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TITLE: Lung Injury Etiology, Risk Factors, and Morbidity of Single and Repeated Lo

PRINCIPAL INVESTIGATOR: Dr. Drew Helmer

CONTRACTING ORGANIZATION: Baylor College of Medicine, Houston, TX

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Fort Detrick, Maryland 21702-5012

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Distribution Unlimited

# REPORT DOCUMENTATION PAGE

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**4. TITLE AND SUBTITLE**

Lung Injury Etiology, Risk Factors, and Morbidity of Single and Repeated Low-Level Blast Overpressure Exposure

**5a. CONTRACT NUMBER**
W81XWH-19-2-0059

**5b. GRANT NUMBER**
W81XWH-19-2-0059

**5c. PROGRAM ELEMENT NUMBER**

**6. AUTHOR(S)**

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**5d. PROJECT NUMBER**
0011400654

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

**7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

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**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT**

Cardiopulmonary symptoms of shortness of breath and decreased exercise tolerance after return from deployment are a major concern for many veterans of Iraq and Afghanistan. While much of the focus has been on burn pit exposure and particulate matter as causal factors, there is growing evidence supporting a contributing role of blast-related lung injury. Acute blast overpressure (BOP) lung injury resulting in gross injury is well established. This project will address the less known, possible long-term, or latent effects of less severe BOP lung injuries. We plan to target veterans deployed to Iraq and Afghanistan with exposure to blast injuries of varying severity and invite them to participate in a multi-day cardiopulmonary evaluation. Specifically, we hope to characterize the severity and burden of mild BOP lung injury in Iraq/Afghanistan veterans and determine the association between BOP exposure with physiological, peripheral blood, and CTbased markers of cardiopulmonary function.

**15. SUBJECT TERMS**

veteran, lung injury, blast, dyspnea

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | USAMRDC |
| Unclassified | Unclassified | Unclassified | Unclassified | 9 | 19b. TELEPHONE NUMBER *(include area code)* |

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## 1.INTRODUCTION:

Chronic unexplained cardiopulmonary symptoms of shortness of breath and decreased exercise tolerance have been attributed to burn pit smoke and other airborne hazard exposures while the possible contribution of blast exposure, the signature wound of post-9/11 deployments, has not been thoroughly studied. In addition, there is no information on how sub-threshold blast exposures effect pulmonary function and pathogenesis despite several epidemiological reports showing an association with blast and long-term pulmonary deficits. This translational study will define morbidity, or functional cardiopulmonary deficits associated with cumulative BOP exposures along with biophysiomarkers that can help diagnose the deficits.

## 2.KEYWORDS:

Veteran, lung injury, blast, dyspnea, cardiopulmonary function, translational research

## 3.ACCOMPLISHMENTS:

1. ***Major activities include:***
    a. Project revisions and approvals due to Dr. Helmer's transfer
    b. Transfer of project to MEDVAMC and BCM
    c. Regulatory approvals
    d. Assembly and education of team members
    e. Characterization and retrospective analysis of clinical cohort (i.e., potentially eligible participants)
    f. Integration of partnered project teams with weekly meetings
2. ***Specific objectives include:***
    a. Finalize data collection tools
    b. Identify potential participants
    c. Initiate recruitment, enrollment, and evaluation
    d. Initiate specimen sharing and data collection and analysis
3. ***Significant results or key outcomes***
    a. None to date (due to COVID-19 hold)

4. ***Other achievements***
    a. Better integration of partnering project teams and deeper analysis of clinical data informing the study
    b. Abstract at the American Thoracic Society meeting co-authored by PI's and Co-Is that is informing the research design (https://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2020.201.1_MeetingAbstracts.A4337)
5. ***Training and professional development***
    a. Assembly, education, and cohesion/integration of the project team through weekly meetings and sharing knowledge, skills, and information
6. ***Dissemination of findings***
    a. Nothing to report
7. ***Plans for next reporting period (10/1/2020-9/30/2021)***
    a. Initiate enrollment and data collection (pending release of COVID-19 administrative hold)
    b. Finalize manuscript reporting retrospective review of clinical experience with blast lung injury among potentially eligible participants
    c. Submit several abstracts to national meetings related to retrospective review of clinical experience with blast lung injury among potentially eligible participants
    d. Share preliminary findings at the VA/DoD Airborne Hazards Symposium (anticipated May 2021)

**Explicit list of the major goals of the project as stated in the approved SOW.**

**Specific Aim 2 (Clinical): (months 1-32)**

*Leveraging the unique clinical experience of the WRIISC/AHBPCE, i.) Characterize the severity and burden of mild BOP lung injury in Iraq/Afghanistan Veterans, and ii.) Determine the association between BOP exposure with physiological and CT-based markers of cardiopulmonary function.*

**Regulatory approvals:**

Regulatory approval was delayed due to Dr. Helmer's (PI) transfer from VA-New Jersey Healthcare System and Veterans' Biomedical Research Institute in East Orange, NJ, to Michael E. DeBakey VA Medical Center and Baylor College of Medicine in August 2019. Despite this disruption, important milestones were met.

| | |
|---|---|
| *Project modifications made and approved* | *accomplished 8/2019 (prior to funding)* |
| *Grant successfully transferred* | *accomplished 9/2019 (prior to funding)* |
| *Finalize data collection tools* | *accomplished 12/2019* |
| *Finalize IRB approvals* | *accomplished 1/2020* |
| *Finalize HRPO approval* | *accomplished 6/2020* |

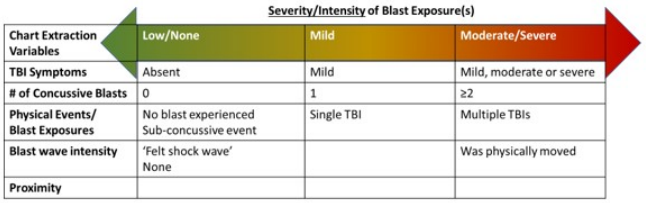
**Subtask 2.1: Human participant enrollment, consent, evaluation and data collection, and data entry. (months 7-32)**

This subtask remains substantially delayed due to COVID 19 and the administrative hold on in-person clinical research across the entire Veterans Health Administration (initiated in 3/2020). VA-New Jersey Health Care System (site of participant recruitment and evaluation) maintains an administrative hold on this protocol. A risk assessment describing how to safely re-open this protocol has been created and submitted to the Research and Development Committee at VA-NJHCS, but the protocol has not yet been approved to reopen.

***Potential participants identified from WRIISC patients and AHOBPR  accomplished 9/2020 (months 7-9)***

The team has identified and characterized the cohort of potentially eligible patients previously evaluated by the team at VA-NJHCS. Analysis is ongoing to further develop preliminary evidence of key clinical outcomes and blast characteristics from this clinical experience to refine the prospective evaluation and inform the broader scientific and clinical community of risk parameters and clinical outcomes of blast-related lung injury. To

support our alternative strategy of recruiting from the Airborne Hazards and Open Burn Pit Registry we have obtained the proper data use agreements.




| Variable | Low/None | Mild | Mod/Severe |
|---|---|---|---|
| Cases (n, %) | 170 | 51 | 46 |
| TBI Mild (n, %) | - | 49 | 45, 97.8% |
| TBI Mod (n, %) | - | 1 | 1, 2.% |
| TBI Severe (n, %) | - | 1 | 0 |
| # Concussive Blasts | - | Single = 51 | Two = 11; ≥ 3 = 35 |
| Physically moved (n, %)* | 5, 2.9% | 20, 39.2% | 18, 39.1% |
| Proximity < 50 m (n, %)* | 20, 11.8% | 39, 76.5% | 33, 71.7% |
| Male sex (n, %) | 134, 78.8% | 47, 92.2% | 42, 91.3% |
| Smoking (never, former, current) | 89, 52, 28 | 27, 16, 8 | 15, 20, 11 |
| Age (Median, [IQR]) | 41 [34, 50] | 36 [31, 44] | 37 [32.9, 42.8] |
| BMI (Median, [IQR]) | 30.3 [27.3, 34.2] | 30.6 [28.1, 35.4] | 30.0 [26.7, 34.8] |
| Post-Deploy Length years (Median, [IQR]) | 8.5 [5.3, 11.4] | 8.3 [6.4, 11.7] | 8.6 [5.7, 10.6] |

*Physically moved responses = n/a, yes, no/missing info
*Proximity responses = n/a, <50, 50-100, >200

***20 participants completed (cumulative=20 participants) (months 7-12)***

Due to the administrative hold due to COVID 19, no participants have been contacted, enrolled, or evaluated.

**Subtask 2.2: Human participants' data cleaned and primary analysis (months 7-32)**

Due to the administrative hold due to COVID 19, no participants have been contacted, enrolled, or evaluated.

Retrospective analysis of the baseline, clinical evaluation of potentially eligible patients has proceeded with full team involvement. Analysis is ongoing and a manuscript summarizing the findings from the clinical cohort is in preparation.

**Specific Aim 3 (Pre-clinical + Clinical): (Months 7-32)**

***Using a combined approach, i.) Assay animal and human sera for pro- and anti- inflammatory makers and evaluate their association with indices of cardiopulmonary function, and ii.) Correlate the functional deficits associated with BOP exposure in clinical and pre-clinical studies and develop injury risk curves from the pre-clinical data.***

The integration of the partnered project teams has been accelerated. We have initiated joint team meetings on a weekly basis to more rapidly translate and apply findings from both animal work and retrospective analysis of clinical experience across the projects. This includes identifying novel biomarkers to explore in blood samples and from anatomical and functional assessments.

**Subtask 3.1: Transfer 90 human blood samples to WRAIR (months 7-32)**

**Subtask 3.2: Run assays on pre-clinical and clinical specimens and collect data (months 7-32)**

Both of these subtasks are on hold due to the administrative COVID-19 hold.

**4.IMPACT:**

***What was the impact on the development of the principal discipline(s) of the project?***

Nothing to Report.

***What was the impact on other disciplines?***

Nothing to Report.

***What was the impact on technology transfer?***

Nothing to Report.

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

Nothing to Report.

**5.CHANGES/PROBLEMS:**

Change 1: The transfer of the project from VA-NJHCS and VBRI to MEDVAMC and BCM with Dr. Helmer's (PI) move was reported and approved prior to the start of the project.

Change 2: The COVID-19 pandemic resulted in a VHA-wide administrative hold on all in-person clinical research. This protocol remains on hold, as described above, pending VA-NJHCS approval of the risk assessment and plan for re-opening the protocol. The VA-NJHCS is actively working with facility leadership to resolve any residual concerns and move to reopen the protocol in a manner that protects the safety of participants and research personnel.

Change 3: The COVID-19 administrative hold has decreased the expenditures on participant reimbursement and use of supplies. In addition, this has reduced the need for research team member travel.

There have been no significant changes in human subjects activities. Initial approvals were obtained:

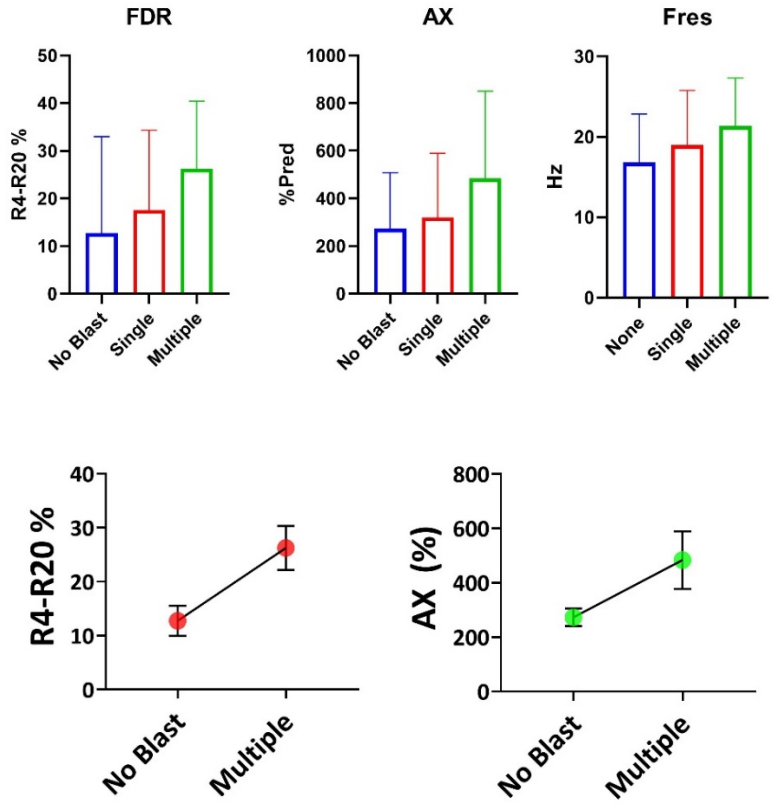
- VANJHCS- April 15, 2020
- MEDVAMC/BCM- March 25, 2020
- HRPO- June 5, 2020

**6.PRODUCTS:**

- Abstract at the American Thoracic Society meeting co-authored by PI's and Co-Is that is informing the research design (https://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2020.201.1_MeetingAbstracts.A4337)

Rationale: Self-reported blast exposure during military deployment to Iraq and Afghanistan is associated with symptoms of dyspnea and exercise intolerance among participants in a national registry. The purpose of our study was to evaluate the association between physician verified blast exposure and lung function assessed via pulmonary function testing (PFT) and forced oscillation technique (FOT).
Methods: We performed a retrospective chart review in 204 Iraq and Afghanistan veterans referred for dyspnea evaluation. Electronic medical records were reviewed by a physician using a standardized chart extraction tool to determine the presence and severity of blast exposure, with severity defined by traumatic brain injury associated with blast. We examined the association of select PFT (TLC, FRC, and RV/TLC) and FOT variables (R4-R20, AX, and Fres) with blast, adjusted for smoking history, BMI and cumulative deployment length.

Blast (none, single or multiple exposure) was used to evaluate the presence of a dose-response relationship.
Results: Median age was 40 years (IQR: 32, 47) and time since deployment was 7.8 (5.1, 10.0) years. Blast was indeterminate in 10.8% (n = 22), not present in 55.9% (n = 114), single exposure in 19.6% (n = 40), or multiple exposure in 13.7% (n = 28). Complete PFT and FOT data were available in 96.1% (n = 196) and 44.6% (n = 91), respectively. We observed no association between blast and PFT variables. In comparison to no blast, multiple exposures were associated with greater AX (β = 205.2; 95% CI: 42.3, 368.1; p = 0.01) and Fres (β = 33.9; 95% CI: 7.3, 60.6; p = 0.01), but not for R4-R20 (β = 11.0; 95% CI: -0.5, 22.5; p = 0.06). No associations were observed when comparing single exposure to none. In comparison to a single exposure, multiple blast exposure was associated with greater AX (β = 194.5; 95% CI: 14.2, 374.7; p = 0.04), but not for Fres (β = 25.1; 95% CI: -4.4, 54.6; p = 0.10) nor R4-R20 (β = 10.0; 95% CI: -2.7, 22.7; p = 0.12).
Conclusions: In our models adjusted for smoking history, BMI and cumulative deployment length, multiple blast exposures were associated with greater small airway dysfunction as defined by FOT. Our findings suggest that blast exposure of sufficient intensity may have a profound effect on the small airways that may not be readily apparent on PFT. Future work is necessary to confirm these findings and understand the mechanism of injury.




**7.PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

***Name: Drew A. Helmer, MD, MS***

Project Role: Principal Investigator

Researcher Identifier (e.g. ORCID ID): vhahouhelmed

Nearest person month worked: 2

Contribution to Project: Leads the project

Funding Support: Funding contributed by VA

***Name: Michael Falvo, PhD***

Project Role: Lead Site Investigator VA-NJHCS

Researcher Identifier (e.g. ORCID ID): https://orcid.org/0000-0001-9348-6676

Nearest person month worked: 2

Contribution to Project: Leads project activities at VA-NJHCS site

Funding Support: Funding contributed by VA

***Name: Israel Christie, PhD***

Project Role: Statistician

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 1

Contribution to Project: Design data collection approach and plan analyses

Funding Support: Funding from this project

***Name: Jennifer Thernkorn, PhD***

Project Role: Research Scientist

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 2

Contribution to Project: Blast-related content expertise, study design and data collection

Funding Support: Funding from this project

***Name: Jason Aguilar***

Project Role: Research Assistant

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 1

Contribution to Project: project, regulatory, and dissemination support

Funding Support: Funding contributed by VA

***Name: Will van Doren***

Project Role: Research Assistant

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 2

Contribution to Project: project, regulatory, and dissemination support

Funding Support: Funding contributed by VA

***Name: Jackie Klein, MS***

Project Role: Laboratory Coordinator

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 2

Contribution to Project: exercise physiology and data collection expertise

Funding Support: Funding contributed by VA

***Name: Sean Hu, MD***

Project Role: Medical Resident

Researcher Identifier (e.g. ORCID ID): N/A

Nearest person month worked: 1

Contribution to Project: Chart abstraction to support manuscript

Funding Support: No Funding

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to Report.

**What other organizations were involved as partners?**

Walter Reed Army Institute for Research

Bethesda, MD

Sujith Sajja, PhD is the PI of the partnered project (W81XWH-19-2-0058). As proposed and funded, Dr. Sujith and his team actively collaborate on this project and utilize their facilities to complete the collaborative activities described in the statement of work and the protocols.

**8.SPECIAL REPORTING REQUIREMENTS ◦COLLABORATIVE AWARDS:**

This is a partnered project. Dr. Sajja (PI, W81XWH-19-2-0058) will submit a separate, complementary annual report.

**9.APPENDICES:**

Not applicable.