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

PRINCIPAL INVESTIGATOR: Dr. Drew Helmer, MD, MS

CONTRACTING ORGANIZATION: Baylor College of Medicine, Houston, TX

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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 CT based markers of cardiopulmonary function. This is the third annual summary and substantial progress has been made in recruitment and data collection. A no cost extension was requested and approved.

15. SUBJECT TERMS
veteran, lung injury, blast, dyspnea

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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 affect 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 blast overpressure (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. Identification of participants
- b. Recruitment, enrollment, and evaluation of participants
- c. Data collection
- d. Identification of new participant pool

2. Specific objectives include:

- a. Identify potential participants
- b. Initiate recruitment, enrollment, and evaluation
- c. Initiate specimen sharing, data collection and analysis

3. Significant results or key outcomes from 10/1/2022-9/30/2023

- a. Mailed 346 invitation letters
- b. Screened 100 respondents
    - i. 54 were determined to be eligible
- c. 34 participants were enrolled in the past year,
- d. 32 studies were completed in the past year.

4. Total significant results or key outcomes from 10/1/2022-9/30/2023

- a. Mailed 668 invitation letters (since start of study)
- b. Screened 245 respondents
    - i. 124 were determined to be eligible

c. 72 participants were enrolled
d. 69 studies were completed

5. Other achievements

a. Identified potential participants from the Airborne Hazards & Open Burn Pit Registry (AHOBPR) (n=9008)
    i. Determined based on geographic proximity, smoking status, self-reported exclusionary conditions, and self-reported blast exposure
    ii. No blast n=2180; Yes blast n=6779
b. Requested regulatory approval to recruit participants from a VA Clinical Sciences Research and Development (CSRD) – funded project "Pulmonary Vascular Dysfunction after Deployment-Related Exposures study" (PI – Falvo)
    i. Overlap in population allows for coordinated recruitment and data collection

6. Training and professional development

a. Assembly, education, and cohesion/integration of the project team through biweekly meetings and sharing knowledge, skills, and information

7. Dissemination of findings

a. Abstract presented at Military Health Sciences Research Symposium in August 2023

8. Plans for next reporting period (10/1/2023-9/30/2024)

a. Recruit, enroll and evaluate more participants to achieve target enrollment of 90 participants
    i. Travel is now allowed (after COVID restrictions) and we have begun recruitment of Veterans previously evaluated at the War Related Illness and Injury Study Center (WRIISC)/Airborne Hazards Burn Pits Center of Excellence (AHBPCE) at VA-New Jersey Health Care System (VANJHCS)
b. Complete analysis of physiology data
c. Complete analysis of blast characteristics and comparison of classification schema
d. Integrate findings to identify and test for associations between blast characteristics and lung function and symptoms.

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:

The VANJHCS site made an amendment on October 2021 to request modification of 1) the exclusion criteria around recent chest CT history, and 2) sequence of experimental procedures allowing to obtain the CT scan at a later date.

The second VANJHCS site amendment was made in March 2022 to clarify the study exclusion criteria to exclude individuals who have been previously diagnosed with cancer (other than non-melanoma skin cancer and to add an additional submaximal breathing test to assess airway inflammation.

The third VANJHCS site amendment was made in August 2022 to exclude individuals who are prescribed and consistently using systemic immunomodulator medication.

The VANJHCS site made the fifth amendment in October 2021 for modifications of 1) the exclusion criteria around recent chest CT history, and 2) sequence of experimental procedures allowing to obtain the CT scan at a later date. This will allow Veterans who had low dose CT scans to participate in the study earlier that previously allowed. Furthermore, For Veterans who are able and willing to volunteer for our multi-day visit but have had a recent CT scan that necessitates a waiting period (i.e., 4- or 12-months depending on type), we would like to be

able to proceed with all other study procedures and then separately schedule a CT scan for our study when the appropriate time interval has elapsed.

The sixth VANJHCS site amendment was made in March 2022 to clarify the study exclusion criteria to exclude individuals who have been previously diagnosed with cancer (other than non-melanoma skin cancer and to add an additional submaximal breathing test to assess airway inflammation.

The seventh VANJHCS site amendment was made in August 2022 Amendment to exclude individuals who are prescribed and consistently using systemic immunomodulator medication to ensure the integrity of the blood analysis. Potential participants who are in the midst of an acute exacerbation of their lung disease will be asked to delay study participation for a minimum of 3 months. Three months should allow the participant to recover from any acute symptoms that may affect the results of study procedures.

Amendment January 2023: Protocol was edited to allow for a third night in the hotel for Veterans who were traveling great distances to participate in the study.

Amendment May 2023: Protocol was edited to clarify the language around maximum mileage reimbursement that a participant can receive. In the situation that a potential participant lives more then 200 miles away from the East Orange facility, but refuses train/airfare and prefers to drive, we will limit maximum reimbursable mileage to 200 miles each way (400 round trip). At 66 cents a mile, limiting the mileage will prevent excessive, and potentially coercive, compensation.

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

Over the course of the study (since 2021), we mailed 668 invitation letters (since start of study)

b. Screened 245 respondents
    i. 124 were determined to be eligible
c. 72 participants were enrolled
d. 69 studies were completed

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

Quality assurance check performed on the data collection and the interpretation of the blast exposure information. Refined the adaptation and scoring of the MN BEST blast exposure assessment. Conduct biweekly blast status adjudication.

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.

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

Specimens have been collected and processed on site at VA-NJHCS and are being stored in a -80C freezer. They will be batch shipped to Dr. Sajja's lab when 100% of specimens have been collected.

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

This aim and subtasks are currently in progress.

4.IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
Abstract was presented at MHSRS as an oral presentation. Further analysis is underway to identify key items from the Salisbury Blast Interview to create a clinically relevant assessment of self-reported blast characteristics not tied directly to acute neurologic symptoms and of clinical relevance and utility.
Published retrospective analysis of blast in WRIISC/AHBPCE cohort.
Abstract presented at American College of Sports Medicine as a poster.

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:

Nothing to report.

6.PRODUCTS:

1. Abstract- accepted for presentation and orally delivered at the Military Health System Research Symposium in Kissimmee, FL in August 2023 (see appendix).

3. Abstract- accepted for presentation and poster was presented at the American College of Sports Medicine Meeting in Denver, CO in May 2023 (see appendix).

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: T. David Wu, MD
Project Role: Co-Investigator

Researcher Identifier (e.g. ORCID ID): https://orcid.org/ 0000-0003-4906-3232
Nearest person month worked: 1
Contribution to Project: Pulmonary subject matter expertise for evaluation, study design and data collection
Funding Support: No funding

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: 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 (Left for Pulmonary Fellowship but is still involved with manuscript preparation)
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Contribution to Project: Chart abstraction to support manuscript
Funding Support: No Funding

Name: Nicole Piskura
Project Role: Research Assistant
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Nearest person month worked: 2
Contribution to Project: Data collection, pulmonary function testing and cardiopulmonary exercise testing
Funding Support: Funding contributed by VA

Name: Amanda Wentz, MS
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Nearest person month worked:
Contribution to Project: Data collection, pulmonary function testing and cardiopulmonary exercise testing
Funding Support: Funding contributed by VA

Name: Gregory Pappas, PhD
Project Role: Data Scientist
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 2
Contribution to Project: Data analyses, statistical plans
Funding Support: Funding contributed by VA

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.APPENDIX:

Abstract presented at Military Health System Research Symposium.
Title: TBI classification and self-reported blast characteristics are strongly correlated in Veterans of Iraq and Afghanistan

Authors: Israel Christie, PhD[1], Thomas Alexander, MS[2], Duncan Ndirangu[2], Jacqueline Klein-Adams, MS[2], Anays Sotolongo, MD[2], Nisha Jani, PhD[2], David Wu, MD[1], Helene Domanski, MS[2], Matthew Watson, MS[2], Jason Aguilar[1], Nancy Eager, RT[1], Bishoy Sami, MS[2], Michael Falvo, PhD[2], VenkatasivasaiSujith Sajja, PhD[3], Drew Helmer, MD[1]

[1] Michael E. DeBakey VA Medical Center and Baylor College of Medicine, Houston, TX

[2] VA New Jersey Healthcare System, East Orange, NJ

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Introduction:

Traumatic Brain Injury (TBI) is considered a signature wound of US military personnel deployed to Iraq and Afghanistan since 2001. Most of these injuries are classified as mild and were caused by blast overpressure damage from improvised explosive devices and other explosions. While TBI has been the primary focus of clinical care and research related to adverse health effects from blast exposure, other body systems and tissues are also at risk, especially those with density differentials and air-filled organs, such as ears, lung, heart and intestines.

Prior to the development and implementation of wearable blast sensors in active duty military personnel, millions of Service Members deployed to combat theater. According to the TBI Center of Excellence, more than 400,000 experienced TBIs with majority of them attributed to blast exposure. While no objective, concurrently collected data exist to characterize these blast exposures, self-reported information may be helpful in categorizing severity of blast to approximate the blast overpressure strength. This in turn may aid in risk stratification of individuals for persistent or latent adverse health problems.

Two classifications of TBI provide clues to blast severity as reflected in self-reported acute symptoms and signs of TBI: the VA/DoD Classification of TBI Severity Index (VATBISI) and the Minnesota Blast Exposure Screening Tool (MN-BEST). These instruments allow for structured retrospective description of the acute events reflecting possible TBI. The MN-BEST summarizes multiple blast events by asking about the three most severe episodes while the VATBISI can be applied to each event separately. The Salisbury Blast Interview (SBI) is a newer tool for capturing the characteristics of the blast event separate from the acute neurologic signs and symptoms, each blast event is captured separately.

In an ongoing prospective study to characterize the association between blast exposure and lung structure and cardiopulmonary function, we have applied each of these instruments to characterize the blast experience of participants. In this analysis, we review the experience of the first 52 participants and compare TBI classifications according to the VATBISI and MN-BEST, and self-reported blast characteristics from the SBI to better understand the potential utility of these instruments to classify the blast exposure of US military personnel without individual monitoring data.

Materials and Methods:

Fifty-two Veterans deployed to Iraq or Afghanistan after October 2001 were enrolled in a prospective observational clinical study to evaluate the relationship between blast exposure and cardiopulmonary function. Forty individuals (77%) reported one or more blast experiences; Twelve individuals (23%) denied having any blast exposure and are excluded from this analysis.

We used semi structured interviews to characterize up to three, most severe individual blast episodes according to VATBISI (Did Not Meet Criteria (DNMC), mild, moderate, severe) and MN-BEST (DNMC, Mild- Type 0, Mild- Type 1, Mild- Type 2, Moderate, Severe) TBI severity criteria and SBI. Items of the SBI addressed perceived domains of blast exposure: wind intensity (wind), disturbance of debris (debris), ground shaking or moving (ground), perception of blast overpressure (pressure), elevation of temperature (temperature), and volume of sound (sound). Each item had domain specific narrative response options of increasing severity/intensity valued 0-5.

We briefly characterize the participants reporting any blast exposures. We then classified each blast episode according to the different TBI classifications following published criteria. We then used Kendall's Tau to assess correlation between these two classification systems and to assess the correlations between SBI item responses and TBI classification according VATBISI and MN-BEST.

Results:

The forty participants included in this analysis were mostly male (39 (98%)) and Caucasian (33 (82%)) or Hispanic (5 (12%)) with a mean age of 43 years (SD 9) and a mean of 42 self-described blast experiences (SD 106). 13 (32%) participants reported one, 9 (22%) reported two, and 18 (45%) reported three or more blast exposures. We characterized 85 blast experiences for a mean of 2.12 (SD 0.88) blasts per participant.

Considering blast episodes as the unit of analysis 44 of 80 blast episodes (5 excluded due to missing data) did not meet TBI criteria (mild or more severe) according to VATBISI and 37 of 84 (1 excluded due to missing data) did not meet TBI criteria (mild or more severe) according to MN-BEST. Agreement between VATBISI and MN-BEST TBI classifications at the blast episode level was high (Kendall's Tau = 0.72, $z = 7.13$, $p < 0.001$).

Salisbury blast characteristic items most strongly associated with VATBISI TBI classification (DNMC, mild, moderate, severe) included pressure ($T = 0.50$, $z = 4.88$, $p < 0.001$), sound ($T = 0.36$, $z = 3.56$, $p < 0.001$) and ground ($T = 0.34$, $z = 3.40$, $p = 0.001$). The correlations between VATBISI and other blast characteristic items (wind, debris, temperature) were less than 0.30.

Salisbury blast characteristics most strongly associated with MN-BEST TBI classification (DNMC, Mild- Type 0, Mild- Type 1, Mild- Type 2, Moderate, Severe) included sound ($T = 0.50$, $z = 5.30$, $p < 0.001$), pressure ($T = 0.44$, $z = 4.73$, $p < 0.001$), ground ($T = 0.38$, $z = 4.09$, $p < 0.001$), temperature ($T = 0.38$, $z = 3.83$, $p < 0.001$), and wind ($T = 0.30$, $z = 3.1$, $p = 0.001$). The correlation between MN-BEST and the SBI debris item was 0.24 (p 0.009).

Conclusions:

Self-reported blast characteristics captured by the SBI and TBI classifications based on VATIBISI and MN-BEST were correlated, supporting the convergent validity of these instruments and indicating a possible latent indicator of blast severity. The two classifications for TBI were highly correlated (T 0.72) in this sample of blast exposed US Veterans of Iraq and Afghanistan deployments. In addition, self-reported perceptions of blast characteristics including perception of the overpressure wave, volume of sound and perceived ground shaking/moving were moderately correlated with TBI severity according to either schema (Ts 0.30-0.50). For the millions of Service Members deployed before wearable sensors for blast overpressure exposure were developed, self-reported blast experience is the only available information to assess their exposure. This analysis supports the clinical utility of using the studied instruments in assigning a blast severity measure to individual blast episodes for studies of long-term health effects of blast exposure.

Learning Objectives

Learning Objective 1: Apply validated assessments of traumatic brain injury and blast exposure.

Learning Objective 2: Understand the correlations among VATBISI and MN-BEST classification schema and Salisbury Blast Interview blast experience items.

Learning Objective 3: Describe the importance of self-reported assessments of blast exposure for health risk stratification and research.

Abstract presented at American College of Sports Medicine

Evaluation of Inter-rater Agreement for Identifying Dysfunctional Breathing in Cardiopulmonary Exercise Testing

Jacquelyn Klein-Adams[1], Matthew Watson[1], Thomas Alexander[1], Drew Helmer[3], Michael Falvo[1-2]
[1]War Related Illness and Injury Study Center, VA New Jersey Health Care System, East Orange, NJ
[2]Rutgers New Jersey Medical School, Newark, NJ
[3]Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey VA Medical Center, Houston, TX

PURPOSE: Dysfunctional breathing (DB) during exercise describes alterations in the breathing pattern that contributes to dyspnea and impairs quality of life. There is presently no gold standard set of criteria to define DB, but erratic depth (VT) and rate (Rf) are defining features. Here we examine agreement among three ACSM Certified Clinical Exercise Physiologists (CEPs) in identifying DB during maximal cardiopulmonary exercise testing (CPET).

METHODS: Breath-by-breath CPET data were retrospectively analyzed from 64 adults (6 female; 40.8±9.0 years) who volunteered for a research study. VT and Rf (y-axes) were plotted against minute ventilation (x-axis) for each individual and independently reviewed and coded (DB present or not). Blinded results were sent to a colleague and aggregated for analysis. Interrater reliability analysis using the Fleiss kappa statistic (two-way mixed; absolute agreement) was performed to assess consistency among the three CEPs in identifying DB. CPET performance (VO_2 peak, VE/VCO_2 slope, $PetCO_2$) was also compared between those with and without DB via independent t-tests.

RESULTS: There was moderate agreement between CEPs for determination of DB, K= 0.52 (95%CI: 0.38, 0.66), $p < 0.001$. Using the mode, DB was present in 60% of our sample. Overall, subjects endorsed 'severe' (Borg: 5.5±1.8) shortness of breath at peak exercise. CPET performance was similar between groups for each of the measured parameters, VO_2 peak, VE/VCO_2 slope, $PetCO_2$ ($p > 0.05$).

CONCLUSIONS: Three CEPs displayed moderate agreement in identifying DB in our sample when employing a standard definition. Despite the subjective nature of determining DB, the identification of its

presence in 60% of our sample may warrant greater attention in the interpretation of CPET in individuals with unexplained dyspnea; especially when other parameters appear normal.
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