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The Medical Research Council dyspnea scale in the estimation of disease severity in idiopathic pulmonary fibrosis

Spyros A. Papiris[a,*], Zoe D. Daniil[a], Katerina Malagari[b], Giorgos E. Kapotsis[a], Christina Sotiropoulou[a], Joseph Milic-Emili[c], Charis Roussos[a]

[a]*Department of Critical Care and Pulmonary Services, National and Capodistrian University of Athens, ''Evangelismos'' Hospital, 45-47 Ipsilantou Street, Athens 10675, Greece*
[b]*Department of Radiology, National and Capodistrian University of Athens, Athens, Greece*
[c]*Meakins-Cristie Laboratories, McGill University, Montreal, Quebec, Canada*

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Summary *Background*: Medical Research Council (MRC) chronic dyspnea scale, used for the estimation of disability due to dyspnea, may serve as a simple index of disease severity and extent in patients with idiopathic pulmonary fibrosis (IPF). However, its relationship with other commonly used measures has not been evaluated.

Methods: The association of MRC chronic dyspnea scale with lung function indices and high-resolution computerized tomography (HRCT) scores such as the total interstitial disease score (TIDs) and the fibrosis score (Fs) was examined in 26 untreated patients with IPF sequentially recruited over a period of 3 years. The aim of this observational study was to explore the relationship between dyspnea, impairment of lung function and CT estimation of disease severity in patients with IPF.

Results: The MRC dyspnea score was significantly associated with FVC, FEV_1, TLC, DLCO, PaO_2, and $PaCO_2$ and with both HRCT scores. In multiple regression analysis only the FVC (OR = 0.85, 95% CI = 0.75–0.95, $P = 0.004$) and $PaCO_2$ (OR = 0.69, 95% CI = 0.50–0.95, $P = 0.02$) correlated with dyspnea. Furthermore, both TIDs and Fs were negatively associated with FVC, FEV_1, TLC and PaO_2. In multiple regression analysis only the FVC correlated with both TIDs ($r^2 = 0.57$, $P = 0.0001$) and Fs ($r^2 = 0.46$, $P = 0.0005$).

Conclusions: These observations suggest that the MRC dyspnea scale could offer useful information about the estimation of severity in patients with IPF. Furthermore

*Corresponding author. Critical Care Department, 45-47 Ipsilantou street, ''Evangelismos'' Hospital, GR 10675, Athens, Greece, Tel:++302107201952; fax:++302107293470.
E-mail address: papiris@otenet.gr (S.A. Papiris).

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among functional indices the FVC seems to be the best estimator of disease severity and extent.

Introduction

Exertional dyspnea is the most prominent and disabling symptom in patients with idiopathic pulmonary fibrosis (IPF).[1,2] Estimation of dyspnea by the Medical Research Council (MRC) chronic dyspnea scale is simple to administer and has been used for many years for grading the effects of breathlessness on daily activities.[3] This scale has been particularly used in patients with chronic obstructive pulmonary disease (COPD) in whom it has proved to be useful and complementary to FEV_1 in the classification of disease severity.[4] However, the relationship of (MRC) chronic dyspnea scale to other commonly used measures has not been evaluated in IPF patients.

Lung function parameters provide useful information in the assessment of status and progress in IPF.[5] High-resolution computerized tomography (HRCT) is a sensitive means for diagnosing IPF,[6,7] and also has been increasingly used for quantification of the disease severity. To the best of our knowledge, there are no studies in which the simple and self-administered MRC chronic dyspnea scale has been associated with lung function parameters, radiological estimates of disease severity and extent (HRCT scores) in IPF.

The aim of the current study was to explore the association between MRC chronic dyspnea scale, lung function indices and HRCT scores in IPF patients. In addition, we studied the association between HRCT scores and lung function indices.

Methods

Subjects

The population studied consisted of 26 untreated patients (15 males, aged 41–80 yr), with clinical and radiological features of IPF. They were recruited sequentially from the respiratory outpatient clinic over a period of 3 years. All patients fulfilled the criteria for the diagnosis of IPF established by the American Thoracic Society, the European Respiratory Society, and the American College of Chest Physicians.[1] Histological features of usual interstitial pneumonia (UIP) were confirmed by video-assisted thoracoscopic biopsy in 22 patients. Fourteen patients were never smokers, 3 current smokers and 9 ex-smokers. The study was approved by the institutional ethics committee and informed consent was obtained from each patient.

Pulmonary function tests

The lung function tests included FEV_1, FVC, FEV_1/FVC ratio, total lung capacity (TLC), residual volume (RV) and DLCO. TLC and RV were measured by the helium dilution method with a Master Screen apparatus (Erich Jaeger GmbH, Wuerzburg, Germany), and DLCO by the single breathholding helium dilution method.[8,9] Measurements were expressed as percentages of predicted values.[8,9] In all patients, the arterial PaO_2 and $PaCO_2$ were also measured at rest.

Dyspnea

Dyspnea was assessed by the modified MRC chronic dyspnea self-administered questionnaire that consists of six questions about perceived breathlessness: [3,11] category 0, no dyspnea; category 1, slight degree of dyspnea (troubled by shortness of breath when hurrying on the level or walking up a slight hill); category 2, moderate degree of dyspnea (walks slower than people of the same age on the level because of breathlessness); category 3, moderately severe degree of dyspnea (has to stop because of breathlessness when walking at own pace on the level); category 4, severe degree of dyspnea (stops for breath after walking about 100 yards or after a few minutes on the level); category 5, very severe degree of dyspnea (too breathless to leave the house or breathless when dressing or undressing).

HRCT

The HRCT examination was performed within a 1-month interval from the pulmonary function tests and lung biopsy. The CT scans were performed using either a Somaton HiQ or a Somaton Plus scanner (Siemens, Erlanger, Germany). All patients underwent conventional computed tomography scanning of the chest, using a 10-mm section thickness at 10-mm intervals. The HRCT scans were obtained at six predetermined levels: large vessels, aortic arch, tracheal carina, pulmonary hilum, pulmonary venous confluence, and 1 cm above the right dia-

phragm. Scans were performed with 1–1.5 mm section thickness and a 1–2 s scanning time during breath holding at end inspiration. These scans were reconstructed with a high spatial frequency algorithm and viewed at window levels appropriate for pulmonary parenchyma (level −500 to −700 Hounsfield units: width 1000–1600 Hounsfield units).

CT scoring: Two independent experienced readers (SP, KM), without any knowledge of the clinical and functional findings, examined the HRCT scans. The HRCT scoring included the extent of: (a) ground glass opacities without evidence of bronchiolectasis and bronchiectasis, the pure ground glass score (PGGs); (b) ground glass opacities with coexisting bronchiolectasis and bronchiectasis, the ground glass score (GGs); (c) fine reticulation; and (d) coarse reticulation. Finally, the composite extent scores calculated were the fibrosis score (Fs), composed by the sum of fine and coarse reticulation and the total interstitial disease score (TIDs) composed by the sum of all the above-mentioned scores (PGGs+GGs+Fs). Extent of involvement was assessed by the HRCT slices using a visual method, similar to that used previously by other investigators, [7,10–13] recording the relative proportion of all the above findings to within 5%. Scores from the six HRCT slices were summed and divided by the total number of slices to calculate the average extent score for each of the variables. Similar methods of scoring have been used by Staples and coworkers,[10] Lee and coworkers,[11] and Wells and co-workers.[7,12] Evaluations of HRCT and scoring were done separately and mean values from the two readers were included for correlations.

Statistical analysis

Results are presented as mean ± SEM. In a univariate analysis, the relationships were examined through correlation analysis. For the MRC dyspnea score, since it is an ordinal categorical variable, the Spearman rank correlation coefficient was calculated, as it is more appropriate for such type of data. For the HRCT scores Pearson correlation coefficient was utilized for normally distributed data while the Spearman rank correlation coefficient was otherwise used. If both examined variables were normally distributed then the Pearson correlation coefficient was used to describe the relationship, otherwise the rank correlation coefficient was used. Differences between smokers and never smokers were also examined in all above-mentioned variables using the *t*-test for independent samples, where appropriate, or by the Wilcoxon Ranks Sum test. Variables significantly correlated with HRCT and MRC scores were further used as explanatory variables in a multivariate analysis. For the HRCT scores a backward stepwise multiple linear regression analysis was performed. A natural logarithmic transformation in TID score and disease duration was made a priori to achieve normality. For MRC score, which is an ordinal categorical variable, generalized linear models were fitted and the best was selected through multiple stepwise logistic regression analysis for ordinal response.[14] A P-value < 0.05 was considered statistically significant. Analysis was performed using the SAS System software.

Interobserver variability in grading HRCT extent of involvement was quantified using the paired *t*-test and kappa value for the nearest to 5% reading. Kappa coefficient expresses the agreement between observers after removal of the component of agreement attributable to chance.

Results

Twenty-six patients (15 males, aged 41–80 yr) were studied. All patients claimed some degree of dyspnea (MRC score > 0) and all were ambulatory (nobody with MRC score of 5). There were 7 patients with MRC grade 1 dyspnea, 11 patients with MRC grade 2 dyspnea, 6 patients with MRC grade 3 dyspnea and 2 patients with MRC grade 4 dyspnea. HRCT scores and lung function data are shown in Table 1. No emphysema was evident in the HRCTs. Most patients had a restrictive lung function pattern characterized by a decrease in TLC (80% of patients) and FEV_1/FVC ratio $\geqslant$ 75% (100% of patients). The DLCO was decreased in 92% of them.

Table 1 Radiographic and lung function data at presentation.

	Patients ($n = 26$)
PGGs (%)	0* (0–18)*
Fs (%)	28 ± 3
TIDs (%)	33 ± 3
FEV_1 (% pred)	79 ± 3
FVC (% pred)	79 ± 3
FEV_1/FVC (ratio)	86 ± 1
TLC (% pred)	66 ± 3
DLCO (% pred)	49 ± 3
PaO_2 (mmHg)	73 ± 4
$PaCO_2$ (mmHg)	37 ± 1

PGGs= pure ground glass score; Fs=fibrosis score; TIDs=total interstitial disease score.Data are presented as means ± SEM.

*Median and range.

No significant differences were observed between smokers and never-smokers in HRCT, MRC dyspnea scores and lung function data. There were no significant differences between the two observers in the estimation of HRCT scores for the TID and *F* scores. Kappa values indicated good agreement between the two observers for the Fs (0.50), and the TIDs (0.66).

Correlation between MRC dyspnea score, lung function parameters and HRCT scores

The MRC dyspnea score was negatively correlated with all lung function parameters studied except RV and FEV_1/FVC ratio (Table 2).

Among the HRCT scores studied, the MRC dyspnea score was positively correlated with both TIDs ($r_S = 0.60$, $P = 0.003$) and Fs ($r_S = 0.49$, $P = 0.02$). However, in multiple stepwise regression analysis with MRC dyspnea score as the dependent variable and lung function parameters and HRCT scores as the independent variables FVC (Odds ratio=0.85, 95% CI: 0.75–0.95, $P = 0.004$) and $PaCO_2$ (Odds Ratio=0.69, 95% CI: 0.50–0.95, $P = 0.02$) were selected as the only parameters that significantly (negatively) correlated with the dyspnea grade (Figs. 1A and B).

Correlation between HRCT scores and lung function parameters

No significant correlation was found between the PGG score and any lung function indices studied. However, both TIDs and Fs were negatively correlated with FVC, FEV_1, TLC and PaO_2 (Table 3). According to multiple stepwise regression analysis, among these four lung function indices, only FVC correlated significantly with both the Fs ($r^2 = 0.46$, $P = 0.0005$) and the TIDs ($r^2 = 0.57$, $P = 0.0001$).

Table 2 Significant Spearman's correlation coefficients (r_S) of MRC dyspnea scale to lung function data.

Lung function data	r_S	*P*-value
FVC (% pred)	−0.75	0.0001
PaO_2 (mmHg)	−0.73	0.0001
FEV_1 (% pred)	−0.64	0.0004
TLC (% pred)	−0.62	0.0007
DLCO (% pred)	−0.56	0.005
$PaCO_2$ (mmHg)	−0.47	0.01

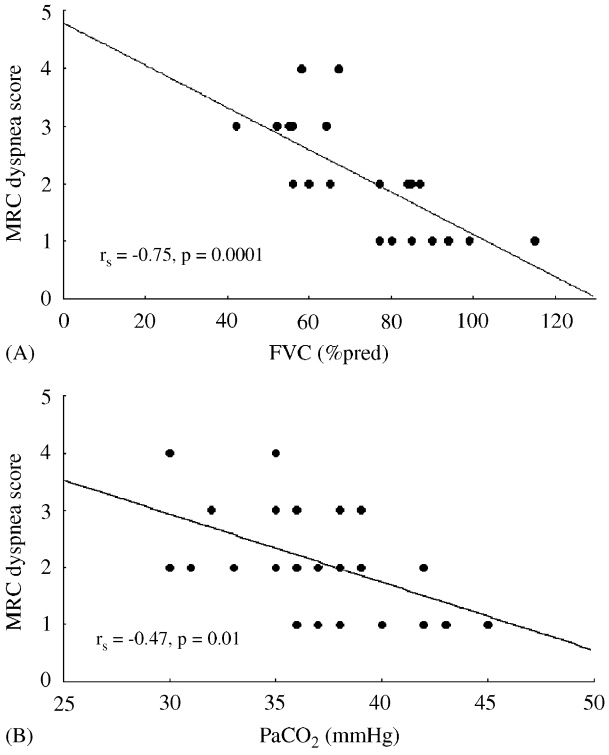

Figure 1 Relationship between MRC dyspnea score and FVC (Rank correlation coefficient $r_s = -0.75$, $P = 0.0001$) (A) and $PaCO_2$ (Rank correlation coefficient $r_s = -0.47$, $P = 0.01$) (B). Each solid circle represents results from one subject.

Discussion

The purpose of this study was to determine the level of association between disability due to breathlessness categorized by the MRC dyspnea scale and other variables used to evaluate the disease severity and extent in patients with IPF. The first finding was that the MRC dyspnea score was significantly associated with FVC, PaO_2, FEV_1, TLC, DLCO and $PaCO_2$ and with TIDs and Fs, indices that reflect the global radiological extent and fibrosis stage of IPF, respectively. Even though all patients with IPF demonstrate a progressive worsening of dyspnea that affects their overall health status,[1] few studies have correlated the MRC chronic dyspnea scale to physiological and radiological estimates of disease severity and extent. In the study by Martinez and co-workers[15] it was found that chronic dyspnea, assessed as the baseline dyspnea index (BDI) is far better contributor to the quality of life in these patients than the lung function variables studied (FEV_1 and FVC). In this study the clinical rating used to quantify chronic dyspnea differed from the MRC dyspnea scale. However, Mahler and Wells have shown that the

Table 3 Significant Spearman's correlation coefficients (r_S) of HRCT scores to lung function data ($n = 22$)

Lung function data	TIDs		Fs	
	r_S	*P*-value	r_S	*P*-value
FVC (% pred)	−0.69	0.0004	−0.68*	0.0005
FEV_1 (% pred)	−0.59	0.004	−0.53	0.01
TLC (% pred)	−0.76	0.0001	−0.64*	0.001
PaO_2 (mmHg)	−0.59	0.004	−0.64*	0.002

*Pearson correlation coefficient.

BDI, and MRC chronic dyspnea scale were highly correlated.[16]

The correlation between HRCT scores and dyspnea score found in this study is in agreement with Hartley and co-workers.[17] They reported a good correlation between a complex computer-derived index of lung parenchyma density based on the HRCT scan and both the FVC and the level of dyspnea in patients with IPF. Our findings are also in agreement with those reported by Staples and co-workers[10] and Terriff and co-workers[18] who found a correlation between HRCT scores and severity of dyspnea, though their dyspnea scales were different from the MRC chronic dyspnea scale used in the present study.

The second finding was that both TIDs and Fs were significantly associated with FVC, FEV_1, TLC and PaO_2. In the studies of Staples and Terriff mentioned above TLC and DLCO but not FVC correlated with the HRCT scores.[10,18] However, Terriff and co-workers evaluated only the significance of ground glass or reticulation, but not the global extent of the disease in HRCT. In more recent studies,[5,19–21] based on global HRCT estimates of disease severity and extent, it has been shown that this morphological parameter correlates well with indices of functional lung impairment and chronic dyspnea in only one of them, though a very different dyspnea scale has been used in that study.[20] In the study of Xaubet and co-workers the FVC was found to be a significant and independent correlate of HRCT abnormalities as in the present study. However, they also found that the DLCO was significantly correlated with the severity of the disease.[5] Furthermore, in the study by Wells and co-workers[20] it has been shown that the global extent of IPF, assessed in terms of HRCT, best correlated with DLCO ($r = -0.68$), though the correlation with FVC ($r = -0.37$) was also significant. In the study of Brantly and coworkers[21] FVC and DLCO correlated equally well ($r = -0.66$ for both). The above discrepancies among previous studies and the present results are difficult to explain but may be related to the variable course of the disease, to the fact that somewhat different methodologies have been used[5,7,10,18,19,21] and also to the fact that some previous works included patients with interstitial lung disease associated with conditions such as connective tissue disorders.[7,10,24]

Finally, according to the multiple stepwise regression analysis, only FVC was selected as significant predictor in virtually all relationships studied. This is not surprising given the fact that the extent of pulmonary fibrosis with concurrent increase in pulmonary elastance is necessarily reflected by decreased FVC and concurrent increase in work of breathing leading to dyspnea.[22] Furthermore, the HRCT indices of global lung disease used in this study correlate well with FVC, which decreases progressively with disease duration. The importance of FVC in IPF could be higher if a good predictive ability for survival could be demonstrated. In this regard, however, controversy still exists. While some studies have confirmed that baseline FVC offers independent predictive ability in determining the risk of death,[23–25] others[26,27] have not. Probably the main reason of this controversy relates to the fact that the cause of death in IPF is multifactorial since mortality is due to respiratory failure only in the 39% of patients, the majority as a single cause but still a minority overall.[28] Recent studies have shown that changes in clinical and physiological variables and among them changes in dyspnea score and FVC, over 6 and 12 months may offer more accurate prognostic information.[29,30]

The fact that $PaCO_2$ was selected as the second significant predictor of dyspnea indicates that the more the patients hyperventilate the more dyspnea they have, which is in line with the fact that virtually every patient with IPF will develop dyspnea, first on exertion and next at rest, as the disease progresses. Indeed, Rampulla and coworkers found that the most frequent symptom limiting exercise capacity in interstitial

lung disease is dyspnea.[31] It should also be noted that although patients with restrictive pulmonary disease often hyperventilate, this phenomenon is most common in patients with interstitial lung disease.[32] This suggests some role to lung parenchymal fibro-inflammatory milieu in the generation of stimuli from the lung parenchyma.

In conclusion, the close correlation observed in the present study between the MRC dyspnea score and some of the most representative functional and radiological indices of disease severity and extent, indicates that the estimation of dyspnea with a simple and self-administered questionnaire is a useful adjunct in the assessment of the clinical status of patients with IPF. However, because of the relatively small size of the population studied, further studies are needed to support our findings. In addition, it would be useful to validate the predictive value of MRC dyspnea score in the disease progression and survival.

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References

1. American Thoracic Society, European Respiratory Society, American College of Chest Physicians, Idiopathic pulmonary fibrosis, diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med* 2000; **161**: 646–64.
2. Schwartz DA, Scott van Fossen D, Davis CS, et al. Determinants of progression in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1994;**149**:444–9.
3. Eltayara L, Becklake MR, Volta CA, et al. Relationship between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;**154**:1726–34.
4. Bestall JC, Paoul EA, Garrod R, et al. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;**54**:581–6.
5. Xaubet A, Agusti C, Luburich P, et al. Pulmonary function tests and CT scan in the management of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998;**158**: 431–6.
6. Orens JB, Kazerooni EA, Martinez FJ, et al. The sensitivity of high-resolution CT in detecting idiopathic pulmonary fibrosis proved by open lung biopsy: a prospective study. *Chest* 1995;**108**:109–15.
7. Wells AU, Hansell DM, Rubens MB, et al. The predictive value of appearances on thin-section computed tomography in fibrosing alveolitis. *Am J Respir Crit Care Med* 1993;**148**: 1076–82.
8. Quanjer PhH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows. Report working party, Standardization of lung function tests, European Community for steel and coal. Official Statement of the European respiratory Society. *Eur Respir J* 1993;**6**(Suppl. 16):5–40.
9. Cotes JE, Chinn DJ, Quanjer PhH, et al. Standardization of the measurement of transfer factor (Diffusing Capacity). Report working party, Standardization of lung function tests, European Community for steel and coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993;**6**(Suppl 16):41–52.
10. Staples CA, Muller NL, Ostrow D, et al. Usual Interstitial Pneumonia: Functional and radiologic correlations. *Radiology* 1987;**162**:377–81.
11. Lee JS, Im J-G, Ahn JM, et al. Fibrosing alveolitis: prognostic implication of ground glass attenuation at high resolution, CT. *Radiology* 1992;**184**:451–4.
12. Wells AU, Rubens MB, du Bois RM, et al. Functional impairment in fibrosing alveolitis: relationship to reversible disease on thin section computed tomography. *Eur Respir J* 1997;**10**:280–5.
13. Muller NM, Mawson JB, Mathieson JR, et al. Sarcoidosis: correlation of extent of disease at CT with clinical, functional and radiographic findings. *Radiology* 1989;**171**: 613–8.
14. Mc Cullagh P, Nelder JA. *Generalized linear models*, 2nd ed. London: Chapman & Hall; 1989.
15. Martinez TY, Pereira CA, dos Santos ML, et al. Evaluation of the short-form 36-item questionnaire to measure health-related quality of life in patients with idiopathic pulmonary fibrosis. *Chest* 2000;**117**:1627–32.
16. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest* 1988;**93**:580–6.
17. Hartley PG, Galvin JR, Hunninghake GW, et al. High-resolution CT-derived measures of lung density are valid indexes of interstitial lung disease. *J Appl Physiol* 1994;**76**:271–7.
18. Terriff BA, Kwan SY, Chan-Yeung MM, et al. Fibrosing alveolitis: chest radiography and CT as predictors of clinical and functional impairment at follow-up in 26 patients. *Radiology* 1992;**184**:445–9.
19. Gay SE, Kazerooni EA, Toews GB, et al. Idiopathic pulmonary fibrosis: predicting response to therapy and survival. *Am J Respir Crit Care Med* 1998;**157**:1063–72.
20. Wells AU, King AD, Rubens MB, et al. Lone cryptogenic fibrosing alveolitis: a functional-morphologic correlation based on extent of disease on thin-section computed tomography. *Am J Respir Crit Care Med* 1997;**155**:1367–75.
21. Brantly M, Avila NA, Shotelersuk V, et al. Pulmonary function and high-resolution findings in patients with an inherited form of pulmonary fibrosis, Hermansky-Pudlak syndrome, due to mutations in HPS-1. *Chest* 2000;**117**:129–36.
22. Renzi GJ, Milic-Emili J, Grassino AE. The pattern of breathing in diffuse lung fibrosis. *Bull Eur Physiopathol Respir* 1982;**18**:461–72.
23. Hubbard R, Johnston I, Britton J. Survival in patients with cryptogenic fibrosing alveolitis. A population-based cohort study. *Chest* 1998;**113**:396–400.
24. Wells AU, Cullinan P, Hansell DM. Et al, Fibrosing alveolitis associated with systemic sclerosis has a better prognosis than lone cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med* 1994;**149**:1583–90.
25. Latsi PI, Wells AU, Bisirtzoglou D, et al. Prognostic determinants in IPF patients with the histological features of usual interstitial pneumonia. *Eur Respir J* 2001;**18**(33): 526S.
26. Douglas WW, Ryu JH, Schroeder DR. Idiopathic pulmonary fibrosis. Impact of oxygen and colchicines, prednisone, or no therapy on survival. *Am J Respir Crit Care Med* 2001;**161**: 1172–8.

27. Mogulcoc N, Brutsche MH, Bishop PW, et al. Pulmonary function in idiopathic pulmonary fibrosis and referral for lung transplantation. *Am J Respir Crit Care Med* 2001;**164**:103–8.
28. Panos RJ, Mortenson R, Niccoli SA, et al. Clinical deterioration in patients with idiopathic pulmonary fibrosis. Causes and assessment. *Am J Med* 1990;**88**:396–404.
29. Collard HR, King Jr. TE, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;**168**:538–42.
30. Latsi PI, du Bois RM, Nicholson AG, Colby TV, Bisirtzoglou D, Nikolakopoulou A, Veeraraghavan S, Hansell DM, Wells AU. Fibrotic idiopathic interstitial pneumonia. The prognostic value of longitudinal functional trends. *Am J Respir Crit Care Med* 2003;**168**:531–7.
31. Rampulla C, Baiocchi S, Dacosto E, et al. Dyspnea on exercise. Pathophysiologic mechanisms. *Chest* 1992;**101**(5): 248S–52S.
32. Kornbluth R, Turino GM. Respiratory control in diffuse interstitial lung disease and diseases of the pulmonary vasculature. *Clin Chest Med* 1980;**1**:91–201.