak pressure had unfavorable hemodynamics responses. Thus, we concluded that a max pressure of 20 cm H2O above PEEP could be used to detect volumetric status. We also determined that shorter duration 10 second [hold] was adequate.

Outcome: Our PV curve utilizes a peak pressure of 20 cm H_2O and hold time of 10 seconds.

Aim 2 key results:

Firstly, a challenge became evident in that PPV cannot be assessed during the PV curve, since PPV requires a breath cycle. However, our preliminary data demonstrated that change in pulse pressure (or delta PP) during a PV curve similarly characterizes hypovolemia (delta PP > 20 mmHg), euvolemia (16 – 20 mmHg) and hypervolemia (<10 mmHg). **Figure 6** shows a brief graphical representation of the overview of our experiments.

The proposed research utilized the pressure-volume loop as a provocative challenge to optimize PEEP and fluid needs. While many endpoints provide some information about fluid responsiveness, there are grey areas and limitations to using current dynamic indices. Specifically, there remains to be an effective endpoint to determine when not to give fluid. Moreover, based on the amplitude of the delta-PP, specific decision support bolus sizes can be prescribed.

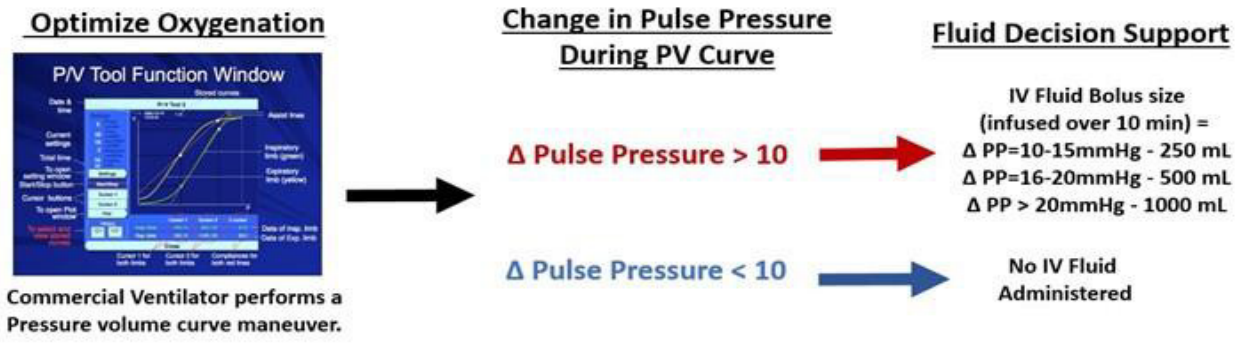

Figure 6. Graphical representation of the overview of our experiments

Data (**Figure 7**) demonstrate the effects of volemic status with and without ALI. A similar pattern occurs in both groups during hypovolemia. One key point that we found was that pulse pressure is low (25 mmHg) during hypovolemia, even before the PV curve. Therefore, this presented a caveat in that if blood pressure and pulse pressure are low: 1) a PV curve really is not necessary and 2) maximal fluid resuscitation should be administered. As volume is repleted (PAOP > 15 mmHg), pulse pressure and its change becomes less significant.

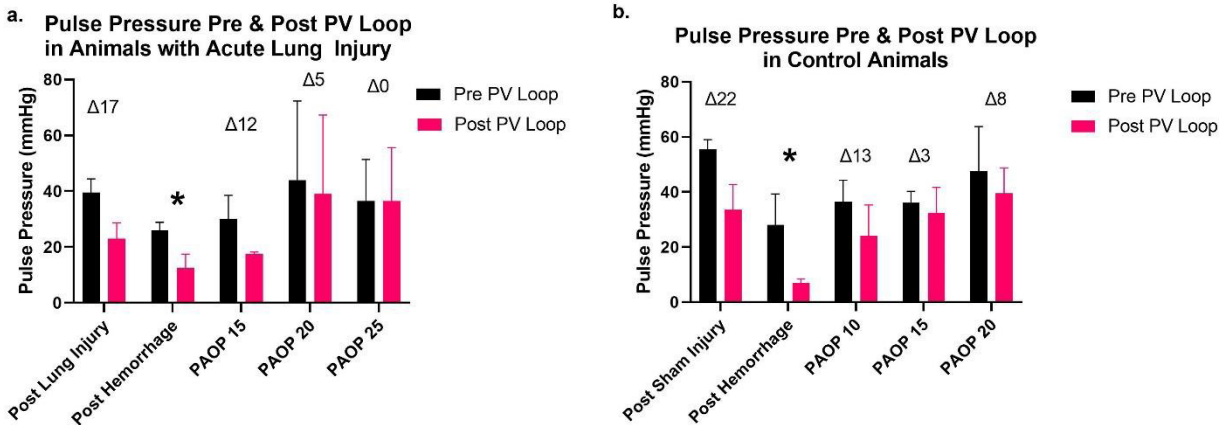

Figure 7. Effects of volemic status with and without ALI

Figure 8 represents individualized experiments demonstrating stroke volume and fluid responsiveness. In both groups, a rapid decrease in stroke volume occurred during hemorrhage. Initial resuscitation based on administering fluid using PAOP showed fluid responsiveness after hemorrhage at moderate PAOP [10 mmHg]. Interestingly, all animals in the ALI group demonstrated fluid responsiveness even at hypervolemic indices, e.g., PAOP 25 mmHg, whereas less than 2/6 of animals in the sham group were responders during hypervolemia. The reason there were differences in starting and ending PAOP between the ALI group and sham was due to higher PEEP in the ALI group. Thus, a PAOP of 10 cmH20 for Sham was equivalent to a PAOP of 15 mmHg. Likewise an ending PAOP of 20 cm H20 for Sham was equivalent to a PAOP of 25 mmHg

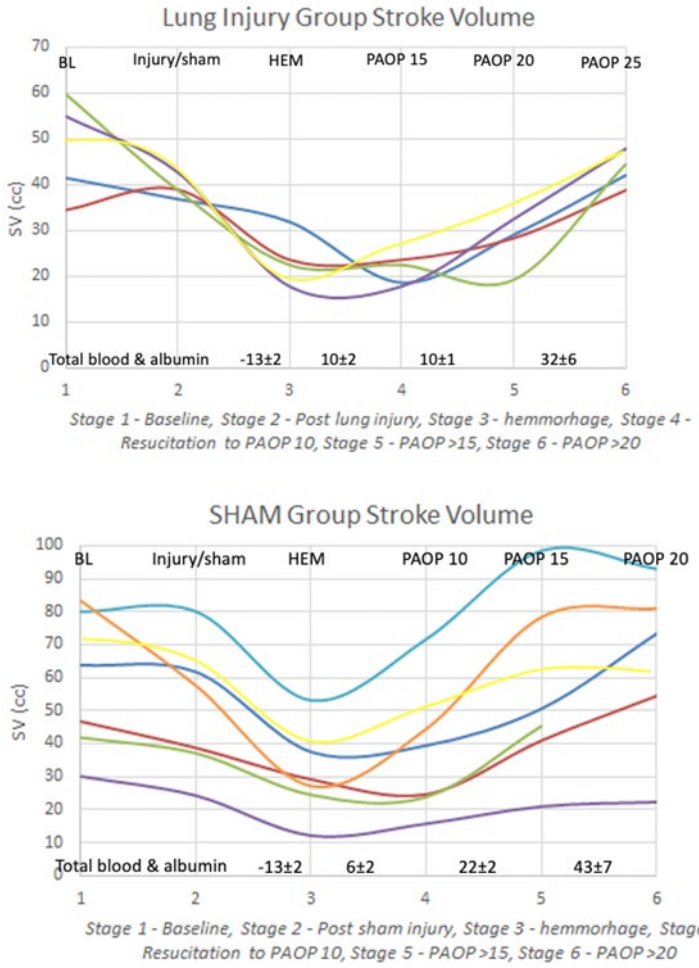

Figure 8. Experiments demonstrating stroke volume and fluid responsiveness

Data also demonstrated the amount of volume that was needed to achieve different levels of 'volemia'. To some extent, both groups of animals [ALI or Sham] had similar volumes [negative or positive] in order to achieve filling pressures PAOP, with the largest volumes needed for hypervolemia PAOP 20-25 mmHg.

Oxygenation: In the Sham group, the PaO2/FIO2 ratio changed little [521plus or minus (±) 50], whereas in the ALI group, the P/F ratio decreased after ALI to 131±25. Thereafter, the P/F improved slightly by the study end [193±72]. By design, PEEP was higher in the ALI group.

Total fluid requirements: Both groups demonstrated a positive fluid balance > 50 mL/kg by the study end, with most of the fluid administration occurring to achieve the hypervolemic endpoint of 20-25 cmH2O.

Outcome: As shown in figure 6, data from this aim were used to generate a decision support table SOC or algorithm [optimizing oxygenation and fluid resuscitation] for Aim 3 studies.

Aim 3 key results:

Development of new model (figure 9)

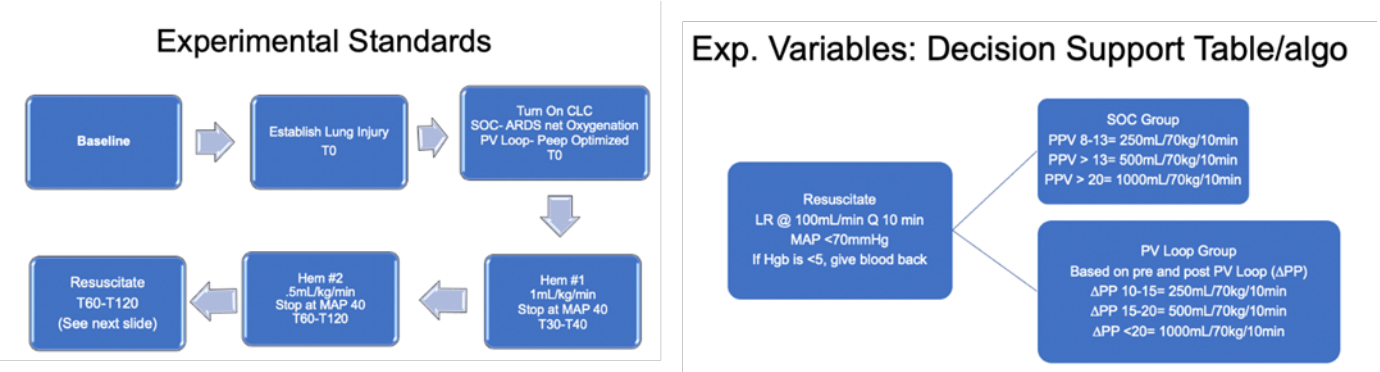

Figure 9. Experimental model and resuscitation groups

Two groups of swine (n=6 per group) were studied. Our model utilized an ALI plus a continuous hemorrhage and resuscitation [using lactated Ringers] to determine the effects of fluid and PEEP optimization. Entry criteria for fluid was set at 70 mmHg blood pressure and either dynamic indices using PPV or a provocative challenge using PV loop.

Outcomes include hemodynamic perfusion indices (e.g., stroke volume, cardiac output) and oxygenation indices (e.g., required FIO2, arterial oxygen saturation, pulmonary edema, and fluid balance). Results demonstrated no difference in total fluid volumes administered or lung edema differences. While we hypothesized that fluid efficiency would have been better in the PV loop curve group, this did not occur.

Additionally, the ending blood pressure [pre versus post MAP] needed to achieve a resuscitation endpoint was significantly reduced in both groups (power (p)<0.05) – see table 1 and 2. Based on this we concluded that both groups inadequately restored hemodynamics. This was a negative finding and likely model dependent. Finally, there were no differences in oxygenation (P/F ratio) between groups. The P/F ratio was 174±39 SOC and 188±55 in the PV curve group.

Summary of SOC Studies

Pig ID	# of Boluses	Starting MAP	Ending MAP	Fluid Given
200y	3 (T60, T80, T110)	72mmHg	59mmHg	2400mL
199y	4 (T60, T80, T100, T110)	75mmHg	58mmHg	2196mL
252y	4 (T60, T80, T90, T110)	83mmHg	72mmHg	2240mL
283y	4 (T70, T80, T100, T110)	87mmHg	34mmHg	3200mL
253y	4 (T60, T80, T90, T100)	67mmHg	36mmHg	1528mL
223y	4 (T70, T80, T90, T100)	80mmHg	59mmHg	900mL

Table 1 – individual standard of care studies pre vs post MAP and total fluid given

Summary of PV Loop Studies

Pig ID	# of Boluses	Starting MAP	Ending MAP	Fluid Given
254y (study ended due to heart failure @ T115)	5 (T70, T80, T90, T100, T110)	82mmHg	38mmHg	1620mL
251y (pig sustained a PE @ T111-112)	6 (T60-T110)	65mmHg	54mmHg	2456mL
281y	6 (T60-T110)	72mmHg	39mmHg	1211mL
280y	6 (T60-T110)	56mmHg	44mmHg	3330mL
284y	6 (T60-T110)	62mmHg	41mmHg	1730mL
228y	6 (T60-T110)	83mmHg	51mmHg	3000mL

Table 2 – individual PV loop studies pre vs post MAP and total fluid given

Standard of Care (SOC) n=6	
Total Fluid Given	2077mL±787mL
Lung Weight	810g±214g
Volume of Fluid in Chest Cavity (n=5)	42mL±62mL
Volume of Fluid in Abdominal Cavity	40mL±18mL

Pressure-Volume Loop (PV Loop) n=6	
Total Fluid Given	2225mL±838mL
Lung Weight	853g±170g
Volume of Fluid in Chest Cavity (n=4)	23mL±11mL
Volume of Fluid in Abdominal Cavity (n=5)	43mL±24mL

Table 3 – Summary table (mean ± SEM) for SOC vs PV loop: total volume and weight

5.0. DISCUSSION:

We developed and tested a model of ALI and hypovolemia in order to optimize oxygenation and fluid resuscitation. Specifically, in these acute anesthetized terminal studies, we demonstrated that a provocative challenge using a PV curve/loop function with a ventilator can identify varying levels of 'volemia'. While many options exist for performing a PV curve, we found that excessive inspiratory pressure results in excessive cardiopulmonary embarrassment. Therefore, we limited our PV curve to 20 cm H_2O above existing PEEP.

Additionally, our studies show that ALI, in face of hypovolemia, volume responsiveness occurs even during hypervolemia. We suggest that this is due to relative hypovolemia [less venous return due to PEEP and higher inspiratory pressure]. Further, while this augments the fluid responsiveness, the lungs seem somewhat protective [oxygenation not worsened]. On the other hand, lung protective strategies in need of fluid, induce a substantial positive balance, e.g., edema.

Our comparison studies SOC vs PV loop algorithm, however, were less positive. Further, we recognized that dynamic indices of resuscitation could not be utilized when performing a PV curve due to lack of mechanical breath cycling. Thus, we incorporated a pulse pressure change [pre vs post PV curve maneuver]. In addition, we determined that there are important caveats that need to be acknowledged using pulse pressure and this maneuver

- Caveat number (#)1: During hemorrhage and hypovolemia, pulse pressure is already low [< 20 mmHg]. Thus, performing a maneuver could aggravate hypoperfusion
- Caveat #2: Despite volume responsiveness, it does not mean that the subject or patient may need volume. This addresses an issue of over resuscitation.

Finally, while this could be a relatively non-invasive means to determine volume status in patients with ALI, the model we used was likely too aggressive. This was evident in the lack of both groups to restore blood pressure. Future studies will adjust the model [less severe bleeding e.g., reduced hemorrhage rate] as well as investigate volume and pressure challenges using the ventilator.

6.0. CONCLUSION:

Animal studies allowed us to develop and test a decision support table linking a fluid recommendation based a PV curve maneuver and pulse pressure. These data showed that a provocative challenge can determine volumetric states. Future studies will explore other indices outside of the change in pulse pressure.

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LIST OF SYMBOLS, ABBREVIATIONS and ACRONYMS

< – less-than
% – percent/percentage
+ – meaning "and"
- Minus
= – equal to
> Greater-than
± plus or minus
Number
ALI – acute lung injury
ARDS – acute respiratory distress syndrome
ASV – adaptive support ventilation
BP – blood pressure
CLC – close loop control
Cm H_2O – centimeters of water
CO – cardiac output
CO_2 – carbon dioxide
CDMRP – Congressionally Directed Medical Research Program
CVP – central venous pressure
DS – decision support
ECG – Electrocardiogram
ETCO2 – end tidal carbon dioxide
e.g. – example
FiO2 – functional inspired oxygen concentration
Hgb – hemoglobin
Hz – Hertz
HLI – heart lung interaction/index
HR – heart rate
JPC6 – Joint Program Committee
IV – intravenous
KCl – Potassium Chloride Injection
Kg – kilograms
LSI – life saving interventions
MAP – mean arterial pressure
mcg/kg/min – micrograms per kilograms per minute
mmHg – millimeter of mercury
mL – milliliter
mL/min – milliliter per min
mL/kg – milliliter per kilogram
Min – minutes
MvO_2 – myocardial oxygen consumption
n – number of particles in the substance; or number of subjects in a study group
PaO2 – partial pressure of oxygen
PAOP – pulmonary artery occlusion pressure
PAP – pulmonary artery pressure

PEEP – positive end expiratory pressure
P/F – ratio of PaO_2/ FIO_2
PID – proportional–integral–derivative controller
PIV – peripheral intravenous line
PP – pulse pressure
PPV – pulse pressure variability
PVI – pleth variability index
PV – pressure volume loop or curve
SBP – systolic blood pressure
SpO2 – saturation of oxygen using plethysmography [pulse oximeter]
SOC – standard of care
SOS – smart oxygenation system
SV – stroke volume
SVV – stroke volume variability
T – Trial
UC – University of Cincinnati
UTMB – University of Texas Medical Branch at Galveston
VCO_2 – production of carbon dioxide per minute
VO_2 – Oxygen consumption per minute