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Lung capillary blood volume and membrane diffusion in idiopathic interstitial pneumonia☆

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KEYWORDS
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DLCO/DLNO;
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Membrane conductance;
Pulmonary arterial pressure

Summary
Rationale: Diffusing capacity of the lung for carbon monoxide (DLCO) is a good marker of disease severity in patients with idiopathic interstitial pneumonia (IIP). The combined diffusing capacity of nitric oxide (DLNO) and DLCO determines the two components of diffusion: membrane conductance (Dm, CO) and pulmonary capillary blood volume (Vc).
Objectives: The aim of this study was to evaluate Vc and Dm, CO in patients with fibrosing IIP in order to determine the relative contribution of membrane resistance and vascular resistance to the loss of DLCO.
Methods: 32 patients with IIP (IPF: $n = 22$, NSIP: $n = 10$) were evaluated using MRC dyspnea scale, plethysmography, combined DLNO/DLCO, 6-min walk test (6 MWT), echocardiography and chest computed tomography (chest CT).
Results: DLCO (41.8 ± 11.9%pred), Dm, CO (40.5 ± 12.7%pred) and Vc (41.9 ± 18%pred) were severely and equally reduced. Dm, CO and Vc were related to MRC scale, FVC, maximal desaturation during 6 MWT, and systolic pulmonary artery pressure (sPAP). There was no correlation with the extent of fibrotic changes on chest CT.
Conclusions: Our main results indicate that Dm, CO and Vc contribute almost equally to DLCO reduction in IIP. Dm, CO and Vc are related to functional indicators of disease severity and to sPAP in agreement with the concept of vascular involvement in IIP.

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Introduction

Idiopathic pulmonary fibrosis (IPF) and non-specific interstitial pneumonia (NSIP) are two idiopathic interstitial pneumonias (IIP) of unknown etiology and poor prognosis.[1] The pathogenesis of lung fibrosis is not clearly understood, but alveolar epithelial cell injury, dysregulation of fibroblasts, vascular injury and aberrant angiogenesis related to vascular remodeling are key elements.[2]

Diffusing capacity of the lung for carbon monoxide (DLCO) is a simple test which evaluates the efficiency of pulmonary gas exchange. It is a valuable tool in the assessment of pulmonary diseases and particularly IPF.[3] Alteration of DLCO may result from changes in gas exchange area, alveolar capillary membrane thickness and ventilation/perfusion relationship in the lung. Since the pulmonary capillary bed also takes part in the gas exchange area, DLCO may also reflect involvement of pulmonary capillaries.

According to the model of Roughton and Forster, DLCO is composed of two resistances arranged in series: [1/DLCO = 1/Dm, CO + 1/(θCo xVc)].[4] Pulmonary membrane diffusing capacity (Dm) for carbon monoxide (Dm, CO) is the CO conductance across the alveolar-capillary tissue membrane and plasma barrier; θCO is the rate of carbon monoxide uptake by whole blood and combination with Hb measured in vitro; Vc is the pulmonary capillary blood volume. The measurement of diffusing capacity of the lung using the transfer gas nitric oxide (NO) and CO together permits to obtain Dm, CO and Vc in a single-breath experiment.[5–7]

The aim of this study was first to measure Vc and Dm, CO in patients with fibrosing IIP in order to determine the relative contribution of membrane resistance and vascular resistance in the loss of DLCO and secondly to study their relations with pulmonary function tests, chest computed tomography (chest CT) and echocardiography.

Patients and methods

Thirty two patients with IIP were included in this prospective study. Inclusion criteria consisted of diagnosis of IPF according to the American Thoracic Society/European Respiratory Society guidelines and/or histopathological evidence for usual interstitial pneumonia, or diagnosis of NSIP (radiographic or histopathological diagnosis). Patients were not included if they had another pulmonary disease (including obstructive disease), left heart failure or a history of pulmonary embolism. Connective tissue diseases were ruled out. No acute exacerbation was observed in the three months preceding inclusion. All patients completed pulmonary function tests. Twenty seven patients completed a modified MRC dyspnea scale. An informed consent was obtained from all patients and approval for the use of these data was provided by the Institutional Review Board of the French learned society for respiratory medicine.

Pulmonary function tests

Resting pulmonary function tests included measurement of lung volumes by plethysmography and single breath diffusion capacity of the lung for carbon monoxide (DLCO) (*Jaeger-Masterlab*® plethysmograph). The reference values used were those of the Official Statement of the European Respiratory Society.[8,9] A 6-min walking test was performed according to ATS guidelines.[10]

DLNO and DLCO

DLNO and DLCO were measured simultaneously during a single breath manœuvre using an automatic apparatus (*Medisoft Dinant*®, Belgium) as described by Aguilaniu et al.[11] The measurements of DLNO/DLCO were accepted if two successive measurements of DLNO and DLCO gave figures within 10%, otherwise a third measurement was performed. Values of Dm, CO and Vc were calculated according to the model of Guénard et al.[7] 1/θNO was assumed negligible, therefore DLNO = Dm, NO. Dm, CO was calculated as Dm, NO/a where a = 1.97 following Graham's law. To calculate Vc, θCO reference from Roughton and Forster was chosen.[4] Hemoglobin concentration was not measured but set at 13.5 g/dL for women and 14.5 g/dL for men. θCO values were multiplied by 13.5/14.9 and 14.5/14.9 respectively. Reference values for DLNO, Dm, CO and Vc used were those established by Aguilaniu et al.[11]

Transthoracic echocardiography

A transthoracic echocardiography was performed at rest, with the patient lying on the left side. Resting measurements included left ventricular diameter and volume as well as left ventricular ejection fraction using the biplane Simpson method. Characteristic of the right ventricle (RV) was also assessed namely, the RV end-diastolic diameter and shortening fraction, tricuspid annular plane systolic excursion (TAPSE), and tricuspid S-waves on Doppler tissue imaging also provided an appreciation of the RV systolic function. We also analysed pulmonary acceleration time, the right ventricular-right atrium gradient on continuous Doppler scans by analysis TR flow, subaortic time-velocity integral of flow and inferior vena cava collapsibility to estimate pressure in the RA. Systolic pulmonary arterial pressure (sPAP) is considered equal to right ventricular systolic pressure in the absence of pulmonary valve stenosis. Right ventricular systolic pressure, and so sPAP can be estimated using continuous wave Doppler.

Chest computed tomography

Chest CT examinations were reviewed by two experienced radiologists unaware of lung function data. Scans were evaluated using a thin section CT (HRCT) scoring system for lung fibrosis, based on ground glass attenuation (HRCT alveolar score) and fibrotic change (HRCT interstitial score) previously described.[12,13]

Statistical analysis

Results are presented as mean ± SD. Following ATS/ERS 2005 guidelines, the lower limits of normal (LLN) were set at the level of 5th percentile (or mean minus 1.645 RSD) of