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Original Research

COPD

Patients With COPD With Higher Levels of Anxiety Are More Physically Active

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Background: **Physical activity (PA) has been found to be an excellent predictor of mortality beyond traditional measures in COPD. We aimed to determine the association between depression and anxiety with accelerometry-based PA in patients with COPD.**
Methods: **We performed a cross-sectional analysis of baseline data from 148 stable patients with COPD enrolled in an ongoing, longitudinal, observational study. We measured PA (total daily step count) with a Stepwatch Activity Monitor over 7 days, depression and anxiety with the Hospital Anxiety and Depression Scales (HADSs), dyspnea with the Shortness of Breath Questionnaire, and functional capacity with the 6-min walk test.**
Results: **Increased anxiety was associated with higher levels of PA such that for every one-point increase in the HADS-Anxiety score there was a corresponding increase of 288 step counts per day ($\beta = 288$ steps, $P < .001$), after adjusting for all other variables. Higher levels of depressive symptoms were associated with lower PA ($\beta = -176$ steps, $P = .02$) only when anxiety was in the model. The interaction term for anxiety and depression approached significance ($\beta = 26$, $P = .10$), suggesting that higher levels of anxiety mitigate the negative effects of depression on PA.**
Conclusions: **The increased PA associated with anxiety in COPD is, to our knowledge, a novel finding. However, it is unclear whether anxious patients with COPD are more restless, and use increased psychomotor activity as a coping mechanism, or whether those with COPD who push themselves to be more physically active experience more anxiety symptoms. Future studies should evaluate for anxiety and PA to better inform how to improve clinical outcomes.**
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Abbreviations: 6MWT = 6-min walk test; CASCADE = COPD Activity: Serotonin Transporter, Cytokine, and Depression Study; HADS = Hospital Anxiety and Depression Scale; HADS-A = Hospital Anxiety and Depression Scale-Anxiety; HADS-D = Hospital Anxiety and Depression Scale-Depression; PA = physical activity; SAM = Stepwatch 3 Activity Monitor

Epidemiologic studies based on self-reported physical activity (PA) show that higher levels of activity are associated with lower risk of incident COPD in smokers and in patients who already have COPD, and with lower risk of acute exacerbations, hospital admissions, and mortality.[1-3] A recent, 4-year, prospective study of patients with COPD showed that objectively measured PA was the best predictor of all-cause mortality compared with a broad range of other prognostic factors, including airflow obstruction, exercise performance, cardiovascular status, nutritional and muscular status, systemic inflammation, health status, depressive symptoms, and dyspnea. Each increase of 1,845 steps per day was associated with a 51% lower risk of death.[4] Objective measures of PA capture what patients actually do vs what they report doing or are capable of doing during a laboratory test.[5] Findings from these studies underscore the critical importance of PA in COPD and the need to better understand how modifiable factors such as psychologic well-being influence PA.

The prevalence of major depression in patients with moderate to severe COPD is approximately 40%.[6] Nearly 20% of patients had episodes of moderate to severe depression prior to their COPD diagnosis.[7] Anxiety disorders, which have considerable overlap

with depressive symptoms, are also prevalent in patients with COPD, with estimates ranging from 10% to 36%.[6,8,9] Patients with higher levels of depressive symptoms report worse physical functioning.[10-14] Similarly, studies that have measured functional capacity using laboratory exercise tests (eg, 6-min walk test [6MWT], symptom-limited cycle, or treadmill) have found that depression is associated with worse functional capacity.[12,15-17] In contrast to these earlier reports that measured functional capacity, a more recent, cross-sectional study from Germany of 170 patients with COPD found that depressive symptoms were not associated with worse PA as measured by accelerometry after adjustment for a number of relevant clinical correlates.[18] Unfortunately, anxiety was not measured in this study by Watz and colleagues,[18] thus, we know very little about the relationship between anxiety (with or without depression) and the level of PA in the daily lives of patients with COPD.

The vicious dyspnea-anxiety-deconditioning spiral has long been acknowledged for a subset of patients with COPD, yet the presumption that anxiety contributes to increased dyspnea with consequent reductions in PA has not been formally tested.[19,20] The relationship between anxiety in patients with COPD and functional capacity remains unclear. A similar number of studies have found that higher anxiety levels are associated with worse functional capacity,[21-23] and a similar number of studies report no relationship between anxiety and functional capacity.[24-26] We are not aware of any published report on the relationship between anxiety and objectively confirmed PA during the daily lives of patients with COPD.

Since recent findings suggest that comorbid anxiety is associated with a greater risk of mortality for patients with COPD,[27] more attention should be directed at understanding anxiety in relation to self-care behaviors and clinical outcomes. Therefore, the purpose of this cross-sectional study was to determine the association between depression and anxiety with accelerometry-based, free-living, ambulatory PA in patients with COPD.

Materials and Methods

Study Design and Settings

The COPD Activity: Serotonin Transporter, Cytokine, and Depression Study (CASCADE) is an ongoing, multisite, prospective, observational study of subjects with COPD who are being followed for 2 years to study the biologic causes and functional consequences of depression. This manuscript is a cross-sectional, descriptive analysis of data from 148 subjects collected at entry to CASCADE. This study was approved by the respective institutional review boards at three clinical sites: the University of Washington, Seattle (approval number 37332); the VA Puget Sound Health Care System (approval number 00240); and the University of Texas Health Science Center at San Antonio/South Texas Veterans Health Care System (approval number HSC20100373H), and was registered with ClinicalTrials.gov (NCT01074515).[28]

Participants

We recruited participants from queries of medical records and pulmonary function tests, chest clinics from the three medical centers, a research database maintained by the investigators, pulmonary rehabilitation programs, better-breathers groups, community pulmonary practices, advertisements, the CASCADE study website, and other referrals. The inclusion criteria were as follows: (1) diagnosis of COPD confirmed by the following: postbronchodilator $FEV_1/FVC < 70\%$, moderate to very severe disease as defined by the GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria ($FEV_1 < 80\%$), age ≥ 40 years, and a significant history of current or past cigarette smoking (> 10 pack-years); (2) stable disease with no acute exacerbations of COPD in the past 4 weeks; and (3) ability to speak, read, and write English. We excluded patients with any of the following conditions: other chronic obstructive lung diseases such as asthma, bronchiectasis, and cystic fibrosis; idiopathic pulmonary fibrosis; uncompensated congestive heart failure (left-sided ventricular dysfunction); primary pulmonary vascular disease; non-COPD-related chronic inflammatory diseases; infectious disease; autoimmune disease; lung cancer or metastatic cancer; chronic renal failure requiring dialysis; chronic uncompensated liver disease; HIV/AIDS; chronic antibiotic use or ongoing infection; chronic oral prednisone use; bipolar disease; psychotic disorders; and any dementia.

Procedures

Informed consent was obtained prior to clinic assessments, which included prebronchodilator and postbronchodilator spirometry, 6MWT, and completion of questionnaires. Participants were asked to wear an activity monitor for 7 days, beginning after their initial clinic visit. Two days after this clinic visit, a depression and anxiety assessment was completed via telephone by a trained mental-health professional.

Measures

Demographic data included self-reported age, sex, education, income, living situation, and marital status. Disease severity included self-report of chronic conditions (Charlson comorbidity index),

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oxygen supplementation, and spirometry, which was performed according to American Thoracic Society standards[29] using an EasyOne spirometer (ndd Medical Technologies Inc). Postbronchodilator values were used. Functional capacity was assessed using the 6MWT according to the American Thoracic Society guidelines.[30] Dyspnea was measured with the Shortness of Breath Questionnaire.[31] Psychologic well-being was measured with the Hospital Anxiety and Depression Scale (HADS).[13] A score ≥ 8 on either scale indicates clinically relevant anxiety (HADS-A) or depression (HADS-D).

PA was measured with a Stepwatch 3 Activity Monitor (SAM) (OrthoCare Innovations LLC) fastened above the right ankle. The SAM is a dual-axis accelerometer linked to a microprocessor sensor that continuously records gait cycles (strides); stride counts are doubled to represent steps. The SAM has been validated for use in patients with COPD[32] and is highly accurate in measuring steps across a range of speeds compared with other accelerometers on the market.[33-35] Participants were asked to wear the SAM during waking hours for 7 days. The SAM was programmed to record in 1-min epochs; a valid day was defined as having ≥ 10 h (600 min) of monitor wear. Total step-count per day was the primary PA variable. Patients wore the accelerometer for a median of 7 days. Seasonality was also considered in the analysis since PA has been shown to vary by season.[36,37]

Data Analysis

We used descriptive statistics to describe the sample and used Pearson correlations for the bivariate correlations. We used independent *t* tests to compare highly anxious and depressed participants to those with low levels of depression and anxiety (HADS-A and HADS-D ≥ 8) on total step counts. We used multivariate linear regression models to examine the relationships between depression and anxiety with total step counts. We performed diagnostic tests to ensure that the models met the assumptions for linear regression (eg, partial correlation plots, standardized residuals, DFITs statistics, leverage, and influence). We also log transformed the outcome variable, step counts; the model remained robust to outliers. All analyses were conducted using SPSS, version 15.0 (IBM). A *P* value < .05 was considered statistically significant.

Table 1—*Sample Characteristics (N = 148)*

Variables	Results
Sociodemographics	
Age, mean (SD), y	66.5 (8.8)
Female sex	33 (22)
Education	
High school or less	38 (26)
Some college or more	110 (74)
Income, USD	
< 20,000/y	68 (47)
≥ 20,000/y	79 (53)
Marital status	
Partnered	79 (53)
Unpartnered	69 (47)
Live alone	37 (25)
BMI, mean (SD), kg/m^2	28.2 (6.4)
Disease severity	
FEV_1/FVC, mean (SD)	0.44 (0.12)
FEV_1 % predicted, mean (SD)	41.7 (15.7)
O_2 supplementation	59 (40)
≥ 5 y since COPD diagnosis	76 (51)
Number of comorbidities, mean (SD)	0.75 (0.91)
Physical functioning, mean (SD)	
6MWT, ft	1,059 (416)
Total steps/d	6,079 (3,718)
Psychologic well-being, mean (SD)	
HADS-D score, 0-21	5.3 (4.0)
HADS-A score, 0-21	5.5 (4.1)
Symptoms, mean (SD)	
Shortness of Breath Questionnaire score, 0-120	28.5 (17.7)

Data given as No. (%) unless otherwise indicated. 6MWT = 6-min walk test; HADS = Hospital Anxiety and Depression Scale; HADS-A = Hospital Anxiety and Depression Scale-Anxiety; HADS-D = Hospital Anxiety and Depression Scale-Depression; O_2 = oxygen; USD = US dollars.

Results

Patient Characteristics

Table 1 includes the summary of the demographic and baseline characteristics of the 148 patients included in the analysis. The cohort (78% men) had a mean FEV_1 % predicted of 42% and few comorbidities. Overall, participants were relatively high functioning and had relatively low depressive and anxiety symptoms. Approximately 32% and 29% of patients scored higher than 8 points on the HADS-A and HADS-D, respectively. Mean SAM wear time did not differ between subjects who had high- or low-anxiety symptoms (874 min vs 899 min, $P = .29$)

Bivariate Unadjusted Associations

PA as measured by total step count had small to moderate significant correlations ($r = 0.14$-0.57, $P < .05$) with age, sex, disease severity (FEV_1 % predicted and oxygen supplementation), 6MWT, dyspnea, and anxiety (Table 2). PA was not significantly correlated with depressive symptoms ($r = 0.01$). Depression and anxiety were highly correlated ($r = 0.64$) as expected, but neither was correlated with functional capacity. Patients with high levels of anxiety (HADS-A > 8) accrued an average of 1,681 more steps per day compared with patients who had low or no anxiety (mean ± SD, 7,215 ± 4,189 vs 5,534 ± 3,358, $P < .01$).

Multivariate Regression Models

Results from the six multivariate regression models predicting PA-total steps per day with disease severity, dyspnea, functional capacity, and psychologic well-being are summarized in Table 3. Model 1, which included age, sex, airflow obstruction, and oxygen use, explained 20% of the variance in total steps. Models 2 and 3 showed that dyspnea and functional capacity were significantly associated with PA, adjusting for all variables from model 1. In Model 4, dyspnea and functional capacity remained significantly associated with PA, whereas depression was not. In model 5, depression was significantly associated with worse PA

Table 2—*Bivariate Correlations (N = 148)*

Variable	Total Steps	Age	Sex	FEV1 % Predicted	O_2 Use	6MWT	Dyspnea	HADS-D	HADS-A
Total steps/d	1.00	…	…	…	…	…	…	…	…
Age	−0.25[a]	1.00	…	…	…	…	…	…	…
Sex	0.14[b]	−0.07	1.00	…	…	…	…	…	…
FEV_1 % predicted	0.32[c]	0.10	0.05	1.00	…	…	…	…	…
O_2 use	−0.19[a]	0.02	−0.01	−0.36[c]	1.00	…	…	…	…
6MWT	0.57[c]	−0.21[a]	0.08	0.33[c]	−0.26[a]	1.00	…	…	…
Dyspnea	−0.42[c]	−0.11	0.01	−0.37[c]	0.29[c]	−0.41[c]	1.00	…	…
HADS-D	0.01	−0.25[a]	0.11	0.10	0.02	0.04	0.26[a]	1.00	…
HADS-A	0.24[a]	−0.38[c]	0.29[c]	0.14[b]	−0.03	0.07	0.21[a]	0.64[c]	1.00

See Table 1 legend for expansion of abbreviations.
[a]$P < .01$.
[b]$P < .05$.
[c]$P < .001$.

(β = −176 steps, $P = .02$) and anxiety was conversely associated with higher levels of PA (β = 288, $P < .001$) after adjusting for all other variables. In a separate model, we also tested the interaction between anxiety and depression and found a positive coefficient, albeit not significant at .05 (β = 26, $P = .10$), suggesting that if a patient was depressed, higher levels of anxiety would mitigate the negative effects of depression on PA.

Since dyspnea could potentially mediate the relationship between anxiety and PA, we tested for this effect in two ways. First, we removed dyspnea from model 6 and found that the coefficients were basically similar to model 5, suggesting that dyspnea did not mediate the relationship between anxiety and PA. Second, anxiety did not have a significant relationship with dyspnea ($P = .22$), another general criterion for

Table 3—*Multivariate Regression Models Predicting Physical Activity, Total Steps per Day (N = 148)*

	Unstandardized Coefficients		Standardized Coefficients			
Variable	β	SE	β	*P* Value	R^2	ΔR^2
Model 1					0.20	0.20
Age, per y	−116	32	0.74	<.001		
Male sex	955	668	0.11	.16		
FEV_1 % predicted[a]	76	19	0.32	<.001		
O_2 use	−547	608	−0.07	.37		
Model 2[b]					0.32	0.12
Dyspnea, SOBQ	−79	16	−0.38	<.001		
Model 3[b]					0.42	0.10
Dyspnea, SOBQ	−52	16	−0.25	.001		
6MWT, ft	3	0.68	0.38	<.001		
Model 4[b]					0.42	0
Dyspnea, SOBQ	−51	17	−0.24	.003		
6MWT, ft	3	0.68	0.38	<.001		
Depression, HADS-D	−23	65	−0.03	.73		
Model 5[b]					0.47	0.04
Dyspnea, SOBQ	−57	16	−0.27	.001		
6MWT, ft	3	0.65	0.39	<.001		
Depression, HADS-D	−176	76	−0.19	.02		
Anxiety, HADS-A	288	80	0.32	<.001		
Model 6[c]					0.42	…
6MWT, ft	4	0.64	0.48	<.001		
Depression, HADS-D	−228	77	−0.25	.004		
Anxiety, HADS-A	257	83	0.29	.002		

ΔR^2 = change in R^2; SOBQ = Shortness of Breath Questionnaire. See Table 1 legend for expansion of other abbreviations.
[a]For each 1% change in FEV_1.
[b]Models 2-5 included age, sex, FEV_1% predicted, and supplemental O_2 use.
[c]Dyspnea excluded from model 6; comparing models 5 and 6 provides a test of mediation to examine whether dyspnea mediates the relationship between the anxiety and physical activity.

dyspnea to be viewed as a mediating factor. The addition of seasonality did not change any of the coefficients for all models and thus the presented data do not include seasons.

Discussion

A key novel finding of this study is that anxiety was significantly and independently associated with increased ambulatory PA in patients with severe COPD, even after adjusting for relevant covariates including demographics, disease severity, functional capacity, dyspnea, and depression. To our knowledge, this finding has not been published elsewhere. We performed a number of diagnostic tests to ensure that the models met the assumptions for linear regression, and, thus, we believe these findings are valid and not due to data errors or artifacts. Also, the increased PA in patients with higher anxiety levels was not due to increased wear time, as patients with high and low levels of anxiety wore the device for the same duration. We also found that depression was associated with less PA only when we adjusted for anxiety.

The discovery that for each one-point increase in anxiety score on the HADS-A in these patients with COPD, there was a corresponding increase of 288 steps per day surprised us. These findings are especially interesting, since published data suggest a positive relationship between anxiety and dyspnea,[26,38] which are presumed to bear negative consequences on PA in patients with COPD.[39] Increased dyspnea and low levels of anxiety were associated with decreased daily step counts (data not shown), but found no indication of an interaction. In addition, a test for dyspnea as a mediator of the relationship between anxiety and PA was negative, suggesting that anxiety and PA are directly related.

Interestingly, our novel finding in patients with COPD is supported by two small studies of primates and adults with panic disorder. Vinot and colleagues[40] found that in nonhuman primates, anxiety was associated with greater spontaneous locomotor activity. A study by Sakamoto and colleagues[41] found that a small sample of adults (14 women, two men) with panic disorder symptoms had high locomotor activity as measured by wrist actigraphy. Thus, it is plausible that the increased spontaneous psychomotor activity is a behavioral manifestation of the restlessness associated with increased anxiety, a coping mechanism, or that patients with a high level of anxiety do not effectively leverage energy conservation strategies and are accruing steps with nongoal-directed ambulatory activities. It is also possible that patients who are anxious and hypervigilant may see lung disease as something that they can and should conquer and that the increased PA may reflect this effort to maintain a high level of activity at all costs. The clinical implications for these observations are interesting because anxiety as a comorbid disorder is associated with increased mortality,[27] while increased PA is associated with lower mortality[4] in patients with COPD. Perhaps mild levels of anxiety that result in higher daily step counts and less sedentary time may be salubrious[42]; this conjecture would need to be confirmed in future studies.

The associations among PA, depression, and use of supplemental oxygen also deserve attention. Similar to the study by Watz and colleagues,[18] we also found that depression was not a significant predictor of PA. However, when we adjusted for anxiety in the final model, a high level of depressive symptoms was associated with worse PA. Depression and anxiety appear to have different effects on PA with anxiety, attenuating the negative impact of depression on total step counts. Our findings suggest that future prediction models of PA should include adjustments for anxiety. Use of supplemental oxygen was not associated with fewer total-step count in our study. This finding is somewhat contrary to typical assumptions by clinicians that patients who carry or roll their oxygen tanks are less likely to be physically active, but is consistent with one other published study.[43]

Limitations

Our findings may have limited generalizability to other patients with COPD who experience comorbidities that have an underlying inflammatory process, since we excluded these individuals from the parent study. In addition, patients who were using prednisone chronically were excluded. Alternatively, these exclusions may have provided a level of control over other comorbidities to isolate the effects of anxiety on PA. This was a cross-sectional analysis, thus, it is not clear if increased PA is a behavioral manifestation of anxiety or a coping mechanism for anxiety, or if patients who push to remain active experience more anxiety due to increased dyspnea with activities. In addition, it is possible that we did not have sufficient power in this study to detect an interaction between increased dyspnea and low levels of anxiety. Another limitation is that our activity monitor may have also captured involuntary nonambulatory activity that is typically associated with highly anxious states. Our sample was predominantly men, tended to have higher functioning, had low mean scores for anxiety and depression, was committed to a longitudinal research study, and thus may not be representative of the larger population of patients with COPD. Future investigations could examine change in anxiety state and its relationship with PA. Additional spatial-location data (eg, GPS to triangulate with accelerometer data) will help establish whether the increased PA is occurring outdoors or indoors associated with activities of daily living.

Conclusions

We conclude that anxiety is associated with increased daily PA in a selected sample of patients with COPD. It is unclear whether patients with COPD who have higher levels of anxiety are more restless and use increased psychomotor activity as a coping mechanism, or whether those with COPD who push themselves to be more physically active experience more anxiety symptoms. The clinical implications of these observations are interesting because anxiety as a comorbid disorder is associated with increased mortality in patients with COPD, whereas increased PA is associated with lower mortality in that group. Based on our results, future COPD studies should include objective measures of PA and systematic evaluations for anxiety to better inform clinicians about how to improve the management and clinical outcomes of these patients.

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