Impaired lung transfer factor in fibromyalgia syndrome

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Received on November 19, 2015; accepted in revised form on February 8, 2016.

Clin Exp Rheumatol 2016; 34 (Suppl. 96): S114-S119.

Key words: fibromyalgia, lung

Funding: this study was supported by funds from our Department.

Competing interests: none declared.

ABSTRACT

Objective. *The aim of this study was to evaluate whether pulmonary diffusing capacity is impaired in patients with fibromyalgia (FM) as it is in those with other diseases characterised by autonomic nerve system (ANS) dysfunction such as type 1 diabetes.*

Methods. *Forty-five consecutive antinuclear antibody (ANA)-negative female Caucasian patients aged 50.1± 5.6 years with FM and compared with 45 healthy female control volunteers matched in terms of age and body mass index (BMI). The autonomic function has been evaluated by means of standard electrocardiography (ECG), finger blood pressure respiration, and muscle sympathetic nerve activity (MSNA) at rest and during a stepwise tilt test up to 75°. Their autonomic profiles were drawn up on the basis of MSNA, plasma catecholamine levels, and spectral indices of cardiac sympathetic and vagal modulation, and sympathetic vasomotor control computed by means of the spectrum analysis of RR and systolic arterial pressure (SAP) variability. Lung volumes and dynamic spirometry parameters were assessed by means of plethysmography. All of the patients were clinically evaluated and completed the FQI and COMPASS questionnaire.*

Results. *There was no difference in lung volumes between the FM patients and healthy controls, but DLCO (83±4 vs. 96±5; p<0.001), Kco (84±5 vs 98±5; p<0.001), DM (12.7±2.4 vs 13.6±1.8; p<0.05) and Vc (48±3.9 vs 65±7; p<0.001) were significantly reduced in the patients.*

The COMPASS-31, RCS and pain VAS scores significantly correlated with DLCO, Kco and Vc with the correlation being particularly close in the case of Vc. Furthermore, univariate Cox proportional hazard analysis showed that the three scores were all significantly associated with an increased risk of impaired DLCO (respectively, χ^2 16.21, p<0.0005; χ^2 7.09, p<0.005; χ^2 6.37, p<0.01).

Conclusion. *FM impairs DLCO mainly as a result of a reduction in Vc, and that this defect is inversely proportional to the severity of the dysfunction suggesting a relationship between impaired DLCO and autonomic nerve dysfunction.*

Introduction

Fibromyalgia syndrome (FM) is a chronic pain disorder characterised by symptoms of morning stiffness, fatigue, depression, non-restorative sleep and reduced cognitive performance (1), some of which are worsened by emotional distress, meteorological changes, insomnia and strenuous activity (2). Some of the patients' symptoms, as well as their physical and psychological characteristics, can be attributed to autonomic nervous system (ANS) dysfunction (3-6), which is frequent because their sympathetic nervous system (SNS) is persistently hyperactive (especially at night), but hypoactive in response to stress (7, 8). This paradox is in line with the principle that continuous over-stimulation of β-adrenergic receptors causes desensitisation and down-regulation (9). Neurotransmitter abnormalities may cause greater pain perception, fatigue, sleep/mood dysfunction and memory problems (10), and both reductionist and holistic hypotheses have been formulated to support the hypothesis of ANS dysfunction in FM patients (11).

It has been demonstrated that ANS dysfunction in patients with type 1 diabetes mellits can induce functional alterations in the regulation of pulmonary microvascular tone and the distribution of pulmonary blood filling, and that the distribution of alveolar ventilation may also be negatively affected by autonomic neuropathy: both of these factors may be responsible for impaired

lung carbon monoxide diffusing capacity (DLCO) (12, 13).

The aim of this study was to evaluate whether pulmonary diffusing capacity is impaired in patients with FM as it is in those with other diseases characterised by ANS dysfunction such as type 1 diabetes (12, 13).

Methods

Forty-five consecutive anti-nuclear antibody (ANA)-negative female Caucasian patients aged 50.1±5.6 years with FM diagnosed on the basis of the 1990 American College of Rheumatology (ACR) criteria (1) were enrolled between October 2014 and April 2015, and compared with 45 healthy female control volunteers matched in terms of age and body mass index (BMI). The study was approved by the local Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki, and informed consent was obtained from all the subjects before they underwent any study procedure.

After they had stopped taking any vasodilators for at least two weeks.

The autonomic function have been evaluated as previously reported (5, 6) by means of standard electrocardiography (ECG), finger blood pressure respiration, and muscle sympathetic nerve activity (MSNA) at rest and during a stepwise tilt test up to 75°. Their autonomic profiles were drawn up on the basis of MSNA, plasma catecholamine levels, and spectral indices of cardiac sympathetic and vagal modulation, and sympathetic vasomotor control computed by means of the spectrum analysis of RR and systolic arterial pressure (SAP) variability. Arterial baroreflex function was evaluated using the SAP/RR spontaneous sequence technique, index a, and the gain in the MSNA/diastolic pressure relationship during the stepwise tilt test.

The controls were not smokers or alcohol users or drug abusers, and none were affected by any medical, neurological or psychiatric disorders or musculoskeletal pain.

Pulmonary function tests

Lung volumes and dynamic spirometry parameters were assessed by means of plethysmography (VMAX227 Autobox V6200, Sensor Medics; Yorba Linda, CA) in accordance with the European Respiratory Society (ERS) criteria (14).

Transfer factor (the carbon monoxide diffusion capacity of the lung, DLCO) was measured using the single breath technique (Transfer Test, Morgan Kent, UK), in accordance with the recommendations of the ERS (14). Double measurements were accepted when the estimates of DLCO and effective alveolar volume differed by 5%. DLCO was measured using low (CO 0.25%; He 14%, O_2 20%) and high oxygen concentrations (CO 25%; He 14%, O_2 85-75%), a breath-holding time of at least 10 seconds, and a washout volume of 0.75 L. The interval between measurements was five minutes, and the tests were performed in a sitting position. DLCO was adjusted for the level of carboxyhaemoglobin (COHb) measured using a blood gas analyser (Critical Care Laboratory Synthesis 35, Instrumentation Laboratory, Paderno Dugnano, Italy) and the following equation (16):

Adjusted DLCO = COHb – measured DLCO (1 + (%COHb/100))

The carbon monoxide transfer factor coefficient (Kco) was derived from the following equation:

Kco = DLCO/alveolar volume.

The flow sensor was calibrated before each test using a three-litre syringe.

The two components of lung transfer, alveolar-capillary membrane (DM) and pulmonary capillary blood volume (Vc), were calculated using the equation of Roughton and Foster (17) and the reference equations proposed by European Community of Coal and Steel report (14).

All of the respiratory tests were conducted by a single examiner (MR), and their variability and reproducibility were within the previously described ranges for these parameters (14).

Symptom assessments

All of the participants completed the Compositive Autonomic Symptom Score (COMPASS-31) (18), the simplified 31-item of COMPASS, which leads to higher scores in FM patients and has a high significant correlation with the fibromyalgia impact questionnaire (FIQ) (19). It quantifies orthostatic intolerance, the vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor domains, and gives a total score of 0-100.

The number of tender points (TPs) was counted using Wolfe's protocol (1), which gives a total score of 0-18, and the intensity of somatic pain was assessed using a 100 mm visual analogue scale (VAS)

The severity of Raynaud's phenomenon was evaluated using the Raynaud's Condition Score (RCS), an ordinal scale ranging from zero to10 that measures the level of difficulty experienced by patients (20).

Videocapillaroscopy of the hands was performed in all of the patients using "Video Cap" (DS MEDICA with 100x optical probe) and the results were evaluated according to the current guidelines (21).

Statistical analysis

The data were analysed using SPSS v. 6.1 software (SPSS, Chicago, IL, USA) and expressed as mean values and standard deviations. The anthropometric data, pulmonary function test results, and symptom scores were analysed using an unpaired Student's *t*-test. The Mann-Whitney U-test and Spearman's rank correlation were used as appropriate. Prognostic factors were evaluated using Cox's proportional hazards analysis of the variables that may influence the DLCO impairment. A p-value of <0.05 was considered significant.

Results

The patients, who had a mean FM duration of 5.1±3.4 years and a mean number of 14.8±2.8 TPs, had significantly higher COMPASS-31 (36.3±17.1 *vs*. 12.7±9.2; $p<0.0001$), RCS (6.3±2 *vs*. 2.1±1.3; $p<0.0001$) and pain VAS scores (6.5±2 *vs*. 2±1; $p<0.0001$) than the controls (Table I).

Table II shows the anthropometric data and pulmonary function tests. There was no difference in lung volumes between the FM patients and healthy controls, but DLCO (83±4 *vs*. 96±5; $p<0.001$), Kco (84±5 *vs*. 98±5; $p<0.001$), DM

Table I. Baseline symptom scores and number of tender points in FM patients and healthy controls

	FM patients (n=45)	Healthy controls (n=54)	*p*
Disease duration, years	5.1 ± 3.4	-	-
COMPASS-31 score	36.3 ± 17.1	12.7 ± 9.2	0.0001
Raynaud's condition score	6.3 ± 2	2.1 ± 1.3	0.0001
Pain VAS score	6.5 ± 2	2 ± 1	0.0001
No. of tender points	14.8 ± 2.8	-	-

Table II. Anthropometric data and pulmonary function tests of FM patients and healthy controls

	FM patients (n=45)	Healthy controls (n=54)	*p*
Age, years	50.1 ± 5.6	49.8 ± 6.1	0.80
BMI, Kg/h^2)	25.9 ± 3.1	26.3 ± 2.5	0.47
VC, % of predicted	88 ± 6	89 ± 5	0.37
FEV1, % of predicted	91 ± 6	90 ± 7	0.45
TLC, % of predicted	93 ± 7	91 ± 6	0.13
RV, % of predicted	91 ± 5	92 ± 6	0.67
DLCO, % of predicted	83 ± 4	96 ± 5	0.0001
Kco, % of predicted	84 ± 5	98 ± 5	0.0001
DM, mL/min/mmHg	12.7 ± 2.4	13.6 ± 1.8	0.05
Vc, mL	48 ± 3.9	65 ± 7	0.0001

Mean values ± SD. BMI: body mass index; VC: vital capacity; FEV1: forced expiratory volume in one second; TLC: total lung capacity; RV: residual volume; DLCO: transfer factor of the lung; Kco: transfer lung coefficient; DM: diffusing capacity of the alveolar membrane; Vc: volume of blood in alveolar capillaries.

Table III. Correlations between symptom scores, transfer factor of the lung (DLCO), transfer lung coefficient (Kco) and volume of blood in alveolar capillaries (Vc).

	R	*p*
COMPASS-31 *vs*. DLCO	-0.68	0.001
Kco	-0.53	0.05
Vc	-0.81	0.0001
Raynaud's condition score *vs*. DLCO	-0.55	0.05
Kco	-0.54	0.05
Vc	-0.74	0.0001
Pain VAS score *vs*.DLCO	-0.58	0.01
Kco	-0.55	0.05
Vc	-0.76	0.0001

(12.7±2.4 *vs*. 13.6±1.8; p<0.05) and Vc (48±3.9 *vs*. 65±7; *p*<0.001) were significantly reduced in the patients.

The COMPASS-31, RCS and pain VAS scores significantly correlated with DLCO, Kco and Vc (Table III), with the correlation being particularly close in the case of Vc (Fig. 1). Furthermore, Univariate Cox proportional hazard analysis showed that the three scores were all significantly associated with an increased risk of impaired DLCO (respectively, χ^2 16.21, *p*<0.0005; χ^2 7.09, *p*<0.005; χ^2 6.37, *p*<0.01).

Raynaud's phenomenon had been previously diagnosed by means of capillaroscopy in 16 of the 45 FM patients (35%), who had significantly lower DLCO (77±4 *vs* 83±5, *p*<0.001), Kco (80±5 *vs*. 84±4, *p*<0.01) and Vc values (46±3.5 *vs*. 50±2.8, *p*<0.001), and significantly more TPs (16.5±1.3 *vs*. 13.1±2.5, *p*<0.001) than those without Raynaud's phenomenon (Table IV).

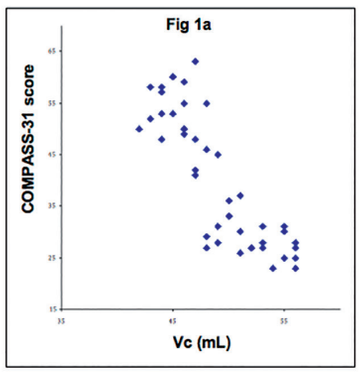
Discussion

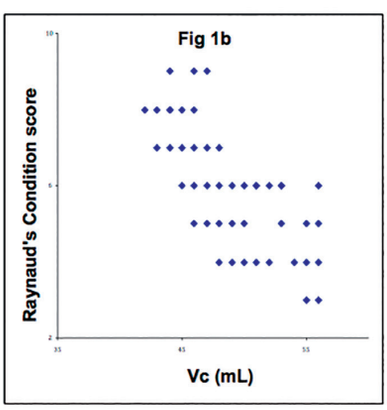
Our data show that FM impairs DLCO mainly as a result of a reduction in Vc, and that this defect is inversely proportional to the severity of the dysfunction suggesting a relationship between impaired DLCO and autonomic nerve dysfunction.

The autonomic nervous system is a complex network that works below the level of consciousness to maintain homeostasis, and regulate the function of various organs and glands by ensuring the equilibrium of antagonistic sympathetic/parasympathetic stimuli. A large number of studies have shown altered pain perception and processing in FM patients, and the neuroendocrine dysfunctions associated with FM can be explained by an alteration in central sensitivity (22, 23). Sensitisation of the nociceptive neurons in the dorsal horn due to the activation of N-methyl-D-aspartic acid receptors, and the inhibition of pain due to the ineffective functioning of the descending inhibitory system, are probably pathogenic for hypersensitivity to all kinds of stimuli (24).

The idea that FM is a sympathetically maintained pain syndrome is based on the findings of controlled studies showing sympathetic hyperactivity in FM patients, whose pain is submissive to sympathetic blockade and rekindled by norepinephrine injections (25).

Dysautonomia may also explain the multi-systemic features of FM, although attempts to quantify possible abnormalities of cardiovascular autonomic regulation have led to only partial and sometimes contradictory results. A microneurography study by Elam *et al*. (26) found no difference in muscle sympathetic nerve activity between FM patients and healthy controls in the recumbent position or during cold pressor stimulation, whereas the results of other studies indicate increased sympathetic activity. It has been found that a guanethedine-induced selective sympathetic blockade reduces pain and the number of TPs (27), and studies based on the power spectrum analysis of heart rate variability have shown increased sympathetic and decreased parasympathetic modulation (28-30). Duschek *et al*. found evidence of an association between the functional features of the baroreflex and pain sensitivity (31): reduced baroreflex func-





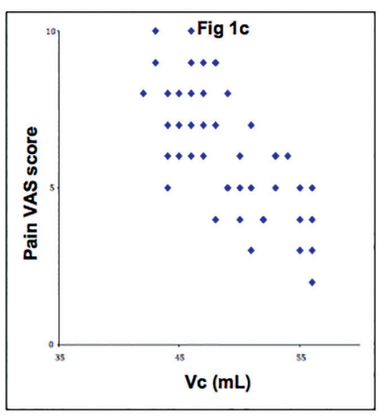


Fig. 1. Spearman rank correlations between symptom scores and volume of blood in alveolar capillaries (Vc): **a**) Vc *vs*. COMPASS-31 score (r = -0.81, $p<0.0001$); **b**) Vc *vs*. Raynaud's condition score (r = -0.74, $p<0.0001$); **c**) Vc vs pain VAS score (r = -0.75, $p<0.0001$).

Table IV. Transfer factor of the lung (DLCO), transfer lung coefficient (Kco) and volume of blood in alveolar capillaries (Vc) in 54 FM patients with or without Raynaud's phenomenon.

	Raynaud's phenomenon		
	YES (n=16)	NO (n=29)	*p*
DLCO, % of predicted	77 ± 4	83 ± 5	0.001
Kco, % of predicted	80 ± 5	84 ± 4	0.01
Vc, mL	46 ± 3,5	50 ± 2.8	0.0001
DM, mL/min/mmHg	12.8 ± 2	13.3 ± 3	0.55
No. of tender points	16.5 ± 1.3	13.1 ± 2.5	0.001

tion in FM patients may be involved in ineffective ascending pain inhibition, and this may contribute to the hyperalgesia characterising the disorder (32). Vaeroy *et al*. (33) measured skin temperature and blood flow responses to intense auditory stimulation and the cold pressor test, and found lower responses in FM patients, thus indicating reduced sympathetically mediated vasoconscriction.

The dysautonomia in FM patients can be characterised by unrelenting sympathetic hyperactivity throughout the day, associated with a deranged sympathetic response to different stressors (30). It is known that sleep greatly influences autonomic function, and increased sympathetic tone at night may be due to sleep disorders or alterations in ANS regulation.

The most important finding of this study is the presence of impaired DLCO manly due to a greater reduction in Vc than in DM, which is inversely proportional to the severity of autonomic nerve dysfunction.

There are only two previously published studies of DLCO in FM patients (34, 35), probably because this index is not routinely measured. Both that DLCO is lower because of a reduction in DM, the authors does not have an explanation for this finding but they suggested that this may be related to the pathogenesis of periodic breathing during sleep that often characterises FM patients (34, 35).

Unlike the findings of previous studies (34, 35), our data confirm that FM patients have reduced DLCO, but we found that this was due to the greater impairment of Vc rather than DM. This may be explained by the fact that previously studies involved a smaller numbers of patients and the presence of Raynaud's phenomenon was ignored, although another factor is that in this study our patients stopped vasodilator therapy some days before they underwent the tests.

The percentage of FM patients with Raynaud's phenomenon in our study is in line with that reported in previous papers (36).

The FM patients were characterised autonomic nerve dysfunction, and local ischemia may explain the occurrence of Raynaud's phenomenon in some patients. FM patients have functional microcirculation and morphological abnormalities, and the abnormal pattern of reactive hyperemia is due to greater sympathetic tone leading to increased vasoconstriction (37). Stress and chronic pain enhance sympathetic activity by altering cardiovascular responses and inducing arterial wall stiffening and endothelial dysfunction (38). Patients with FM have impaired endothelial-dependent and flow-mediated dilation caused by decreased endothelial NO activity, which directly regulates large artery stiffness (39). They also show a distinctive vascular cold response caused by relative ischemia due to an increase in endothelin-1 levels, which further enhances vasospasm and thus creates a vicious circle (40).

It is also worth noting that the autonomic cardiac dysfunction characterised by Raynaud's phenomenon precedes the development of fibrosis in patients with systemic sclerosis (41).

An ANS dysfunction could be responsible for impaired DLCO, may be predicted by administering a questionnaire

such as COMPASS-31 that assesses the degree of autonomic dysfunction (42-45). Autonomic cardiac neuropathy could induce functional alterations in the regulation of pulmonary microvascular tone and the distribution of pulmonary blood filling, which would cause a reduction in Vc. The distribution of alveolar ventilation may be negatively influenced by autonomic neuropathy, thus contributing to the reduction of DLCO due to reduced DM.

Our data show that, like other diseases characterised by a autonomic nerve dysfunction, FM impairs DLCO mainly as a result of a reduction in Vc, and that this defect is inversely proportional to the severity of the dysfunction.

Our data seem to suggest the studying DLCO and its components may be useful in FM patients with greater autonomic nerve dysfunction. It may also be useful in evaluating the efficacy of vasodilating therapy in the subgroup of these patients with full-blown Raynaud's phenomenon.

Study limitations

Beause of the relatively small number of FM patients, further studies are necessary to confirm the relationship between impaired DLCO and autonomic nerve dysfunction.

Clinical usefulness

Our findings certainly contribute to improving our understanding of the pathophysiology of FM, and seem to indicate the usefulness of studying DLCO and its components in the follow-up of FM patients with greater autonomic nerve dysfunction and or full-blown Raynaud's phenomenon.

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