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

PRINCIPAL INVESTIGATOR: 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

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
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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 10/1/2021-9/30/2022***

a. Mailed 201 invitation letters
b. Screened 85 respondents
    i. 52 were determined to be eligible
c. 30 participants were enrolled in the past year,
d. 30 studies were completed in the past year.

***4. Total significant results or key outcomes from 3/1/2021-9/30/2022 (since full approval)***

a. Mailed 322 invitation letters

b. Screened 146 respondents
    i. 70 were determined to be eligible
c. 38 participants were enrolled
d. 37 studies have been 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 September 2022

***8. Plans for next reporting period (10/1/2022-9/30/2023)***

a. Recruit, enroll and evaluate more participants to achieve target enrollment of 90 participants
    i. Travel is now allowed 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. Preliminary analysis of physiology data collected
c. Preliminary analysis of blast characteristics and comparison of classification schema

## 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 last 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.

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

After reviewing and updating research protocols and processes, VA-New Jersey Health Care System (site of participant recruitment and evaluation) sent out the mailing of 55 letters to potential participants on 11/22/2021, 44 letters on 01/12/2022, and 51 letters on 02/3/2022, 51 letters on 08/4/2022. Of the 201 potential participants contacted, 85 were screened and 52 were eligible for the study. Thirty veterans were enrolled in the study by September 29, 2022, and 30 evaluations have been completed.

***Potential participants identified AHOBPR accomplished 9/2021 (months 7-9)***
The alternative strategy of recruiting from the Airborne Hazards and Open Burn Pit Registry was initiated as of 09/2021. Determined based on geographic proximity, smoking status, self-reported exclusionary conditions, and self-reported blast exposure, 9008 of potential participants have been identified. This strategy was initially focused on potentially eligible AHOBPR participants who live within 100 miles of VANJHCS given the hesitancy to travel participants longer distances due to COVID at the time. Once COVID incidence decreased, recruitment prioritized potential participants who were previously evaluated at the WRIISC/AHBPCE at VANJHCS.

***30 participants completed (cumulative=30 participants) (months 7-12)***
Thirty participants have been evaluated and their studies completed as of September 29, 2022, with twelve months of active study period (October 2021 – September 2022). More potential participants have been identified through the AHOBPR and from the "Pulmonary Vascular Dysfunction after Deployment-Related Exposures" study.

## 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 50% and then 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 accepted to MHSRS but was unable to be presented due the meeting being cancelled due to COVID. Manuscript is in progress.

***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:

No problems have occurred. Minor changes to NJ protocol described above.

## 6.PRODUCTS:

1. Abstract- accepted for presentation and poster was presented at MHSRS in September 2022.
2. Publication- Therkorn, J.H., Hu, S., Sotolongo, A.M. et al. Relationship between clinician documented blast exposure and pulmonary function: a retrospective chart review from a national specialty clinic. Respir Res 23, 153 (2022). https://doi.org/10.1186/s12931-022-02071-0

## 7.PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

***Name: Drew A. Helmer, MD, MS***
Project Role: Principal Investigator
Researcher Identifier (e.g. ORCID ID): eraCommons- 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 (Left the project in March 2022)***

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: 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 (Returned from Military Leave in January 2022)***
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 (Left the project in October 2021 and then returned to the project August 2022)***
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)***
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

***Name: Immanuelle Azebe-Osime, MS (Left the project to attend Medical School June 2022)***
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: project, regulatory, and dissemination support
Funding Support: No Funding

***Name: Nicole Piskura***
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 2
Contribution to Project: Data collection, pulmonary function testing and cardiopulmonary exercise testing
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.APPENDICES: (Please see attached for Poster and Published Article)

Abstract presented at MHSRS.
"Retrospective review of clinically documented blast exposure does not demonstrate an association with abnormal pulmonary function test metrics in clinically evaluated Veterans of Iraq and Afghanistan"

Presenter: Drew A. Helmer, MD, MS
Co-authors:
Michael Falvo, PhD
Sujith Sajja, PhD
Jen Therkorn, PhD
Israel Christie, PhD
Tianshi (David) Wu, MD
Sean Hu, MD

Abstract:
Acute blast lung injury is a well described phenomenon resulting from exposure to high blast overpressure waves created by explosives. It is usually associated with other severe trauma and requires intensive and often prolonged care. US servicemembers deployed to Iraq and Afghanistan after 2001 were frequently exposed to blast overpressure waves, but usually of lower intensity. Mild traumatic brain injury is recognized as a signature wound of these deployments, but other organs, particularly those with apposed tissues of differential densities, such as the lung, are also vulnerable to injury. Analysis of self-reported blast exposure
(yes or no) and symptoms of dyspnea and decreased exercise tolerance from the VA/DoD Airborne Hazards and Open Burn Pit Registry detected a moderate association (adjusted odds ratio 1.66, 95%CI 1.5-1.7) between these variables controlling for potential confounding factors. We report findings from cohort of veterans of Iraq and Afghanistan clinically evaluated at the New Jersey War Related Illness and Injury Study Center (NJ WRIISC) at VA-New Jersey Health Care System in East Orange, NJ, testing for associations between clinician documented blast exposure and objective metrics of pulmonary function.

Study Design, Sample and Setting: Retrospective medical record review of 311 veterans deployed to Iraq or Afghanistan after 2001 who completed a comprehensive evaluation at a tertiary center specializing in unexplained, deployment-related health concerns between 2011 and 2019.
Veterans referred to the NJ WRIISC endorse chronic multi-system symptoms that remain unexplained secondary to work-up at the

Veteran's respective VA Medical Center and is refractory to therapy. Comprehensive evaluations are performed by an interdisciplinary team that is tailored to the Veteran yet consists of the following basic elements: 1) medical history review and physical examination, 2) occupational and environmental medicine history, 3) pulmonary function test (PFT) with bronchodilator, 4) neuropsychological or psychological evaluation, and 5) standardized intake questionnaire packet.

All Veterans, irrespective of chief complaint, underwent complete PFT in accordance with published guidelines. PFT was performed in the morning in a semi-fasted state after an overnight withdrawal of bronchodilators (if applicable). Tests were performed in the following order: 1) spirometry, 2) lung volumes via body plethysmography, 3) diffusing capacity of carbon monoxide via the single-breath technique (DLCO), and 4) post-bronchodilator spirometry. Published reference equations were used for interpretation and reporting of spirometry, lung volumes, and DLCO (hemoglobin corrected).

Veterans did not undergo a standardized assessment of blast exposure during their clinical evaluation. However, each Veteran underwent a one-on-one exposure evaluation in which blast and other exposures were explicitly addressed. Exposure to blast was also likely to be discussed during 1) TBI screening conducted by a neuropsychologist or mental health provider, 2) history and physical conducted by a physician or nurse practitioner, and 3) cardiopulmonary evaluation by a pulmonologist. Text from the clinical notes of these encounters provided the data used for characterizing blast exposure.

An a priori chart abstraction process was designed by a multidisciplinary working group of clinicians and scientists with expertise in pulmonary medicine, internal medicine, environmental and occupational medicine, neuropsychology, and exercise physiology. Key variables were abstracted from the clinical notes to characterize blast severity. Veterans were assigned to one of three blast exposure groups: none (n=210), single mild (n=53), or multiple mild (n=48). Individuals (n=3) with moderate or severe blast and were not included in the analysis.

Analysis focused on key metrics from pulmonary function tests: Total Lung Capacity (TLC; % predicted), Forced Expiratory Volume at 1 second (FEV1; % predicted),% change in FEV1 after bronchodilator (%FEV1 PB), the FEV1 to Forced Vital Capacity ratio (FEV1/FVC) and the corrected DLCO (% predicted).

The sample included 261 (84.2 %) men; mean age 40.6 (SD 9.7); mean body mass index 30.4 (SD 5.2); 53 (17.0%) current, 105 (33.8%) former, and 153 (49.2%) never smokers; 206 (66.2%) Army, 18 (5.8%) Navy, 39 (12.5%) Marine, 43 (13.8%) Air Force, 1 (0.3%) Coast Guard; mean 8.6 (SD 3.8) years since deployment; and 14.4 (SD 8.6) months of cumulative deployment. After adjusting for age, gender, height, weight, race/ethnicity, pack years, post deploy length, body mass index, cumulative deployment length and branch of service, neither single mild blast exposure nor multiple mild blast exposures were statistically different from no blast exposure (all p values 0.11-0.96 without correction for multiple comparisons).

In this retrospective analysis of medical records, veterans deployed to Iraq and Afghanistan demonstrated no statistically significant association between single mild or multiple mild clinician documented blast exposures and objective measures of pulmonary function on clinical pulmonary function testing. This is in contrast to the findings from self-reported data from a large cohort previously published in which blast exposure was captured as "yes" or "no", i.e., without characterization of severity or repeated exposure. Other published reports of blast lung injury focused on individuals with multiple traumatic injuries from blast; the NJ WRIISC cohort comprised almost completely of veterans with mild blast exposure. Limitations of the current study include lack of a consistent and explicit focus on characterizing blast exposure during the clinical evaluations, related difficulty consistently abstracting blast intensity and relevant characteristics from the clinical documentation and a heterogeneous sample with regard to potentially confounding characteristics. Strengths include the large sample of veterans deployed to Iraq and Afghanistan with pulmonary function tests and the expert clinical setting. Further research is necessary to better characterize blast exposure among military service members and veterans and examine the potential persistent and latent effects of blast overpressure exposure on cardiopulmonary health.

Abstract Disclaimer:
The views expressed in this abstract are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

Learning Objectives:

1) Assess the state of the science around persistent cardiopulmonary effects of blast overpressure exposure, especially around self-reported exposure and symptoms.
2) Describe the strengths and limitations of retrospective analysis of medical record documentation of blast overpressure exposure.
3) Discuss the importance of objective pulmonary function metrics in assessing the potential effects of blast-related lung injury.

# Retrospective review of clinically documented blast exposure does not demonstrate an association with abnormal pulmonary function test in clinically evaluated Veterans of Iraq and Afghanistan

Mike Falvo, PhD[1,2], Sujith Sajja, PhD[3], Jen Therkorn, PhD[1,2], Israel Christie, PhD[4,5], Tianshi (David) Wu, MD[4,5], Sean Hu, MD[4], Drew Helmer, MD,MS[4,5]

Airborne Hazards Burn Pits Center of Excellence, VA -New Jersey Healthcare System, East Orange, NJ [1], Rutgers New Jersey Medical School, Newark, NJ [2], The Geneva Foundation supporting Blast Induced Neurotrauma Branch, Walter Reed Army Institute of Research, Silver Spring, MD [3], Center for Innovations in Quality, Effectiveness and Safety (IQuESt), Michael E. Debakey VA Medical Center, Houston, TX [4], Baylor College of Medicine, Houston, TX [5]

**Background:** Service member exposure to explosive blast overpressure waves is common with considerable attention to traumatic brain injury (TBI) and neuropsychological sequalae. Less is known about the impacts on the respiratory system, particularly long-term effects, despite vulnerability to overpressure. Using a national registry, we previously observed an independent relationship between self-reported blast exposure and respiratory symptoms; however, the impact on objective measures of pulmonary function is poorly understood.

**Methods:** 307 post-9/11 Veterans were referred to our national specialty center for post-deployment health concerns underwent a comprehensive multi-day evaluation that included complete pulmonary function testing (PFT), occupational and environmental medicine history, neuropsychological or psychological evaluation. We developed an a priori chart abstraction process and template to classify Veterans into blast exposure groups: (1) none, (2) single-mild, or (3) multiple-mild. This template focused primarily on clinician documented notes of blast related TBI that were used as proxy for blast overpressure injury to thorax. PFT variables characterizing flow (FEV1%; %ΔFEV1), volume (TLC%), diffusion (DLCO%) and respiratory mechanics (forced oscillometry) were selected for analysis.

**Results:** Veterans (40.5 ± 9.7 years; 16.3% female) were referred 8.6 ± 3.6 years after their last deployment and presented with considerable comorbid conditions and health problems (e.g., 62% post-traumatic stress, 55% dyspnea). After chart abstraction, Veterans were assigned to none (n = 208), single mild (n = 52) and multiple mild (n = 47) blast exposure groups. Among the blast exposed, clinicians documented 73.7% were < 50 m from the blast and 40.4% were physically moved by blast. PFT outcome measures were similar across all groups (p value range: 0.10–0.99).

**Conclusions:** In this referred sample of deployed Veterans, PFT measures of flow, volume, diffusion, and respiratory mechanics were not associated with clinician documented blast exposure per the retrospective chart abstraction.

Table 1. Blast characteristics identified from chart abstraction process and resultant blast grouping assignments.
Notes: *According to CDC blast injury definitions [10]. TBI = traumatic brain injury. PTSD = posttraumatic stress disorder.

| Study Assigned Blast Grouping | Overall (n = 307) | | No Blast (n = 208) | | Single Mild (n = 52) | | Multiple Mild (n = 47) | |
|---|---|---|---|---|---|---|---|---|
| Blast Characteristics | n | % | n | % | n | % | n | % |
| Proximity to Blast | | | | | | | | |
| Not applicable | 153 | 49.8 | 140 | 67.3 | 7 | 13.5 | 6 | 12.8 |
| < 50 m | 97 | 31.6 | 24 | 11.5 | 40 | 76.9 | 33 | 70.2 |
| 50-100 m | 19 | 6.2 | 12 | 5.8 | 1 | 1.9 | 6 | 12.8 |
| 101-200 m | 7 | 2.3 | 5 | 2.4 | 2 | 3.8 | 0 | 0.0 |
| > 200 m | 19 | 6.2 | 15 | 7.2 | 2 | 3.8 | 2 | 4.3 |
| Missing data | 12 | 3.9 | 12 | 5.8 | 0 | 0.0 | 0 | 0.0 |
| Number of Sub Concussive Blasts | | | | | | | | |
| Not applicable | 75 | 24.1 | 70 | 33.7 | 0 | 0.0 | 1 | 2.1 |
| 0 | 89 | 29.0 | 62 | 29.8 | 17 | 32.7 | 10 | 21.3 |
| 1 | 11 | 3.6 | 6 | 2.9 | 4 | 7.7 | 1 | 2.1 |
| > 1 | 111 | 36.2 | 45 | 21.6 | 31 | 59.6 | 35 | 74.5 |
| Missing data | 25 | 8.1 | 25 | 12.0 | 0 | 0.0 | 0 | 0.0 |
| Number of Concussive Blasts | | | | | | | | |
| 0 | 208 | 67.8 | 208 | 100.0 | 0 | 0.0 | 0 | 0.0 |
| 1 | 52 | 16.9 | 0 | 0.0 | 52 | 100.0 | 0 | 0.0 |
| 2 | 12 | 3.9 | 0 | 0.0 | 0 | 0.0 | 12 | 25.5 |
| ≥ 3 | 35 | 11.4 | 0 | 0.0 | 0 | 0.0 | 35 | 74.5 |
| Missing data | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| TBI Symptoms | | | | | | | | |
| Absent | 208 | 67.8 | 208 | 100.0 | 0 | 0.0 | 0 | 0.0 |
| Mild | 98 | 31.9 | 0 | 0.0 | 52 | 100.0 | 46 | 97.9 |
| Moderate | 1 | 0.3 | 0 | 0.0 | 0 | 0.0 | 1 | 2.1 |
| Missing data | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| PTSD Associated with Blast | | | | | | | | |
| Not applicable | 35 | 10.5 | 24 | 11.5 | 4 | 7.7 | 3 | 6.4 |
| Yes | 26 | 8.5 | 9 | 4.3 | 12 | 23.1 | 5 | 10.6 |
| Maybe | 65 | 19.9 | 25 | 12.0 | 16 | 30.8 | 20 | 42.6 |
| No | 102 | 33.2 | 66 | 31.7 | 18 | 34.6 | 18 | 38.3 |
| Missing data | 87 | 28.3 | 84 | 40.4 | 2 | 3.8 | 1 | 2.1 |
| Blast Related Symptom or Injury* | | | | | | | | |
| Not applicable | 198 | 64.5 | 171 | 82.2 | 15 | 28.8 | 12 | 25.5 |
| Primary | 30 | 9.8 | 6 | 2.9 | 11 | 21.2 | 13 | 27.7 |
| Secondary | 6 | 2.0 | 1 | 0.5 | 3 | 5.8 | 2 | 4.3 |
| Tertiary | 25 | 8.1 | 3 | 1.4 | 13 | 25.0 | 9 | 19.1 |
| Quaternary | 23 | 7.5 | 2 | 1.0 | 10 | 19.2 | 11 | 23.4 |
| Missing data | 25 | 8.1 | 25 | 12.0 | 0 | 0.0 | 0 | 0.0 |
| Physically Moved by Blast | | | | | | | | |
| Not applicable | 89 | 29.0 | 89 | 42.8 | 0 | 0.0 | 1 | 2.1 |
| Yes | 45 | 14.7 | 5 | 2.4 | 23 | 44.2 | 17 | 36.2 |
| No | 147 | 47.9 | 89 | 42.8 | 29 | 55.8 | 29 | 61.7 |
| Missing data | 26 | 8.5 | 25 | 12.5 | 0 | 0.0 | 0 | 0.0 |

Disclaimer: The views expressed in this abstract are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

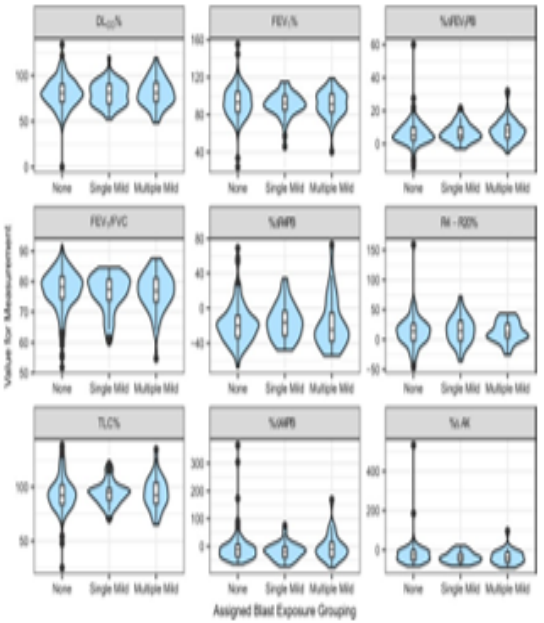


Fig. 4 Violin plots of pulmonary function test findings across assigned blast exposure groups. Blast exposure group assignments are as follows: none (n = 208), single mild (n = 52), and multiple mild (n = 47). The plots represents the range for each of the nine respective variable x and measurement units are dependent on variable type. Total Lung Capacity (TLC%; %predicted), Forced Expiratory Volume at 1 s (FEV1%; % predicted),% change in FEV1after bronchodilator (%ΔFEV1FB), the FEV1to Forced Vital Capacity ratio (FEV1/FVC), the corrected DLCO (DLCO%, % predicted), difference in resistance between 5 and 20 Hz (R5-R20%), % change in resistance area after bronchodilator (%ΔAX), and % change in resistance and reactance at the lowest frequency (4 Hz) after bronchodilator (%ΔRFB and %ΔXFB)

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# Relationship between clinician documented blast exposure and pulmonary function: a retrospective chart review from a national specialty clinic

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## Abstract

**Background:** Service member exposure to explosive blast overpressure waves is common with considerable attention to traumatic brain injury (TBI) and neuropsychological sequalae. Less is known about the impacts on the respiratory system, particularly long-term effects, despite vulnerability to overpressure. Using a national registry, we previously observed an independent relationship between self-reported blast exposure and respiratory symptoms; however, the impact on objective measures of pulmonary function is poorly understood.

**Methods:** 307 Veterans referred to our national specialty center for post-deployment health concerns underwent a comprehensive multi-day evaluation that included complete pulmonary function testing (PFT), occupational and environmental medicine history, neuropsychological or psychological evaluation. We developed an a priori chart abstraction process and template to classify Veterans into blast exposure groups: (1) none, (2) single-mild, or (3) multiple-mild. This template focused primarily on clinician documented notes of blast related TBI that were used as proxy for blast overpressure injury to thorax. PFT variables characterizing flow ($FEV_1$%; %Δ$FEV_1$), volume (TLC%), diffusion ($DL_{CO}$%) and respiratory mechanics (forced oscillometry) were selected for analysis.

**Results:** Veterans (40.5 ± 9.7 years; 16.3% female) were referred 8.6 ± 3.6 years after their last deployment and presented with considerable comorbid conditions and health problems (e.g., 62% post-traumatic stress, 55% dyspnea). After chart abstraction, Veterans were assigned to none (n = 208), single mild (n = 52) and multiple mild (n = 47) blast exposure groups. Among the blast exposed, clinicians documented 73.7% were < 50 m from the blast and 40.4% were physically moved by blast. PFT outcome measures were similar across all groups (*p* value range: 0.10–0.99).

**Conclusions:** In this referred sample of deployed Veterans, PFT measures of flow, volume, diffusion, and respiratory mechanics were not associated with clinician documented blast exposure per the retrospective chart abstraction

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methodology applied. Yet, these clinical findings suggest future research should determine and assess distinction between Veteran recollections of perceived blast experiences versus overpressure wave exposure to the respiratory system.

## Introduction

Approximately 8 in 10 combat injuries in recent conflicts have an explosive blast etiology [1] which includes air blast wave propagation from improvised explosive devices (IED). IEDs are a distinguishing feature of the conflicts in Iraq and Afghanistan [2] and well-recognized to induce traumatic brain injury (TBI) [3]. However, organ systems other than the brain, such as the lungs, ears and the gastrointestinal tract, are uniquely vulnerable to blast overpressure (i.e., rapidly changing pressure gradient) yet long term outcomes and effects of exposures on these systems have been understudied relative to TBI [4]. Recent studies have begun to investigate the association between blast overpressure during deployment and pulmonary outcomes. Pugh and colleagues conducted a retrospective review of Veterans Affairs (VA) medical encounters between 2003 and 2011 and observed an increasing prevalence of chronic obstructive pulmonary disease and asthma among those deployed in support of combat operations in Iraq and Afghanistan [5]. In their analyses, an association between TBI and chronic lung disease was observed; the authors cautiously interpreted this association as potential evidence of a role for blast exposure with TBI diagnosis serving as a proxy for IED blast exposure.

Using data from the national VA Airborne Hazards and Open Burn Pit Registry, we previously observed an independent association (adjusted odds ratio 1.66, 95% CI 1.5–1.7) between IED blast exposure and cardiopulmonary symptoms, even after adjustment for potential confounding factors such as burn pit smoke exposure and smoking [6]. This study was limited by reliance on a dichotomous, self-reported representation of blast exposure, and did not assess physiological outcomes. An alternative methodology to classify blast exposure was recently described by Zell-Baran et al. [7] who developed a 'blast exposure intensity score' that was the sum of the product of deployment length (months) and frequency (days·month$^{-1}$) of IED blasts and controlled detonations. Investigators observed an unadjusted association between their blast exposure severity score and lung clearance index (marker of ventilation heterogeneity) in 71 deployed individuals that was interpreted as evidence for a link between blast exposure and small airways injury. Whereas scoring instruments and standardized interviews exist to assess blast-related TBI and associated neuro-psychological sequelae beyond self-report [8, 9], the validity of these approaches have not been assessed in the context of adverse respiratory system effects.

This study examined whether pulmonary function was associated with clinician-documented blast exposure during deployment among a large cohort of deployed Veterans referred for specialty evaluation. We first developed a rigorous chart abstraction process and associated template with a multi-disciplinary team of clinicians and scientists. Clinical encounter notes were then reviewed to establish blast exposure case assignment with emphasis on TBI clinician notes as a proxy for physiological effect from blast exposure. Pulmonary function was then compared across blast exposure groups adjusting for confounding factors. We hypothesized that a history of blast exposure during deployment would be associated with impaired pulmonary function variables in a dose-dependent manner.

## Methods

### Sample description

The present cohort is comprised of combat deployed Veterans (n = 601) referred to our national post-deployment health clinic (New Jersey War Related Illness and Injury Study Center (NJ WRIISC) [10]) between 2011 and 2019 who underwent pulmonary function testing (PFT) as part of their multi-day clinical evaluation as previously described [11]. We limited the present analysis to those Veterans deployed in support of operations to Southwest Asia and Afghanistan starting in 2001 (n = 315). Additional exclusion criteria included subjects with deployment lengths less than one month or missing deployment history (n = 4). As this was a retrospective review of medical records that did not require contacting patients, a waiver of consent was obtained. Ethics approval was obtained from the VA New Jersey Health Care System Research & Development Committee (#01298).

### Clinical evaluations

Comprehensive evaluations performed by an interdisciplinary team were tailored to the Veteran yet consist of the following basic elements: (1) medical history review and physical examination, (2) occupational and environmental medicine history, (3) PFT with bronchodilator, (4) neuropsychological or psychological evaluation, and (5) standardized intake questionnaire packet. By design, Veterans referred to the NJ WRIISC endorse chronic symptoms that remain unexplained secondary to work-up at

the Veteran's home VA Medical Center. Depending on presenting symptoms, Veterans may also receive additional specialty testing as clinically indicated, including specialized pulmonary testing.

All Veterans, irrespective of chief complaint, underwent complete PFT in accordance with published guidelines [12] using commercially available equipment (Cosmed Quark PFT, Q-Box, i2M; Rome, Italy). PFT was performed in the morning in a semi-fasted state after an overnight withdrawal of bronchodilators (if applicable) as previously described [11]. Tests were performed in the following order: (1) spirometry, (2) lung volumes via body plethysmography, (3) diffusing capacity of carbon monoxide via the single-breath technique ($DL_{CO}$), and (4) post-bronchodilator spirometry. Published reference equations were used for interpretation and reporting of spirometry [13], lung volumes [14], and $DL_{CO}$ [15] (hemoglobin corrected [16]). Beginning in 2013, Veterans typically also underwent additional cardiopulmonary testing including the forced oscillation technique (FOT) before and after bronchodilator (400 µg salbutamol via spacer) as previously described [11].

Analysis of pulmonary function focused on the following outcomes from the pulmonary function tests: total lung capacity (TLC%; % predicted), forced expiratory volume in 1 s ($FEV_1$%; % predicted), % change in $FEV_1$ after bronchodilator (%Δ$FEV_1$PB), the $FEV_1$ to forced vital capacity ratio ($FEV_1$/FVC), the hemoglobin-corrected $DL_{CO}$ ($DL_{CO}$%, % predicted), frequency dependence of resistance (R4–R20%), % change in reactance area after bronchodilator (%ΔAX), and % change in resistance and reactance at the lowest frequency (4 Hz) after bronchodilator (%ΔR4PB and %ΔX4PB). These variables were selected to provide broad representation of pulmonary flow, volume, diffusion, and mechanics.

#### Initial blast exposure assessment and characterization

Aside from self-report (yes/no) to blast exposure as indicated on the intake questionnaire, Veterans did not undergo a routine and standardized assessment of blast exposure during their clinical evaluation. However, each Veteran underwent a one-on-one exposure evaluation with an occupational and environmental medicine physician or other trained physician during which blast and other exposures were specifically inquired about. Exposure to blast was also frequently discussed with a provider during other components of the clinical evaluation such as: (1) TBI screening conducted by a neuropsychologist or mental health provider, (2) history and physical conducted by a physician or nurse practitioner, and/or (3) cardiopulmonary evaluation by a pulmonologist. Text from the clinical notes of these encounters provided the source of information for characterizing blast exposure.

#### Retrospective chart review to characterize blast exposure

An a priori chart abstraction process was designed by a multidisciplinary working group of NJ WRIISC clinicians and scientists with expertise in pulmonary medicine, internal medicine, environmental and occupational medicine, neuropsychology, and exercise physiology. Although several instruments are available to evaluate neuropsychological sequelae of TBI (blast-related and non-blast-related) (e.g., [8, 9]), the working group was unable to identify an existing instrument designed to assess the impact of blast exposure on the cardiopulmonary system. Therefore, we developed a process and tool for extracting key variables from the clinical notes to derive an assessment of blast exposure.

A chart reviewer template was developed to guide the chart abstraction process. This template consisted of preselected key variables: (1) proximity to blast (< 50 m, 50–100 m, 101–200 m, > 200 m); (2) number of subconcussive and concussive blasts; (3) severity of acute symptoms for TBI caused by blast (absent, mild, moderate) [17]; (4) PTSD associated with blast (yes, maybe, no); (5) CDC blast injury definitions (primary: injury from blast pressure wave, secondary: injury from resultant projectiles, tertiary: injury from being moved by blast wind, quaternary: all other blast related injuries such as burns) [18]; (6) and whether or not the patient was physically moved by the blast (yes, no). One chart reviewer (clinician) read through each patient's record to abstract responses for each key variable from the WRIISC clinicians' documentation of blast exposures (n = 311). Two additional researchers (non-clinicians) reviewed and abstracted information from a random selection of 10% of the charts using the same template. Blinded to the initial reviewer's results, this allowed for assessment of interrater reliability for the chart abstraction instrument.

Initially, reliability, completeness, and consistency of the clinical notes for the key variables of interest of the chart abstraction process were unclear; upon further examination of the abstracted data, the variables for number of concussive blasts and TBI severity were selected to define blast exposure groupings. These variables were selected because they were the most complete and they provided the most consistent blast exposure assessment according to the interrater agreement of the chart abstraction process (> 92% agreement; Additional file 1: Table S1). Blast exposure groupings were defined as follows: (1) none (no TBI symptoms nor concussive blasts identified), (2) single mild blast exposure (one concussive blast incident identified with mild TBI symptoms), and (3) multiple mild blast exposures (more than one concussive blast incident identified with mild TBI symptoms). Single and multiple moderate/severe blast exposures were defined in the same manner, except were

based on moderate/severe TBI symptoms. For a thorough reporting of the interrater agreement results, see Additional file 1: Table S1.

#### Comorbid conditions and health problems

Patient charts were reviewed to abstract the International Classification of Disease-9 and -10 (ICD9/ICD10) codes present in the WRIISC clinician's notes. ICD9 codes were converted to ICD10 codes to organize into comorbid condition and health problem groupings [19]. Comorbid condition and health problem groupings were determined by a physician (DAH) consistent with ICD taxonomy. Patients were counted as having a comorbid condition and health problem if one or more constituent ICD code was present and we calculated the frequency of each comorbidity in the sample. All comorbid conditions and health problems with a prevalence > 10% in the study sample are reported.

#### Data and statistical analysis

Assessments for differences among blast exposure groupings for patient characteristics were conducted with the Kruskal–Wallis test for continuous variables followed by Dunn test for post-hoc multiple comparisons. Fisher's exact test was used to assess for association between categorical patient characteristics and blast grouping. The interrater reliability analysis for the chart abstraction was conducted using Gwet's AC2 with linear weighting [20, 21]. A more comprehensive analysis using multivariable linear regression models to assess the effect of blast exposure on specific pulmonary function outcomes was also pursued and described in the Additional file 1. All analyses were conducted using the R software for statistical computing [22].

## Results

#### Blast characteristics

After the chart abstraction process, all subjects were categorized according to blast group as follows: none (n = 208), single mild blast exposure (n = 52), and multiple mild blast exposures (n = 47) (Table 1). Due to a low representation of moderate/severe blast exposure in this dataset (n = 4), these subjects were excluded from further analyses. Specific, abstracted blast characteristics generally aligned well with assigned blast category. For example, the experience of being physically moved by the blast was far more common among those with "single mild" (44.2%) or "multiple mild" blasts (36.2%) compared to those with "no blast" (5%). Similarly, experiencing higher order blast effects (secondary, tertiary or quaternary effects according to the CDC classification [18]) was not applicable in 82.2% of those with no blast (and not documented in 12.0%), while everyone classified with one or more blast had documentation related to higher order blast effects and > 70% experienced one or more of these effects. All analyses presented below use the "no blast," "single mild," and "multiple mild" blast groups.

#### Patient characteristics

Patient characteristics are presented in Table 2. Overall, the mean group age was 40.5 ± 9.7 (mean ± SD) years, evaluated 8.6 ± 3.8 years after last deployment, mostly male, never or former smokers, and non-Hispanic white and with a mean body mass index of 30.4 ± 5.2 kg/m$^2$. Median total deployment duration was found to be statistically significantly different across blast groups [H (Kruskal Wallis test statistic) = 6.05, p = 0.03] with the multiple mild blast exposure group having a significantly longer total deployment length as compared to the group with no blast exposure [Z (post hoc Dunn's test statistic) = 2.28, p = 0.03]. Blast exposure group was also associated with military branch (p = 0.001) and sex (p = 0.03). None of the remaining characteristics were statistically significantly different across groups. Also presented in Table 2 are 21 different comorbid condition and health problem groupings with > 10% prevalence in the study sample. The most common were PTSD (62%) and dyspnea (55%); none of which were statistically significantly different across blast groups. Self-reported lower respiratory symptoms (scored as none (24.8%), mild (22.1%), moderate (15.6%), and severe (15.3%), percentages from the overall sample) were also similar across blast groups (p = 0.71).

#### Pulmonary function test findings

The overall trends and distribution of data, as indicated by the shape and location of the violin plots and inner boxplots, were similar across the three blast groups for each of the nine selected pulmonary function test outcomes (Fig. 1). To support and complement these qualitative findings, statistical analyses comparing these pulmonary function outcomes across blast groups are described and presented in the Additional file 1: Supplemental Statistical Analyses, Tables S2–S4. Overall, there were no differences across groups for any outcome measure, irrespective of the level of model adjustment (all p values 0.10–0.99 without correction for multiple comparisons). A more thorough reporting of results for additional parameters for lung volumes, diffusion, airflow, and FOT are included in Additional file 1: Tables S5–S7.

## Discussion

We hypothesized lung injury from mild blast exposure during deployment will result in impaired pulmonary function. In the absence of standardized instruments to classify blast exposure to the thorax, we first developed

**Table 1** Blast characteristics identified from chart abstraction process and resultant blast grouping assignments

| Study assigned blast grouping | Overall (n = 307) | | No blast (n = 208) | | Single mild (n = 52) | | Multiple mild (n = 47) | |
|---|---|---|---|---|---|---|---|---|
| **Blast characteristics** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| Proximity to Blast | | | | | | | | |
| Not applicable | 153 | 49.8 | 140 | 67.3 | 7 | 13.5 | 6 | 12.8 |
| < 50 m | 97 | 31.6 | 24 | 11.5 | 40 | 76.9 | 33 | 70.2 |
| 50–100 m | 19 | 6.2 | 12 | 5.8 | 1 | 1.9 | 6 | 12.8 |
| 101–200 m | 7 | 2.3 | 5 | 2.4 | 2 | 3.8 | 0 | 0.0 |
| > 200 m | 19 | 6.2 | 15 | 7.2 | 2 | 3.8 | 2 | 4.3 |
| Missing data | 12 | 3.9 | 12 | 5.8 | 0 | 0.0 | 0 | 0.0 |
| Number of sub-concussive blasts | | | | | | | | |
| Not applicable | 71 | 23.1 | 70 | 33.7 | 0 | 0.0 | 1 | 2.1 |
| 0 | 89 | 29.0 | 62 | 29.8 | 17 | 32.7 | 10 | 21.3 |
| 1 | 11 | 3.6 | 6 | 2.9 | 4 | 7.7 | 1 | 2.1 |
| > 1 | 111 | 36.2 | 45 | 21.6 | 31 | 59.6 | 35 | 74.5 |
| Missing data | 25 | 8.1 | 25 | 12.0 | 0 | 0.0 | 0 | 0.0 |
| Number of concussive blasts | | | | | | | | |
| 0 | 208 | 67.8 | 208 | 100.0 | 0 | 0.0 | 0 | 0.0 |
| 1 | 52 | 16.9 | 0 | 0.0 | 52 | 100.0 | 0 | 0.0 |
| 2 | 12 | 3.9 | 0 | 0.0 | 0 | 0.0 | 12 | 25.5 |
| ≥ 3 | 35 | 11.4 | 0 | 0.0 | 0 | 0.0 | 35 | 74.5 |
| Missing data | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| TBI symptoms | | | | | | | | |
| Absent | 208 | 67.8 | 208 | 100.0 | 0 | 0.0 | 0 | 0.0 |
| Mild | 98 | 31.9 | 0 | 0.0 | 52 | 100.0 | 46 | 97.9 |
| Moderate | 1 | 0.3 | 0 | 0.0 | 0 | 0.0 | 1 | 2.1 |
| Missing data | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| PTSD associated with blast | | | | | | | | |
| Not applicable | 31 | 10.1 | 24 | 11.5 | 4 | 7.7 | 3 | 6.4 |
| Yes | 26 | 8.5 | 9 | 4.3 | 12 | 23.1 | 5 | 10.6 |
| Maybe | 61 | 19.9 | 25 | 12.0 | 16 | 30.8 | 20 | 42.6 |
| No | 102 | 33.2 | 66 | 31.7 | 18 | 34.6 | 18 | 38.3 |
| Missing data | 87 | 28.3 | 84 | 40.4 | 2 | 3.8 | 1 | 2.1 |
| Blast related symptoms or injury* | | | | | | | | |
| Not applicable | 198 | 64.5 | 171 | 82.2 | 15 | 28.8 | 12 | 25.5 |
| Primary | 30 | 9.8 | 6 | 2.9 | 11 | 21.2 | 13 | 27.7 |
| Secondary | 6 | 2.0 | 1 | 0.5 | 3 | 5.8 | 2 | 4.3 |
| Tertiary | 25 | 8.1 | 3 | 1.4 | 13 | 25.0 | 9 | 19.1 |
| Quaternary | 23 | 7.5 | 2 | 1.0 | 10 | 19.2 | 11 | 23.4 |
| Missing data | 25 | 8.1 | 25 | 12.0 | 0 | 0.0 | 0 | 0.0 |
| Physically moved by blast | | | | | | | | |
| Not applicable | 89 | 29.0 | 88 | 42.3 | 0 | 0.0 | 1 | 2.1 |
| Yes | 45 | 14.7 | 5 | 2.4 | 23 | 44.2 | 17 | 36.2 |
| No | 147 | 47.9 | 89 | 42.8 | 29 | 55.8 | 29 | 61.7 |
| Missing data | 26 | 8.5 | 26 | 12.5 | 0 | 0.0 | 0 | 0.0 |

*According to CDC blast injury definitions [18]. *TBI* traumatic brain injury, *PTSD* posttraumatic stress disorder

a standardized approach to characterize blast exposure derived from clinical interviews with emphasis on TBI as a proxy for physiological effect from blast exposure. After assigning Veterans to exposure groups (i.e., none, single- or multiple-mild), we evaluated whether group assignment was associated with select pulmonary function

**Table 2** Patient characteristics, comorbid conditions and health problems across assigned blast groupings

| | Overall (n = 307) | | No blast (n = 208) | | Single mild (n = 52) | | Multiple mild (n = 47) | | p-value*** |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | |
| Age (years) | 40.5 | 9.7 | 41.0 | 9.8 | 39.4 | 9.4 | 39.2 | 9.2 | 0.25 |
| Height (m) | 1.8 | 0.1 | 1.7 | 0.1 | 1.8 | 0.1 | 1.8 | 0.1 | 0.11 |
| Weight (kg) | 93.8 | 18.9 | 92.4 | 18.1 | 98.2 | 16.0 | 94.8 | 24.2 | 0.13 |
| BMI (kg/m$^2$) | 30.4 | 5.2 | 30.2 | 5.0 | 31.1 | 4.9 | 30.5 | 6.2 | 0.57 |
| Cumulative deployment duration (months) | 14.4 | 8.6 | 13.4 | 7.7 | 14.8 | 7.8 | 18.1 | 11.8 | 0.03 |
| Post-deployment duration (years) (Missing data: n = 1, 0.3%) | 8.6 | 3.8 | 8.4 | 3.9 | 8.9 | 3.5 | 8.8 | 3.4 | 0.74 |
| | **Median** | **IQR** | **Median** | **IQR** | **Median** | **IQR** | **Median** | **IQR** | |
| Smoking pack years* (Missing data: n = 11, 3.6%) | 0 | 0, 9 | 0 | 0, 9 | 0 | 0, 9 | 4 | 0, 10 | 0.08 |
| | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | |
| Sex | | | | | | | | | |
| Male | 257 | 83.7 | 166 | 79.8 | 48 | 92.3 | 43 | 91.5 | 0.03 |
| Female | 50 | 16.3 | 42 | 20.2 | 4 | 7.7 | 4 | 8.5 | |
| Missing data | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | |
| Race/Ethnicity | | | | | | | | | |
| Non-Hispanic White | 193 | 62.9 | 123 | 59.1 | 37 | 71.2 | 33 | 70.2 | 0.18 |
| Non-Hispanic Black | 19 | 6.2 | 15 | 7.2 | 1 | 1.9 | 3 | 6.4 | |
| Non-Hispanic Other | 5 | 1.6 | 4 | 1.9 | 1 | 1.9 | 0 | 0.0 | |
| Hispanic | 57 | 18.6 | 37 | 17.8 | 10 | 19.2 | 10 | 21.3 | |
| Unknown | 33 | 10.7 | 29 | 13.9 | 3 | 5.8 | 1 | 2.1 | |
| Missing data | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | |
| Branch | | | | | | | | | |
| Army | 203 | 66.1 | 128 | 61.5 | 35 | 67.3 | 40 | 85.1 | 0.001 |
| Air Force | 42 | 13.7 | 38 | 18.3 | 2 | 3.8 | 2 | 4.3 | |
| Marine | 39 | 12.7 | 21 | 10.1 | 13 | 25.0 | 5 | 10.6 | |
| Navy | 18 | 5.9 | 16 | 7.7 | 2 | 3.8 | 0 | 0.0 | |
| Missing data | 5 | 1.6 | 5 | 2.4 | 0 | 0.0 | 0 | 0.0 | |
| Smoking status | | | | | | | | | |
| Never | 150 | 48.9 | 109 | 52.4 | 27 | 51.9 | 14 | 29.8 | 0.06 |
| Former | 104 | 33.9 | 67 | 32.2 | 16 | 30.8 | 21 | 44.7 | |
| Current | 53 | 17.3 | 32 | 15.4 | 9 | 17.3 | 12 | 25.5 | |
| Missing data | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | |
| Lower respiratory symptoms** | | | | | | | | | |
| None | 76 | 24.8 | 51 | 24.5 | 16 | 30.8 | 9 | 19.1 | 0.71 |
| Mild (1/3) | 68 | 22.1 | 45 | 21.6 | 11 | 21.2 | 12 | 25.5 | |
| Moderate (2/3) | 48 | 15.6 | 35 | 16.8 | 6 | 11.5 | 7 | 14.9 | |
| Severe (3/3) | 47 | 15.3 | 31 | 14.9 | 6 | 11.5 | 10 | 21.3 | |
| Missing data | 68 | 22.1 | 46 | 22.1 | 13 | 25.0 | 9 | 19.1 | |
| Comorbid conditions and health problems (> 10% prevalence) | | | | | | | | | |
| PTSD | 190 | 61.9 | 125 | 60.1 | 35 | 67.3 | 30 | 63.8 | 0.81 |
| Dyspnea | 170 | 55.4 | 118 | 56.7 | 31 | 59.6 | 21 | 44.7 | 0.28 |
| Other sleep problems (Insomnia, restless legs syndrome, etc.) | 107 | 34.9 | 78 | 37.5 | 15 | 28.8 | 14 | 29.8 | 0.38 |
| Hearing loss/tinnitus | 101 | 32.9 | 65 | 31.3 | 24 | 46.2 | 12 | 25.5 | 0.07 |
| Axial pain | 95 | 30.9 | 65 | 31.3 | 15 | 28.8 | 15 | 31.9 | 0.95 |
| Headache/migraine | 91 | 29.6 | 58 | 27.9 | 19 | 36.5 | 14 | 29.8 | 0.65 |

**Table 2** (continued)

| | n | % | n | % | n | % | n | % | |
|---|---|---|---|---|---|---|---|---|---|
| Depression | 82 | 26.7 | 55 | 26.4 | 15 | 28.8 | 12 | 25.5 | 0.92 |
| Sleep apnea | 81 | 26.4 | 48 | 23.1 | 20 | 38.5 | 13 | 27.7 | 0.08 |
| Fibromyalgia | 78 | 25.4 | 50 | 24.0 | 18 | 34.6 | 10 | 21.3 | 0.24 |
| Irritable bowel syndrome | 75 | 24.4 | 49 | 23.6 | 17 | 32.7 | 9 | 19.1 | 0.39 |
| Extremity pain | 72 | 23.5 | 47 | 22.6 | 11 | 21.2 | 14 | 29.8 | 0.53 |
| Upper respiratory issues (Rhinitis, sinusitis, etc.) | 70 | 22.8 | 48 | 23.1 | 12 | 23.1 | 10 | 21.3 | 0.98 |
| Traumatic brain injury | 63 | 20.5 | 44 | 21.2 | 9 | 17.3 | 10 | 21.3 | 0.89 |
| Neuropathy | 63 | 20.5 | 40 | 19.2 | 12 | 23.1 | 11 | 23.4 | 0.72 |
| Cognitive problems | 61 | 19.9 | 35 | 16.8 | 16 | 30.8 | 10 | 21.3 | 0.08 |
| Fatigue | 54 | 17.6 | 32 | 15.4 | 12 | 23.1 | 10 | 21.3 | 0.49 |
| Vitamin D deficiency | 47 | 15.3 | 31 | 14.9 | 7 | 13.5 | 9 | 19.1 | 0.57 |
| Cough | 42 | 13.7 | 28 | 13.5 | 10 | 19.2 | 4 | 8.5 | 0.31 |
| Asthma | 41 | 13.4 | 32 | 15.4 | 6 | 11.5 | 3 | 6.4 | 0.27 |
| Gastroesophageal reflux disease | 38 | 12.4 | 26 | 12.5 | 6 | 11.5 | 6 | 12.8 | 1.00 |
| Other pain | 35 | 11.4 | 24 | 11.5 | 6 | 11.5 | 5 | 10.6 | 1.00 |

*Due to non-normality, data are presented as median and interquartile range. **Self-reported cough, wheeze and/or dyspnea ≥ twice per week. ***To assess differences among blast groups, Kruskal–Wallis test followed by Dunn test for post hoc multiple comparisons was used for continuous variables while Fisher's exact test was used for categorical variables. *BMI* body mass index, *PTSD* posttraumatic stress disorder

outcomes by comparing the overall trends and distribution of data (Fig. 1) as well as through statistical analyses (Additional file 1). Overall, with the current approach, we did not observe an association between clinician-documented blast exposure and objective measures of pulmonary function in this sample of deployed Veterans referred for specialty evaluation.

As highlighted by the National Academies of Sciences, Engineering, and Medicine, "…there is a striking absence of data on the long-term pulmonary outcomes of exposure to blast (pg. 138; [23])." In a case series of 11 civilians who survived a bus terrorist explosion, most were reported to have normal cardiopulmonary function one year after their injury [24]. A direct comparison to the present study's results is difficult given substantial differences in injury severity and length of follow-up. However, given that pulmonary function was similar across groups, the present study's findings may be considered consistent with that of Hirshberg and colleagues [24]. Zell-Baran et al. [7] observed greater lung clearance index, suggestive of small airway injury, among previously deployed individuals (n = 71) with higher blast exposure intensity scores. This association was no longer significant after adjustment and no other pulmonary function parameters were considered. In the present analysis, we did not observe an association with blast exposure and any pulmonary function outcome, including multiple indices of small airway function via oscillometry. This inconsistency may be related to several factors, including the study design, as well as differences in blast exposure characterization. For example, in addition to IED blast exposures, Zell-Baran and colleagues included frequency of exposure to controlled detonations, which the present study was unable to ascertain. Looking beyond IED exposure is important as past research indicates that repetitive, low level blast exposures such as from routine training with weapons can lead to chronic cumulative pathophysiological effects [25, 26].

There are two major limitations with this study: (1) potential contributors to errors in blast exposure assessment, and (2) confounding due to underlying comorbid conditions and health problems. In assessing blast exposure, it is challenging to disentangle recollections of prior blast exposures versus experiences. Martindale et al. [27] highlighted that psychological stress associated with blast experiences (i.e., hearing/seeing a blast) during deployment mediates symptom reporting, potentially resulting in reporting of symptoms similar to TBI regardless of whether a TBI or other physical trauma has occurred [27, 28]. A second interrelated issue is the reliance on TBI as a proxy for blast overpressure wave impact on the pulmonary system. Recent evidence suggests that TBI symptomatology is not necessarily indicative of blast exposure severity [27], prompting calls to update TBI classification schemes to better align with physiological outcomes [23]. Third, patients' recollections of blasts and/or clinical documentation may be biased towards more memorable blast experiences. Objective measurement of the blast-overpressure experienced by an individual will be the least biased assessment possible.

The observed lack of an association between blast exposure and objective measures of pulmonary function

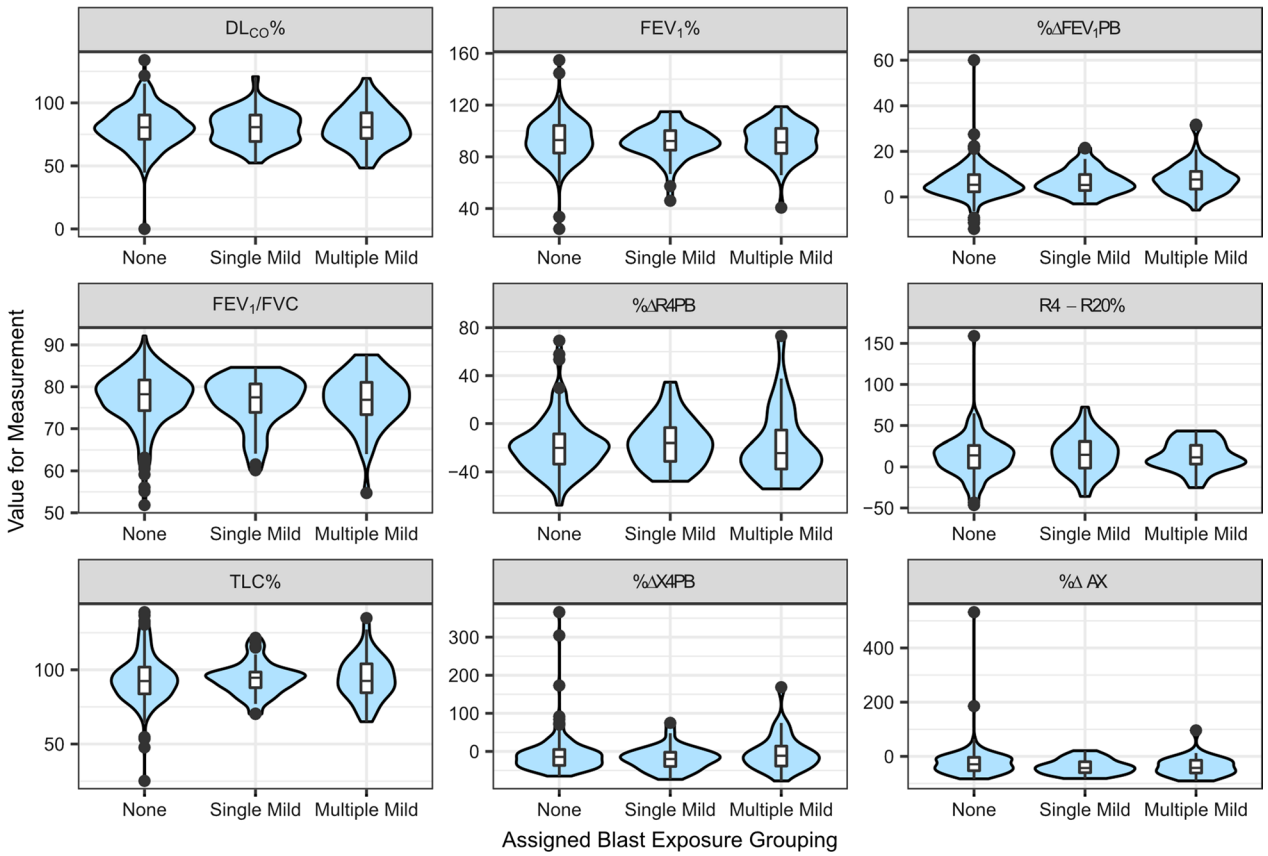


**Fig. 1** Violin plots of pulmonary function test findings across assigned blast exposure groups. Blast exposure group assignments are as follows: none (n = 208), single mild (n = 52), and multiple mild (n = 47). The y-axis represents the range for each of the nine respective variables and measurement units are dependent on variable type: Total Lung Capacity (TLC%; % predicted), Forced Expiratory Volume at 1 s ($FEV_1$%; % predicted), % change in $FEV_1$ after bronchodilator (%ΔFEV1PB), the $FEV_1$ to Forced Vital Capacity ratio ($FEV_1$/FVC), the corrected DLCO ($DL_{CO}$%, % predicted), difference in resistance between 4 and 20 Hz (R4–R20%), % change in reactance area after bronchodilator (%ΔAX), and % change in resistance and reactance at the lowest frequency (4 Hz) after bronchodilator (%ΔR4PB and %ΔX4PB)

in the present analysis may also be attributable to various confounding factors intrinsic to the examination of a clinical sample. Foremost, Veterans referred to the NJ WRIISC have chronic, unexplained symptoms, including dyspnea and many other symptoms and deployment-related concerns. The presence of multiple and diverse comorbid conditions and health problems may have compromised the ability to detect the association between blast exposure and measure of long-term pulmonary function. Similarly, almost 20% of the sample were current smokers and about one third were former smokers albeit with a minimal pack-year history (Table 2). While we did control for smoking pack years and BMI in the adjusted models with no meaningful differences in results relative to unadjusted models, we did not control for comorbid conditions and health problems (Additional file 1). The use of past clinicians' notes allowed us to assess the presence of comorbid conditions and health problems using ICD9/10 codes at one point in time, but the relationships among these comorbidities, blast exposure and pulmonary function were not clear. Future prospective studies should ask explicitly about the presence and onset of each comorbidity of interest to control for potential confounders.

This study exhibited strengths in its design and offers important insight for future research. This is a large well-described single site cohort evaluated by a multidisciplinary team of subspecialty clinicians obtained approximately 9 years after deployment. The high inter-rater reliability (> 92%) for the variables we abstracted from the medical record to define blast exposure are reflected in Table 1. Characteristics of blast exposure generally aligned well with concussive symptoms and blast experience. Because this work has illustrated the ability to consistently abstract relevant clinician notes, the key to improving future work will be improving accuracy of the interview for the targeted purpose assessing blast overpressure wave exposure to pulmonary system.

## Conclusions

In this retrospective analysis of medical records, Veterans deployed to Iraq and Afghanistan with or without clinician-documented mild blast exposure demonstrate similar pulmonary function. Reliance on clinical interviews tailored to evaluate blast-related TBI as a proxy for blast-related thoracic injury may have impacted our ability to differentiate between groups. However, our approach could be modified for future investigations designed to distinguish between blast *exposures* versus *experiences*. Moreover, the clinical findings and experience presented herein may also aid the design and development of prospective controlled studies to better characterize potential blast exposure persistent and latent effects on cardiopulmonary health.

#### Abbreviations

BMI: Body mass index; CDC: Centers for Disease Control and Prevention; CI: Confidence interval; $DL_{CO}$: Diffusing capacity of carbon monoxide via the single-breath technique; FEV1: Forced expiratory volume in 1 s; FOT: Forced oscillation technique; FVC: Forced vital capacity; IED: Improvised explosive devices; ICD: International Classification of Diseases; IRR: Inter-rater reliability; NJ WRIISC: New Jersey War Related Illness and Injury Study Center; PB: Post bronchodilator; PTSD: Post-traumatic stress disorder; PFT: Pulmonary function test; TLC: Total lung capacity; TBI: Traumatic brain injury; VA: Veterans Affairs.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-022-02071-0.

**Additional file 1.** Contains the following supplemental tables as described in the manuscript text: (1) **Table S1.** Key variables used for retrospective chart abstraction process and interrater reliability. (2) **Table S2.** Number of subjects in regression models and additional number (%) of subjects excluded in adjusted models due to incomplete predictors data. (3) **Table S3.** Model fit results by outcome measure and model type. (4) **Table S4.** Model fit results (effect estimate and (p-value)) by outcome measure and model adjustment for blast exposure group (any mild blast exposure) vs. reference group (no blast exposure). (5) **Table S5.** Additional pulmonary function test findings: lung volumes and diffusion. (6) **Table S6.** Additional pulmonary function test findings: spirometry. (7) **Table S7.** Additional pulmonary function test findings: forced oscillation technique.

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#### Author contributions

JHT contributed to the data analysis/interpretation and drafting/revising of work. SH contributed to data acquisition, interpretation and drafting of work. AMS contributed to conception and design of the work. IC contributed to data analysis and interpretation and drafting of work. TDW contributed to data interpretation and drafting of work. WVD contributed to data acquisition and analysis. VSSSS contributed to concept and design of work, data interpretation and drafting of work. NJ contributed to work conception and design. JKA contributed to data acquisition and analysis. DAH contributed to work conception, design, data interpretation and drafting of work. MJF contributed to work conception/design, data acquisition/analysis/interpretation and drafting of work. All authors have approved the submitted version of the manuscript and agree to be personally accountable for their own contributions and any questions related to work accuracy/integrity. All authors read and approved the final manuscript.

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#### Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available or available in de-identified form as these our clinical data from electronic health records.

## Declarations

#### Ethics approval and consent to participate

This protocol was exempt from IRB review but monitored under the purview of the VA New Jersey Health Care System's Research & Development Committee (#01298).

#### Consent for publication

Not applicable

#### Competing interests

The authors declare that they have no competing interests.

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## Publisher's Note