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Assessing dyspnea and its impact on patients with connective tissue disease-related interstitial lung disease

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Abstract

Rationale—Dyspnea is the cardinal symptom in patients with any type of interstitial lung disease (ILD); however, there are limited data on dyspnea among patients with connective tissue disease-related ILD (i.e., CTD-ILD).

Objectives—To explore the utility of two dyspnea instruments (the University of California San Diego Shortness of Breath Questionnaire [UCSD] and the Dyspnea-12 [D-12]) and use their scores to examine the impact of dyspnea on the lives of patients with CTD-ILD.

Methods—Subjects were enrolled from the Autoimmune Lung Database (ALD) at National Jewish Health. Chronbach's alpha was used to assess the internal consistency reliability of the two dyspnea questionnaires. We used the Multi-Dimensional Health Assessment Questionnaire [MDHAQ] as a measure of health status and examined associations between health status and dyspnea by using Pearson product-moment correlation and linear regression.

Results—The internal consistency reliability of each of the two dyspnea questionnaires was excellent (alpha=0.9 for each). There were significant correlations between either of the two dyspnea measures and MDHAQ components. While controlling for ILD severity, dyspnea as assessed by the UCSD, was a significant predictor of physical function (p=0.04), psychological well-being (p=0.005), and fatigue (p=0.02); dyspnea as assessed the D-12, was a significant predictor of psychological well-being (p=0.01) and global status (p=0.03).

Conclusion—Dyspnea significantly affects day-to-day functioning and global well-being in patients with CTD-ILD. The UCSD and D-12 yield meaningful information about these patients that measures of pulmonary physiology can not. Future studies should examine other performance characteristics of these self-report measures in patients with CTD-ILD.

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Keywords

interstitial lung disease; connective tissue disease; dyspnea; patient-assessed outcomes

Introduction

The connective tissue diseases (CTD) have a number of potential extra-articular manifestations, including lung injury, and any of the lung's compartments—airways, the parenchyma or interstitium, vasculature, or pleura—may be independently or simultaneously affected. Interstitial lung disease (ILD) is a common lung manifestation of CTD—it can be a particularly prominent aspect of systemic sclerosis (SSc), rheumatoid arthritis (RA), as well as the myositis spectrum of disease—and the resultant dyspnea can be extremely debilitating. When viewed histologically, ILD associated with CTD (i.e., CTD-ILD) most often comprises a combination of lower zone-predominant inflammation and scar (fibrosis). ILD is not only common—seen in nearly 25% of patients with CTD—it is debilitating, and among all-comers, survival is only 60% at 10 years from diagnosis.[1,2]

Several instruments have been designed to capture the effect dyspnea has on patients with lung disease.[3,4] Among patients with idiopathic ILD (i.e., unrelated to CTD), dyspnea induces physical inactivity and a number of adverse downstream effects including deconditioning, loss of independence, along with impaired emotional well-being and overall quality of life (QOL).[5-8] Although ILD is a common manifestation of CTD and dyspnea, its principal symptom, is burdensome and intrusive, questionnaires that assess dyspnea are rarely used in clinical practice or as research endpoints in studies enrolling subjects with CTD-ILD.[9,10] This may, in part, be due to limited information regarding the presence and perception of dyspnea in these patients, a knowledge gap that makes the question of what the most appropriate tool to assess dyspnea in this population impossible to answer. To our knowledge only two published studies that enrolled subjects with CTD-ILD have systematically investigated dyspnea and its relationship with other outcome measures.[9,10] Both of them included only subjects with SSc and suggested that dyspnea is a driver of QOL and functional status.

The Health Assessment Questionnaire (HAQ) is a self-report instrument originally developed to assess and monitor health status and well-being in patients with RA.[11] A multidimensional derivative of it—the MDHAQ[12,13]—has been found to be useful to capture such information in patients with various autoimmune and arthritic conditions.[14] Advantages of the MDHAQ include its applicability across an array of conditions, its potential use as part of routine clinical care, and its brief, yet comprehensive composite summation index (termed "routine assessment of patient index data" [RAPID]—a score encompassing function, pain, and global status). The RAPID was recently validated for use in RA as a disease activity measure.[15,16] A different derivative of the HAQ (the HAQ DI), focused solely on assessing one's ability to perform activities of daily living, has been administered to subjects with SSc (including those with ILD[10] or pulmonary arterial hypertension[17]); however, the MDHAQ has yet to be administered to any cohort of subjects with CTD-ILD. Many components of the MDHAQ would seem to capture the scope of impairment among patients with CTD-ILD (regardless of the underlying CTD), and its broad applicability makes it an attractive self-report instrument for research.

We conducted this study with two aims in mind: 1) to further explore the effects of dyspnea in a cohort of subjects with CTD-ILD; and 2) to examine the appropriateness, internal consistency reliability, and utility of two dyspnea instruments—the University of California San Diego Shortness of Breath Questionnaire (UCSD)[3] and the Dyspnea-12 (D-12))[18] in

this patient group. We hypothesized that each of the two dyspnea questionnaires would have acceptable internal consistency reliability. Further, because dyspnea affects physical health and emotional well-being in patients with CTD-ILD, we hypothesized that scores from the two dyspnea questionnaires would correlate significantly with day-to-day functioning and global well-being (as measured by various components of the MDHAQ) and would yield meaningful information—beyond what measures of pulmonary physiology can provide—about CTD-ILD patients.

Methods

Subjects

The study sample was composed of consecutive subjects with CTD-ILD enrolled in the Institutional Review Board (IRB)-approved Autoimmune Lung Database (ALD) at National Jewish Health during 2009. The CTD diagnoses were made by a board-certified rheumatologist (AF) in accordance with applicable American College of Rheumatology criteria. The diagnosis of ILD was made by board-certified pulmonologists with expertise in ILD and on the basis of clinical, radiologic, and where available, pathologic criteria. Subjects enrolled in the ALD completed the MDHAQ, UCSD, and D-12 at each visit prior to physician evaluation. Pulmonary function tests were performed according to ATS/ERS criteria.[19-21] The protocol was approved by the National Jewish Health IRB, and given the retrospective design, granted exemption from full review.

Questionnaires

The MDHAQ—The MDHAQ is a modification of the original HAQ[11] and is a self-report instrument that includes items which assess the extent of difficulty with activities of daily living; it also includes visual analogue scales for pain and global status, along with scale scores for fatigue, psychological distress, morning stiffness, and change in status over the last week. Thus, the MDHAQ yields seven scale scores (0-10, with 10 connoting greater impairment), five of which are the physical function (FN), pain, psychological well-being, fatigue, and patient-assessed global status. The FN, pain, and patient-assessed global status scores are summed to give the “RAPID3” subscale, scored 0-30. The MDHAQ takes about 10 minutes for patients to complete and less than one minute to analyze and score.[13]

The UCSD SOB Questionnaire—The UCSD is a 24-item instrument composed of 21 items that ask respondents to rate the severity of dyspnea while doing various activities; another item asks how limiting dyspnea is; and the final two items focus on fear associated with overexerting or with dyspnea itself.[3] Simple summation scoring is used to yield scores from 0-120, with higher scores corresponding to greater impairment.

The D-12—The D-12 is a unidimensional questionnaire with 12 items derived from direct patient consultation and a systematic search of relevant literature on the language that patients use to describe dyspnea.[18] Hierarchical modeling and subsequent Rasch analysis was used to pare down the initial pool of 81 items to 12. The D-12 provides a global score of breathlessness severity that incorporates both “physical” and “affective” aspects. The score is calculated using simple summation of the responses for each item (0 “mild” to 3 “severe”); thus, the total score ranges from 0 to 36, with 36 representing maximal severity.

Statistical Analysis

Baseline data are presented as percentages or means with standard deviations as appropriate. We used Cronbach’s alpha to estimate internal consistency reliability of the two dyspnea questionnaires. Pearson product-moment correlation was used to examine the relationship between different outcomes. We used linear regression to further examine relationships

between pulmonary physiology, MDHAQ component scores and dyspnea scores. Specifically, we built two multivariable models for each of the FN, Psychological distress, Fatigue, and Global MDHAQ components (dependent variables in each model): one model had as predictors UCSD scores and percentage of predicted normal for race/age/gender/height forced vital capacity (FVC%), and the other model had D-12 scores and FVC%. This allowed us to examine the association between dyspnea and the four MDHAQ components while controlling for ILD severity (with FVC%). We elected not to include both FVC% and percent predicted diffusing capacity of the lung for carbon monoxide (DLCO%) in each linear regression model to avoid problems with collinearity, given the strong correlation ($r=0.8$, $p<0.0001$) between FVC% and DLCO%. We considered a p value < 0.05 as statistically significant. All analyses were performed by using SAS, version 9.1.3 (SAS Institute; Cary, NC).

Results

Forty-eight subjects were enrolled; their baseline data are presented in Table 1. The internal consistency reliability of each of the two dyspnea questionnaires was excellent (alpha = 0.9 for each). Table 2 displays correlations between outcome measures. There was moderately strong correlations between components of the MDHAQ. FVC% correlated significantly with physical function (FN) but with no other component of the MDHAQ; DLCO% did not correlate with any MDHAQ component. There was moderately strong correlation between scores from the two dyspnea instruments. There were significant correlations between either of the two dyspnea measures and FN, psychological well-being, fatigue, and patient-assessed global status. Table 3 shows the results of the linear regression analyses. While controlling for ILD severity, dyspnea as assessed by the UCSD, was a significant predictor of physical function, psychological well-being, and fatigue; as assessed by the D-12, dyspnea was a significant predictor of psychological well-being and patient-assessed global status.

Discussion

In this study, we administered self-report questionnaires to subjects with CTD-ILD and found significant correlations among their scores. To our surprise, in this cohort, lung function (as measured by FVC% or DLCO%) was not significantly associated with psychological well-being, fatigue, or global status insofar as the MDHAQ assesses these domains; however, as expected, dyspnea was associated with each of these domains.

To our knowledge, this is the first study in which the MDHAQ has been administered to patients with CTD-ILD; thus, there are no published data available for direct comparison. However, the MDHAQ component scores from this cohort are similar to published scores from patients in a general rheumatology clinic. In a study by Pincus and Sokka,[22] weighted average scores from the FN, patient-assessed global status and Fatigue components of the MDHAQ for 332 subjects with either RA, systemic lupus erythematosus, or SSc were 2.8, 4.4, and 4.9 respectively, whereas corresponding mean scores from our cohort were 2.3, 4.7, and 4.8. In our cohort, the RAPID score—a composite of the FN, PN, and Global components—suggested moderate severity (high severity > 12).[22] Investigators have used other HAQ derivatives in patients with CTD. For example, Baron and colleagues[9] observed that dyspnea (as assessed by using items from the HAQ and a modified version of the Pulmonary Functional Status and Dyspnea Questionnaire[23]) was associated with HAQ scores, as well as physical and mental health status (as measured by the SF-36) in 151 subjects with SSc. It is unclear whether those subjects had ILD; despite their mean FVC% of 90 (well within normal range), we might presume some of them did.

The UCSD was originally developed for use in patients with COPD.[3] Our work represents the first systematic evaluation of this tool for use in the assessment of activity-related dyspnea in patients with CTD-ILD. Ferreira and colleagues used the UCSD and other dyspnea questionnaires to assess the effects of pulmonary rehabilitation in 99 patients with various forms of ILD—three had CTD-ILD.[24] In that study, only 29 subjects completed the UCSD, and their mean score at baseline was 54.7. Mean FVC% and DLCO% were not given for this subgroup, so their disease severity is not known, and we are unable to make comparisons with our results. In other studies, investigators have observed that subjects with moderately severe (e.g., Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage II) chronic obstructive pulmonary disease (COPD) have mean UCSD scores in the mid-50s, and patients with GOLD stage III COPD (e.g., percent predicted FEV-1 of 25%) have mean scores of 65.[25] Although there is no staging system for ILD, given their FVC% and DLCO%, subjects in our study would be considered to have mild to perhaps moderate ILD, and their mean UCSD score of 45.7 makes sense.

We observed that dyspnea correlated with multiple components of the MDHAQ, including day-to-day functioning, psychological well-being, fatigue, and global status. One reason for this is that both the MDHAQ and dyspnea questionnaires are self-report, and scores from self-report measures have an inherently greater likelihood to be associated with each other than do outcomes with differing characteristics (e.g., a score from a self-report measure and a laboratory test value). Another reason is that among patients with CTD-ILD, dyspnea is the predominant respiratory symptom—it is bothersome and intrusive; the significant correlations between MDHAQ components and dyspnea scores bolsters the notion that dyspnea is one driver of many aspects of CTD-ILD patients' physical and mental health and global well-being.

Although focused on a similar symptom, the two dyspnea questionnaires actually capture different information about shortness of breath. The UCSD might best be regarded as a dyspnea "status" instrument, assessing how short of breath one becomes while performing various (predominantly day-to-day) activities. The D-12 was developed based on the responses from patients with a variety of cardiopulmonary diseases, including ILD; thus, its items are deemed to be relevant to the experience of dyspnea regardless of underlying disease. In contrast to other dyspnea questionnaires (including the UCSD), the D-12 is not activity dependent; it measures the direct impact that dyspnea has on a patient. Given this, it is not surprising that D-12 scores did not correlate significantly with pulmonary physiology. Furthermore, this well explains the results of the linear regression analyses: the UCSD score was a significant predictor of day-to-day functioning (the D-12 was not), and the D-12 score was a significant predictor of global sense of well-being (the UCSD was not). These analyses also suggest that no matter the disease severity (recall we controlled for disease severity in our models), dyspnea significantly impacts health status domains that are important to patients. The low R-square values suggest there are factors besides dyspnea and ILD severity that affect variability in the four health status domains—we suspect these factors are related to the underlying CTD. For example, fatigue is a well-known symptom of CTD, and our data suggest components other than dyspnea and ILD severity contribute to that symptom.

The primary limitation of the current study is the potential for tertiary referral bias. This potential limitation is present in any study generated in such a medical center. We would argue that because of the complexity of the combination of diseases in patients with CTD-ILD, along with the potentially toxic medications used to treat them, a great number of patients with CTD-ILD will be cared for in a referral center. Further, based on their pulmonary physiology, our subjects had mild to at most moderate ILD; thus, they are likely representative of CTD-ILD patients in the general population. The majority of subjects had

systemic sclerosis; unfortunately, we did not have enough data to analyze subgroups based on type of CTD separately. Hopefully, we can address this in future, larger, prospective studies. Despite these potential limitations, we believe this study has generated data useful for the study of patients with CTD-ILD. Specifically, we observed that scores from two dyspnea questionnaires—instruments that measure different but important aspects of shortness of breath—and a CTD-specific questionnaire (the MDHAQ) provide meaningful information not captured by measures of pulmonary physiology. Thus, this study begins the validation process for MDHAQ, UCSD, and D-12 scores as measures of health status and dyspnea in patients with CTD-ILD. Future studies should assess the ability of scores from these instruments to discriminate between subjects with differing severities of ILD and with differing underlying CTD. It will also be important to use health status and dyspnea questionnaires in longitudinal fashion to help define CTD-ILD trajectory and finally to establish the minimum score change over time that is clinically meaningful (i.e., the MID) for each of these instruments.

In conclusion, the self-report measures—MDHAQ, UCSD, and D-12—are tools useful in the assessment of patients with any of a wide spectrum of CTD-ILD. Most importantly, these measures yield meaningful information that measures of pulmonary physiology can not. Not surprisingly, dyspnea is strongly associated with day-to-day functioning and global well-being in this patient population. Future studies should examine other performance characteristics of these self-report measures in patients with CTD-ILD.

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Table 1

Baseline characteristics

	N=48
Age, yrs ± SD	52.8 ± 19.7
Female:Male (%)	74:26
Race (%)	
White	77
Black	4
Hispanic	17
Asian	0
Other	2
CTD (N)	
Systemic sclerosis	20
Rheumatoid arthritis	8
Undifferentiated CTD	7
Poly-/dermatomyositis	7
Systemic lupus erythematosus	3
Primary Sjögren's syndrome	3
FVC%	72.1±21
FEV1%	73.7±21
DLCO%	51.6±21
MDHAQ components	
FN	2.3±1.8
PS	2.7±2.2
Pain	4.2±3.2
Fatigue	4.8±3.2
Global	4.7±2.3
RAPID	11.2±6.6
Stiff in AM	32.5±38.8
Joints	9.8±9.2
Dyspnea questionairres	
D12	12.3±10.2
UCSD	45.7±26.6

CTD = connective tissue disease; FVC% = percent of predicted normal value for forced vital capacity; FEV1% = percent of predicted normal value for forced expiratory volume at one second; DLCO% = percent of predicted normal value for diffusing capacity for carbon monoxide; MDHAQ = Multi-dimensional Health Assessment Questionairre; FN = physical function; PS = psychological well-being component; RAPID = scale composed of FN, Pain, and patient-assessed global components; D12 = Dyspnea 12; UCSD = University of San Diego Shortness of Breath Questionairre

Table 2

Pearson product-moment correlation coefficients for associations between outcome measures

	FVC%	DLCO%	6MWD	BDI	TrailsA	TrailsB	WMVP1	WMVP2	DVtime	DVerror	Animal	Clock	GAD	PHQ	FSS	PSQI
FVC%	1.0	0.44	0.44	0.22	−0.11	0.10	0.33	0.24	0.33	−0.16	−0.11	0.31	−0.34	−0.25	−0.11	−0.54*
DLCO%	-	1.0	0.28	0.17	−0.30	−0.003	0.32	0.10	−0.21	−0.13	−0.29	0.46	−0.48	−0.18	−0.24	−0.42
6MWD	-	-	1.0	0.65†	0.57*	0.53*	−0.07	−0.01	0.41	0.47*	−0.04	0.46	−0.04	−0.32	−0.57*	−0.37
BDI				1.0	0.35	0.47*	−0.36	−0.22	0.55†	0.34	−0.33	0.13	−0.12	−0.26	−0.54*	−0.10
TrailsA	-	-	-	-	1.0	0.4*	0.002	0.12	0.46*	0.52*	0.22	0.30	−0.95	−0.25	−0.43*	−0.07
TrailsB	-	-	-	-	-	1.0	−0.22	−0.02	0.35	0.19	−0.08	0.23	−0.15	−0.30	−0.30	−0.35
WMVP1	-	-	-	-		-	1.0	0.87‡	−0.19	−0.15	0.37	0.38	−0.51*	−0.26	−0.01	−0.09
WMVP2	-	-	-	-		-	-	1.0	0.01	0.13	0.42	0.42	−0.47*	−0.34	−0.008	−0.04
DVtime	-	-	-	-		-	-	-	1.0	0.40	0.06	0.21	−0.18	−0.35	−0.34	−0.13
DVerror	-	-	-	-		-	-	-	-	1.0	0.07	0.16	0.15	−0.10	−0.32	0.09
Animal	-	-	-	-		-	-	-	-	-	1.0	0.31	−0.24	−0.17	0.10	0.23
Clock	-	-	-	-		-	-	-	-	-	-	1.0	−0.40	−0.67†	−0.21	−0.17
GAD	-	-	-	-		-	-	-	-	-	-	-	1.0	0.59†	0.38	0.29
PHQ														1.0	0.53*	0.59†
FSS															1.0	0.37
PSQI																1.0

FVC%=percent predicted forced vital capacity; DLCO%=percent predicted diffusing capacity of the lung for carbon monoxide, 6MWD=distance walked during the six-minute walk test; BDI=Baseline Dyspnea Index; TrailsA=Trail Making Test Form A; TrailsB=Trail Making Test Form B; WMVP1=Wechsler Memory Scales-Third Edition Verbal Pairs 1; WMVP2=Wechsler Memory Scales-Third Edition Verbal Pairs 2; DVtime=Digit Vigilance Test Time; DVerror=Digit Vigilance Test Errors; Animal=Animal Fluency Test; Clock=Clock Drawing Test; GAD=General Anxiety Questionnaire; PHQ=Patient Health Questionnaire (8 items); FSS=Fatigue Severity Scale; PSQI=Total score from the Pittsburgh Sleep Quality Index

*p<0.05

†p<0.01

‡p<0.0001

Table 3

Multivariable analyses examining relationships between MDHAQ components and either pulmonary physiology or dyspnea. Each model includes one of the dyspnea measures (either D12 or UCSD) and FVC%

Outcome Model Predictors	R-Square of Model	Point Estimate	Standard Error	P value
FN Component				
Model #1	0.15			
D12		0.03	0.03	0.3
FVC%		−0.02	0.01	0.1
Model #2	0.23			
UCSD		0.02	0.01	0.04
FVC%		−0.01	0.02	0.7
PS Component				
Model #1	0.21			
D12		0.08	0.03	0.01
FVC%		0.02	0.01	0.3
Model #2	0.24			
UCSD		0.04	0.01	0.005
FVC%		0.04	0.02	0.04
Global Component				
Model #1	0.14			
D12		0.1	0.04	0.03
FVC%		0.02	0.02	0.5
Model #2	0.08			
UCSD		0.04	0.02	0.1
FVC%		0.03	0.03	0.3
Fatigue Component				
Model #1	0.11			
D12		0.1	0.05	0.06
FVC%		0.02	0.03	0.5
Model #2	0.16			
UCSD		0.06	0.03	0.02
FVC%		0.05	0.03	0.1

FN = physical function component; PS = psychological well-being component; Global = patient-assessed global component; RAPID = scale composed of FN, Pain, and Global components; D12 = Dyspnea 12; UCSD = University of San Diego Shortness of Breath Questionairre