Isolated Small Airway Dysfunction and Ventilatory Response to Cardiopulmonary Exercise Testing

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BACKGROUND: The effect of isolated small airway dysfunction (SAD) on exercise remains incompletely characterized. We sought to quantify the relationship between isolated SAD, identified with lung testing, and the respiratory response to exercise. METHODS: We conducted a prospective evaluation of service members with new-onset dyspnea. All subjects underwent plethysmography, diffusing capacity of the lung for carbon monoxide (D_{LCO}), impulse oscillometry, high-resolution computed tomography (HRCT), and cardiopulmonary exercise testing (CPET). In subjects with normal basic spirometry, D_{LCO}, and HRCT, SAD measures were analyzed for associations with ventilatory parameters at submaximal exercise and at maximal exercise during CPET. RESULTS: We enrolled 121 subjects with normal basic spirometry (ie, FEV_1, FVC, and FEV_1/FVC), D_{LCO}, and HRCT. Mean age and body mass index were 37.4 ± 8.8 y and 28.4 ± 3.8 kg/m^2, respectively, and 110 (90.9%) subjects were male. The prevalence of SAD varied from 2.5% to 28.8% depending on whether FEV_3/FVC, $FEF_{25-75\%}$, residual volume/total lung capacity, and R5-R20 were used to identify SAD. Agreement on abnormal SAD across tests was poor (kappa = −0.03 to 0.07). R5-R20 abnormalities were related to higher minute ventilation ($\dot{V}_E$) and higher $\dot{V}_E$/maximum voluntary ventilation (MVV) during submaximal exercise and to lower $\dot{V}_{O_2}$ during maximal exercise. After adjustment for differences at baseline, there remained a trend toward a relationship between R5-R20 and an elevated $\dot{V}_E$/MVV during submaximal exercise (β = 0.04, 95% CI −0.01 to 0.09, P = .10), but there was no significant association with $\dot{V}_E$ during submaximal exercise or with $\dot{V}_{O_2}$ during maximal exercise. No other SAD measures showed a relationship with ventilatory parameters. CONCLUSIONS: In 121 subjects with normal basic spirometry, D_{LCO}, and HRCT, we found poor agreement across tests used to detect SAD. Among young, healthy service members with postdeployment dyspnea, SAD as identified by lung function testing does not predict changes in the ventilatory response to exercise. *Key words: small airway dysfunction; ventilatory response; exertional dyspnea; cardiopulmonary exercise testing.* [Respir Care 2020;65 (10):1488–1495. © 2020 Daedalus Enterprises]

Introduction

The effects from small airway dysfunction (SAD) are difficult to quantify because patients rarely present with isolated SAD, leading some to dub the small airways the "quiet zone."[1] An accepted standard measure therefore does not exist.[2,3] Studies relating SAD to the ventilatory response to exercise have enrolled older subjects with COPD and tobacco/environmental exposures,[4-6] where relationships are confounded by the presence of gas-exchange and large-airway abnormalities and are exaggerated by the loss in elastic recoil inherent to the aging process.

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Furthermore, these studies each used different tests to assess the small airways.[4,5,7,8] In fact, the prevalence of SAD is reported to vary with the test used for assessment,[9] a fact confirmed by the recent results from the ATLANTIS study.[2]

Active-duty service members often present with exercise-related dyspnea during and after deployment to Southwest Asia.[10-14] Elevated levels of geologic and inorganic dusts have been documented in this region,[15] and tobacco use generally increases during deployment,[16,17] putting active-duty service members at risk for SAD. One study reported a high prevalence of SAD in soldiers with postdeployment respiratory symptoms,[18] and others have identified airway disease as the most common diagnosis among active-duty service members with postdeployment respiratory complaints.[19,20] Lastly, because active-duty service members are required to exercise and to pass bi-annual fitness testing, SAD that is silent in a sedentary individual may manifest as exercise limitation.

The Study of Active-Duty Military for Pulmonary Disease Related to Environmental Deployment Exposures (STAMPEDE III) was initiated to systematically assess service members returning from Southwest Asia with new-onset dyspnea.[10,20,21] All subjects enrolled were tested with spirometry, plethysmography, diffusing capacity of the lung for carbon monoxide (D_{LCO}), impulse oscillometry, high-resolution computed tomography (HRCT), and cardiopulmonary exercise testing (CPET). Thus, STAMPEDE III enrolled otherwise healthy, active subjects exposed to tobacco and particulate matter and provides the opportunity to isolate the physiologic effects from SAD in a younger, healthy population. We used data from STAMPEDE III to evaluate different measures of SAD and to test whether isolated SAD is associated with respiratory response on CPET.

QUICK LOOK

Current knowledge

Data indicating that small airway dysfunction (SAD) leads to changes in the ventilatory response to exercise are confounded by the presence of abnormal large airway resistance or abnormal gas exchange in the subjects studied. Patients rarely present before more extensive respiratory abnormalities accrue, so the effect from isolated SAD on the ventilatory response to exercise is largely unknown.

What this paper contributes to our knowledge

In a young, active population with exercise limitations who had normal FEV_1, FVC, FEV_1/FVC, diffusion capacity, and high-resolution computed tomography scans at rest, SAD measures were not independently associated with the ventilatory response to exercise. Our data suggest that, when assessing a population with exercise limitations, isolated SAD abnormalities do not predict a change in the ventilatory response to exercise.

Methods

This prospective evaluation was approved by the Brooke Army Medical Center Institutional Review Board (#363715), and all study participants provided written informed consent. Enrollment began at Brooke Army Medical Center in 2012; in 2015 the Walter Reed National Military Medical Center opened as a satellite study site (IRB #385625-2). Subjects were service members who presented with new-onset dyspnea or exercise limitation after deployment to Southwest Asia (ie, Iraq, Afghanistan, or Kuwait). Individuals with a pre-deployment medical history of any physician-diagnosed pulmonary or cardiac disease were excluded. Those unable to run on a treadmill were also excluded. Participants completed a questionnaire detailing deployment history, airborne exposures, smoking, pulmonary symptoms, and medical treatment (see the supplementary materials at http://www.rcjournal.com). Comprehensive testing, as part of the ongoing STAMPEDE III study,[21] includes full pulmonary function testing (spirometry, plethysmography, D_{LCO}), impulse oscillometry, HRCT (inspiratory and expiratory images with 1- and 3-mm slices), and CPET. To assess the effect that isolated SAD has on the respiratory response to exercise, we focused our evaluation on subjects with normal spirometry, D_{LCO}, and HRCT (Fig. 1).

Pulmonary Function Testing

Participants performed spirometry and D_{LCO} according to American Thoracic Society (ATS) standards, using a VMax spirometer (CareFusion, Yorba Linda, California).[22,23] D_{LCO} was done with methane (CH_4) as the tracer gas. VMax body plethysmography (CareFusion) was used to determine total lung capacity (TLC) and residual volume (RV).[24] Oscillatory

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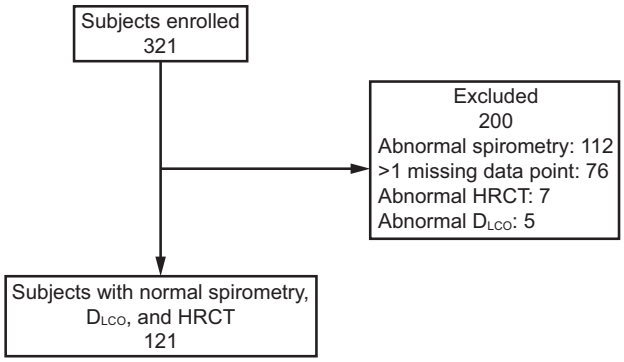

Fig. 1. Flow chart. D_{LCO} = diffusing capacity of the lung for carbon dioxide; HRCT = high-resolution computed tomography.

resistance was obtained using system software (CareFusion MasterScreen IOS; San Diego, California). Testing was performed according to published guidelines, and measurements of R5 (total respiratory resistance), R20 (proximal resistance), X5 (distal capacitive reactance), Fres (resonant frequency), and AX (reactance area) were recorded.[25,26] We considered the following tests to be measures of small airway function: forced expiratory flow during the middle half of the FVC maneuver ($FEF_{25-75\%}$),[27,28] forced expiratory volume in the first 3 s (FEV_3)/FVC,[29] RV/TLC,[28,30] and R5-R20, which is calculated as $[(R5 - R20)/R5] \times 100$.[25,26]

Cardiopulmonary Exercise Testing

All subjects had an incremental treadmill exercise test (Bruce protocol)[31] performed according to guidelines published by the ATS and American College of Chest Physicians.[32] A treadmill was used in lieu of a cycle ergometer to simulate the running required for physical fitness testing in the military. The subjects exercised to exhaustion. During the warm-up, exercise, and recovery phases of the test, expired gas analysis was performed using the Medgraphics Platinum Elite series (MCG Diagnostics, St. Paul, Minnesota). Oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), tidal volume, breathing frequency, and minute ventilation ($\dot{V}_E$) were directly measured. Parameters reflecting cardiac function measured or calculated included maximum heart rate, maximum $\dot{V}_{O_2}$, ventilatory anaerobic threshold, heart rate response, and electrocardiogram.

Our primary outcome was respiratory response assessed by measuring ventilatory equivalents for carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$) and oxygen ($\dot{V}_E/\dot{V}_{O_2}$) and minute ventilation as a percentage of maximum voluntary ventilation ($\dot{V}_E$/MVV; MVV was measured prior to initiation of CPET) during submaximal exercise. Submaximal exercise was chosen at 25 mL/kg/min $\dot{V}_{O_2}$ because it represents the 10th to the 20th percentile ranking of $\dot{V}_{O_2}$ for fit men and women between the ages of 26 and 45 years old[33] and should therefore be achievable by the majority of participants. Respiratory response was also assessed at rest and maximum $\dot{V}_{O_2}$.

Reference Values

In accordance with ATS recommendations,[34] we used the data from NHANES III[35] for interpretation of spirometry in African-American, White, and Hispanic subjects. NHANES III does not include data for Asian-American subjects, so we used regression equations established by Korotzer et al[36] for this population. NHANES III includes equations for FEV_1, FVC, FEV_1/FVC, and $FEF_{25-75\%}$, but not for FEV_3/FVC. Reference values for FEV_3/FVC were taken from Hansen et al.[29] Equations for RV/TLC were taken from data published by Crapo et al,[37] with a correction factor of 0.88 to adjust for non-White races.[38] For D_{LCO}, we used the equations published by Miller et al.[39]

We used 150% as the upper limit and 80% as the lower limit of normal for R5 and R20/R5 respectively, based on the manufacturer's recommendations.[20,40] An alternative threshold using a fixed upper limit for abnormality for R5-R20 is 0.76 cm H_2O/L/s, which was taken from data on SAD following exposure to dust during the World Trade Center disaster.[41] Analysis was done using both the manufacturer's criteria and the World Trade Center criteria, given the absence of consensus on the optimal reference thresholds for impulse oscillometry.

Statistics

Normally and nonnormally distributed variables are displayed by mean ± SD and median with intra-quartile range, respectively. Comparisons between continuous variables were made using the independent samples *t*-test and the Mann-Whitney *U* test for normally and nonnormally distributed variables, respectively. All categorical comparisons were made using the Fisher exact test. Pearson correlation coefficients were used to assess bivariate relationships between linear variables, and kappa statistics were used to measure agreement between categorical variables. To adjust for possible confounders, we used linear regression when appropriate. All data analysis was performed with SPSS 22.0 (SPSS, Chicago, Illinois).

Results

Between June 2012 and December 2016, 260 and 61 subjects were enrolled at Brooke Army Medical Center and Walter Reed National Military Medical Center, respectively (Fig. 1). There were 121 (37.7%) subjects (Fig. 1) with normal spirometry, D_{LCO}, and HRCT (for specific HRCT findings; see the supplementary materials at http://www.rcjournal.com). Baseline demographics, labs, exposures, and diagnoses made during deployment are listed in Table 1. On

Table 1. Demographics/Diagnoses for Subjects With Normal Spirometry, D_{LCO}, and HRCT

Age, y	37.4 ± 8.8
Body mass index, kg/m^2	28.4 ± 3.8
Tobacco use*	
Prior	34 (33.7)
During	31 (3.7)
Male	110 (90.9)
Race	
White	86 (71.1)
African-American	18 (14.9)
Hispanic	17 (14.0)
Hemoglobin, g/dL	14.8 ± 1.1
Deployment duration, months	12.5 ± 6.2
Prior deployments	1.5 (0.0–3.0)
Exposures	
Sand	99 (98.0)
Chemicals	47 (5.5)
Smoke	96 (98.0)
Burn pits	97 (98.0)
Conditions diagnosed during deployment	
Allergies	31 (31.3)
Asthma	18 (18.0)
Upper respiratory infection	31 (31.0)

Data are presented as *n* (%), mean ± SD, or median (interquartile range). *n* = 121 subjects.
* 40 (39.6%) used tobacco either before or during deployment.
D_{LCO} = diffusing capacity of the lung for carbon monoxide
HRCT = high-resolution computed tomography

Table 2. Lung Function Testing

Spirometry/Plethysmography	Measurement
FVC, L	5.0 ± 0.9 (99.2 ± 12.1)
FEV_1, L	4.0 ± 0.7 (97.9 ± 11.6)
FEV_1/FVC	0.08 ± 0.05
$FEF_{25-75\%}$, L/s	3.8 ± 1.0 (95.6 ± 22.0)
RV/TLC	0.27 ± 0.16
Diffusion capacity	
D_{LCO}, mL/min/mm Hg	32.6 ± 7.1 (98.8 ± 18.8)
D_{LCO}/V_A, mL/min/mm Hg/L	5.2 ± 1.0 (105.1 ± 21.7)
Impulse oscillometry	
R5-R20, %	85.2 ± 11.0
Small airway abnormalities	
Abnormal FEV_3/FVC	10 (9.2)
Abnormal $FEF_{25-75\%}$, %	3 (2.5)
Abnormal R5-R20, %*	34 (28.8)
Abnormal RV/TLC, %	14 (11.8)

Data are presented as *n* (%) or mean ± SD. *n* = 121 subjects.
*R5-R20 = [(R5-R20)/R5]×100 (from Ref. 40), < 80.0% considered abnormal; using the alternative threshold of R5-R20 > 0.76 cmH_2O/L/s, the number of abnormals is 30 (25.4%) (from Ref. 41).
$FEF_{25-75\%}$ = forced expiratory flow during the middle half of the FVC maneuver
RV = residual volume
TLC = total lung capacity
FEV_3 = forced expiratory volume in 3 s
D_{LCO} = diffusing capacity of the lung for carbon monoxide
V_A = alveolar volume

a linear scale (1 = never, 2 = ≤ 2 times/week, 3 = 2–5 times/week, and 4 = daily), subjects rated symptoms of dyspnea, wheezing, cough, sputum production, and decreased exercise after deployment. For the 121 subjects with normal lung testing and HRCT, mean ± SD scores for each symptom were 3.1 ± 0.9, 2.3 ± 1.1, 2.7 ± 1.1, 2.1 ± 1.0, and 3.1 ± 1.0, respectively.

Lung function testing is listed in Table 2. Prevalence of abnormality in small airway function ranged from 3 (2.5%) to 34 (28.8%) subjects, depending on the test used for identification. Kappa values (−0.03 to 0.07; for details on specific relationships; see the supplementary materials at http://www.rcjournal.com) indicate no agreement on small airway abnormality across tests.

Table 3 lists age, body mass index, baseline FEV_1, and MVV when each SAD measure is normal versus abnormal. Subjects with an abnormal $FEF_{25-75\%}$ had significantly lower FEV_1 values, and those with abnormal RV/TLC and R5-R20 had lower and higher body mass index values, respectively. Overall values for anaerobic threshold and maximum $\dot{V}_{O_2}$ during exercise were 26.4 ± 6.3 and 37.3 ± 6.6 mL/kg/min respectively, and O_2-pulse at maximum $\dot{V}_{O_2}$ was 19.8 ± 3.7 mL/beats/min. End-tidal P_{CO_2} at submaximal exercise (25 mL/kg/min) was 45.6 ± 3.4 mm Hg, and $\dot{V}_E/\dot{V}_{CO_2}$ values at anaerobic threshold and maximum $\dot{V}_{O_2}$ were 25.4 ± 3.1 and 28.5 ± 4.4, respectively.

Table 4 shows CPET results during submaximal exercise ($\dot{V}_{O_2}$ = 25 mL/kg/min) and during maximal exercise when SAD by each measure is normal versus abnormal. At submaximal exercise, breathing frequency and tidal volume were significantly lower when $FEF_{25-75\%}$ and RV/TLC were abnormal, respectively, and $\dot{V}_E$ and $\dot{V}_E$/MVV were higher when R5-R20 was abnormal. During maximal exercise, $\dot{V}_E$ and $\dot{V}_E/\dot{V}_{CO_2}$ were higher in subjects with abnormal FEV_3/FVC, and, $\dot{V}_{O_2}$ was significantly lower in subjects with abnormal R5-R20.

We used linear regression to adjust for differences seen at baseline. No regression was required for FEV_3/FVC given a lack of baseline differences between groups. After adjusting for FEV_1 at baseline, an abnormal $FEF_{25-75\%}$ remained significantly associated with breathing frequency during submaximal exercise (β = 9.0, 95% CI 2.3–15.6, P = .01). After adjusting for body mass index at baseline, an abnormal RV/TLC was no longer significantly associated with tidal volume during submaximal exercise. For an abnormal R5-R20, after adjusting for body mass index at baseline, there remained a trend toward a relationship with $\dot{V}_E$/MVV during submaximal exercise (β = 0.04, 95% CI −0.01 to 0.09, P = .10). Abnormal R5-R20 was no longer significantly associated with $\dot{V}_E$ at submaximal exercise or with $\dot{V}_{O_2}$ at max exercise.

Because thresholds of abnormality for $FEF_{25-75\%}$, RV/TLC, and R5-R20 have not been established using

Table 3. Demographics and Lung Function According to Small Airway Dysfunction

	FEV_3/FVC		$FEF_{25-75\%}$		RV/TLC		R5-R20	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Subjects, *n*	99	10	118	3	105	14	84	34
Age, y	37.0 ± 8.8	36.6 ± 5.7	37.6 ± 8.8	30.3 ± 7.5	37.5 ± 8.8	36.0 ± 9.7	37.6 ± 8.1	36.2 ± 9.9
Body mass index, kg/m^2	28.4 ± 3.7	28.5 ± 3.3	28.4 ± 3.6	29.6 ± 11.5	28.7 ± 3.6	26.4 ± 4.8†	27.9 ± 3.7	30.0 ± 4.0‡
FEV_1, % predicted	97.6 ± 12	97.1 ± 7.8	98.3 ± 11	79.5 ± 0.8*	94.7 ± 14	98.4 ± 11	98.4 ± 11	96.4 ± 13
MVV, L/min	157 ± 34	162.3 ± 37	157 ± 35	144 ± 22	157 ± 35	149 ± 35	159 ± 35	152 ± 35

Data are presented as mean ± SD. $n = 121$ subjects.
* $P < .001$.
† $P = .03$.
‡ $P = .007$.
FEV_3 = forced expiratory volume in 3 s
$FEF_{25-75\%}$ = forced expiratory flow during the middle half of the FVC maneuver
RV = residual volume
TLC = total lung capacity
R5-R20 = [(R5 − R20)/R5] × 100 (from Ref. 42)
MVV = maximum voluntary ventilation

Table 4. Respiratory Response at Submaximal Exercise and at Peak Exercise

	FEV_3/FVC		$FEF_{25-75\%}$		RV/TLC		R5-R20	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Submaximal Exercise ($\dot{V}_{O_2}$ = 25 mL/kg/min)								
Subjects, *n*	97	8	110	3	98	13	80	32
f, breaths/min	27.4 ± 5.6	27.8 ± 6.3	27.2 ± 5.7	20.0 ± 1.0	26.8 ± 5.4	29.3 ± 7.8	26.3 ± 5.6	28.8 ± 5.8
Tidal volume, L	2.1 ± 0.5	2.2 ± 0.4	2.1 ± 0.5	2.5 ± 0.8	2.2 ± 0.5	1.9 ± 0.4*	2.1 ± 0.5	2.1 ± 0.6
$\dot{V}_E$	57.1 ± 14	55.0 ± 16	56.6 ± 14	48.7 ± 14	56.7 ± 14	53.9 ± 15	54.5 ± 13	61.4 ± 16†
$\dot{V}_E/\dot{V}_{O_2}$	25.6 ± 3.8	26.9 ± 3.9	27.5 ± 20	22.3 ± 1.9	27.6 ± 21	26.0 ± 4.5	27.8 ± 23	26.2 ± 4.3
$\dot{V}_E/\dot{V}_{CO_2}$	25.4 ± 2.4	25.8 ± 3.2	25.1 ± 2.7	22.7 ± 4.1	25.0 ± 2.7	26.2 ± 2.7	25.0 ± 2.7	25.4 ± 2.8
$\dot{V}_E$/MVV, %	38.5 ± 13	36.4 ± 14	38.0 ± 13	35.5 ± 16	38.2 ± 13	37.3 ± 11	36.1 ± 12	42.6 ± 14
Peak Exercise								
Respiratory exchange ratio	1.20 ± 0.1	1.28 ± 0.1	1.20 ± 0.1	1.15 ± 0.1	1.20 ± 0.1	1.20 ± 0.1	1.20 ± 0.1	1.17 ± 0.1
$\dot{V}_{O_2}$, mL/kg/min	38.9 ± 7.3	38.9 ± 7.7	38.7 ± 7.4	44.3 ± 10	38.3 ± 6.9	41.5 ± 10	39.9 ± 7.8	36.3 ± 6.2†
f, breaths/min	43.0 ± 8.3	45.7 ± 8.7	42.6 ± 8.4	39.0 ± 10	42.2 ± 8.1	43.2 ± 10	42.9 ± 8.3	41.7 ± 8.8
Tidal volume, L	2.8 ± 0.6	3.1 ± 0.5	2.9 ± 0.7	3.3 ± 1.1	2.9 ± 0.7	2.6 ± 0.7	2.9 ± 0.7	2.8 ± 0.7
Minute ventilation	117 ± 25	140 ± 18†	119 ± 26	120 ± 4.6	120 ± 26	109 ± 20	121 ± 26	115 ± 26
$\dot{V}_E/\dot{V}_{O_2}$	34.6 ± 5.7	38.9 ± 6.1	35.0 ± 5.8	32.1 ± 5.1	35.2 ± 5.7	33.0 ± 6.0	35.4 ± 5.7	33.8 ± 5.8
$\dot{V}_E/\dot{V}_{CO_2}$	28.6 ± 4.5	30.3 ± 2.9*	28.5 ± 4.4	27.7 ± 4.7	28.4 ± 4.5	29.2 ± 3.4	28.9 ± 3.4	27.5 ± 6.1
$\dot{V}_E$/MVV, %	76.9 ± 19	89.1 ± 18	77.9 ± 20	85.1 ± 16	78.4 ± 20	75.3 ± 18	78.0 ± 18	78.1 ± 22

Data are presented as mean ± SD. $n = 121$ subjects.
* $P = .02$.
† $P = .05$.
FEV_3 = forced expiratory volume in 3 s
$FEF_{25-75\%}$ = forced expiratory flow during the middle half of the FVC maneuver
RV = residual volume
TLC = total lung capacity
R5-R20 = [(R5 − R20)/R5] × 100 (from Ref. 42)
f = breathing frequency
$\dot{V}_E$ = minute ventilation
MVV = maximum voluntary ventilation

robust data sets, we checked for linear relationships between each measure and outcomes on CPET, again controlling for differences at baseline. Percent of predicted $FEF_{25-75\%}$ was no longer associated with breathing frequency at submaximal exercise ($P = .23$), and percent of predicted RV/TLC was still unrelated to tidal volume at submaximal exercise ($P = .16$). R5-R20 was not associated with $\dot{V}_E$ ($P = .97$) or $\dot{V}_E$/MVV

($P = .13$) during submaximal exercise, nor was it associated with maximum $\dot{V}_{O_2}$ ($P = .32$). Lastly, we noted differences in baseline and exercise variables in relation to R5-R20 abnormalities using the World Trade Center cut-off (see the supplementary materials at http://www.rcjournal.com). However, after adjusting for differences at baseline (FEV_1 percent of predicted, MVV, and body mass index), R5-R20 at this cut-off for abnormality was not significantly related to any exercise values on CPET.

Discussion

We studied young, active subjects with complaints of exertional dyspnea and evidence of isolated SAD on lung function testing. Our findings suggest that the prevalence of SAD ranges from 2.5% to 28.8% depending on the lung testing used, and there is poor agreement across tests. After adjusting for confounders at baseline, SAD showed little (if any) relationship to the respiratory response to exercise.

In our cohort, we found that an abnormal $FEF_{25-75\%}$ was associated with a lower breathing frequency during submaximal exercise. Of those studied, only 3 subjects had an abnormal $FEF_{25-75\%}$. It is unclear why an abnormal $FEF_{25-75\%}$ would lead to a decrease in breathing frequency, so this finding is unlikely to have clinical importance. The relationship between RV/TLC and exercise variables was eliminated after adjustment for body mass index. Associations between FEV_3/FVC, $\dot{V}_E$, and $\dot{V}_E/\dot{V}_{CO_2}$ at maximum $\dot{V}_{O_2}$ are difficult to interpret given the absence of differences during submaximal exercise. Subjects with an abnormal FEV_3/FVC had a higher respiratory exchange ratio and $\dot{V}_E$/MVV during maximal exercise, which might imply greater effort in this group and could account for the differences in $\dot{V}_E$ and $\dot{V}_E/\dot{V}_{CO_2}$ seen at maximum $\dot{V}_{O_2}$. However, the differences in respiratory exchange ratio and $\dot{V}_E$/MVV at maximum $\dot{V}_{O_2}$ were not significant.

In our population, R5-R20 showed a significantly lower ventilatory reserve during submaximal exercise and a lower maximum $\dot{V}_{O_2}$. When controlling for body mass index, this relationship was largely eliminated. Incidentally, body mass index remained significantly associated with both ventilatory reserve during submaximal exercise ($\beta = 0.01$, 95% CI 0.01–0.02, $P < .001$) and maximum $\dot{V}_{O_2}$ ($\beta = -0.84$, 95% CI −1.2 to −0.52, $P < .001$) in regression analysis. Weight is known to affect impulse oscillometry via changes in chest wall compliance and airway closure or atelectasis, so it seems likely that an abnormal R5-R20 is a surrogate for an increased body mass index.[25,42] Body mass index in turn affects ventilatory reserve and maximum $\dot{V}_{O_2}$.[32]

There are several possible explanations for why we could not identify a relationship between SAD and ventilatory response on CPET. First, we may have used the wrong cutoff points to define SAD. Although $FEF_{25-75\%}$,[27,28] FEV_3/FVC,[29] RV/TLC,[28,30] and R5-R20[25,26] have all been used to assess the small airways, with the exception of FEV_3/FVC, thresholds for abnormality have not been derived from large, well-defined data sets. For all 4 measures, there are limited data correlating the thresholds that we used for abnormality with clinical outcomes. We attempted to control for this by analyzing linear relationships between each SAD measure and outcomes on CPET, and by using different thresholds for R5-R20. Still, we were unable to detect a correlation between SAD and CPET variables, making inappropriate thresholds an unlikely explanation for the absence of significant findings.

Second, SAD may affect the ventilatory response to exercise without showing changes in the outcome variables we analyzed ($\dot{V}_E/\dot{V}_{CO_2}$, $\dot{V}_E/\dot{V}_{O_2}$, $\dot{V}_E$, $\dot{V}_E$/MVV). Elbehairy et al[7] compared smokers with peripheral airway dysfunction (but without COPD) to healthy controls. They found no differences between $\dot{V}_E/\dot{V}_{CO_2}$, $\dot{V}_E/\dot{V}_{O_2}$, $\dot{V}_E$, and $\dot{V}_E$/MVV at submaximal exercise levels, but they did see early differences in respiratory resistance, inspiratory work, and dyspnea using electromyography and advanced pressure monitoring. Although it is possible that we would have detected similar changes in subjects with SAD had we used the same advanced testing, we believe that this is unlikely. Their group found clear differences at maximal exercise levels between smokers with peripheral airway dysfunction and controls (ie, respiratory exchange ratio, $\dot{V}_E$/MVV, maximum $\dot{V}_{O_2}$), suggesting an earlier limitation to exercise. We found no such differences at maximum $\dot{V}_{O_2}$, making it less likely that the subjects with SAD in our cohort were doing a significant amount of additional inspiratory work earlier in exercise, thus resulting in dyspnea.

Lastly, it is possible that the absence of findings is related to the population we studied. Given their deployment exposures, they may be at increased risk for SAD,[18-20] but the current literature does not define the overall burden of disease (eg, expected prevalence and SAD severity). When testing for subtle abnormalities in lung function, there will be overlap with normal.[43] If the true prevalence of abnormality is low, positive predictive value will decrease and abnormalities will be less likely to reflect real disease. The poor correlation across SAD measures supports this explanation. Likewise, because we compared our findings with those of other symptomatic service members with similar exposures, rather than healthy controls without symptoms, real differences in the respiratory response to exercise may have been difficult to isolate on CPET. Finally, peripheral resistance and lung elastic recoil decline with age,[29,44] and it may be that isolated SAD has less effect on younger individuals than on older individuals.

This study has several limitations. First, the absence of exercise flow-volume loops and dyspnea scores limits our ability to correlate subtle mechanical limitations related to SAD, like dynamic hyperinflation, to symptoms.[45] However,

others have used models similar or identical to ours to study the relationship between SAD and exercise limitations, so our approach was reasonable.[4,5,7,8] Second, we chose to compare SAD to respiratory response on CPET to establish clinical importance. If the clinical burden from SAD was tracked using different outcome measures (eg, symptoms, clinic visits, and medication use), FEV_3/FVC, $FEF_{25-75\%}$, RV/TLC, or impulse oscillometry might have revealed important relationships. For example, the ATLANTIS study established an association between some of the same measures we used and clinical outcomes in asthma subjects.[2] Third, because we did not report a formal diagnosis of asthma, exercise-induced bronchoconstriction, or allergies, it is unclear if and how the presence of any of these diagnoses affects our results. Lastly, our data are most applicable to younger patients with dyspnea who have findings of isolated SAD on lung testing. In this specific population, markers for SAD do not predict changes in the ventilatory response to exercise during CPET.

Conclusions

We studied a large military population with respiratory symptoms following deployment to Southwest Asia. We found evidence of SAD among subjects with normal spirometry, D_{LCO}, and HRCT. Agreement across SAD tests was poor, and the presence of isolated SAD did not predict the ventilatory response to exercise as measured during CPET. The finding of isolated SAD on lung function testing in younger subjects with dyspnea is of uncertain clinical importance.

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