

CT-Parametric Response Mapping Identifies Four Radiographic Signatures in Small Cohorts of Post-9/11 Veterans with Chronic Bronchiolitis and Symptomatic Veterans with Gulf War Veterans Illness

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RATIONALE: A subset of soldiers deployed to southwest Asia develop deployment-related chronic (or “constrictive”) bronchiolitis (DR-CB) characterized by persistent small airway inflammation and fibrosis. Inhalational insults are suspected, yet the inciting agents and resultant pathophysiology remains uncertain. Definitive diagnosis of DR-CB requires surgical lung biopsy and no treatments have been identified. Parametric response mapping (PRM) is a computational CT analytic technique that measures differences in lung density on a voxel by voxel basis using paired inspiratory and expiratory high-resolution CT scans (HRCTs). Dynamic differences in density characterize each voxel as representing: a) normal lung, b) functional small airways disease (fSAD), c) parenchymal disease, or d) emphysema. The objective of this study was to compare the CT-PRM radiographic signatures of post 9/11 soldiers with DR-CB relative to Veterans with Gulf War Veterans Illness (GWVI) experiencing respiratory symptoms.

METHODS: Pre-existing HRCTs were obtained from 18 post-9/11 soldiers diagnosed with DR-CB (Vanderbilt University) and 15 Veterans diagnosed with GWVI (New Jersey WRIISC). Each HRCT underwent PRM using an established methodology to quantify the percent of lung identified as: a) normal (PRM^{Norm}); b) functional small airways disease (PRM^{fSAD}); c) parenchymal disease (PRM^{PD}); and d) emphysema (PRM^{Emph}). Cutoffs for abnormal PRM signatures were defined using 95% confidence intervals derived from a non-military control cohort.

RESULTS: We identified four CT-PRM signatures in both post-9/11 Veterans with DR-CB and Veterans with GWVI: 1) “Normal” (4/18 with DR-CB; 2/15 with GWVI); 2) “High fSAD” (7/18 with DR-CB; 5/15 with GWVI); 3) “High PD” (2/18 with DR-CB; 4/15 with GWVI), and “Mixed” (high fSAD and PD; 5/18 with DR-CB; 4/18 with GWVI). PRM^{Emph} was mildly increased in some Veterans with GWVI. Additional exploratory analysis was performed to assess for potential relationships between PRM signatures and other standard clinical parameters.

CONCLUSIONS: Our data identifies four CT-PRM signatures in post-9/11 soldiers with biopsy evidence of DR-CB and Veterans with GWVI. The finding of increased PRM^{fSAD} in most subjects suggests that the histopathologic abnormalities identified in the soldiers with DR-CB are functional and may be similarly present in Veterans with GWVI. Evidence of elevations in PRM^{fSAD} and PRM^{PD} (or both) may suggest that more than one type lung injury has occurred. These findings advance our understanding of DR-CB and GWVI and may allow us to non-invasively assess the incidence, prevalence, and natural history of these conditions and (hopefully) their response to potential treatments.

Self-reported sleep apnea among Female US Servicemembers in the Airborne Hazard Open Burn Pit Registry

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RATIONALE: Sleep apnea is a serious health condition characterized by impaired breathing as the body relaxes during sleep. The prevalence of sleep apnea varies by factors such as gender and age, with premenopausal women among the group with lower incidence. Environmental exposures may predispose

individuals to sleep disordered breathing, but this has not been evaluated in veterans. The objective is to examine sleep apnea among deployed female servicemembers by age.

METHODS: The Airborne Hazard and Open Burn Pit Registry (AHOBPR) is a voluntary self-administered questionnaire (SAQ) run in collaboration with the Department of Veteran Affairs (VA) and Department of Defense (DOD). We examined servicemembers who by July 1, 2018, completed the AHOBPR (n=148,712). Sleep apnea was classified based on the AHOBPR question: "How often do you have times when you stop breathing during your sleep?". A response of sometimes, regularly, or frequently was classified as a self-reported diagnosis of disease. A woman was categorized as pre-menopausal if she was under 50 years old at the time of completion of registry questionnaire. All woman 50 and above were classified as menopausal/post-menopausal.

RESULTS: Among AHOBPR participants, 15,044 (10.1%) were female. Among women in the AHOBPR, 20% reported sleep apnea. In the subset of women in the pre-menopausal cohort, who responded to the SAQ, 41% (n=2600) had self-reported sleep apnea, and among menopausal/post-menopausal woman 56% (n=528). Among those who reported sleep apnea, the older cohort was more likely to serve in the Army (72.9% vs 67.0%) and had longer cumulative deployments (mean(SD)=401(312) vs 445(349)). The pre-menopausal group was more likely to currently smoke (6.0% vs 3.8%) and had a BMI that fell in the normal range of 18.5-24.9kg/m² (19.3% vs 16.5%). Compared to pre-menopausal women, the older cohort more frequently self-reported respiratory diagnosis of emphysema, chronic bronchitis and asthma (all P<0.05).

CONCLUSION: Women with sleep apnea tended to be older and had more risk factors such as increased BMI and smoking history. Overall, the prevalence of sleep apnea, based on self-reported data, was much higher than the general population. Additional investigation of possible risk factors such as comorbid lung disease, PTSD, and deployment respiratory hazards is necessary to properly understand the status of sleep apnea among female servicemembers.

Examination of Insomnia and other sleep conditions among deployed US Servicemembers

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RATIONALE: Sleep disturbance and chronic sleep deprivation, defined by the American Academy of Sleep Medicine as <7-8 hours of sleep time per night, is associated with poorer health outcomes including increased cardiovascular risk, mood disorders, metabolic disturbance, pain, cognitive impairment, and mortality risk. Environmental respiratory exposures have also been linked to an increased likelihood of developing sleep disordered breathing. The objective was to examine sleep issues among Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn deployed servicemembers.

METHODS: The Airborne Hazard and Open Burn Pit Registry (AHOBPR) is a voluntary self-administered questionnaire (SAQ) run in collaboration with the Department of Veteran Affairs (VA) and Department of Defense (DOD). We examined servicemembers who by July 1, 2018, completed the AHOBPR (n=146,540). Sleep disordered breathing (SDB) was classified based on the AHOBPR questions: "How often do you have times when you stop breathing during your sleep?" and "How often do you snore?" A response of sometimes, regularly, or frequently was classified as a self-reported diagnosis of disease. For insomnia, "During the past 12 months, have you regularly had insomnia or trouble sleeping?" An answer

yes to this question was classified as self-reported insomnia. “On average, how many hours of sleep do you get in a 24-hour period (Round up 30 minutes or more to the next whole hour)?”. Those who reported 0-5 hours were classified as sleep deprived. Individual deployment segments were combined to determine cumulative length of deployment.

RESULTS: Among Veterans in the AHOBPR, 78.1% (n=114,425) reported snoring, 40.5% (n=59,378) reported sleep disordered breathing, and 46.3% (n=67,877) reported being chronically sleep deprived. The subset reporting some form of sleep abnormality were more likely to be men, have served in the Army, to be in the 30-49 age group and to be overweight (BMI=25-29). Among participants, 81.0% (n=118,809) reported insomnia or trouble sleeping. A majority of these respondents were male (84.9%), under 50 (82.6%), and overweight/obese (81.5%). There was no substantial difference in deployment length when categorized as under or over one year (47.2% vs 52.7%).

CONCLUSION: The majority of the participants of the AHOBPR report some form of sleep issues such as snoring, chronic sleep deprivation, and sleep disordered breathing. The significantly higher prevalence of insomnia in this cohort, compared to 30% among adults in the general population, warrants more research to better assess the nature of their insomnia, which represent a potentially significant comorbidity.

Comparison of measured versus calculated maximum voluntary ventilation for determining ventilatory limitation in Veterans with unexplained dyspnea

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Introduction: Current guidelines from professional societies recommend directly measuring maximum voluntary ventilation (MVV) prior to cardiopulmonary exercise testing to assess the presence of ventilatory limitation. In practice, calculated MVV (cMVV; $FEV_1 \times 40$) is frequently used instead of measured MVV (mMVV) for practical or other reasons. The objective of our study was to compare indices of ventilatory limitation using either mMVV or cMVV among dyspneic veterans.

Methods: Data from deployed veterans referred to our center for unexplained dyspnea were retrospectively reviewed. Veterans who did not undergo exercise testing or who had unacceptable spirometry were excluded. Three commonly used indices of ventilatory limitation were calculated using both mMVV and cMVV: 1) ratio of peak exercise ventilation (VE_{max}) to MVV (VE_{max}/MVV), 2) breathing reserve ($BR = 1 - VE_{max}/MVV$), and 3) absolute difference ($MVV - VE_{max}$). Ventilatory limitation was defined as: 1) $VE_{max}/MVV \geq 0.80$, 2) $BR \leq 0.15$, and $MVV - VE_{max} < 11$ L. Bland-Altman method comparison analysis was performed to assess agreement between cMVV and mMVV across indices.

Results: 147 veterans (90.5% male) were included for analysis and had the following characteristics ([Median (IQR)]; age: 44 (35, 51) years, BMI: 31.1 (27.9, 34.0) kg/m^2 , smoking history: 0.0 (0.0, 5.0) pack-years, and post-deployment length: 10.5 (6.4, 21.0) years). VE_{max} (87.3 [68.9, 102.2]) $L \cdot min^{-1}$, mMVV (107.0 [86.4, 130.2]) $L \cdot min^{-1}$, and cMVV (145.2 [123.6, 166.4]) $L \cdot min^{-1}$ were used for ventilatory limitation indices. The frequency of ventilatory limitation were as follows (mMVV vs. cMVV): VE/MVV : 50.3% vs. 9.7%, BR : 43.8% vs. 5.5%, and $MVV - VE_{max}$: 34.2% vs. 9.5%. For each method comparing mMVV and cMVV, the bias and 95% limits of agreement are reported as follows: 1) VE/MVV : 0.22 [-0.18, 0.63], 2) BR : -0.22 [-0.64, 0.21], and 3) $MVV - VE_{max}$: -35.8 [-92.6, 21.0]. Bland-Altman plots are shown in Figure.

Conclusions: Among our sample, there was poor agreement and considerable variability for ventilatory limitation indices when using either mMVV or cMVV for calculation. Notably, these findings raise concerns regarding current guidelines to detect ventilatory limitation using mMVV. Future studies are necessary to identify sources of this poor agreement as well as optimal indices for assessing ventilatory limitation to exercise in this population.

Physician verified blast exposure is associated with small airway dysfunction in Iraq and Afghanistan Veterans

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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 ($\beta = 205.2$; 95% CI: 42.3, 368.1; $p = 0.01$) and Fres ($\beta = 33.9$; 95% CI: 7.3, 60.6; $p = 0.01$), but not for R4-R20 ($\beta = 11.0$; 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 ($\beta = 194.5$; 95% CI: 14.2, 374.7; $p = 0.04$), but not for Fres ($\beta = 25.1$; 95% CI: -4.4, 54.6; $p = 0.10$) nor R4-R20 ($\beta = 10.0$; 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.

Evaluation of the 2019 ERS Task Force Guidelines for FOT Measurement Replication

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RATIONALE: The European Respiratory Society recently released a Task Force Report on the Technical Standards for Respiratory Oscillometry (King et al. 2019 Eur Resp J), which included recommendations

for the minimum number of technically acceptable replicate forced oscillation (FOT) measurements. New for this report was a recommendation to utilize coefficient of variation (CoV) criteria applied to low-frequency resistance to select three replicate measurements for analysis. The purpose of this study was to evaluate the feasibility of these new criteria in a sample of healthy non-smoking adults.

METHODS: 107 healthy non-smoking adults (25.6 ± 4.0 years; 68.2% female) volunteered for this study. FOT measurements (TremoFlo C-100; Canada) were obtained during 10 consecutive 20-sec volume perturbations using multi-frequency waveforms (5-37Hz), with a minimum 30-sec rest between trials. All testing was performed following calibration in a seated position using an antibacterial filter (ClearFlo F-100 PFT Filter) while wearing a nose clip and keeping hands firmly against cheeks. Artifacts were rejected automatically (i.e., ≥ 2 valid breaths, inspiration and expiration time ≥ 0.35 sec, tidal volume ≥ 100 ml, and coherence ≥ 0.7) and through visual inspection. Total and within-breath resistance and reactance from the impedance spectrum were collected, but replication criteria (CoV $\leq 10\%$) were applied to total resistance at 5Hz (R5) to identify 3 replicate measurements.

RESULTS: A total of 1,070 trials were performed across all participants, of which 1.3% were rejected and excluded from subsequent analysis. All participants were able to achieve criteria within 8 trials. 60.7% met criteria within the first three trials. 21.5% met criteria within the first four trials. 12.1% met criteria within five trials. 5.6% met criteria within 6-8 trials. Average CoV of all available replicate measurements was 5.54 ± 2.6 (range: 0.68 to 9.90). 100% of participants had at least 3 replicate measurements with a CoV $\leq 10\%$.

CONCLUSIONS: The new criteria recommended by the 2019 ERS Task Force Guidelines appears feasible for our sample of healthy adults. The majority of participants met criteria within the first 3 trials, and over 80% of our sample met criteria within 4 trials. Based on our findings, pulmonary function laboratories may consider discarding the first trial for practice. Future studies are necessary to evaluate these guidelines in patient populations.