

The Role of EDD (Exercise Capacity, Dyspnea, and Diffusing Capacity of Lungs for Carbon Monoxide) Index in Pulmonary Fibrosis Secondary to Scleroderma

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ARTICLE INFO

Article type:
Original Article

Article history:
Received: 09 Apr 2016
Revised: 04 Jun 2016
Accepted: 17 Aug 2016

Keywords:
High Resolution CT Scan
Lung Function Tests
Pulmonary Fibrosis
Scleroderma

ABSTRACT

Introduction: Pulmonary involvement secondary to Systemic Sclerosis (SSc) is the major cause of morbidity and mortality in SSc patients. We designed this study to determine the correlation of important lung function parameters with lung High Resolution CT (HRCT) scan findings.

Materials and Methods: Thirty-two consecutive diffuse SSc patients with pulmonary fibrosis were enrolled in this cross-sectional study. Patients with pulmonary fibrosis secondary to other causes, previous restrictive lung disease, and history of smoking were excluded. Complete lung function evaluation was performed. The EDD (Exercise capacity, Dyspnea, and Diffusing capacity of lungs for carbon monoxide) index was determined. The Warrick score was calculated based on lung HRCT findings.

Results: The mean age of the patients was 39.18 years \pm 9.39 (SD). Seventeen (53%) patients were in EDD stage 1 (score: $0 \leq \text{score} \leq 3$), 9 patients (28%) in stage 2 ($3 < \text{score} \leq 6$), and 6 patients (19%) in stage 3 ($6 < \text{score} \leq 9$). The mean Warrick score was 10.84 ± 6.94 (SD). There was statistically significant correlation between EDD index and Warrick score ($r=0.72$, $P=0.001$). Also there was statistically significant strong correlation between EDD stages and Warrick scores ($r=0.8$, $P=0.002$).

Conclusion: The results of this study revealed that EDD may be a valuable representative marker of lung involvement in SSc and in the future, it can be a suitable and safe alternate modality comparing lung HRCT in our clinical practice and close follow-up.

► Please cite this paper as:

Shariaati Sarabai J, Attaran D, M.Lari Sh, Nazari P, Akhlaghi S, Bahadori A. The Role of EDD (Exercise Capacity, Dyspnea, and Diffusing Capacity of Lungs for Carbon Monoxide) Index in Pulmonary Fibrosis Secondary to Scleroderma. J Cardiothorac Med. 2016; 4(4): 516-521.

Introduction

Systemic sclerosis (SSc) (scleroderma) is a collagen vascular disease with unknown etiology which is clinically characterized by excessive fibrosis of skin and internal organs (1,2). The two principal categories of SSc regarding to the clinical and laboratory presentations are diffuse

(with progressive skin induration and pulmonary fibrosis) and limited (usually with long-standing Raynaud's phenomenon and sclerodactyly) (3-5).

Variety of organ complications are accompanied with diffuse SSc including: renal disease, cardiac involvements, and pulmonary

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complications (6). Among these problems, pulmonary involvement is now the leading cause of morbidity and mortality in SSc (1). Following the pulmonary involvement, more than 50% of patients develop dyspnea (7, 8). The interstitial pulmonary fibrosis in SSc is detected by restrictive ventilatory defect (low vital capacity and total lung capacity) (7). Additionally, decrease of diffusing capacity of lungs for carbon monoxide (DLco), is the earliest finding of pulmonary fibrosis in SSc (9). Exercise limitation is a major finding in SSc patients due to the increase of dead space ventilation and the gas exchange abnormalities. We can evaluate exercise performance of patients with six-minute walk distance (6MWD) test (10).

High-resolution CT scan (HRCT) of lung has simplified the diagnosis of the extent and pattern of pulmonary involvement in SSc (7). It has been reported that about 60-90% of patients with SSc, demonstrate the pulmonary abnormalities in lung HRCT (11-14). The main pulmonary findings in lung HRCT are: areas of ground glass opacity, poorly defined subpleural nodules, reticular pattern of attenuation, honeycombing and traction bronchiectasis (15, 16). Warrick and colleagues developed and published a semi-quantitative scoring method in 1991 for pulmonary involvement in diffuse SSc (17).

As it has been proved previously, the extent of pulmonary fibrosis on lung HRCT has significant correlation with pulmonary function test abnormalities (7). In this study, we decided to propose a model consisting of important clinical and laboratory pulmonary parameters in SSc patients including: Exercise capacity, Dyspnea, and DLco, defined as EDD index. Additionally, we try to show the association of this index with the severity of pulmonary involvement demonstrated on lung HRCT. The main idea of this proposed model was originated from an evaluation index in patients with chronic obstructive pulmonary disease (COPD) presented by Celli and colleagues (18).

Materials and Methods

Subjects

Thirty-two consecutive diffuse SSc patients (according to the criteria of American College of Rheumatology- ACR) (19) with pulmonary involvement were enrolled in this cross-sectional study. Patients with following criteria were excluded: pulmonary fibrosis secondary to other reasons, previous restrictive lung disease, pulmonary hypertension due to other causes, musculoskeletal pain, peripheral vascular involvement, obesity, and history of smoking. All patients underwent a detailed medical interview and complete physical examination. The severity of skin stiffness was determined in patients according to the modified Rodnan skin score which was

applied by pinching the skin in 17 different body area (20). Additionally the severity of Reynaud's phenomenon was assessed by Reynaud's Condition Score (RCS) (21). The study was approved by ethics committee of Mashhad University of Medical Sciences (MUMS). All patients gave their written informed consent for participating in this study.

Lung function tests

Standard body plethysmography according to the American Thoracic Society guideline (ATS) (22) was performed in patients (ZAN 500 Plethysmograph, nSpire Health Ltd., Longmont, Co, USA). Total lung capacity (TLC) and DLco were recorded. Every participant performed 6MWD test in a 30-meter flat indoor corridor according to ATS guidelines (23). For determining the severity of dyspnea in participants, the modified medical research council (MMRC) scale (18) was applied which was graded between zero and four based on the patient's description as following:

Grade 0: "I only get breathless with strenuous exercise".

Grade 1: "I get short of breath when hurrying on the level or walking up a slight hill".

Grade 2: "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level".

Grade 3: "I stop for breath after walking about 100 yards or after a few minutes on the level".

Grade 4: "I am too breathless to leave the house" or "I am breathless when dressing".

The EDD index

As shown in the Table1, the proposed EDD index was calculated in patients according to the 6MWD, DLco, and MMRC findings.

Additionally the EDD stage was determined as following:

Stage 1: $0 \leq \text{score} \leq 3$

Stage 2: $4 \leq \text{score} \leq 6$

Stage 3: $7 \leq \text{score} \leq 9$

Table 1. The EDD index in scleroderma lung fibrosis

Parameter	Stage			
	0	1	2	3
6MWD	≥ 350	250-349	150-249	<150
DLco	$\geq 80\%$	60-79%	40-59%	<40%
MMRC	0-1	2	3	4

6MWD: 6 minute walk distance, DLco: diffusing capacity of lungs for carbon monoxide, MMRC: modified medical research council

HRCT of lung

HRCT studies performed using a Somatom sensation 16 Siemens Munich, Germany CT scanner. The scans of the chest were acquired with patients in supine position and with lungs at end inspiration. The area of the scans ranged

from the lung apices to bases, with 0.75 mm collimation, 1- to 2- mm slice thickness at 10 mm increments. The Warrick score (Table 2) consists a severity score ranging from 0 (normal) to 15 (all lesions present) and an extension score ranging from 0 (normal) to 15 (more than nine pulmonary segments involved). A total Warrick score was obtained by summing the severity and the extension scores (17, 24, 25).

Table 2. The Warrick score in scleroderma lung fibrosis according to lung HRCT findings

Parenchymal alteration	Severity score
Ground glass opacities	1
Irregular pleural margins	2
Septal/subpleural lines	3
Honeycombing	4
Subpleural cysts	5
No. of lung segments	
1-3	1
4-9	2
>9	3

* With the courtesy of Journal of Rheumatology (17).

Warrick scores of pulmonary abnormalities were carried out in a blinded manner by 2 independent pulmonologists and 1 radiologist and discordant scores were reviewed by a fourth core reader to produce a final consensus score.

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS version 11.5, Chicago, IL, USA). Descriptive statistics were used to summarize the demographic characteristics and pulmonary function test parameters in SSc patients. The continuous data are presented as percentages and means \pm SDs. Verifying the normality of continuous variables, the one-sample Kolmogorov-Smirnov test was used. Pearson and Spearman correlation coefficients were calculated. A p-value of less than 0.05 was considered significant.

Results

All of the patients were female. The demographic characteristics of patients are shown in Table 3. The frequency of different stages of EDD index is shown in Figure 1.

Table 3. The demographic characteristic of patients

Date	Value *
Age (years)	39 \pm 9.40
BMI (kg/m ²)	23.60 \pm 4.70
Duration of disease (years)	6.60 \pm 4.25
TLC (% pred.)	70 \pm 22
DLco (%)	77.75 \pm 22.60
Spo2 (%)	97.70 \pm 5.60
6MWD (m)	375 \pm 52.70
Warrick score	10.50 \pm 7

*Data are presented as mean \pm SD.

BMI: body mass index, TLC: total lung capacity, DLco: diffusing capacity of lungs for carbon monoxide, SpO₂: saturation of oxygen, 6MWD: 6 minute walk distance.

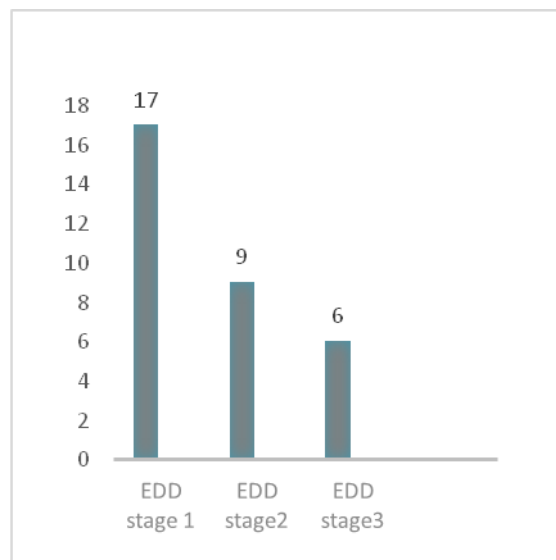


Figure 1. The frequency of different stages of EDD index in patients

Twenty- three (72%) patients had the MMRC grades 2 and 3. There was statistically significant moderate correlation between Warrick score and the age of the patients ($r=0.45$, $P=0.01$).

The correlations of important pulmonary function test parameters and Warrick score are shown in Table 4. As it was expected, the Warrick score had significant inverse correlations with the main spirometry factors like DLco and TLC, 6MWD, and MMRC.

Table 4. The correlation of Warrick score and important pulmonary function test parameters in scleroderma lung fibrosis

Parameter	Correlation coefficient (r)	P value
DLco	-0.70	0.001
RV	-0.20	0.89
TLC	-0.60	0.01
FEV1	-0.60	0.001
FVC	-0.70	0.01
Spo ₂	-0.65	0.001
6MWD	-0.80	0.001
MMRC	-0.77	0.001

DLco: diffusing capacity of lungs for carbon monoxide, RV: residual volume, TLC: total lung capacity, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, SpO₂: saturation of oxygen, 6MWD: 6 minute walk distance, MMRC: modified medical research council.

There was statistically significant strong correlation between EDD and Warrick scores as shown in Figure 2 ($r=0.72$, $P=0.001$). Means that with the progression of pulmonary impairment evaluated by the patient's symptom, exercise capacity, and pulmonary function test, the severity of lung HRCT abnormalities will be increased. Also there was statistically significant strong correlation between EDD stages and Warrick scores ($r=0.8$, $P=0.002$).

Additionally, we found statistically significant correlations between Warrick scores and severity of skin stiffness in patients as shown in Figure 3.

There were no significant correlations between the duration of scleroderma with 6MWD and MMRC ($r= -0.2$ and $P=0.1$, $r=0.3$ and $P=0.3$, respectively).

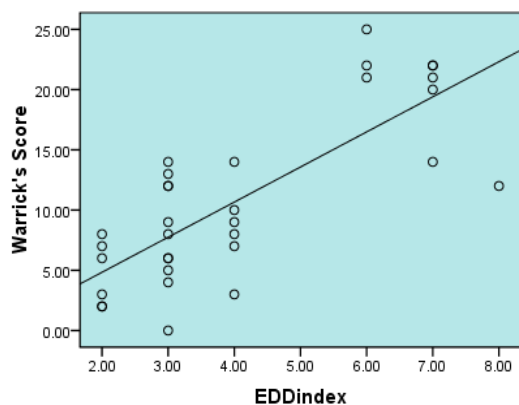


Figure 2. The correlation of Warrick's scores and EDD index in scleroderma lung patients ($r=0.72$, $P=0.001$)

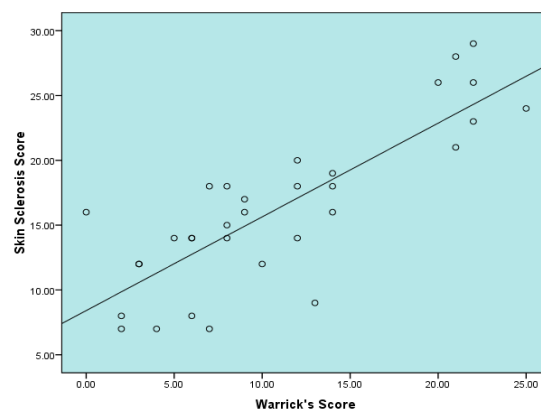


Figure 3. The correlation of Warrick score and skin sclerosis score in scleroderma lung patients ($r= 0.8$, $P= 0.001$)

Discussion

In this study we proposed a model for evaluating the lung function parameters in SSc pulmonary fibrosis consisting of Exercise capacity, severity of Dyspnea, and DLco, named as EDD index. We found a statistically significant correlation between EDD index and Warrick score in lung HRCT. Also the correlations of Warrick score in lung HRCT with skin stiffness score and Raynaud's phenomenon were statistically significant.

Since pulmonary involvement and its complications in SSc are now the main cause of morbidity and mortality, therefore early detection and proper treatment play an important role in the management of SSc lung fibrosis (26). Pulmonary involvement in setting of diffuse scleroderma is mainly pulmonary fibrosis that approximately 40% of all SSc patients suffered from restrictive lung disease (1). Dyspnea with varying degrees of severity is the most common symptom in diffuse SSc patients (27). In our study, 72% of patients had dyspnea with a considerable severity score according to the MMRC scaling score, which was concordant with previous studies considering frequency of this symptom in diffuse SSc patients (26). A restrictive lung disease is an inevitable consequence of pulmonary fibrosis in diffuse SSc. Due to increased dead space ventilation and diffusing abnormalities, exercise limitation is frequently encountered in SSc patients. Although there are some limitations in performing 6MWD in SSc patients (especially those with musculoskeletal pain and peripheral vascular involvement), 6MWD has still emerged a practical tool for assessment of exercise capacity in SSc patients (27). We found a statistically significant correlation between duration of SSc-related musculoskeletal disease and 6MWD measurements.

As we mentioned earlier, DLco plays a pivotal role in early diagnosis of pulmonary fibrosis in diffuse SSc (7). Besides DLco, other pulmonary

function parameters reflecting underlying pulmonary fibrosis are impaired (7). We proposed a model consisting of important pulmonary function parameters in diffuse SSc. By considering the exercise capacity, dyspnea, and DLco the scoring of pulmonary involvement, known as EDD index, was carried out. The EDD index was completely correlated with duration of rheumatologic disease.

It is now well documented that lung HRCT has a valuable role in early detection of pulmonary involvement in diffuse SSc. The Warrick scoring system consisting of the distribution and severity of fibrosis has been established before as a useful tool for determining the severity of pulmonary fibrosis in diffuse SSc. Warrick and colleagues showed that this scoring system has significant correlation with pulmonary function tests (17). In our study, the EDD index had significant correlation with Warrick scores in lung HRCT. With the progression in EDD scores, the total Warrick scores were increased significantly. To the best of our knowledge, there are no studies concerning a group of pulmonary function parameters in evaluating the scleroderma lung disease. Since we found significant correlation between the EDD index and lung HRCT findings, we propose that EDD index can be used in clinical practice, that in situations that lung HRCT is not available or for evaluating in more close intervals.

This study has some limitations. Firstly, it is a small sample size study. Therefore if we could expand the number of diffuse scleroderma patients, the analysis of our data would be more precise. Secondly, we recommend to measure and evaluate serum antinuclear antibodies in our patients and add this parameter to EDD index as well.

Conclusion

Pulmonary involvement is the major cause of morbidity and mortality in diffuse scleroderma. Complete pulmonary function tests and lung HRCT have paramount roles in early diagnosis and

treatment of patients. In this study, we proposed a severity index score based on pulmonary function tests consisting of exercise capacity, dyspnea severity, and DLco. This model was named as EDD index that has significant correlations with lung HRCT. We recommend using this index in our clinical practice for management of SSc patients with pulmonary fibrosis.

Acknowledgment

This study was financially supported by MUMS (code number: 88832). The authors wish to thank to M.Aalami and M.Tamizi for their wonderful assistance in performing the study.

Conflict of Interest

The authors declare no conflict of interest.

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