Forced oscillation technique in veterans with preserved spirometry and chronic respiratory symptoms

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A B S T R A C T

Purpose: To evaluate the utility of the forced oscillation technique (FOT) among military veterans with preserved spirometry and chronic unexplained respiratory symptoms.
Methods: 178 veterans referred for evaluation of unexplained respiratory symptoms completed pulmonary function testing and FOT. Preserved spirometry was defined as FEV_1/FVC, FEV_1 and $FVC \geq$ 5th percentile. Frequency dependence of resistance (R4-R20) and reactance area (AX) were assessed via FOT, and R4-R20 $\geq$ 20% and AX $\geq$ 95th percentile were considered abnormal.
Results: Spirometry was preserved in 71.3%, of whom 124 had acceptable FOT data. 93 of 124 (75.0%) veterans with preserved spirometry had one or more abnormal findings on FOT. Veterans with abnormal R4-R20 and/or AX had reduced FVC, FEV_1, FEF_{25-75}, and diffusing capacity (% predicted) in comparison to those with Normal FOT ($p = 0.030$ to $p < 0.001$).
Conclusions: In our referral sample, distal airway dysfunction in the presence of preserved spirometry appears common and may represent an at-risk group requiring closer surveillance.

1. Introduction

Oscillometry was first described by Dubois et al. (1956) as a tool to measure lung function using sinusoidal sound waves of single frequencies superimposed on tidal breathing to determine respiratory impedance. Presently, the forced oscillation technique (FOT) and its variant, impulse oscillometry, utilize multifrequency pressure oscillations (2–48 Hz) applied at the mouth to assess the mechanical properties of the airways and lung parenchyma. Several comprehensive reviews describing FOT technique, commonly reported parameters and interpretation have been previously published (Goldman et al., 2005; Goldman, 2001; Shirai and Kurosawa, 2016; Bickel et al., 2014). In general, FOT's ease of use (i.e., tidal breathing) and distal airway sensitivity is often juxtaposed to spirometry's effort-dependence and distal airway insensitivity, but remains an area of active debate (Berger et al., 2015a). FOT's adoption as a clinical screening tool has been furthered hindered by a lack of technical standardization and universally accepted references values (Kalchiem-Dekel and Hines, 2018). Notwithstanding these challenges, there is growing interest among clinicians and scientists regarding the clinical utility of FOT.

FOT does have specific indications for use, such as for the evaluation of patients exposed to occupational and environmental hazards when spirometry is preserved (Oppenheimer et al., 2007). Though exposure to airborne hazards is exceedingly common in military personnel deployed to Iraq and Afghanistan, FOT has been understudied in this population. Deployment-related exposures include elevated levels of fine particulate matter from natural (i.e., sand, dust storms) and anthropogenic sources (i.e., burn pit smoke, diesel exhaust), as well as regional air pollution (Engelbrecht et al., 2009). Such exposure, along with unique characteristics of military service (i.e., combat, blast exposure, strenuous physical activity) (Falvo et al., 2015), may place deployed personnel at greater risk for post-deployment health consequences. Although many of these veterans return from deployment with persistent frustrating respiratory symptoms, spirometry is often preserved, and the exact cause(s) of respiratory symptoms often remains unknown (Falvo et al., 2018; Holley et al., 2016; Morris et al., 2014).

Respiratory symptoms in the presence of preserved spirometry have been investigated in at-risk groups such as 'healthy smokers' (Regan et al., 2015; Woodruff et al., 2016) and adults with occupational

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exposure (Oppenheimer et al., 2007; Berger et al., 2015b). In a recent manuscript involving the "SubPopulations and InteRmediate Outcome Measures In COPD Study" (SPIROMICS), approximately 50% of current or former smokers endorsed respiratory symptoms despite having preserved spirometry. These subjects were more likely to have respiratory exacerbations, decreased 6-minute walk time and evidence of subclinical lung disease (Woodruff et al., 2016). Since a significant proportion of the distal airways must be obstructed before a reliable reduction in FEV_1 is observed (Cosio et al., 1978), these findings raise concern as to whether distal airway dysfunction undetected by spirometry will eventually manifest as frank lung disease, particularly among those with risk factors (Hnizdo and Vallyathan, 2003).

In the present study, we retrospectively examined a sample of symptomatic Iraq and Afghanistan veterans referred to our national post-deployment tertiary evaluation clinic for respiratory symptoms and/or exposure concerns. During a multi-day, interdisciplinary evaluation, patients underwent clinically indicated cardiopulmonary assessments including FOT. We hypothesized that symptomatic Iraq and Afghanistan veterans with preserved spirometry would have evidence of distal airway dysfunction when measured by FOT, and these veterans would have poorer pulmonary function.

2. Material and methods

2.1. Sample description

Clinical data from 178 deployed Iraq and Afghanistan veterans referred to our national post-deployment specialty clinic (War Related Illness and Injury Study Center [WRIISC]) within the Veterans Health Administration were retrospectively analyzed under an IRB approved protocol (VA New Jersey Health Care System #01298) and waiver of consent. Eligibility for referral to the WRIISC requires the following: 1) combat deployed, 2) chronic multi-system symptoms that remain unexplained after a standard work-up at veteran's local medical center, 3) treatment non-responsive, 4) and safe to travel for outpatient services. An interdisciplinary team of clinicians evaluate referral requests from the veteran's health care provider and determine eligibility. Clinical evaluations span multiple days and if chronic respiratory symptoms are present, the evaluation includes standardized, clinically indicated cardiopulmonary assessments.

2.2. Intake questionnaire

All veterans complete a standardized intake questionnaire packet prior to clinical evaluation, which includes medical history review, tobacco use, current symptoms, and their top three health concerns. Although the questionnaire is designed to capture many post-deployment health issues, we extracted those questions pertaining to the respiratory system, including the frequency of cough, wheeze and shortness of breath using a Likert-type scale (i.e., never, yearly, monthly, weekly, biweekly, or daily) within the past 6 months, as well as shortness of breath intensity (i.e., none, mild, moderate, or severe). Under medical history review, veterans are provided a list of conditions and diseases and respond to the question, "Have you ever been told by a physician you have any of the following conditions or diseases?" Conditions pertaining to the respiratory system were extracted. Deployment history (i.e., dates and locations) and exposures (i.e., yes/no) were also obtained via questionnaire, and confirmed by clinical interview. Current medication use was extracted from the computerized medical record system.

2.3. Pulmonary function

Testing was performed in the morning (8-10a) in a semi-fasted state, abstinent from caffeine and nicotine products for the past 4 h, and after an overnight withdrawal of bronchodilators (if applicable). Testing

Table 1
Characteristics of veterans with preserved spirometry and deployment history.

Characteristic	
No. of patients	127
Age, years, mean ± SD	44.1 ± 9.7
Body mass index, kg/m², mean ± SD	30.9 ± 5.3
Sex, male, n (%)	110 (86.6%)
Ethnicity/Race	
Non-Hispanic White, n (%)	87 (68.5%)
Hispanic or Latino White, n (%)	13 (10.2%)
Non-Hispanic Black, n (%)	6 (4.7%)
Unknown/Other, n (%)	21 (16.5%)
Tobacco Use[a]	
Current, n (%)	16 (12.8%)
Former, n (%)	52 (41.6%)
Never, n (%)	57 (45.6%)
Pack-years, median (IQR)	0.6 (0.0, 6.5)
Iraq/Afghanistan Deployment(s)	
Total deployment length, months, median (IQR)	12.0 (6.0, 18.0)
Multiple deployments, n (%)	55 (44.7%)
Post-deployment length, years, median (IQR)	11.5 (6.3, 23.9)

Notes: Continuous variables presented as mean ± SD or median (interquartile range [IQR]). Categorical variables presented as number and percent of sample.

Table 2
Self-reported respiratory conditions and deployment-related exposures obtained from questionnaire intake packet, and current respiratory medication among veterans with preserved spirometry.

Characteristic	No. of Patients/Total No. of Patients	%
Self-reported conditions:		
Asthma, n (%)	43/123	35.0%
Allergies, n (%)	65/124	52.4%
Chronic sinusitis, n (%)	30/124	24.2%
Chronic bronchitis, n (%)	26/124	21.0%
Emphysema/COPD, n (%)	9/124	7.3%
Asbestosis/Silicosis, n (%)	1/124	0.8%
Pneumonia, n (%)	32/127	25.8%
Sleep apnea, n (%)	63/127	50.8%
Self-reported exposures:		
Blast overpressure, n (%)	72/122	59.0%
Smoke from burn pits, n (%)	105/120	87.5%
Sand and dust, n (%)	112/116	96.6%
Petrochemicals, n (%)	118/124	95.2%
Regional air pollution, n (%)	62/109	56.9%
Respiratory symptoms (≥ 2 days·wk^{-1}):		
Shortness of breath, n (%)	86/126	68.3%
Cough, n (%)	52/126	41.3%
Wheeze, n (%)	48/125	38.4%
Respiratory medications:		
Antihistamine, n (%)	37/127	29.1%
Bronchodilator, n (%)	39/127	30.7%
Inhaled corticosteroid, n (%)	21/127	16.5%
Nasal spray, n (%)	28/127	22.0%

Notes: Questionnaire item responses were missing for some veterans.

followed published recommendations (Miller et al., 2005a) and included: 1) measurement of exhaled nitric oxide (FeNO; NIOX Mino or Vero), 2) FOT, 3) spirometry, 4) lung volumes, and 5) diffusing capacity of carbon monoxide using the single-breath technique (DL_{CO}). FOT and spirometry were re-assessed post-bronchodilator (400 μg salbutamol via spacer). Published reference equations were used for spirometry (Hankinson et al., 1999) lung volumes (Stocks and Quanjer, 1995), and DL_{CO} (Miller et al., 1983) (hemoglobin corrected (MacIntyre et al., 2005)). Preserved spirometry was defined as FEV_1/FVC, FEV_1 and $FVC \geq$ the lower limit of normal (LLN (Hankinson et al., 1999)). All testing was performed by trained technicians using published

Table 3

Pulmonary function test results in veterans with preserved spirometry (n = 127).

	No. of Patients	Mean ± SD	Median (IQR)	< 5th Percentile (LLN)	> 95th Percentile (ULN)
FeNO, ppb	113	18.2 ± 9.2	17.0 (11.0, 24.0)	–	0 (0%)
TLC, % predicted	126	96.2 ± 13.3	94.9 (87.9, 100.6)	12 (9.4%)	9 (7.1%)
RV, % predicted	126	77.5 ± 33.7	73.8 (49.8, 99.2)	54 (42.5%)	10 (7.9%)
FRC, % predicted	126	90.0 ± 22.4	88.5 (73.8, 103.2)	25 (19.7%)	4 (3.1%)
RV/TLC, %	126	23.7 ± 9.3	24.0 (16.2, 29.7)	49 (38.6%)	1 (0.8%)
FRC/TLC, %	126	46.9 ± 8.5	45.9 (41.1, 52.2)	24 (18.9%)	5 (3.9%)
FEV$_1$, % predicted	127	100.9 ± 11.6	100.5 (92.0, 114.3)	0 (0%)	–
FVC, % predicted	127	100.9 ± 11.0	100.4 (107.8, 91.8)	0 (0%)	–
FEV$_1$/FVC, %	127	79.3 ± 3.9	79.5 (76.7, 81.9)	0 (0%)	–
FEF$_{25-75}$, % predicted	127	104.7 ± 23.9	101.2 (89.3, 121.9)	2 (1.6%)	–
DL$_{CO}$, % predicted	113	88.5 ± 16.4	88.7 (78.7, 100.1)	24 (18.9%)	1 (0.8%)
FEV$_1$, % post-BD change	123	5.4 ± 4.9	4.6 (2.6, 8.0)	–	9 (7.1%)[a]
FVC, % post-BD change	123	2.0 ± 4.4	1.6 (-1.1, 4.4)	–	5 (4.0%)[a]
FEF$_{25-75}$, % post-BD change	123	17.2 ± 14.1	16.1 (8.7, 23.7)	–	–

Definition Abbreviations: IQR = interquartile range (25%, 75%); SD = standard deviation; LLN = lower limit of normal; ULN = upper limit of normal; FeNO = fractional exhaled nitric oxide; ppb = parts per billion; TLC = total lung capacity; RV = residual volume; FRC = functional residual capacity; FEV$_1$ = forced expiratory volume in one second; FVC = forced vital capacity; FEF$_{25-75}$ = mid-expiratory flow; DL$_{CO}$ = diffusing capacity of carbon monoxide; post-BD = post-bronchodilator.

Notes: Continuous data are presented as mean ± standard deviation and median (interquartile range), and categorical data are presented as frequency (percentage). A dash (-) indicates no recommended LLN or ULN. [a] ≥ 12% and 200 ml increase from pre-bronchodilator values.

Table 4

Forced oscillation technique results in veterans with preserved spirometry (n = 124).

	Mean ± SD	Median (IQR)	> 95th Percentile (ULN)	Post-BD Normalization
R4, hpa·s·L^{-1}	3.93 ± 1.5	3.63 (2.91, 4.74)	55 (44.3%)	34 (28.1%)
R4, % predicted	117.3 ± 40.7	109.6 (86.2, 134.82)		
R4, % post-BD change[a]	−14.7 ± 19.5	−16.5 (−28.2, −3.8)		
R20, hpa·s·L^{-1}	3.24 ± 0.9	3.17 (2.59, 3.74)	51 (41.1%)	26 (21.5%)
R20, % predicted	110.9 ± 30.4	107.2 (87.8, 126.7)		
R20, % post-BD change[a]	−10.6 ± 14.9	−11.4 (−19.7, −2.7)		
R4-R20, %[b]	13.0 ± 19.8	14.3 (1.5, 26.9)	48 (38.7%)	24 (19.8%)
R4-R20, % post-BD change[a]	−4.2 ± 16.3	−3.6 (−15.1, 5.6)		
AX, hpa·s·L^{-1}	10.8 ± 11.6	7.19 (4.47, 12.68)	88 (71.0%)	28 (23.7%)
AX, % predicted	235.6 ± 193.8	183.5 (113.7, 268.7)		
AX, % post-BD change[a]	−24.7 ± 35.2	−31.0 (−46.5, −3.7)		
Fres, Hz	16.1 ± 5.5	15.43 (11.62, 19.45)	87 (70.2%)	31 (25.6%)
Fres, % predicted	123.8 ± 36.9	118.6 (98.8, 142.2)		
Fres, % post-BD change[a]	−13.1 ± 19.2	−13.1 (−26.1, −1.6)		

Definition of Abbreviations: IQR = interquartile range; SD = standard deviation; ULN = upper limit of normal; Post-BD = post-bronchodilator; R4 = resistance at 4 Hz; R20 = resistance at 20 Hz, R4-R20 = (R4-R20)/R4 * 100; AX = reactance area; Fres = resonant frequency.

Notes: Continuous data are presented as mean ± standard deviation and median (interquartile range), and categorical data are presented as frequency (percentage). A dash (-) indicates no predicted value or bronchodilator cut-off is available. Post-BD normalization was defined as an observed pre-bronchodilator value > ULN that then became ≤ ULN post-bronchodilator (except for R4-R20 which utilized a cut-off value of 20%). [a]Bronchodilator responses for R4, R20, and Fres were missing or unacceptable for three patients (n = 121), and bronchodilator responses for AX were missing or unacceptable for nine patients (n = 118). [b] R4-R20 ≥ 20%.

Table 5

Non-parametric correlations, Spearman's rho, between FOT indices and pulmonary function measures in veterans with preserved spirometry.

	R4	R20	R4-R20	AX	Fres	FeNO	TLC	RV	FRC	FEV$_1$	FVC	FEV$_1$/FVC	FEF$_{25-75}$	DL$_{CO}$
R4	–	0.73†	0.61†	0.75†	0.69†	−0.02	−0.26*	0.05	−0.33†	−0.41†	−0.34†	−0.30†	−0.45†	−0.20*
R20		–	−0.02	0.49†	0.33†	−0.11	−0.34†	−0.05	−0.23*	−0.40†	−0.34†	−0.26*	−0.43†	−0.18
R4-R20			–	0.63†	0.71†	0.02	−0.11	0.11	−0.34†	−0.23*	−0.22*	−0.13	−0.23*	−0.16
AX				–	0.90†	−0.06	−0.25*	0.15	−0.36†	−0.44†	−0.39†	−0.22*	−0.44†	−0.23*
Fres					–	0.01	−0.17	0.12	−0.34†	−0.34†	−0.28*	−0.29*	−0.39†	−0.22*

Notes: Spearman's rank-order correlation coefficients (ρ) are reported in each cell. All variables are in their respective units. *$p < 0.05$, †$p < 0.001$.

guidelines (Miller et al., 2005a; Dweik et al., 2011; Miller et al., 2005b; Wanger et al., 2005; Oostveen et al., 2003), equipment (Cosmed Quark PFT and Q-Box; Rome, Italy) was calibrated prior to each test, and data were quality inspected and interpreted by a pulmonologist.

2.4. Forced oscillation technique (FOT)

FOT maneuvers (8 s) were performed per recommendations (Oostveen et al., 2003) using optimized pseudorandom noise between 4–48 Hz and a piezoresistive pressure transducer (Cosmed Quark i2M) that was calibrated according to manufacturer recommendations. All testing was performed in an upright seated position with chin slightly elevated while wearing a nose clip. Patients were instructed to maintain a tight seal on the mouthpiece, firmly support cheeks with their hands, and avoid swallowing and glottis closure. Pressure-flow tracings were viewed in real-time by the technician to identify errors. An average of three technically acceptable (i.e., free of errors and coherence ≥ 0.7 at 4 Hz and ≥ 0.9 at 20 Hz) and reproducible (< 10% variability)

Table 6

Comparison of exhaled nitric oxide and spirometric variables by FOT patterns.

	Normal FOT	Abnormal R4-R20	Abnormal AX	Abnormal R4-R20 and AX	P-Value*
No. of patients	31[a]	5[b]	45[c]	43[d]	
FeNO, ppb					
Median (IQR)	18.0 (13.3, 24.0)	12.0 (11.0, 17.5)	15.0 (11.0, 24.0)	17.0 (11.8, 26.8)	0.568
Mean ± SD	19.0 ± 8.3	13.8 ± 3.4	17.9 ± 9.5	19.2 ± 9.9	
Mean difference (95% CI)	0 (ref)	5.2 (−2.7, 13.1)	1.1 (−3.5, 5.7)	−0.2 (−5.1, 4.7)	
FEV_1, % predicted					
Median (IQR)	108.0 (100.5, 114.2)	99.5 (85.6, 107.5)	99.2 (91.7, 106.5)†	94.4 (88.0, 105.8)†	< 0.001
Mean ± SD	100.9 ± 11.6	109.3 ± 11.9	97.2 ± 13.4	98.9 ± 8.9	
Mean difference (95% CI)	0 (ref)	12.2 (0.4, 24.0)	10.4 (5.6, 15.1)	12.2 (7.0, 17.5)	
FVC, % predicted					
Median (IQR)	106.2 (98.8, 115.3)	95.4 (90.1, 107.2)	98.1 (91.4, 104.9)†	95.5 (91.1, 104.9)†	0.001
Mean ± SD	108.0 ± 13.0	98.0 ± 9.5	99.2 ± 9.5	97.5 ± 8.8	
Mean difference (95% CI)	0 (ref)	10.0 (-4.1, 28.4)	8.9 (3.7, 14.0)	10.6 (5.5, 15.6)	
FEV_1/FVC, %					
Median (IQR)	81.1 (77.3, 82.0)	76.3 (73.4, 83.3)	79.3 (77.1, 82.4)	78.6 (75.6, 81.7)	0.341
Mean ± SD	79.3 ± 3.9	80.2 ± 3.8	78.0 ± 6.0	79.5 ± 3.3	
Mean difference (95% CI)	0 (ref)	2.3 (−1.7, 6.3)	0.7 (−0.9, 2.3)	1.6 (−0.3, 3.4)	
FEF_{25-75}, % predicted					
Median (IQR)	117.6 (93.9, 132.4)	95.9 (67.2, 129.1)	101.2 (91.0, 110.8)	94.8 (82.3, 120.4)†	0.009
Mean ± SD	117.2 ± 23.0	97.7 ± 34.3	101.6 ± 16.4	99.4 ± 25.8	
Mean difference (95% CI)	0 (ref)	19.5 (−4.5, 43.5)	15.6 (6.6, 24.6)	17.8 (6.2, 29.4)	
FEV_1, % post-bronchodilator change					
Median (IQR)	4.2 (2.2, 5.4)	8.9 (4.1, 14.0)	4.4 (1.9, 7.1)	6.1 (3.6, 9.1)	0.139
Mean ± SD	4.4 ± 3.2	9.0 ± 5.2	4.6 ± 4.5	6.0 ± 4.4	
Mean difference (95% CI)	0 (ref)	−4.6 (-8.3, -1.0)	−0.2 (-2.1, 1.6)	−1.7 (-3.5, 0.2)	
FVC, % post-bronchodilator change					
Median (IQR)	1.8 (−1.2, 3.5)	3.8 (−2.6, 11.7)	1.5 (−1.2, 4.2)	1.6 (−1.0, 4.5)	0.850
Mean ± SD	1.6 ± 2.7	4.3 ± 7.6	1.4 ± 3.8	2.1 ± 5.0	
Mean difference (95% CI)	0 (ref)	−2.6 (-6.4, 1.1)	0.3 (-1.3, 1.7)	−0.5 (-2.5, 1.5)	
FEF_{25-75}, % post-bronchodilator change					
Median (IQR)	13.7 (3.8, 21.9)	21.8 (12.5, 41.1)	16.1 (6.4, 20.8)	17.4 (12.1, 26.6)	0.160
Mean ± SD	13.8 ± 12.1	25.1 ± 5.6	15.3 ± 11.9	19.3 ± 11.8	
Mean difference (95% CI)	0 (ref)	−11.5 (−25.6, 2.5)	−1.7 (−7.4, 4.1)	−5.7 (−11.6, 0.1)	

Definition of Abbreviations: IQR = interquartile range (25%, 75%); SD = standard deviation, CI = confidence interval; FeNO = fractional exhaled nitric oxide; ppb = parts per billion; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; FEF_{25-75} = mid-expiratory flow.

Notes: Data are presented only for patients who had acceptable tests: [a] FeNO (n = 24); [b] post-bronchodilator change (n = 4); [c] FeNO (n = 43), post-bronchodilator change (n = 41); [d] FeNO (n = 38). *Kruskal-Wallis Test. †Dunn's test with Bonferroni correction for comparison with Normal FOT.

maneuvers were used for further analysis (Oostveen et al., 2003).

FOT resistance and reactance measurements are available across the range of frequencies (4–48 Hz), but we delimited our analysis to two integrative indices (Goldman, 2001) for resistance and reactance: 1) frequency dependence of resistance (R4-R20), and 2) reactance area (AX). The frequency dependence of resistance, or R4-R20, was measured by calculating the difference between resistance at 4 and 20 Hz, expressed as a relative percent (R4-R20 = (R4 − R20)/R4 * 100). R4-R20 values ≥ 20% were operationally defined as an abnormal (Zaidan et al., 2018). Reactance area (AX) was calculated as the integrated low-frequency reactance between 4 Hz and the resonant frequency. AX values ≥95th percentile (Oostveen et al., 2013) were considered abnormal. R4-R20 and AX are commonly used FOT parameters to reflect nonuniformity of airflow distribution and distensibility, respectively, and are used herein to reflect distal airway function (Oppenheimer et al., 2007; Skloot et al., 2004). Additional FOT measures were interpreted using published reference equations by Oostveen et al. that account for sex, age, height and weight (Oostveen et al., 2013), which also included criteria for a positive bronchodilator response for selected variables (c.f., Table 5 in (Oostveen et al., 2013)). Specifically, a relative change (Δ = [Pre − Post]/Pre *100) for resistance at 4 Hz (R4; -32.8%) and reactance area (AX; -56.0%) were used to denote a positive bronchodilator response.

We identified *a priori* four FOT patterns of interest among veterans with preserved spirometry: 1) R4-R20 < 20% and AX < ULN (Normal FOT), 2) R4-R20 ≥ 20% and AX < ULN (Abnormal R4-R20), 3) R4-R20 < 20% and AX ≥ ULN (Abnormal AX), and 4) R4-R20 ≥ 20% and AX ≥ ULN (Abnormal R4-R20 and AX). FOT patterns 2–4 provide an index of distal airway dysfunction and afford separate analysis of resistance, reactance, or combined abnormality.

2.5. Statistical Analysis

Patient characteristics were summarized by medians, interquartile ranges (IQR) and percentages. Differences in pulmonary function were compared between FOT patterns (i.e., Normal FOT, Abnormal R4-R20, Abnormal AX, and Abnormal R4-R20 and AX) using Kruskal-Wallis tests. For significant results, we performed *post hoc* testing between patterns using Dunn's test with Bonferroni multiple comparison adjustment. Additionally, differences in FOT (R4-R20 and AX) were compared across shortness of breath intensity levels (i.e., none, mild, moderate and severe) using the same approach. Mean differences and 95% confidence intervals were also reported. Spearman's correlation coefficients were calculated to determine associations between FOT and pulmonary function data. Analyses were performed using IBM SPSS Statistics (v25).

Table 7
Comparison of lung volumes and diffusing capacity by FOT patterns.

	Normal FOT	Abnormal R4-R20	Abnormal AX	Abnormal R4-R20 and AX	P-Value*
No. of patients	31[a]	5	45	43[b]	
TLC, % predicted					
Median (IQR)	98.1 (89.1, 111.5)	93.8 (81.4, 97.0)	93.9 (86.4, 99.9)	93.9 (86.8, 99.6)	0.345
Mean ± SD	100.2 ± 14.7	90.1 ± 11.0	94.5 ± 13.4	94.8 ± 11.5	
Mean difference (95% CI)	0 (ref)	10.1 (−4.0, 24.2)	5.7 (−0.8, 12.2)	5.3 (−0.8, 11.5)	
RV, % predicted					
Median (IQR)	67.1 (45.1, 95.2)	48.6 (31.9, 91.7)	76.5 (47.6, 98.9)	74.3 (63.6, 102.6)	0.311
Mean ± SD	70.4 ± 34.2	59.1 ± 31.6	78.5 ± 37.2	80.6 ± 27.4	
Mean difference (95% CI)	0 (ref)	11.3 (−22.0, 44.6)	−8.1 (−25.0, 8.9)	−10.2 (−24.6, 4.2)	
FRC, % predicted					
Median (IQR)	91.5 (81.9, 104.5)	79.6 (58.1, 101.9)	91.8 (74.6, 107.8)	79.2 (68.4, 95.0)	0.041
Mean ± SD	93.8 ± 17.9	79.9 ± 22.7	93.5 ± 24.9	82.2 ± 17.8	
Mean difference (95% CI)	0 (ref)	13.9 (−4.3, 32.2)	0.4 (−10.1, 10.9)	11.7 (3.2, 20.1)	
RV/TLC, %					
Median (IQR)	21.1 (13.4, 27.1)	16.4 (12.0, 31.6)	24.0 (15.0, 29.0)	25.8 (19.8, 31.1)	0.168
Mean ± SD	21.2 ± 9.4	20.7 ± 11.3	23.2 ± 9.4	26.0 ± 8.8	
Mean difference (95% CI)	0 (ref)	0.5 (-9.0, 10.0)	−2.0 (-6.4, 2.4)	−4.8 (−9.1, −0.5)	
FRC/TLC, %					
Median (IQR)	46.4 (41.8, 54.4)	44.9 (35.9, 53.7)	46.9 (41.3, 54.6)	42.1 (39.2, 50.0)	0.077
Mean ± SD	47.6 ± 7.3	44.8 ± 9.0	48.8 ± 9.2	44.0 ± 7.4	
Mean difference (95% CI)	0 (ref)	2.8 (−4.7, 10.2)	−1.2 (−5.2, 2.8)	3.6 (0.1, 7.1)	
DL_{CO}, % predicted					
Median (IQR)	94.3 (84.1, 107.7)	79.0 (65.3, 99.7)	83.8 (72.9, 91.3)†	85.9 (76.2, 102.3)	0.033
Mean ± SD	94.7 ± 15.3	81.3 ± 18.0	83.8 ± 13.7	88.0 ± 16.9	
Mean difference (95% CI)	0 (ref)	8.4 (−3.8, 30.5)	10.9 (3.8, 18.0)	6.7 (−1.6, 15.0)	

Definition of Abbreviations: IQR = interquartile range (25%, 75%); SD = standard deviation, CI = confidence interval; TLC = total lung capacity; RV = residual volume; FRC = functional residual capacity; DL_{CO} = diffusing capacity of carbon monoxide.
Notes: Data are presented only for patients who had acceptable tests: [a] Lung volumes (n = 30) and diffusing capacity (n = 26); [b] Diffusing capacity (n = 37).
*Kruskal-Wallis Test. †Dunn's test with Bonferroni correction for comparison with Normal FOT.

3. Results

3.1. Sample description

Baseline clinical characteristics and deployment histories are shown in Table 1. Among our referral cohort, 71.3% (n = 127) had preserved spirometry and 28.7% (n = 51) had abnormal spirometry. Please see Supplemental Material for clinical characteristics of veterans with abnormal spirometry excluded from additional analyses (Supplemental Tables 1 and 2), including FOT and pulmonary function results (Supplemental Tables 3 and 4).

Among veterans with preserved spirometry, the median time since deployment was 11.5 years (IQR: 6.3, 23.9), which was calculated as the difference between the date of their clinical evaluation (median; IQR: 4/2016; 3/2015, 7/2017) and date of return from their most recent deployment (median; IQR: 4/2004; 6/1991, 12/2009). Approximately 36.2% were deployed between 1990–1999, 40.9% were deployed between 2000–2009, and 22.8% were deployed between 2010 – 2015.

Self-reported respiratory conditions, symptoms, deployment-related exposures, and current respiratory medications were obtained via questionnaire and their frequencies are summarized in Table 2. Veterans' top health concerns were (in rank-order): pain (60.2%), respiratory symptoms (46.3%), other symptoms/conditions (41.5%), physical fatigue (26.8%), gastrointestinal symptoms (25.2%), and mental health (18.7%).

3.2. Pulmonary function

Results of complete pulmonary function testing are reported in Table 3 (n = 127). Individual data failing to meet quality data were excluded from analyses and the number of patients for each variable is provided within the table. FOT results from three patients were excluded due to failure to obtain acceptable maneuvers; therefore, only acceptable FOT data (n = 124) are reported in Table 4. A positive bronchodilator response for R4 and AX was observed in 15.3% (19/124) and 43.2% (51/118), respectively. Bivariate associations between FOT variables of interest and pulmonary function variables are reported in Table 5.

3.3. FOT patterns

One or more FOT parameters (R4-R20, AX) were abnormal in 75% of our sample (93/124). Veterans were classified into one of the following four groups: 1) Normal FOT (n = 31), 2) Abnormal R4-R20 (n = 5), 3) Abnormal AX (n = 45), and 4) Abnormal R4-R20 and AX (n = 43). Using the Kruskal-Wallis test, group differences were observed for FEV_1, FVC, FEF_{25-75}, and DL_{CO} (Tables 6 and 7), but not for other measures. Dunn's post-hoc tests adjusted for multiple comparisons demonstrated that veterans with Abnormal R4-R20 and AX had reduced FEV_1 ($p < 0.001$), FVC ($p = 0.001$), and FEF_{25-75} ($p = 0.006$) relative to Normal FOT, and veterans with Abnormal AX had reduced FEV_1 ($p = 0.002$), FVC ($p = 0.012$), FEF_{25-75} ($p = 0.050$), and DL_{CO} ($p = 0.030$) relative to Normal FOT. No other between-group differences were noted. Mean differences, using Normal FOT as the reference group, are reported in Tables 6 and 7. With respect to symptoms, we observed no relationship between R4-R20 ($p = 0.0507$) and AX ($p = 0.051$) and shortness of breath characterized by self-reported severity (mild, moderate, or severe).

3.4. Supplemental material

Results of additional assessments (i.e., bronchoprovocation with methacholine and high-resolution computed tomography) were
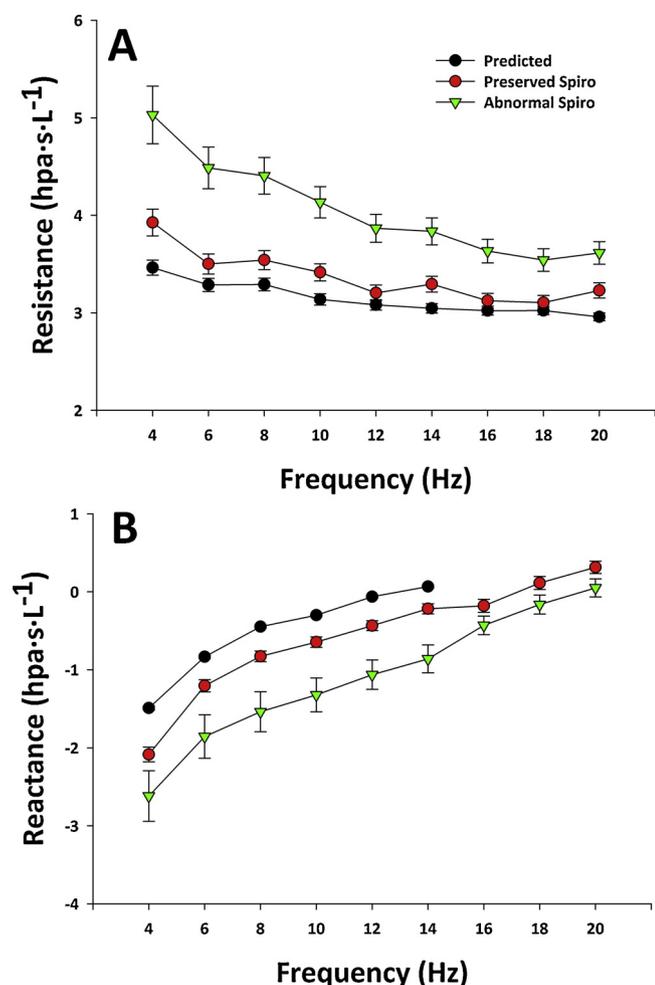
Fig. 1. Forced oscillation technique derived (A) airway resistance and (B) reactance across frequencies (4–20 Hz).
Notes: Resistance (Fig. 1A; circles) and reactance (Fig. 1B; triangles) measures are expressed as mean ± SE for veterans with preserved spirometry (n = 127) and abnormal spirometry (n = 51). Normal predicted values (Oostveen et al., 2013) that account for age, sex, height and weight are also plotted for comparison purposes. Note that predicted values for reactance at 16–20 Hz are unavailable and therefore not included in Fig. 1B.

performed only on a subset of our sample with preserved spirometry and are reported in the Supplemental Material (c.f., Supplemental Tables 5 and 6).

4. Discussion

The majority (71.3%) of our sample of deployed Iraq and Afghanistan veterans with respiratory symptoms had preserved spirometry. Among those with preserved spirometry, 75% (n = 93) have FOT patterns characterized by frequency dependence of resistance or elevated reactance area (n = 50) or both (n = 43). Additional FOT findings of airway dysfunction in this sample include elevated low-frequency resistance and reactance as well as bronchodilator reversibility and normalization. That spirometry is preserved in this sample suggests these abnormalities most likely reflect distal airway dysfunction. FVC, FEV_1, FEF_{25-75}, and DL_{CO} were also reduced in those with FOT abnormalities; however, this reduction is of uncertain clinical relevance given that spirometric indices remained within normal limits. Nonetheless, these findings along with persistent respiratory symptoms (Table 2) suggest that deployed veterans with preserved spirometry, yet distal airway dysfunction as defined by FOT parameters, may represent an at-risk group requiring closer surveillance.

Morris et al. (2013) have highlighted that the biggest challenge in the evaluation of military personnel with post-deployment respiratory symptoms are those with preserved spirometry. Findings from our group and others (Falvo et al., 2018; Holley et al., 2016; Morris et al., 2014; King et al., 2011) reinforce this statement, and underscore the challenge for the clinician in determining whether additional diagnostic evaluations, including potential invasive options, are warranted and appropriate for the symptomatic patient with preserved spirometry. For example, King et al. described a case series of 49 soldiers with unexplained dyspnea and exercise intolerance who underwent open lung biopsy after traditional cardiopulmonary work-up was unremarkable, including 88% (43 of 49) with preserved spirometry (King et al., 2011). In this regard, FOT may provide unique clinical utility in determining which patient might require additional work-up. In Fig. 1, we illustrate a comparison of FOT resistance and reactance values among deployed veterans with preserved and abnormal spirometry, as well as predicted normative values. An interesting pattern emerges whereby veterans with preserved spirometry have greater resistance and reactance values than predicted and appear to approach FOT values of veterans with abnormal spirometry. The cross-sectional nature of the present study precludes further interpretation of these data, but appear to support the presence of distal airway dysfunction among veterans with preserved spirometry. Moreover, inverse associations between FOT indices and pulmonary function measures (Table 5) further suggest that FOT measures provide meaningful insight.

Among veterans with preserved spirometry, 39% (Table 4) had abnormal frequency dependence of resistance. These findings support recent work by Hines et al. (2018) who also found abnormal frequency dependence of resistance in 39% (14/36) of a sample of deployed Persian Gulf War (1990–1991) veterans referred for specialty evaluation with normal spirometry. Although there are differences between these studies (e.g., age of veterans, FOT type, test sequence, interpretative strategy), these similarities are interesting given unique characteristics of the deployed veteran population. Unlike the study by Hines et al. (2018), we also considered AX in our operational definition of distal airway dysfunction, which resulted in a greater frequency of abnormality (75%) overall. Using a multi-parameter approach is consistent with similar studies in civilians examining the prevalence of distal airway dysfunction among at-risk adults with preserved spirometry. For example, Jetmalani et al. (2018) found that 51% of their sample of current or former smokers with preserved spirometry had one or more FOT abnormalities (i.e., R5, R20, R5-R20, X5). Similarly, 68% of a sample exposed to the World Trade Center dust and fumes with preserved spirometry demonstrated one or more FOT abnormalities (i.e., R5, R20, R5-R20, or AX) (Oppenheimer et al., 2007). Across these studies, FOT defined distal airway dysfunction comprised measures of both resistance and reactance. Historically, both resistance and reactance values were thought to be affected similarly in disease states (van Noord et al., 1989); however, this view has been challenged in recent years (Aronsson et al., 2015; Karayama et al., 2017). To explore this question further, we separated veterans with preserved spirometry into four groups to examine the effects of isolated or combined abnormalities in resistance and reactance on pulmonary function.

Veterans with Abnormal AX had lower FEV_1, FVC, FEF_{25-75}, and DL_{CO} than those with Normal FOT, and veterans with both Abnormal R4-R20 and AX had reduced FEV_1, FVC, and FEF_{25-75} relative to veterans with Normal FOT (Tables 6 and 7; Fig. 2). Veterans with Abnormal R4-R20 had similar pulmonary function to that of Normal FOT; however, very few veterans (n = 5) met these criteria. Our data suggest that distal airway dysfunction in our sample appears to be driven predominantly by abnormalities in reactance. There are several lines of evidence that support this view. For example, AX was abnormal in 71% of veterans with preserved spirometry as opposed to 38.7% with abnormal R4-R20 (Table 4). This is also supported by multi-frequency plots of resistance and reactance (Fig. 1) whereby reactance values in those with preserved spirometry more closely approximate those with
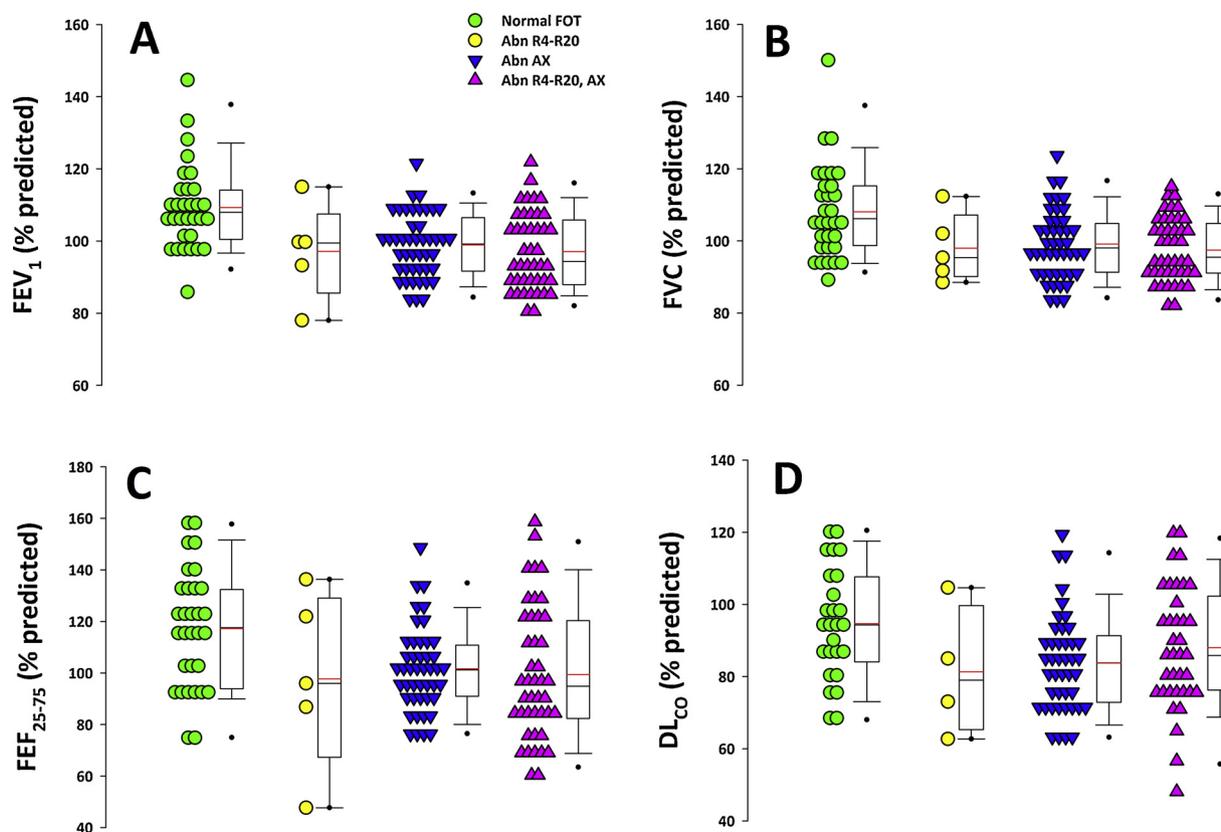
Fig. 2. Dot and box plots representing veterans with preserved spirometry for selected pulmonary function variables by FOT patterns of distal airway function. *Definition of Abbreviations:* FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, FEF_{25-75} = mid-expiratory flow; DLCO = diffusing capacity of carbon monoxide; FOT = forced oscillation technique; R4 = resistance at 4 Hz; R20 = resistance at 20 Hz, R4-R20 = (R4-R20)/R4 * 100; AX = reactance area. *Notes:* Dot plots represent individual results for (A) FEV_1, (B) FVC, (C) FEF_{25-75}, and (D) DL_{CO} represented as a percent of predicted value (Hankinson et al., 1999; Miller et al., 1983). Adjacent box plots represent the median, 25th and 75th percentiles along with mean (red horizontal line) values by group. Groups were determined *a priori* via FOT patterns: Normal FOT, Abnormal R4-R20, Abnormal AX, and Abnormal R4-R20 and AX. Please see methods for details on group assignment. Normal FOT was used as the reference group and the remaining three groups represent distal airway dysfunction.

abnormal spirometry. Additionally, the frequency of a positive bronchodilator response for AX was almost three-fold higher than R4 (43.2% vs. 15.3%), and AX was more strongly associated with pulmonary function measures than measures of resistance (Table 5).

Reactance has been shown to decrease (more negative) with the severity of obstruction (van Noord et al., 1989), and some studies report a stronger association with FEV_1 than measures of resistance (van Noord et al., 1989; Malmberg et al., 2000). In COPD, measures of reactance are more closely associated with pulmonary function test measures of air trapping and airflow limitation (Tse et al., 2016; Kolsum et al., 2009), as well as risk of future exacerbation (Yamagami et al., 2018), than measures of resistance. In addition to obstructive indices, recent studies suggest that reactance may also be more closely associated with high-resolution computed tomography (HRCT) patterns than resistance. For example, Karayama et al., (2017) found that the percentage of low attenuation areas on HRCT were significantly associated with reactance measures, but not resistance, in patients with COPD. Similar findings were also reported in patients with systemic sclerosis, whereby AX – but not measures of resistance – was associated with HRCT patterns of ground glass opacities and fibrosis (Aronsson et al., 2015). HRCT patterns of decreased attenuation and ground glass opacities are suggestive of emphysematous and interstitial changes, and these features are commonly associated with reductions in DL_{CO}. In fact, Fujii et al. (2015) found that more negative reactance values were associated with worse DL_{CO} in patients with interstitial lung disease, and no associations were observed with measures of resistance. That reduced DL_{CO} was only observed among those with Abnormal AX in the present study appears to support this earlier work.

Although the present study highlights the potential clinical utility of FOT, adoption in routine clinical care has been historically difficult due to: (1) the absence of longitudinal studies, (2) variability of FOT implementation due to patient factors (e.g., cheek support, glottis closure), and (3) limited reference values from diverse populations (See Kalchiem-Dekel and Hines, 2018) for review). Additionally, more than 15 years have passed since the first international guidelines on FOT have been published (Oostveen et al., 2003), and as a result, interpretative strategies presently lack consensus. Therefore, the operational definitions used in the present study for abnormal R4-R20 and AX, albeit frequently used, may have resulted in over- or under-classification of abnormality. Unlike FOT, there is greater consensus around spirometry with respect to reference values and interpretative strategies Miller et al. (2005b) that are not only diagnostic, but provide prognostic information concerning morbidity and mortality. FOT's future utility as a clinical screening tool remains subject to debate (Berger et al., 2015a) until additional studies and greater consensus is achieved.

Notwithstanding the limitations of a cross-sectional study, a notable limitation to the present study is referral bias of our sample. Veterans evaluated at our center are treatment seeking and report a variety of respiratory and non-respiratory symptoms. Due to the clinical nature of our center, we lack data on non-treatment seeking asymptomatic deployed veterans, a very important comparison group. In addition, our sample is predominantly non-Hispanic white men. For these reasons, the generalizability of our study's findings to the larger deployed population may be limited. It is also important to note that data used for the present analysis were not collected for research purposes, but abstracted from the clinical evaluation. As our center is a national referral

center, we also lack longitudinal follow-up. Additionally, clinically indicated tests such as HRCT images of the chest and bronchoprovocation studies are only available on a subset of our sample (details provided in Supplemental Material). The absence of these complete data, as well as invasive studies (i.e., lung biopsy), preclude our ability to validate our operational definition of distal airway dysfunction in our sample.

5. Conclusions

In conclusion, 71% of deployed Iraq and Afghanistan veterans referred to our national post-deployment center for chronic unexplained respiratory symptoms had preserved spirometry. Among those with preserved spirometry 75% had distal airway dysfunction, as defined as one or more FOT abnormalities, and these individuals had reduced pulmonary function for some (FEV_1, FVC, FEF_{25-75}, and DL_{CO}), but not all measures of standard pulmonary function testing. Airway reactance rather than resistance appears most affected as reflected by a greater rate of abnormality and bronchodilator responsiveness in the AX measure. Overall, our findings support prior recommendations (Oppenheimer et al., 2007) for the assessment of distal airway function via FOT when evaluating patients exposed to environmental hazards who have preserved spirometry. Given that less than one-third of our sample had been prescribed bronchodilators prior to evaluation, there may also be an opportunity to validate early therapy in this cohort. Further studies into FOT are needed to investigate the clinical significance of distal airway dysfunction in symptomatic individuals and to eventually guide therapy, especially in at-risk populations.

Declarations of interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resp.2018.11.012.

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