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W81XWH-13-2-0006

TITLE:

Transportable Life Support for Treatment of Acute Lung Failure Due to Smoke Inhalation and Burns

PRINCIPAL INVESTIGATOR:

Andriy Batchinsky, MD

RECIPIENT:

The Geneva Foundation
Tacoma, WA 98402

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14. ABSTRACT This proposal compares 3 currently marketed extracorporeal gas exchange (ECGE) devices as means to treat lung failure. Objective: assess the capacity of the Hemolung, Cardiohelp and PECLA to lower injurious ventilator settings during transport of combat casualties with lung failure. Hypothesis: when used in conjunction with mechanical ventilation respiratory therapy with the Hemolung, or Cardiohelp, or PECLA permits a 50% or more reduction in minute ventilation. Specific aims: 1) Compare therapeutic efficiency of each ECGE device to reduce minute ventilation in model of ARDS due to smoke inhalation and burns in swine; 2) compare gas exchange efficiency and benchmark the ECGE devices; 3) compare expression of local (lung) and systemic inflammatory mediators; 4) assess safety of ECGE devices. Study design: prospective randomized study in 40 animals (10 for each device/group and controls).					
15. SUBJECT TERMS none provided					
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1. INTRODUCTION:

The purpose of this work is to carry out a comprehensive benchmarking study of three existing minimally invasive extracorporeal lung support (ECLS) devices, also known as extracorporeal gas exchange (ECGE) or extracorporeal CO₂ removal devices (ECCO₂R), which have high potential for fielding. The miniaturized self-operating and portable ECGE systems we will compare are: Hemolung (Alung Technologies, Pittsburgh, PA), Pumpless Extracorporeal Lung Assist (PECLA) system, and the Cardiohelp (Maquet Cardiopulmonary, USA). We will address the following requirements: 1) therapeutic feasibility to replace at least 30%-50% of the ventilatory function of the injured lung; 2) potential to reduce mechanical ventilator settings and improve outcome; 3) clinical practice guidelines and therapeutic indications for use; and 4) implications of weight, size, and logistics of ECGE therapy. This technology is envisioned to be used as an autonomous, minimally invasive adjunct to mechanical ventilation (MV) and without a need for constant supervision by providers or for specialized staff training. Applicability of ECGE technology is expected at levels II-III, during en-route care, and at higher echelons as needed. We will provide practical guidelines for use of ECGE in casualties with various degrees of respiratory failure due to any reason but also as specific to casualties with inhalation injury and burns. We will develop a revolutionary new approach to management of patients with lung failure which is based on sound physiology and a recent complete re-evaluation of maximally lung-protective ventilatory strategies with the aim of providing life-sustaining and effective respiratory support during transport of *mechanically ventilated combat casualties with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) due to inhalation injury and burns.*

2. KEYWORDS:

Lung failure; acute respiratory distress syndrome acute lung injury; mechanical ventilation; Extracorporeal Gas Exchange (ECGE); Pumpless Extracorporeal Lung Assist (PECLA), Hemolung, NovaLung, Cardiohelp.

3. OVERALL PROJECT SUMMARY:

The primary objective of this project is to evaluate the therapeutic efficiency of the ECGE devices to decrease mechanical ventilation requirement in a swine model of ARDS due to smoke and burn. The secondary objectives are: 1) to develop practice guideline protocols for minimally invasive use of the ECGE devices; 2) to compare gas exchange efficiency and benchmark the ECGE devices; 3) to compare expression of local (lung) and systemic inflammatory mediators in control and ECGE-treated animals; 4) to assess safety of ECGE devices and complication rates, circuit interventions, and adjustments during therapy; 5) to determine coagulation profile during ECGE therapy.

The project commenced on 30 March 2013. The first priority was to accomplish Specific Aim 1 objective 1a and to receive approval for the animal use addendum. This task has

been accomplished. The animal protocol has been approved by the USA ISR IACUC and reviewed and approved by ACURO. The animal ordering and supply purchase plan has been developed.

To address Milestone 1, "First consensus conference of international experts on minimally invasive ECLS use," took place at the 12th International Conference on Complexity in Acute Illness (ICCAI) in Budapest, Hungary August 8 ó 11, 2013. This conference included a comprehensive round table with participation of international experts representing USA, Hungary, Germany, Italy, France and Ukraine. The conference included a specialized half-day session (funded by this grant) focusing directly on emerging need and indications for partial lung support using ECGE devices. Position paper is being written and work on the manuscript summarizing this first introductory meeting is ongoing.

Work has begun on accomplishing Milestone 2, "Report on device performance and efficiency for each ECGE device." At no cost to the project we added an additional arm of experiments using the Hemolung ECGE device in conscious spontaneously breathing sheep. Addenda entitled: "Effects of Low-Flow-CO₂-Removal in Experimental Lung Injury in Sheep" and "Treatment of an Inhalation Injury via Mechanical Ventilation with Continuous Spontaneous Breathing" were approved by USAISR IACUC with subsequent approval by ACURO. Work on this arm consisting of 15 animals randomized between one group treated with the Hemolung + a model of non-invasive ventilation (BIPAP) and another group treated with spontaneous breathing via BIPAP, is nearing completion. The reason for this addition to the protocol is logistical but also, importantly, innovatively scientific. Logistically, the ISR had a temporary delay with animal housing (swine specifically) as well as long delay with space available for research due to a Government shutdown. This caused major delays with our ability to start the work in pigs. However, sheep space was not affected and so the priority during this period was to include an aspect of use of ECGE devices in conjunction with spontaneously breathing patients. This approach is completely innovative and is directly applicable to a condition when a combat casualty has partial lung damage and still is able to breathe in-part spontaneously only needing some assistance with ventilation. Another condition we focused this addendum on is a scenario when mild or moderate lung failure occurs and partial lung support is carried out with ECGE and avoiding intubation, full anesthesia and fully invasive mechanical ventilation. In this case the subject would be placed on non-invasive mechanical ventilation. Although sheep in our experiments had a tracheostomy (an equivalent of an intubation) that was performed due to technical reasons (smoke delivery and maintenance of a safe airway over days of the experiment in conscious state) and the same treatment in humans would be carried out with a face mask only and without any form of intubation. The addendae and innovative objectives were approved by the GOR in a timely manner.

In addition, progress was made towards Specific Aim 3, Objective 3. Local (bronchoalveolar lavage) and systemic (plasma) cytokine analysis in the "Sheep" arm of the study is ongoing. Also, progress was made towards Specific Aim2 Objectives 2a and 2b. Use of the Hemolung device in sheep permitted us to assess gas exchange efficiency of this device. Data analysis is presently ongoing. Finally, we underwent training on the use of the Maquet PALP device which is the second device we will benchmark. The device itself was delivered also with a delay but now is available for use.

The third device, the NovaLung Mini Lung Petite, will replace the PECLA interventional lung assist device as it is less invasive, veno-venous and the most recently produced equipment. Our lab will be the first to test this device in the USA and preparation of the paperwork to receive these devices is still ongoing causing a delay in the start of the benchmarking experiments. We envision overcoming this delay by August of 2014. In summary, overall we made solid progress on the grant, non-withstanding that the progress of our research was hampered by the government shutdown and delays with housing of animals at the USA ISR veterinary support division. We are happy with the progress made and will work diligently toward the successful continuation of this study.

4. KEY RESEARCH ACCOMPLISHMENTS:

- We hired a research fellow Dr. Slava Belenkiy, MD
- 1st consensus conference of international experts on minimally invasive ECLS use took place at the 12th International Conference on Complexity in Acute Illness (ICCAI) in Budapest, Hungary August 8 ó 11, 2013
- Animal use protocols were approved by the USA ISR IACUC and ACURO
- Practice guidelines for minimally invasive use of ECGE as adjuncts to MV have been started
- Gas exchange efficiency of the Hemolung device is evaluated in the sheep arm of the study, data analysis is ongoing
- Local (lung) and systemic (serum and plasma) cytokines are measured

5. CONCLUSION:

Burns are significant for combat casualty care. Between 2003 and 2005 the annual rate of combat explosion increased from 18% to 69%. Prevalence of ARDS in combat burns was 30% with resulting mortality of 30%. Developing standard practice guidelines on the use of minimally invasive ECGE devices will allow standardization of the use of these devices while reducing requirement for the mechanical ventilation. We were able to conduct a unique study in a novel setting of treating lung injury with partial lung support via continuous positive pressure ventilation (CPAP and BIPAP), a form of non-invasive ventilation permitting to preserve the natural respiration of patients taking advantage of the ability of the body to compensate for injury in conscious state. This means that during injury, a patient will be able to cough, and evacuate pulmonary debris while being supported with partial non-invasive mechanical ventilation with or without partial lung support via an ECGE device (the two groups of studies in sheep). Most importantly, initiation of minimally invasive partial lung support using a dialysis-like 15F intravenous catheter will permit earlier initiation of therapy for the failed lung potentially preventing exacerbation of lung injury due to invasive and injurious intubation and invasive mechanical ventilation. We are assessing the efficiency of the Hemolung ECGE device in conscious state which will lead to the possibility of treating combat casualties without mechanical ventilation and without anesthesia and full incapacitation of natural pulmonary toilet reflexes. In addition, our research enabled us to measure inflammatory mediators in sheep which will enable us to assess the lung protective role of ECGE devices.

We plan to proceed with animal experiments as scheduled in order to accomplish tasks as described in the statement of work.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

a. List all manuscripts submitted for publication during the period covered by this report resulting from this project.

b. Lay Press: nothing to report

(1) Peer-Reviewed Scientific Journals:

1. Belenkiy SM, Berry JS, Batchinsky AI, Kendrick C, Necsoiu C, Jordan BS, Salinas J, Cancio LC. The Non-invasive Carbon Dioxide Gradient (NICO2G) during Hemorrhagic Shock. *Shock*. 2014 Mar 21. Epub ahead of print. PMID: 24667626
2. Belenkiy SM, Buel AR, Cannon JW, Sine CR, Aden JK, Henderson JL, Liu NT, Lundy JB, Renz EM, Batchinsky AI, Cancio LC, Chung KK. Acute respiratory distress syndrome in wartime military burns: application of the Berlin criteria. *J Trauma Acute Care Surg*. 2014 Mar;76(3):821-7. doi: 10.1097/TA.0b013e3182aa2d21. PMID: 24553555
3. Chou L, Batchinsky A, Belenkiy S, Jing J, Ramalingam T, Brenner M, Chen Z. In vivo detection of inhalation injury in large airway using three-dimensional long-range swept-source optical coherence tomography. *J Biomed Opt*. 2014 Mar;19(3):36018. doi: 0.1117/1.JBO.19.3.036018. PMID: 24664245

(2) Invited Articles:

Position manuscript on the first international consensus meeting of experts on ECGE devices and their therapeutic potential in an invited article by the *Journal Critical Care*: currently in preparation.

(3) Abstracts:

LP Neff, JW Cannon, IJ Stewart, AI Batchinsky, DH Zonies, JC Pamplin, KK Chung. Extracorporeal organ support following trauma: The dawn of a new era in combat casualty critical care. *Journal of Trauma-Injury, Infection, and Critical Care* 75 (2), S120-S129, 2013.

Christy Sine, Slava Belenkiy, Waters J, Andriy Batchinsky, Jeremy Cannon, James Aden, Leopoldo Cancio, Kevin Chung. Abstract 235: Acute Respiratory Distress Syndrome in Burns: Application of the Berlin Definition Definition. *Critical Care Med.* 2013; 41(12):A53.

Scaravilli V, Kreyer S, Linden K, Jordan B, Pesenti A, Cancio L, Batchinsky A. Effects of recirculation of dialysate on carbon dioxide removal capabilities of a membrane lung. *J Crit Care.* 2013 Dec;28(6):e38

Berry J, Mccartt J, Belenkiy . S, Park T, Cap A, Cannon J. Damage control resuscitation in a patient on extracorporeal life support with empyema. *J Crit Care.* 2013 Dec;28(6):e40.

- c. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

2013 Batchinsky AI, "Minimally Invasive Extracorporeal Life Support: a New Paradigm in Treatment of Combat Casualties with Lung Failure" Grand Rounds at the Pittsburgh Department of Surgery and Critical Care, Pittsburgh, PA, May 23, 2013.

2013 Batchinsky AI, "Single and multiorgan support for critical illness: new dimensions of complexity at the bedside" invited podium presentation at 12-th International Conference of the Society for Complex Acute Illness, Budapest, Hungary, Aug. 9, 2013.

2013 Batchinsky AI, "Minimally Invasive Extracorporeal Life Support: a New Paradigm in Treatment of Lung Failure" invited podium presentation at the Department of Pulmonary and Critical Care University of California at Irvine, Irvine, California, Nov. 27, 2013.

2014 Batchinsky AI, "Minimally invasive partial lung support devices" invited podium presentation at the 30-th Annual Children's National Medical Center Extracorporeal Membrane Oxygenation and Advanced Therapies for Acute Respiratory Distress Syndrome Conference, 28 February, Keystone, CO.

2014 Batchinsky AI, "Minimally invasive extracorporeal lung support: what it is and what it is not." Invited lecture at the 31-st Annual Conference on High Frequency Ventilation and Acute Respiratory Distress Syndrome, 28 March, Snowbird, Utah.

7. INVENTIONS, PATENTS AND LICENSES:

Invention disclosure on effect of minimally invasive ECGE on shear stress of shunted blood through the circuit is in preparation.

8. REPORTABLE OUTCOMES:

We have developed an electronic data collection system for any and all vital sign and medical monitor data collected in the animal ICU. The system is in use in the animal ICU daily and we will report on its performance after we analyze the data acquired to date.

9. OTHER ACHIEVEMENTS:

Dr. Batchinsky was elected president of The Society for Complexity in Acute Illness (SCAI).

Dr. Belenkiy was selected for CA-1 (PGY-2) position at the Department of Anesthesiology Residency Program at West Virginia University starting 1 July 2015.

10. REFERENCES:

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2. Kauvar DS, Wolf SE, Wade CE, Cancio LC, Renz EM, Holcomb JB. Burns sustained in combat explosions in Operations Iraqi and Enduring Freedom (OIF/OEF explosion burns). *Burns*. Nov 2006;32(7):853-857.
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5. Kauvar DS, Cancio LC, Wolf SE, Wade CE, Holcomb JB. Comparison of combat and non-combat burns from ongoing U.S. military operations. *J Surg Res*. May 15 2006;132(2):195-200.
6. Wolf SE, Kauvar DS, Wade CE, et al. Comparison between civilian burns and combat burns from Operation Iraqi Freedom and Operation Enduring Freedom. *Ann Surg*. Jun 2006;243(6):786-792; discussion 792-785.
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8. Davies A, Jones D, Bailey M, et al. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. *JAMA*. Nov 4 2009;302(17):1888-1895.
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11. Alpard SK, Bidani A, Conrad SA, Zwischenberger JB. Arteriovenous carbon dioxide removal. *Asaio J*. May-Jun 1998;44(3):223-224.

12. Bein T, Weber F, Philipp A, et al. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. *Crit Care Med.* May 2006;34(5):1372-1377.
13. Batchinsky AI, Jordan BS, Regn D, et al. Respiratory dialysis: reduction in dependence on mechanical ventilation by venovenous extracorporeal CO2 removal. *Crit Care Med.* 227 Jun 2011;39(6):1382-1387.
14. Philipp A, Arlt M, Amann M, et al. First experience with the ultra compact mobile extracorporeal membrane oxygenation system Cardiohelp in interhospital transport. *Interact Cardiovasc Thorac Surg.* Jun 2011;12(6):978-981.
15. Bein T, Phillip A, Zimmermann A, et al. Transportable Extracorporeal Lung Support for Rescue of Severe Respiratory Failure in Combat Casualties. Paper presented at: Western Association for the Surgery of Trauma; February 28, 2012, 2012; Veil, Colorado.
16. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1301-1308.
17. Batchinsky AI, Martini DK, Jordan BS, et al. Acute respiratory distress syndrome secondary to inhalation of chlorine gas. *J Trauma* 2006;60 (5)(5):944-957.
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19. Neff LP, Cannon JW, Stewart IJ, Batchinsky AI, Zonies DH, Pamplin JC, Chung KK. Extracorporeal organ support following trauma: The dawn of a new era in combat casualty critical care. *J Trauma* 2013;75(2):S120-S129.

11. APPENDICES:

None.

QUAD CHARTS:

See attached.

Transportable Life Support for Treatment of Acute Lung Failure Due to Smoke Inhalation and Burns
 ERMS/Log Number: 12340055
 W81XWH-13-2-0006



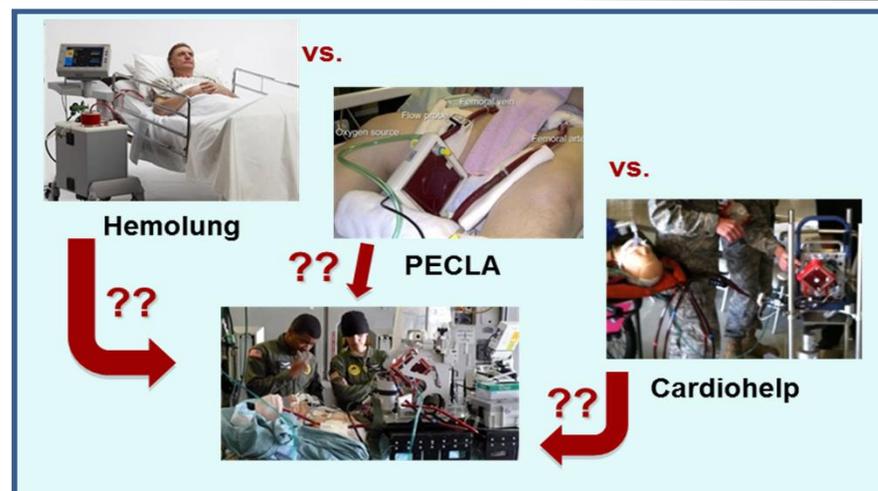
PI: Dr. Andriy Batchinsky Org: The Geneva Foundation/US Army Institute of Surgical Research Award Amount: \$756,062

Study/Product Aim(s)

- Compare therapeutic efficiency of ECGE devices: Hemolung, PECLA, and Cardiohelp to reduce minute ventilation in an animal model of ARDS due to smoke inhalation and burns
- Compare gas exchange efficiency and benchmark the EDGE devices
- Compare expression of pulmonary and systemic inflammatory mediators among groups
- Assess safety of ECGE devices and develop standard heparinization requirements
- Develop standard practice guidelines protocols for minimally invasive use of ECGE devices

Approach

An animal with ARDS from smoke inhalation + 40% cutaneous burn will be randomized to three study arms treated with an ECGE device vs. controls receiving MV alone x5 days per animal: Vent + Hemolung vs. Vent + Cardiohelp vs. Vent + Pumpless Extracorporeal Lung Assist (PECLA)



Accomplishment: Award received 28-MAR-13; animal use addendum to protocol submission approved 12-SEP-13, guidelines on minimally invasive ECLS use pending publication

Timeline and Cost

Activities	CY	13	14	15	16
Experiments on benchmarking ECGE devices		█	█		
Effects on inflammatory mediators		█	█		
Coagulation profile and heparinization requirements		█	█		
Practice guidelines and safety assessment		█	█		
Estimated Budget (\$756K)		\$250	\$251	\$255	\$000

Updated: 11-APR-14

Goals/Milestones

- CY13 Goal** – Begin animal experiments
- X Approve addendum and start experiments
- CY14 Goals** – Benchmark ECGE devices
- X Continue Animal experiments
 - X Study inflammatory mediators
 - X Study coagulation profile, device efficiency and practice guidelines
- CY15 Goal** – Safety assessment and guideline development
- Continue Animal experiments
 - Study inflammatory mediators
 - Study coagulation profile, device efficiency and practice guidelines
- CY16 Goal** – Study completion
- Continue Animal experiments
 - Study inflammatory mediators
 - Study coagulation profile, device efficiency and practice guidelines

Comments/Challenges/Issues/Concerns

Budget Expenditure to Date

Projected Expenditure- Y1: \$259,569
 Actual Expenditure: \$74,255