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Interactions of Closed Loop Control PEEP oxygenation and Fluid Therapy

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14. ABSTRACT

Background: Closed loop control mechanical ventilation has been reported to potentially reduce ventilator weaning time, burden on medical caregivers, and improve comfort during mechanical ventilation. However, the influence of closed loop control PEEP adjustment, on fluid requirements in the acute phase and cardiopulmonary dysfunction, remains unknown. The aim of this study was to investigate the impact of closed loop ventilation and PEEP/FiO2 on decision support-based fluid resuscitation and respiratory mechanics/gas exchange using a clinically relevant ovine model of burn and smoke inhalation.

Methods: Adult female sheep (31-42kg) were surgically prepared 5-7 days prior to the study. Sheep were then subjected to burn (3rd degree and 40 percent of body surface) and smoke inhalation injury under anesthesia and analgesia. During the injury, a pulse-oximeter was placed on the ear to monitor SpO2. After the injury, sheep were randomly assigned into control group (n=5) which received adaptive support ventilation (ASV) and closed loop group (n=6) which received ASV with Intellivent, using the Hamilton S1 ventilator. Sheep were monitored for 48 hours in a conscious state. In the control group, FiO2 and % Minute volume (%MV) were adjusted according to PaO2 and PaCO2 values measured every 3 – 6 hours. The PEEP was fixed at 5 cmH2O. In the Intellivent group, FiO2, PEEP, and %MV were automatically adjusted according to SpO2 and etCO2 changes. The initial fluid rate was 4 mL/kg for 1 h, then the rate was adjusted hourly based on an algorithm using the hourly urinary output. The survival rate, total fluid in, urine output, net fluid balance, severity of pulmonary dysfunction, and hemodynamic changes, were monitored.

Results: All sheep survived in the closed loop group, while 2 out of 5 control group survived 48 hrs, p=0.06. Because only 2 sheep survived in the control group, the data was summarized for first 24hrs. The total amount of infused fluid for 24 hrs in the closed loop and control groups were 4,346mL ± 462 and 3,265± 364 mL, respectively, p=0.10. The total urinary output for 24 hrs was comparable in both groups (1,180 ± 136 mL in the closed loop group vs. 1,107 ± 141 mL in the control group, p=0.72). Net fluid balance was 3,166 ± 505 mL in the closed loop group vs. 2,157 ± 491 mL in the control group, p=0.19. At 24hrs, the PaO2/FIO2 ratio in closed loop group tended to be higher (213 ± 45 mmHg) vs. the control group (135 ±30 mmHg, p=0.20). The respiratory effort (P0.1) was significantly lower in the closed loop group (2.8 vs. 6.4 cmH2O, p=0.02) vs the control group. The PEEP was 11 cmH2O in the closed loop group vs 5 cmH2O in the control group, P<0.01 The tidal volume, respiratory rate, peak airway pressure, and hemodynamic changes were comparable in both groups.

Conclusion: Closed loop control of PEEP/FIO2 is associated with better oxygenation, lower respiratory effort, and greater survival rate of sheep with combined burn and smoke inhalation injury. This is possibly due to higher PEEP used in the closed loop control group, which improves oxygenation, lung compliance and reduces the work of breathing.

15. SUBJECT TERMS
Closed Loop Control, mechanical ventilation, fluid

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TABLE OF CONTENTS

Section

1.0 BACKGROUND

A major challenge for critical care transport of civilian patients and wounded warriors is maintaining perfusion by appropriate fluid therapy in the presence of hypovolemia. An equally challenging task is providing adequate oxygenation in patients with acute lung injury (ALI). The use of positive end-expiratory pressure (PEEP) and increasing fractional inspired oxygen (FiO_2) are fundamental in this approach. Closed-loop-control (CLC) systems are emerging technologies that could potentially treat these challenges and will work in constrained and resource limited environments that occur for the military and civilian remote locations.

Independent CLC systems rely on **physiologic negative feedback loops** to deliver treatment. CLC oxygenation is not commercially available for FiO2 and PEEP in the United States. We have developed a near term closed loop fluid delivery system that maintains pressures and perfusion during multiple hemorrhages e.g., Trauma Tablet and burn shock e.g., Burn Navigator. We have tested the commercially available Hamilton G5 and S1 system, which is approved outside US. We have used the above systems to test and verify algorithms for administering fluid therapy and oxygen. Our past and ongoing work have demonstrated that CLC systems can improve efficacy {maintain target} and efficiency {less resources} when used to treat acute lung injury [ALI], hemorrhage and severe burn injury. Specifically, we found that CLC FiO2/PEEP can better maintain target SpO2 while reducing the FiO2. Our CLC fluid systems for treating hemorrhage and burns attain better target blood pressure and urinary output, respectively, while reducing fluid balance e.g., less edema.

However, multiple CLC systems have the potential to interfere with each other and thus joint synergistic algorithms must be developed for treating poly trauma where hemorrhage and acute lung injury are present. These interactions must be better defined before the CLC systems and algorithms are finalized. Specifically, there are important deleterious interactions that can occur when two CLC's are working at the same time, especially if CLC systems interfere with concomitant disease processes that in turn alter the physiology. Hypovolemia with lung injury is one example **(see figure 1).** Clinically, intravenous fluid therapy is used to restore vascular volume and PEEP is used to improve oxygenation. However, potential antagonistic interactions could occur if two simultaneous CLC systems are used together. For instance, PEEP increases intrathoracic pressure resulting in reduced venous return [decreased blood pressure and urinary output]. This would activate CLC fluid. The excess fluid would leak into damaged lung tissues resulting in low SpO2. CLC PEEP would activate based on the low SpO2 and increase intrathoracic pressure and thereby reduce venous return, worsening the cycle. We suspect that CLC interactions could result in **a positive feedback loop** or decompensatory phase.

This project defined the interactions of closed loop control systems via the following **hypotheses**:

1- *simultaneous use of CLC PEEP & CLC Fluid to treat acute lung injury and hypovolemia will reduce efficacy [inability to maintain target] and poor efficiency [excessive volume and edema].*
2- *use of dynamic indices generated by CLC interactions will provide decision support stop gate tools for clinicians so that fluid and PEEP therapy can more effectively be delivered with limited sequelae.*

We tested these hypotheses in the following specific Aims:
Aim 1. Swine [n=9, per group] treated underwent acute lung injury followed by hemorrhage and assigned to one of two treatment groups: Group 1 = standard of care (SOC) PEEP and SOC Fluid; Group 2 = CLC PEEP alone and CLC Fluid based on blood pressure. In both groups, oxygen [FiO2] was manually titrated to achieve SpO2 93%. The Primary endpoint was time in target blood pressure and fluid balance. Secondary endpoints will include organ injury, edema and blood flow.
Aim 2. Sheep [n=9, per group] underwent an inhalational injury combined with a 40% TBSA burn injury. Sheep were then randomly assigned to fluid [based on UO] plus either SOC PEEP [set at 5 cmH20 and manually titrated FiO2 to achieve O2sat 93%] or CLC PEEP/FiO2 according to ARDSnet to achieve SpO2 93%. Primary endpoints were target UO and fluid balance. Secondary endpoints included organ injury, P/F ratios, lung compliance, edema and other makers of injury.
Aim 3. Was an exploratory aim that incorporated data from CLC algorithms, dynamic indices and other endpoints to develop decision support tools and "stop gates" for assessing CLC interactions and loss of efficacy / efficiency. Specific indices include, Heart Lung Index [HLI], Pleth Variability Index [PVI], production of carbon dioxide [VCO2] and others e.g., Total Fluid Index [TFI] and tissue oximetry [StO2]. In addition, pilot studies were performed to determine the mechanism for differences in survival between the CLC group vs SOC group in sheep [s/p burn + smoke inhalation injury].

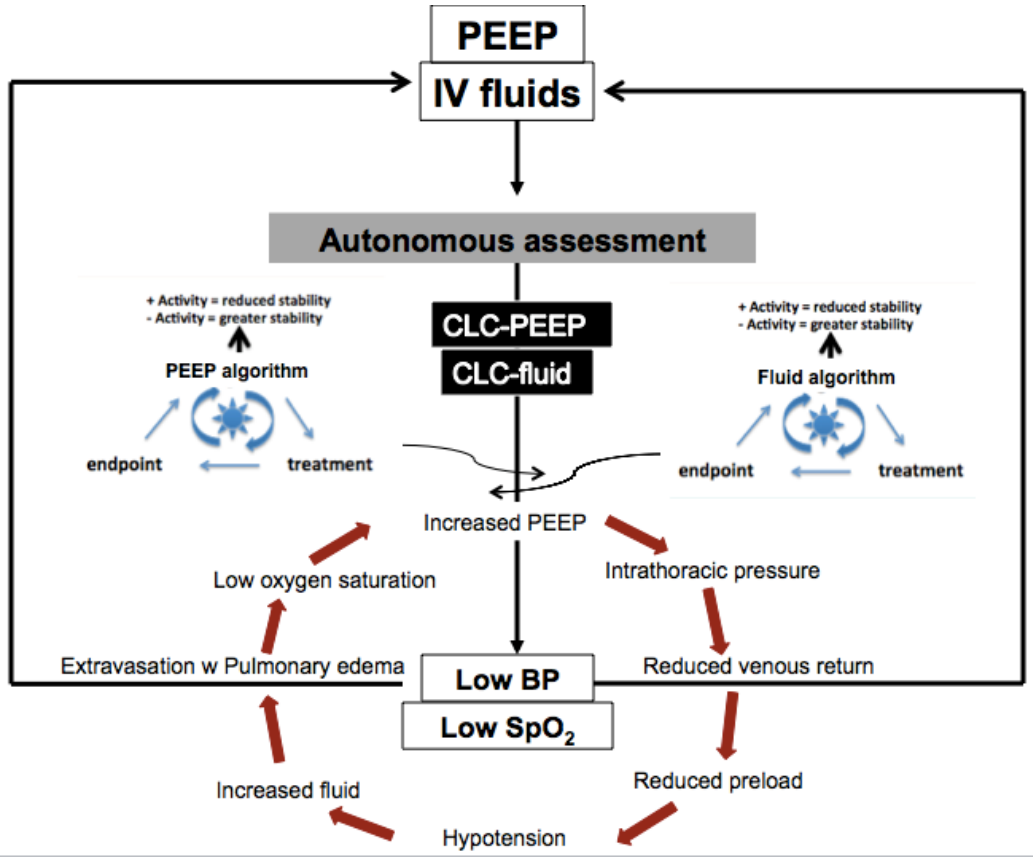


Figure 1. Demonstrates the interaction of closed-loop control PEEP and fluid therapy for treating lung injury and hypovolemia. Potential consequences could result in worsening hypotension and fluid extravasation.

2.0 METHODS

Methodology are separated into two different studies – both of which are in manuscript draft preparation. The references are not completed or updated for this report. Both studies/aims were presented at the MHSRS meeting in 2018 (study 1) and 2019 (study 2), respectively.

The study protocols were reviewed and approved by the University of Texas Medical Branch Institutional Animal Care and Use Committee (IACUC) and United States Air Force Surgeon General Office of Research Oversight & Compliance. Animals were handled and studies were conducted under a program of animal care accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) and in accordance with the "Guide for the Care and Use of Laboratory Animals" (NRC, 2011; in compliance with DoDI 3216.1).

Study #1

Animal preparation:
Twenty-one farm-raised female Yorkshire swine (3-4 months old) were obtained from a U.S. Department of Agriculture licensed vendor (USDA license 74-B-065). All animals were examined by a veterinarian for any possible preexisting pathologies, housed at 23˚C to 25˚C, and quarantined for 2 weeks in 12-h light/dark cycles, while having access to food and water. Prior to the experiment, the animals were fasted for 12-hours.

Anesthesia: On the morning of the study, the swine, while in their enclosure, were brought to the study suite and were administered an intramuscular injection in the hind leg with 2.8 mg/kg ketamine (KetaVed; Vedco Inc, St Joseph, MO), 2.8 mg/kg xylazine (AnaSed; Akorn, Decatur, IL), 5.7 mg/kg Telazol (Zoetis Inc, Kalamazoo, MI) and 0.3 mg buprenorphine (Par Pharmaceutical Cos. Inc, Spring Valley, NY). After deep sedation, each swine was placed in the prone position on the operating table. Three-lead electrocardiogram and pulse oximeter were placed on chest and tail, respectively. An ear vein was cannulated with a 20-gauge intravenous catheter. General anesthesia was induced with 100 mg intravenous (IV) ketamine and 2-5% inhaled isoflurane (Piramidal Healthcare Limited, India) in oxygen via mask. After end-tidal isoflurane was >2%, animals underwent endotracheal intubation. After confirming bilateral breath sounds and end-tidal carbon dioxide by the Capnomac Ultima gas analyzer (Datex-Ohmeda, Finland), the endotracheal tube (ETT) was secured. Swine were then mechanically ventilated using a Drager Narkomed GS anesthesia machine (Draeger Medical, Inc. Telford, PA). Initial tidal volume was set at 10 mL/kg with a respiratory rate of 10 to 15 breaths per minute, and a FiO2 of 0.4. Ventilation was adjusted to maintain an end-tidal CO_2 of 35 mmHg by adjusting the respiratory rate.

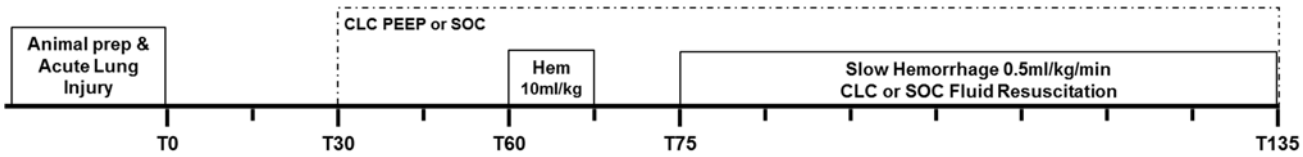
Surgical preparation: A urinary catheter was inserted into the bladder. Cut-down incisions on both femoral triangles were performed, and the femoral arteries were catheterized for pressure monitoring (Monitoring Kit with Flush Device, Abbot Industries, North Chicago, IL), and pulse pressure variability (PPV) calculation. The femoral veins were cannulated for fluid administration. The right neck was dissected, and a 5F single-lumen catheter placed in the right

carotid artery to induce bleeding. The right internal jugular vein was cannulated with a 8F introducer for pulmonary artery and central venous pressure monitoring via a 7.5 F Swan-Ganz catheter (Edwards Lifesciences LLC, Irvine, CA). A Doppler flow probe was placed on inferior vena cava (Transonic Systems, Ithaca, NY). Splenectomy was performed to eliminate possible splenic contraction during hemorrhage. Fluid maintenance during surgical preparation was done with PlasmaLyte A (Baxter, Deerfield, IL) at a rate of 12 mL/kg/hr, and was prewarmed to avoid hypothermia. Hamilton G5 ventilator (Hamilton Medical AG, Bonaduz, Switzerland) was used after surgery, and anesthesia was maintained with an infusion of 80 to 150 μg/kg/min of propofol (Diprivan; Fresenius Kabi USA, LLC, Lake Zurich, IL). A warming blanket was applied to maintain normal body temperature. Animals were monitored to ensure hemodynamic stability during the study, which included temperature, electrocardiography, arterial blood pressure (Hewlett Packard, Model 78534C, Andover, MA), pulse oximetry (Masimo Radical-7; Masimo, Irvine, CA), capnography (Datex-Ohmeda Capnomac Ultima, Finland) and urinary output (BD, BARD Medical, GA). Euthanasia was performed with an IV bolus infusion of 25 mg/kg ketamine followed by 1 to 2 mEq/kg of saturated KCl (Hospira Inc, Lake Forest, IL) on completion of the study protocol.

Study Protocol: A combined acute lung injury and hemorrhagic hypovolemia were induced in a swine model (Figure 1). The acute lung injury was performed prior to randomizing the animals to a CLC of PEEP/FiO_2 & fluid therapy (n =10) or SOC PEEP/FiO_2 & fluid therapy (n =11) followed by hemorrhage. Acute lung injury was induced by surfactant washout and augmented with barotrauma, described in previous publication. Briefly, animals were disconnected from the ventilator circuit, and up to 600 ml of warmed Plasmalyte was instilled from a height of 50 cm into the ETT. The fluid was allowed to dwell for 2-3 minutes, and then drained by gravity. In between each surfactant wash, the ventilator circuit was reconnected, and provided ventilation with a tidal volume of 8 ml/kg and FiO_2 of 1.0 for about 3 minutes and allowed oxygen saturation (SpO_2) to return to baseline. The washout was repeated until the PaO_2/FiO_2 (P/F) ratio was less than 100, followed by a barotrauma injury induced by ventilating animals on pressure control mode with FiO_2 of 1.0, peak inspiratory pressure of 35 mmHg, and PEEP of zero for about 1 hour. Once the injury was established, the ventilation mode was switched to Assisted Support Ventilation (ASV), FiO_2 of 1.0, PEEP of 5 mmH_2O, and $PaCO_2$ was maintained at 35-45 mmHg. After 30 minutes (T30), the lung injury treatment was initiated for the CLC group with CLC of PEEP and FiO2 using Intellivent® with a SpO_2 target of 93-95% and $EtCO_2$ target of 35-45 mmHg. The SOC group used ASV and manual control of PEEP and FiO_2 with the same treatment goals as CLC and PaO_2 goal of >70 mmHg. On the SOC group, FiO_2 was increased in increments of 20% and PEEP by 2 cmH_2O increments, if needed, however, if PPV became > 13, PEEP was decreased by 2 cmH2O, and was not allowed to be increased. Thirty minutes after the lung injury treatment was initiated (T30), a rapid hemorrhage was induced at a rate of 10 mL/kg over 10 minutes. Twenty minutes later (T60), a slow hemorrhage was induced 0.5 mL/kg/min for 90 min. Fluid resuscitation was initiated as the second hemorrhage started with crystalloid based on a fluid closed-loop algorithm (CLC) or decision-support table (SOC) until the end of the protocol. The target blood pressure used on both groups was mean arterial pressure (MAP) of 70 mmHg. Our fluid closed-loop system has been previously described and extensively tested on different type of hypovolemic shock. Briefly, the closed-loop fluid resuscitation consisted of an arterial pressure transducer connected to the vital signs monitor, an algorithm (computer), and an IV infusion pump. Java was used to program the closed-loop software as well as the user

interface. The MAP signal was sampled every 100 Hz, and transmitted to the PID controller algorithm every 5 seconds. The Power Infuser™ (ZOLL Power Infuser modified by Arcos, TX) was used to deliver the fluid intravenously whenever the MAP fell below the set target at a rate of 100 ml/min.
For SOC group, the decision-support table for fluid resuscitation was based on the MAP, and was used every 15 minutes as followed: if MAP less than 30 mmHg, a 28 ml/kg bolus was infused over 10 minutes; if MAP less than 50 mmHg, a 14 ml/kg bolus was infused over 5 minutes; and if MAP was less than 70 mmHg, a 7 ml/kg bolus was infused over 5 minutes.

Hemodynamics, and respiratory parameters were continuously monitored, collected at 1000 Hz and recorded using high-resolution data capture software (PowerLab) for the entirety of the study. Blood gases were obtained every 10 minutes.
Swine Protocol - **Figure 2: Swine CLC study protocol.**



Statistical analysis:
We used key time points on the data analysis: baseline, once injury was stablished, immediately before rapid hemorrhage (hemorrhage #1), immediately before slow hemorrhage (hemorrhage #2), and at the end of the study. Analyses were performed in GraphPad Prism 8 (GraphPad Software, San Diego, CA.). Summary statistics are presented as mean ± standard deviation (SD). Comparison between groups at different time points was performed using a two-way analysis of variance (ANOVA) corrected for repeated measurement with Bonferroni.

Mann-Whitney test to compare continuous data.
Data comparison within a group: comparing different time point used one-way analysis of variance (ANOVA) corrected for repeated measurements with Bonferroni.
All statistical tests were two-sided, and P values less than 0.05 were considered statically significant.

Study #2

Seventeen adult female Merino sheep (approximately 3 years of age and body weight [BW] 30 - 41 kg) were used. The experiments complied with the guidelines of the National Institutes of Health and the American Physiological Society for the care and use of laboratory animals. Animals were group-housed during a 14-day quarantine period at the Animal Research Center and placed in individual metabolic cages upon transferring to the Translational ICU (TICU) for study. Sheep were housed within sight of other sheep in a temperature/humidity-controlled environment with dark/light cycles.

Overview Aim 2. In this series using a sheep model - we induced two severe injuries administered (acute lung injury and burn induced hypovolemia but over 48hr) to all animals that included a 40%

TBSA full thickness burn along with inhalation injury. Two groups of randomized sheep were used CLC group [n=9] vs SOC [n=8]. Fluid resuscitation was identical in both groups.

Experimental Animal Protocol:

Animal preparation: The burn smoke inhalation injury model has been well described in the Translational Intensive Care Unit (TICU). Briefly, Adult female sheep (30–40 kg) were prepared surgically under sterile conditions under general anesthesia. Silastic catheters were placed into the femoral artery and vein for continuous measurement of hemodynamics such as heart rate and systemic arterial blood (MAP) and intermittent sampling of arterial blood and for infusing fluid and pharmacologic agents. A Swan-Ganz thermal dilution catheter (model 93A-131-7F, Edwards Laboratories, Irvine, CA) was placed through the right jugular vein and advanced into the pulmonary artery (PA) to measure pulmonary arterial (PAP), central venous pressures (CVP), cardiac output (CO), mixed venous oxygenation (MVO_2) and blood temperature. After surgery and anesthesia, the sheep had seven days of recovery. The animals were connected to physiological monitors (model 78304A, Hewlett Packard, Santa Clara, CA) and monitored at least three times a day to ensure good recovery i.e., lack of fever, appropriate eating and drinking, well hydrated, good physical appearance, lack of pain. Sheep with evidence of pain (e.g., gritting teeth, lethargic, poor eating, rapidly getting up and down) were treated with buprenorphine. Criteria in order to enter experimental study include: $PaO_2 > 90$mmHg, $PaCO_2$ <36 mmHg, body temperature between 38°C and 40°C, heart rate < 100 beats/min, hematocrit >22 and white blood cell count between 5 and 10 thousand/μL.

Study procedure and measurements: Experiments were conducted in an awake state for 48hr. On the day of experiment (7 days of recovery) and two hours before injury (T minus 2 hr), baseline hemodynamic measurements and blood chemistries in sheep were obtained. Blood (1 mL) was sampled from the PA-catheter for MVO_2 and from the arterial line for blood gas analysis including, PO_2, PCO_2, and pH and for Co-Oximetry that include total hemoglobin (Hb), arterial oxygen saturation (SaO_2) and carboxyhemoglobin (COHb) concentration (model IL 1600, Instrumental Laboratory, Lexington, MA). Sheep have a higher baseline COHb concentration than humans, COHb ≈5-7 %. After a one-hour stable baseline, general anesthesia was induced (at time point, one hour before injury (T minus 1 hr)) to perform a tracheostomy and inhalation injury. Sheep were then administered buprenorphine for pre-emptive analgesia, and then a cuffed tracheostomy tube (10 mm diameter, Shiley, Irvine, CA) was inserted. A Foley catheter was inserted in the urinary bladder to measure urinary output [UO].

Induction of combined burn injury and inhalation injury: General anesthesia continued and sheep received a full thickness burn injury using smoke inhalation injury in the prone position with a modified bee smoker filled with 50g of burning cotton. At time point zero (0 hr), the smoker was connected to the tracheostomy tube via a modified endothracheal tube containing an indwelling thermistor to ensure that the temperature of the smoke did not exceed 40°C. Inhalation injury induction was performed by insufflating cotton smoke (Severe injury) – 5 sets of 12 breaths of cotton smoke will be done (60 breaths total). After each set of smoke inhalations, COHb levels were measured to determine injury severity. Burn injury, 40%, third degree, was performed using a Bunsen burner. After closely shaving the animals' flanks, a 20% total body surface area burn was done on each flank (side). The injury produced a full-thickness burn including both the

epidermis and dermis, which means the nerve endings are destroyed, therefore sheep did not feel pain after the full thickness lesion.

Oxygenation, ventilation and other support: Following inhalation injury, general anesthesia was discontinued. The tracheostomy site was attached to a breathing circuit of the ventilator with side-stream capnography for $ETCO_2$. Initially, all sheep were placed on CMV mode (due to general anesthesia) with 100% oxygen. Since carbon monoxide has an extremely high affinity for hemoglobin and displaces oxygen (200 X more than O_2), a FiO_2 of 1.0 (100% oxygen) was administered to eliminate carbon monoxide. Based on the sheep inhalation injury model, a FiO_2 of 1.0 is needed for two-three hours in order to reduce carbon monoxide to basal levels. Co-Oximetry data was measured every 30 min while the FiO_2 is maintained at 1.0. Once the % COHb returns to basal levels ± 5%, the FiO_2 was set to 0.3. Specific adjustments with modes, PEEP and FiO2 described below.

We anticipated that all sheep with severe inhalation injury would require full mechanical ventilation with oxygenation support within 12 -24 hrs of injury due to worsening pulmonary gas exchange.

CLC for PEEP/FiO2 [n=9] For the closed loop group, the CLC PEEP/FiO2 was activated for Hamilton S1 transport. CLC PEEP and CLC FiO2 used a weighted scale based on the ARDSnet data and current SpO2. Thus, PEEP was primarily increased first to offset high FiO2 needs. However, FiO2 also increased when PEEP exceeded Hamilton's CLC algorithm. As noted earlier, HLI will be disregarded [recorded but not used]; however, we capped the PEEP maximum at 15 cmH2O.

Standard of Care (SOC) protocol [n=8]: We used the Hamilton Ventilator in ASV mode in non-closed loop mode. Oxygenation was managed by setting PEEP to maximum of 5 cmH2O and FiO2 was adjusted to attain PaO2 > 70 mmHg. SpO2 along with arterial blood gas data were recorded. Initial oxygenation setting includes a FiO2 at 0.4 and PEEP of 5 cmH2O. PEEP was not increased further. The FiO_2, therefore was adjusted and recorded according to blood gas analysis (PaO_2 between 70-100, and SaO_2 above 90%). This was performed every 3-6 hrs.

Fluid resuscitation used a decision support protocol that was hourly driven and directed based on varying urinary output (UO). Initial fluid resuscitation began at 0.25 mL/kg/%TBSA per hour (which was 10 mL/kg/hr since it was a 40% TBSA) and used a weighted PID algorithm to increase fluid when UO was low and reduced it when UO normalized. We had 99% compliance with UO determination, fluid rate each hour for 48 hrs using this decision support platform.

Data collection: Hemodynamics, blood analytes, ventilator settings, FiO_2, PEEP and pulmonary mechanics were recorded at (T minus 2hr – baseline awake), general anesthesia before injury (T minus 1hr), induction of inhalation injury at 0 hr, and 3, 6, 12, 18, 24, 30, 36, 42 and 48 hr post injury.

Net fluid balance and target UO. We recorded fluid In, UO and calculated net fluid balance at each time point. We analyzed and compared groups in regard to target UO and cumulative fluid administered.

Pulmonary mechanics: Pulmonary function and acute lung injury score were evaluated by measuring arterial and mixed venous blood gases. Pulmonary shunt fraction was calculated using a standard equation. Work of breathing, peak and plateau airway pressure and compliance was recorded.

Cardiovascular function: We monitored and recorded heart rate, MAP, PAP, CVP, and pulmonary capillary wedge pressure (PCWP). Pulmonary and systemic vascular resistance index was calculated. Cardiac output was measured by the thermodilution technique. In addition to the hemodynamic variables Cardiac index, stroke volume index, left ventricle stroke work index, systemic vascular resistance index, pulmonary vascular resistance index, pulmonary capillary pressure, pulmonary shunt fraction, oxygen delivery and oxygen consumption was calculated.

Other: The lung wet-to-dry ratio, a measure of lung water content and histology, was determined postmortem. All animals were euthanized at 48 hr and lung were harvested following strict adherence to protocol. While this was not intended to be a survival study comparison, there were deaths in the SOC in 50% of the animals. Thus, survival analysis was included.

Additional studies & work: Since survival was statistically significant finding, we performed additional pilot studies to determine the rationale for protection in the CLC group. Thus, we received additional funding to do three more sheep with a focus on cardiopulmonary protection from CLC PEEP/FIO2 with a specific focus utilizing echocardiography [systolic and diastolic function, right heart function]. We will continue to analyze data when comparable groups are done.

3.0 RESULTS

Aim 1 – Study 1: Comparing CLC Oxygenation /PEEP (n=10) versus Standard of Care (n=11) in swine s/p Acute lung injury + hemorrhage [anesthetized study]

Table 1. Fluid balance and laboratory findings

Fluid Balance				
Fluid infused (ml/kg ± SD)		79 ± 22	51 ± 19	**0.002***
Hemorrhage (ml/kg ± SD)		42 ± 5	39 ± 10	0.557
Urine output (ml/kg ± SD)		2.1 ± 1.6	1.8 ± 1.2	0.653
Wet lung weight (mg/kg)		19 ± 3	20 ± 4	0.968
Necropsy fluid (ml/kg ± SD)	Pericardial	0.2 ± 0.1	0.3 ± 0.2	**0.040***
	Thoracic	0.9 ± 0.6	0.6 ± 0.7	0.321
	Abdominal	4.4 ± 2.6	3.6 ± 1.8	0.359
Laboratory				
Hemoglobin (mg/dL)	Baseline	9.6 ± 1.3[a]	9.1 ± 0.7[a]	>0.999
	Injury established	10.1 ± 0.9[a]	9.9 ± 1.2[a]	>0.999
	Hemorrhage # 1	9.4 ± 0.7[a]	9.6 ± 1.5[a]	>0.999
	Hemorrhage # 2	9.6 ± 1.5[a]	9.8 ± 2.3[a]	>0.999
	End of study	5.2 ± 1.0	6.5 ± 1.1	0.107
Lactate (mmol/L ± SD)	Baseline	2.0 ± 0.7[a]	1.7 ± 0.9[a]	>0.999
	Injury established	3.6 ± 1.4[a]	2.9 ± 0.9[a]	>0.999
	Hemorrhage # 1	3.7 ± 2.5[a]	2.7 ± 0.9[a]	>0.999
	Hemorrhage # 2	3.7 ± 2.1[a]	2.4 ± 0.9[a]	0.866
	End of study	6.7 ± 2.1	5.5 ± 2.8	>0.999

[a] p <0.05, within the same group compared to the last time point (end of study).

[b] p <0.05, within the same group compared to baseline

[c] p <0.05, within the same group compared to injury

d p <0.05, within the same group Hemorrhage #1 compared to Hemorrhage #2

Table 2. Pulmonary variables

Pulmonary				
VCO_2 (mL/min ± SD)	Baseline	134 ± 42	148 ± 51	>0.999
	Injury established	137 ± 43	138 ± 51	>0.999
	Hemorrhage # 1	134 ± 23	135 ± 44	>0.999
	Hemorrhage # 2	128 ± 27	131 ± 43	>0.999
	End of study	135 ± 26	135 ± 46	>0.999
Compliance (L/cmH_2O ± SD)	Baseline	24 ± 7[a]	26 ± 10[a]	0.146
	Injury established	13 ± 5[a]	12 ± 4[b]	>0.999
	Hemorrhage # 1	15 ± 4[a]	15 ± 4[b]	>0.999
	Hemorrhage # 2	15 ± 4[a]	16 ± 5[b]	>0.999
	End of study	14 ± 3	15 ± 4	>0.999
MV (L/min ± SD)	Baseline	6 ± 2	6 ± 2[a]	>0.999
	Injury established	6 ± 1	6 ± 2[a]	>0.999
	Hemorrhage # 1	7 ± 1	7 ± 3	>0.999
	Hemorrhage # 2	7 ± 1	7 ± 3	>0.999
	End of study	7 ± 2	8 ± 3	>0.999
Dead space	Baseline	114 ± 35	118 ± 41	>0.999
	Injury established	114 ± 20	116 ± 31	>0.999
	Hemorrhage # 1	128 ± 25	125 ± 29	>0.999
	Hemorrhage # 2	128 ± 24	127 ± 34	>0.999
	End of study	125 ± 18	132 ± 35	>0.999
Ppeak (mmHg ± SD)	Baseline	18 ± 3[a]	18 ± 8[a]	>0.999
	Injury established	37 ± 4[a]	34 ± 6[b]	>0.999
	Hemorrhage # 1	36 ± 7[a]	35 ± 6[b]	>0.999
	Hemorrhage # 2	35 ± 6[a]	33 ± 8[b]	>0.999
	End of study	36 ± 7	32 ± 9	0.764
PEEP (cmH_2O ± SD)	Baseline	1 ± 2[a]	0 ± 0	>0.999
	Injury established	2 ± 4[a]	2 ± 4	>0.999
	Hemorrhage # 1	11 ± 2[ac]	8 ± 3[bc]	>0.999
	Hemorrhage # 2	9 ± 3[ac]	6 ± 4[b]	0.065
	End of study	11 ± 4	5 ± 3	**0.0001***
PaO_2/FiO_2	Baseline	414 ± 146[a]	555 ± 262[a]	0.159
	Injury established	120 ± 84[a]	181 ± 140[b]	>0.999
	Hemorrhage # 1	182 ± 76[a]	196 ± 99[b]	>0.999
	Hemorrhage # 2	172 ± 75[a]	150 ± 93[b]	>0.999
	End of study	207 ± 72	180 ± 73	>0.999
PaO_2 (mmHg ± SD)	Baseline	380 ± 158[a]	445 ± 85[a]	0.236
	Injury established	114 ± 79[a]	145 ± 97[b]	>0.999
	Hemorrhage # 1	94 ± 28[a]	108 ± 52[b]	>0.999
	Hemorrhage # 2	83 ± 14[a]	83 ± 31[b]	>0.999
	End of study	94 ± 38	104 ± 19	>0.999
FiO_2 ± SD	Baseline	0.9 ± 0.2[a]	0.9 ± 0.2	>0.999
	Injury established	1.0 ± 0.1[a]	0.9 ± 0.2	>0.999
	Hemorrhage # 1	0.6 ± 0.2[ac]	0.6 ± 0.3[bc]	>0.999
	Hemorrhage # 2	0.5 ± 0.2[ac]	0.7 ± 0.2	0.297
	End of study	0.5 ± 0.1	0.7 ± 0.2	0.359

Table 3. Cardiovascular variables

Cardiovascular				
		CLC (n = 10)	SOC (n = 11)	p value
Heart Rate (bpm ± SD))	Baseline	96 ± 25[a]	87 ± 23[a]	>0.999
	Injury established	94 ± 20[a]	89 ± 19[a]	>0.999
	Hemorrhage # 1	116 ± 26[a]	100 ± 24[a]	0.497
	Hemorrhage # 2	152 ± 36[a,c,d]	125 ± 36[a,b,c]	0.460
	End of study	172 ± 43	162 ± 35[c]	>0.999
MAP (mmHg ± SD)	Baseline	90 ± 16[a]	91 ± 14[a]	>0.999
	Injury established	69 ±15[a,b]	74 ± 9[a,b]	>0.999
	Hemorrhage # 1	68 ± 14[a,b]	74 ± 11[a,b]	>0.999
	Hemorrhage # 2	55 ±9[a,c,d]	55 ± 8[a,c,d]	>0.999
	End of study	47 ±13	50 ± 6	>0.999
CVP (mmHg ± SD)	Baseline	5 ± 3[a]	3 ± 3	0.411
	Injury established	6 ± 3	5 ± 2	>0.999
	Hemorrhage # 1	7 ± 2	7 ± 2[a,b]	>0.999
	Hemorrhage # 2	5 ± 2	5 ± 3	>0.999
	End of study	8 ± 3	4 ± 2	**0.012***
PAP (mmHg ± SD)	Baseline	17 ± 6[a]	18 ± 8[a]	>0.999
	Injury established	26 ± 6[a]	30 ±9[a]	>0.999
	Hemorrhage # 1	30 ± 6[a]	32 ± 9[a,b]	>0.999
	Hemorrhage # 2	28 ± 6[a]	29 ± 9[a]	>0.999
	End of study	28 ± 7	26 ± 10	>0.999
CO (L/min ± SD)	Baseline	3.9 ± 1.7	3.4 ± 1.0	>0.999
	Injury established	3.2 ± 1.1	3.4 ± 1.2	>0.999
	Hemorrhage # 1	3.1 ± 1.2	3.1 ± 1.1	>0.999
	Hemorrhage # 2	3.2 ± 1.4	2.7 ± 0.7	>0.999
	End of study	3.8 ± 1.2	3.3 ± 1.2	>0.999
SV (ml/min ± SD)	Baseline	42 ± 16[a]	42 ± 21[a]	>0.999
	Injury established	35 ± 11	39 ± 13[a]	>0.999
	Hemorrhage # 1	27 ± 10[a]	32 ± 10	>0.999
	Hemorrhage # 2	23 ± 12[a,c]	23 ± 9[a,c]	>0.999
	End of study	24 ± 12	21 ± 10	>0.999
PPV (% ± SD)	Baseline	12 ± 2[a]	13 ± 5	>0.999
	Injury established	12 ± 8[a]	14 ± 8	>0.999
	Hemorrhage # 1	20 ± 7[a,b]	12 ± 9	0.138
	Hemorrhage # 2	26 ± 8[a]	20 ± 11	0.536
	End of study	30 ± 11	19 ± 10	**0.017***
IVC (L/min ± SD)	Baseline	1.2 ± 1.0[a]	1.2 ± 0.6[a]	>0.999
	Injury established	0.9 ± 0.5	0.9 ± 0.4	>0.999
	Hemorrhage # 1	0.7 ± 0.2[a]	0.8 ± 0.3	>0.999
	Hemorrhage # 2	0.6 ± 0.2[a]	0.6 ± 0.3[a]	>0.999
	End of study	0.7 ± 0.3	0.6 ± 0.2	>0.999
PAOP (mmHg ± SD)	Baseline	5 ± 2[a]	5 ± 3	>0.999
	Injury established	9 ± 3[a]	9 ± 3	>0.999
	Hemorrhage # 1	13 ± 7[a,c]	9 ± 3[a]	0.261
	Hemorrhage # 2	12 ± 7[a]	9 ± 4	0.730
	End of study	14 ± 6	9 ± 4	**0.042***

Aim 2 – Study 2: Comparing CLC Oxygenation /PEEP (n=9) versus Standard of Care (n=8) in sheep s/p 40% TBSA burn and inhalation injury [48 hr conscious study]

Figure 3. Cardiovascular indices: control (standard of care) vs CLC oxygen/PEEP (treatment)

Figure 3a. Mean Arterial Pressure (MAP)

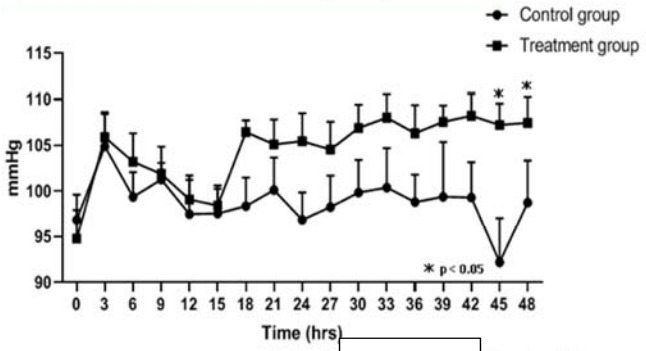


Figure 3b. Heart Rate (HR)

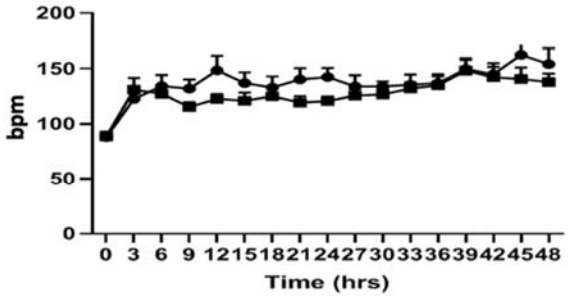
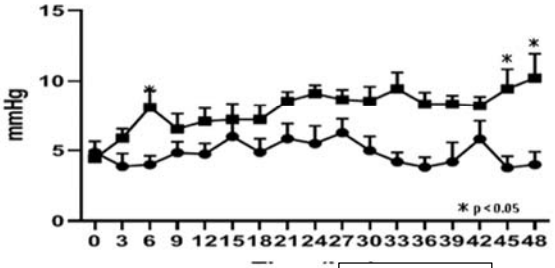


Figure 3c. Central Venous Pressure (CVP)



11

Figure 3d. Systemic Vascular Resistance (SVR)

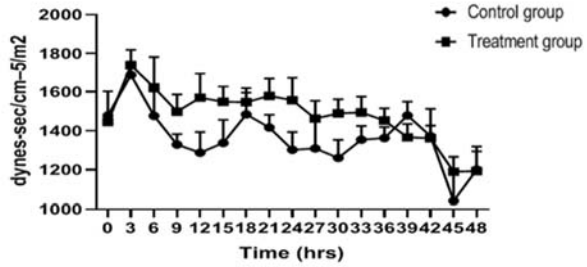


Figure 3e. Stroke Volume Index (SVI)

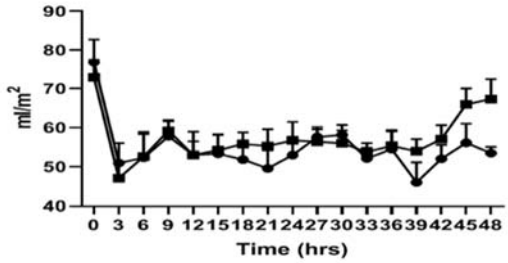
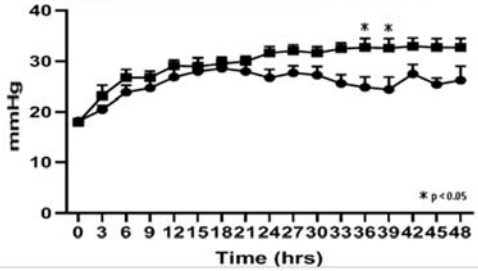


Figure 3f. Pulmonary Artery Resistance (PAP)



12

Figure 4. Pulmonary indices: control (standard of care) vs CLC oxygen/PEEP (treatment)

Figure 4a. Fraction of inspired oxygen (FiO_2)

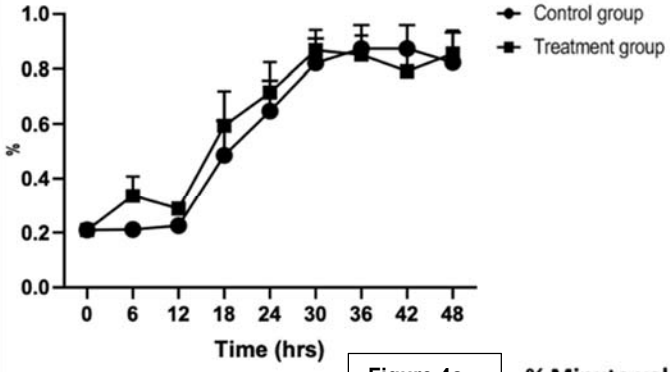


Figure 4b. Positive end-expiratory pressure (PEEP)

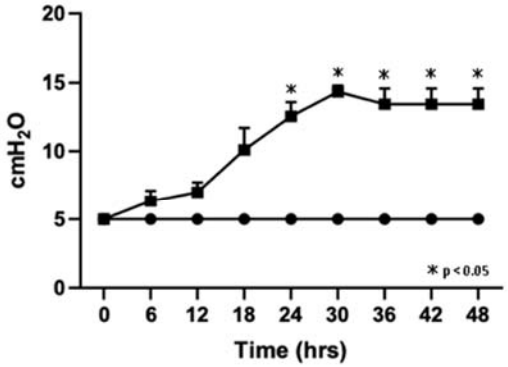


Figure 4c. % Minute volume

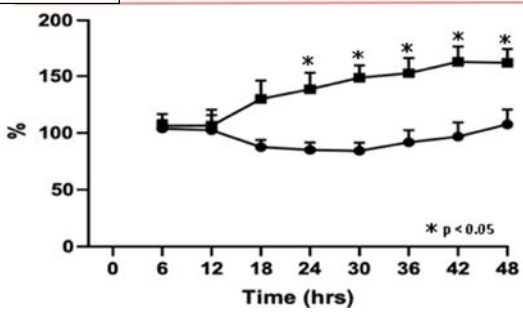


Figure 4d. Respiratory Drive

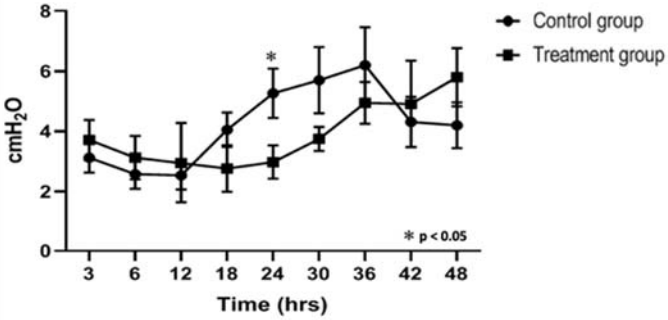


Figure 4e. Dynamic Lung Compliance

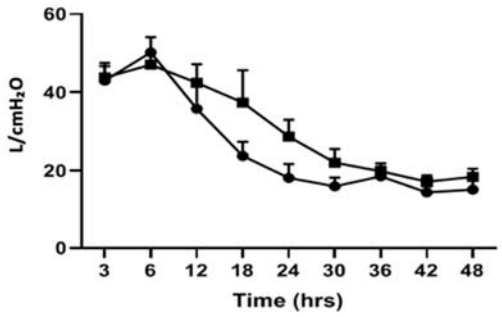


Figure 4f. Peak Airway Pressure

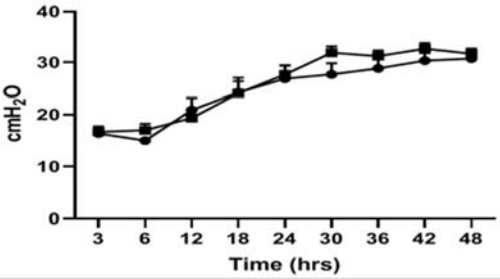
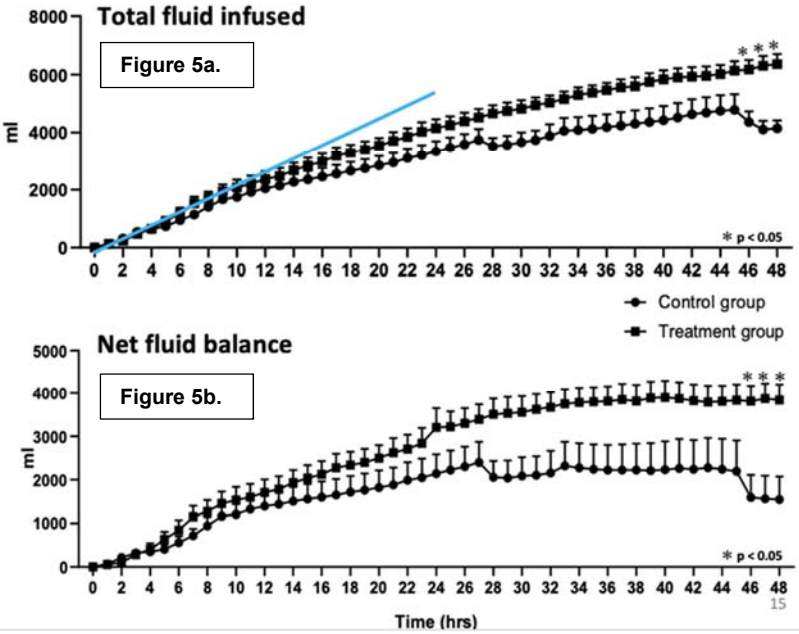


Figure 5. Fluid Balance and Survival: control (standard of care) vs CLC oxygen/PEEP (treatment)

Fluid Balance

- There was no difference on:
  - Infusion rate (ml/h)
  - Urine output (ml)
- The CLC had increased fluid requirement.
- Parkland formula:
  4 ml * % BSA * weight (kg)



15

Control (n = 8) 8 survived 24 hrs
4 survived 48 hrs

CLC (n = 9) → All survived 48hrs

Figure 5c. **Survival Analysis**

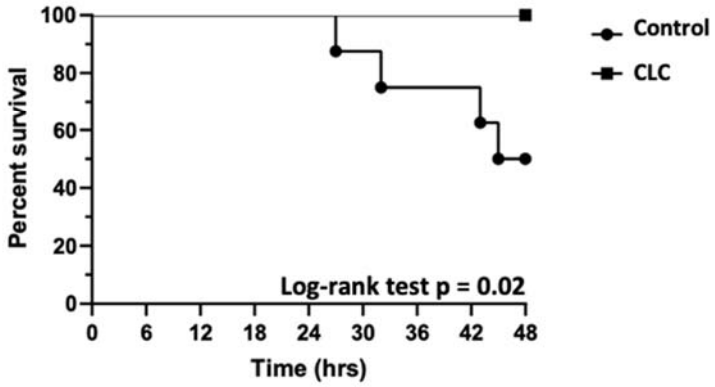


Figure 6. Cardiac work, oxygen extraction and wet/dry wt: control (standard of care) vs CLC oxygen/PEEP (treatment)

Figure 6a. Left Ventricle Stroke Work Index (LVSWI)

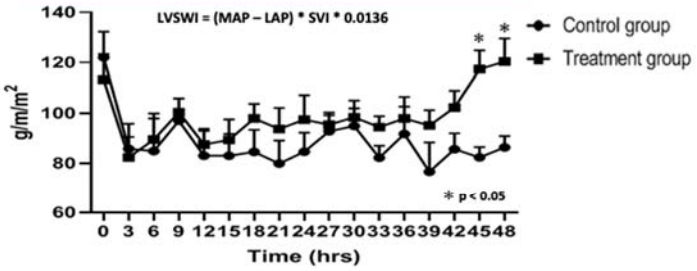


Figure 6b. Oxygen Extraction (VO_2/DO_2)

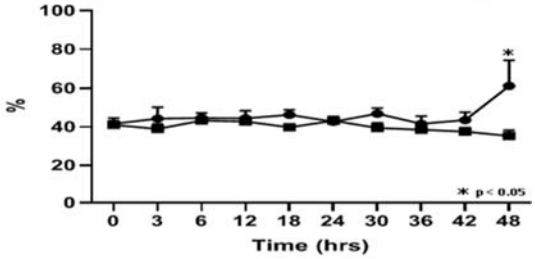
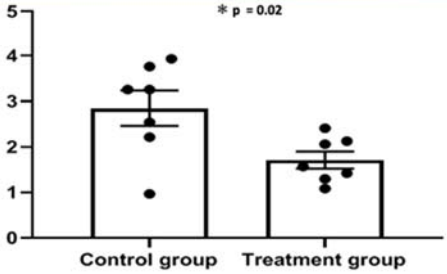


Figure 6c. Heart W/D ratio



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4.0 DISCUSSION

AIM 1 STUDY 1 PORCINE [results: Table 1 – 3]

Discussion: Overall, the measured variables demonstrated small difference between groups suggesting that automated CLC delivers PEEP and fluid therapy as well as SOC. Automation alone is of value as it frees up caregiver time, but our data suggest limited physiologic benefit of CLC. It is of note that the CLC resulted in greater delivery of therapy for similar cardiopulmonary function. Higher levels of PEEP were associated with ASV and more fluid was delivered by the CLC fluid controller. Together, these do provide some support for the hypothesis that competing CL controllers can worsen cardiovascular function and efficiency. Furthermore, making ventilator and fluid adjustments over periods of seconds versus minutes may lead to over therapy.

Our hypothesis was partially rejected: the competing interest of different CLC systems may lead to detrimental cardiopulmonary interaction, and worsen lung injury and fluid overload.

- Cardiovascular: Hemodynamics were similar between the groups, and CLC group did not do worse than the SOC group. It may be important to note that hemodynamics in the CLC group were maintained by delivering fluid overload, which may have decreased diastolic function. However, diastolic function may have a confounding effect of PEEP, which increases intrathoracic pressure and thereby increases CVP and LAP.
- CLC group showed higher CVP/PPV/PAOP at the end of the study. Again, this could be attributed to the higher level of PEEP in the CLC group. No difference was observed on other variables.
- Pulmonary: There was no difference in pulmonary variables except the significantly higher PEEP in the CLC group.
- Fluid overload: More fluid volume was administered in the CLC group. However, there was no difference in total fluid in necropsy in either group. The pericardial fluid on CLC group was higher than the SOC group, which may be attributed to the protective effect of PEEP. Furthermore, no significant difference was observed in the wet lung weight or urine output.
- Despite higher fluid infused (“fluid overload”), there was no significant differences on the cardiopulmonary interaction in either group.
- There was some lung recovery observed in both groups (CLC>SOC) evidenced by the decreasing FiO2 requirements and increasing P/F ratio.
- Greater fluid administration on the CLC group did not lead to a worse lung injury. This may be due to the lung protective effects of PEEP, which may have pushed the fluid out of the lung.
- Significant anemia and hemodilution was observed in both groups at the end of the injury.
- At study end neither the CLC nor the SOC group has sustained target MAP of 70 mmHg.
- Limitations
    - The P/F ratio was recovered during 30 minutes baseline period in both groups.

- It is a strength and a weakness of this study that this model of lung injury and hemorrhage were severe.

AIM2 STUDY 2 OVINE [Results: Figures 3 -6]

Discussion: Severe burn and smoke inhalation injury in sheep induces substantial lung injury and tissue edema; however, this occurs over a period of 12-24 hr. Pathophysiologically, there is direct and indirect injury to bronchi and alveoli from inflammation, mucosal secretion and bronchoconstriction. Furthermore, cardiac strain contributes to further fluid extravasation, which is worsened by large volume resuscitation. Closed-loop control of PEEP attenuates some of the cardiovascular injury. Additionally, PEEP [of 15 cmH2O vs 5 cmH2O (control group)] confers protection in reducing the overall driving pressure while preserving minute ventilation.

We were surprised to observe a survival benefit in the CLC PEEP/oxygenation group. While the precise mechanisms cannot be elucidated by this study, we can infer, based on our data, that CLC PEEP reduces oxygen consumption and improves left ventricular stroke index. Interestingly, myocardial edema was lessened in the CLC PEEP group, suggesting less myocardial injury or some degree of protection. While the CLC PEEP group received more fluid [both groups were administered fluid based on urinary output decision support algorithm], the amount of fluid in the CLC PEEP group did not exceed the Parkland formula.

As outlined in series 1, automation frees up caregiver time. Several studies show improved efficiency and efficacy. While efficiency [less fluid] was not observed, efficacy based on survival was clearly improved in CLC PEEP/oxygenation group. In contrast to series 1, higher levels of PEEP in this series had advantages. Thus, hypothesis partially rejected.

• Closed loop ventilation (FiO2, PEEP and minute volume) reduced lung strain, alleviated cardiac performance and improved 48-h survival in sheep subjected to combined burn and smoke inhalation injuries.

• Driving pressure was much lower in closed loop group that may have resulted in less energy expenditure and reduced cellular/tissue stress including heart muscle (LVSWI was better in CLC PEEP). In support of this speculation, oxygen extraction was lower, indirectly suggesting possible less compromised metabolic rate.

• Incidence of lowest P/F were fewer in CLC PEEP group, suggesting less tissue hypoxia, including heart muscle.

• Higher minute volume and CLC PEEP may be a reason for fewer incidence of lowest P/F ratio, thus preventing severe hypoxia episodes. Higher PEEP could impact myocardial contractility. Higher LVSWI suggests better myocardial contractility (however we acknowledge that LVSWI by itself is not contractility. Echo studies are ongoing to compare this effect.

5.0 CONCLUSIONS

There is an increase need and recognition by the Department of Defense, as well as, rural medical care to push for rapid development of technologies. This would enable care to be delivered in areas where expertise is lacking and resources are limited. Additionally, CLC technologies enhance the management of task force by providing monitoring and treatment for a specific organ system. For example, a CLC device such as an oxygenation support, can automatically monitor and treat oxygenation deficits, which thereby provide the clinician to focus on other tasks e.g., cardiovascular support.

Optimizing care in critical care ill patients, requires a systematic approach. It is most likely that perturbations occur in more than one system e.g, cardiovascular insult and lung injury can occur common in combat casualty or severe trauma. Hemodynamic data is gathered from electronic medical record and variety of monitors, and then integrated by the clinician to make decisions, which often are interdependent.

Single CLC systems have shown greater autonomous control of specific endpoint variables compared to manual adjustment. The interaction of two or more CLC systems, working independently to optimize different physiological systems need to have clinician presence, vigilance and ability to alter or even disengage a CLC system. Acute lung injury by different mechanisms respond differently. Thus, effect of closed loop ventilation should also be tested in different ARDS models induced by various etiologic factors (i.e., sepsis etc.).

6.0 REFERENCES

1. Herrero P, Rawson TM, Philip A, Moore LSP, Holmes AH, Georgiou P. Closed-Loop Control for Precision Antimicrobial Delivery: An In Silico Proof-of-Concept. IEEE Trans Biomed Eng. 2018 Oct;65(10):2231-2236
2. Albrecht S, Frenkel C, Ihmsen H, Schüttler J. A rational approach to the control of sedation in intensive care unit patients based on closed-loop control. Eur J Anaesthesiol. 1999 Oct;16(10):678-87.
3. Liberman MY, Ching S, Chemali J, Brown EN. A closed-loop anesthetic delivery system for real-time control of burst suppression. J Neural Eng. 2013 Aug;10(4):046004.
4. Peter J, Klingert K, Klingert W, Thiel K, Königsrainer A, Grasshoff C, Rosenstiel W, Schenk M. Automated closed-loop management of body temperature using forced-air blankets: preliminary feasibility study in a porcine model. BMC Anesthesiol. 2018 Jul 3;18(1):80
5. Pasin L, Nardelli P, Pintaudi M, Greco M, Zambon M, Cabrini L, Zangrillo A. Closed-Loop Delivery Systems Versus Manually Controlled Administration of Total IV Anesthesia: A Meta-analysis of Randomized Clinical Trials. Anesth Analg. 2017 Feb;124(2):456-464
6. Marques NR, Whitehead WE, Kallu UR, Kinsky MP, Funston JS, Wassar T, Khan MN, Milosch M, Jupiter D, Grigoriadis K, Kramer GC. Physician-Directed Versus Computerized Closed-Loop Control of Blood Pressure Using Phenylephrine in a Swine Model. Anesth Analg. 2017 Jul;125(1):110-116
7. Hundeshagen G, Kramer GC, Ribeiro Marques N, Salter MG, Koutrouvelis AK, Li H, Solanki DR, Indrikovs A, Seeton R, Henkel SN, Kinsky MP. Closed-Loop- and

Decision-Assist-Guided Fluid Therapy of Human Hemorrhage. Crit Care Med. 2017 Oct;45(10):e1068-e1074
8. Hoskins SL, Elgjo GI, Lu J, Ying H, Grady JJ, Herndon DN, Kramer GC. Closed loop resuscitation of burn shock. J Burn Care Res. 2006 May-Jun;27(3):377-85.
9. Rinehart J, Chung E, Canales C, Cannesson M. Intraoperative stroke volume optimization using stroke volume, arterial pressure, and heart rate: closed-loop (learning intravenous resuscitator) versus anesthesiologists. J Cardiothorac Vasc Anesth. 2012 Oct;26(5):933-9
10. Food and Drug Administration, Center for Devices and Radiological Health: MiniMed 670G System approval letter, September 28, 2016. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160017S031a.pdf. Accessed May 28, 2019.
11. Arnal JM, Garnero A, Novotni D, Corno G, Donati SY, Demory D, Quintana G, Ducros L, Laubscher T, Durand-Gasselin J. Closed loop ventilation mode in Intensive Care Unit: a randomized controlled clinical trial comparing the numbers of manual ventilator setting changes. Minerva Anestesiol. 2018;84(1):58-67
12. Absalom AR, Glen JI, Zwart GJ, SChnider TW, Struys MM. Target-Controlled Infusion: A Mature Technology. Anesth Analg. 2016;122(1):70-8
13. Struys MM, Kalmar AF, De Baerdemaeker LE, Mortier EP, Rolly G, Manigel J, Buschke W. Time course of inhaled anaesthetic drug delivery using a new multifunctional closed-circuit anaesthesia ventilator. In vitro comparison with a classical anaesthesia machine. Br J Anaesth. 2005;94(3):306-17
14. Denai MA, Mahfouf M, Ross JJ. A hybrid hierarchical decision support system for cardiac surgical intensive care patients. Part I: Physiological modelling and decision support system design. Artif Intell Med. 2009 Jan;45(1):35-52
15. Berwick D, Downey A, Conett E. National Academies of Sciences, Engineering, and Medicine. 2016. A National Trauma Care System: Integrating Military and Civilian Trauma Systems to Achieve Zero Preventable Deaths After Injury. Washington, DC: The National Academies Press.
16. Johannigman JA, Branson RD, Edwards MG: Closed loop control of inspired oxygen concentration in trauma patients. J Am Coll Surg 2009; 208(5):763-68
17. Parvinian B, Scully C, Wiyor H, Kumar A, Weininger S. Regulatory Considerations for Physiological Closed-Loop Controlled Medical Devices Used for Automated Critical Care: Food and Drug administration Workshop Discussion Topics. Anesth Analg. 2018;126(6):1916-1925
18. Jernigan PL, Hoehn RS, Blakeman TC, Heyl J, Robinson BR, Pritts TA, Branson RD. Portable mechanical ventilation with closed-loop control of inspired fraction of oxygen maintains oxygenation in the setting of hemorrhage and lung injury. Journal of Trauma and Acute Care Surgery. Volume 79(1), July 2015, p 53–59
19. Mehta AB, Syeda SN, Wiener RS, Walkey AJ. Epidemiological trends in invasive mechanical ventilation in the United States: a population-based study. J Crit Care. 2015;30: 1217-1221.
20. Chatburn RL, Mireles-Cabodevila E. Closed-loop control ofmechanical ventilation: Description and classification of targeting schemes. Respir Care. 2011;56:85-102.

21. Wysocki M, Jouvet P, Jaber S. Closed loop mechanical ventilation. J Clin Monit Comput. 2014;28:49-56.
22. Wenstedt EFE, De Bie Dekker AJR, Roos AN, Verberne JJM, Korsten HHM, Schultz MJ, Bindels AJGH. Current practice of closed-loop mechanical ventilation modes on intensive care units—a nationwide survey in the Netherlands.
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