Characterizing the Bioenergetic Profile of White Blood Cells for Utility In Assessing Mitochondrial Dysfunction In Gulf War Illness

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PURPOSE: Gulf War Illness (GWI) is a chronic multi-symptom illness that affects veterans who served during the 1990– 1991 Gulf War. Similar symptoms between GWI and known mitochondrial disorders have sparked investigations into the health of mitochondria in veterans with GWI. The objective of this study is to characterize the bioenergetic profile of peripheral blood mononuclear cells (PBMCs) in veterans with GWI (GWI+) and controls (GWI-) and assess the relationship with symptom severity and physical activity.

METHODS: 55 Gulf War veterans (85.5% male; 55.0±6.7 years) volunteered for this study. GWI case status and symptom severity were determined via the Kansas-Steele Questionnaire (KQ). Self-reported fatigue (Fatigue Severity Questionnaire; FSS) and physical activity (International Physical Activity Questionnaire; IPAQ) were obtained via questionnaire. PBMCs were isolated from whole blood to determine bioenergetic profiles (Seahorse XFp), parameters of which are listed in the table. Between-group differences and associated effect sizes for each parameter and symptom/activity scales were assessed via Mann Whitney U and Hedges' *d*, respectively. Spearman's rank correlation was used to evaluate the relationship between reserve capacity and GWI symptom severity (KQ total score), physical activity (IPAQ kcal/week) and fatigue severity (FSS mean score).

RESULTS: 38 of 55 veterans met case definition for GWI. Self-reported symptom severity, physical activity level, and the profile parameters are reported in the table (mean±SD). Reserve capacity was associated with FSS (ρ = -0.29, p = 0.04), but not for KQ (ρ = -0.26, p = 0.05) nor physical activity (ρ = 0.18, p = 0.18).

CONCLUSIONS: We observed differences in bioenergetic profiles between veterans with and without GWI. GWI+ veterans demonstrated a profile consistent with mitochondrial dysfunction and one that can be potentially used as a diagnostic tool.

Variables and Symptom Severity	GWI- (n = 17)	GWI+ (n = 38)	*p value*	Effect size (d)
Basal	124.1 (37.6)	103.9 (35.2)	.04	-.57
ATP-linked	100.9 (30.8)	83.5 (28.5)	.04	-.59
Proton leak	23.1 (10.5)	19.6 (10.4)	.23	-.33
Maximal Capacity	326.7 (117.2)	240.9 (79.5)	.01	-.91
Reserve Capacity	202.6 (88.1)	137.7 (57.1)	.01	-.94
Non-Mitochondrial	47.3 (16.6)	41.6 (15.9)	.11	-.35
Kansas Score	4.7 (5.4)	34.47 (14.4)	.00	2.37
FSS Score	1.8 (1.2)	4.43 (2.0)	.00	1.44
IPAQ Score	4636.1 (7560.1)	2847.5 (2679.8)	.83	-.37

Pulmonary capillary blood volume and membrane conductance in Iraq and Afghanistan Veterans with deployment-related exposures

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Purpose: We have previously observed an isolated reduction in diffusing capacity of the lung for carbon monoxide (DL_{CO}) to be a common pulmonary function pattern among symptomatic Iraq and Afghanistan Veterans. DL_{CO} measurement reflects both alveolar capillary membrane diffusion (DM_{CO}) and pulmonary capillary blood volume (V_C); therefore, additional techniques (i.e., simultaneous measurement of diffusion of nitric oxide [DL_{NO}]) are necessary to separately examine DM_{CO} and V_C components. The purpose of this preliminary study is to evaluate the utility of the double-gas diffusion technique in Iraq/Afghanistan veterans to better understand the physiological basis of reduced DL_{CO}.

Methods: 20 Iraq/Afghanistan non-smoking veterans (90% male; Age: 36.65 ± 7.3 years; BMI: 30.37 ± 3.8 kg/m^2) volunteered for this study. Complete pulmonary function testing was performed, including the double-gas diffusion technique (DL_{NO}/DL_{CO}) and forced oscillation technique (FOT). Combined reference equations for DL_{CO}, DL_{NO}, DM_{CO}, V_C from the ERS DL_{NO} Task Force were used to calculate predicted and lower 2.5^{th} percentile (LLN). FOT-derived frequency dependence of resistance (R4-R20) and reactance area (AX) were calculated to reflect distal airway function. Spearman's rank correlation was used to examine the relationship between DM and V_C with R4-R20 and AX.

Results: Double-gas diffusion testing results are provided in the table. Reduced V_C ($\leq$ LLN) was observed in 8 of 20 (40%) and DM_{CO} was reduced ($\leq$ LLN) in 2 of 20 (10%) veterans. Vc (% predicted) was inversely associated with distal airway measures (R4-R20: $\rho = -0.72$, $p < 0.001$; AX: $\rho = -0.50$, $p = 0.03$), but DM_{CO} (% predicted) was not (R4-R20: $\rho = 0.45$, $p = 0.05$; AX: $\rho = 0.36$, $p = 0.13$).

Conclusion: In our preliminary analysis, we observed that 40% of our sample demonstrated reduced V_C, which appears to be associated with distal airway dysfunction. Continued investigation in this population appears warranted.

	Observed Mean ± SD [range]	Predicted (%) Mean ± SD [range]
DL_{NO} (mL·min^{-1}·mmHg^{-1})	148.5 ± 24.5 [105.0 – 199.9]	88.9 ± 12.6 [66.0 – 113.0]
DL_{CO} (mL·min^{-1}·mmHg^{-1})	28.5 ± 5.9 [16.3 – 39.0]	83.6 ± 13.6 [58.0 – 108.0]
DL_{NO}/DL_{CO} ratio	5.3 ± 0.6 [4.1 – 6.4]	-
DM_{CO} (mL·min^{-1}·mmHg^{-1})	211.0 ± 83.7 [103.4 – 478.6]	117.0 ± 35.9 [59.0 – 222.0]
V_C (mL)	57.7 ± 14.6 [30.0 – 85.0]	73.2 ± 17.0 [47.0 – 110.0]