

## Non-invasive Diagnostic and Functional Evaluation of Cardiac and Pulmonary Involvement in Systemic Sclerosis

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**Abstract.** *Background:* The aim of the present study was to evaluate the role of non-invasive methods in the early detection of pulmonary and cardiac involvement in Systemic sclerosis (SSc) and to identify clinical and/or instrumental patterns of prognostic value. *Patients and Methods:* Twenty female patients affected by SSc (8 with diffuse cutaneous SSc and 12 with limited cutaneous SSc) were enrolled in our study. Cardiac and pulmonary involvement (respiratory function tests and carbon monoxide lung diffusion [ $DL_{CO}$ ], chest radiography, high resolution computed tomography [HRCT] and lung perfusion magnetic resonance) were evaluated. *Results:* All 18 patients studied with respiratory function tests showed a significant reduction of  $DL_{CO}$ . HRCT was considerably more sensitive than traditional chest radiography (59% versus 28%;  $p < 0.05$ ). Lung perfusion MRI revealed normal findings in 15 patients. Abnormal lung perfusion MRI results were found only in 3 patients. Angina pectoris with electrocardiographic and scintigraphic ischemic changes, severe regional wall motion abnormalities and complex arrhythmias seemed to be associated with poor prognosis. *Conclusion:* Taken together these results indicate that a pulmonary involvement occurs both in limited and in diffuse cutaneous SSc patients and develops, in 83 % of the cases, without any regional lung perfusion abnormality. Furthermore, cardiac involvement is detected in 65 % of the cases as a consequence of a range of noxious events including myocardial ischemia, fibrosis and pressure overload which may result in ventricular dysfunction and arrhythmias. Lung perfusion MRI should be

considered as a complementary diagnostic method for the functional evaluation of these symptoms in systemic sclerosis.

Systemic sclerosis (SSc) is a connective tissue disease of unknown etiology characterized by vascular pathology, especially of the microvasculature, and tissue fibrosclerosis with involvement of the skin, gastrointestinal tract and organs such as the lungs, heart and kidneys.

In a recent study based on the Pittsburgh Data Bank (20), renal involvement was observed in 19%, cardiac in 15% and pulmonary in 16 % of 953 patients. The improved survival obtained in the renal crisis by effective therapy with ACE-inhibitor drugs has made pulmonary fibrosis the most frequent cause of death in SSc, nowadays (7, 19-20).

During the first five-year period from the onset of the disease, 44% of deaths had a cardiac or renal origin compared to 18% in the successive five-year period, with an overall 40% cardiac mortality. Furthermore, a higher mortality rate due to pulmonary fibrosis was present in the second five-year period (32%) when compared to the first five-year period (9%), corresponding to an overall 41% of total deaths (20).

These data demonstrate that, in the heart and in the kidneys, the progression of the functional alterations can lead more rapidly to severe disease and death while the pulmonary damage, although occurring early, proceeds asymptotically toward a large loss of pulmonary volume.

These observations point out the significance of the early detection of organ damage in modifying the course of the disease through an appropriate treatment.

Cardiac involvement is present in more than 80% of SSc patients and consists of various pathological changes including hypertrophy, inflammation and myocardial fibrosis, occasionally associated with segmental necrosis of the myocytes and contraction band necrosis due to severe ischemia and reperfusion injury, despite the absence of obstructive coronary lesions (8, 11, 12, 20, 22, 27).

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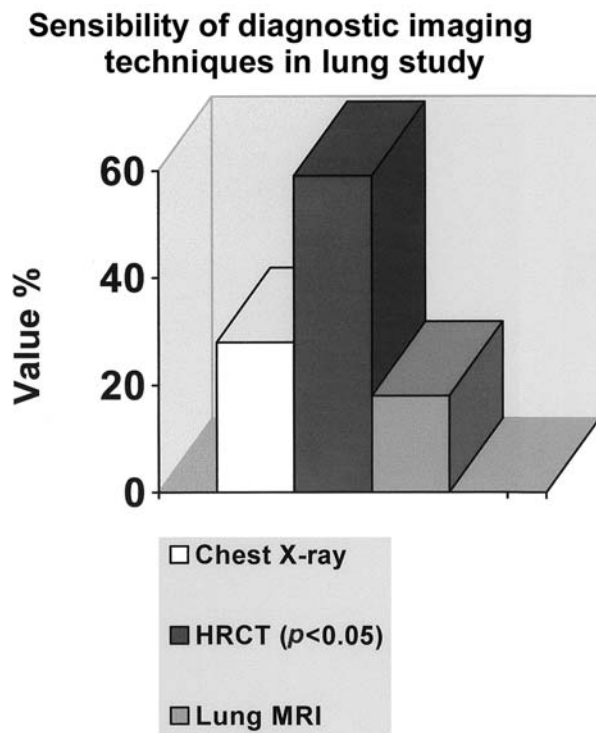


Figure 1. Sensitivity of the radiological diagnostic methods in the study of the lungs.

Pulmonary involvement is extremely frequent and consists of interstitial pulmonary disease, ranging from active inflammatory alveolitis to pulmonary fibrosis and pulmonary hypertension, which occurs as an isolated vasculopathy predominantly in the limited cutaneous SSc and results from pulmonary fibrosis or cardiac involvement more commonly in diffuse cutaneous SSc (4, 8-11, 16, 25). In addition, although a range of investigations, including Doppler echocardiography, pulmonary function testing and imaging techniques, is employed to evaluate asymptomatic SSc patients with isolated slightly elevated systolic pulmonary artery pressure (sPAP), open questions remain concerning its clinical significance and the appropriate treatment and the timing of initiation (8).

Diagnostic evaluation with standard thoracic radiography yields limited information. Considerably more accurate information is offered by high resolution computed tomography (HRCT): a "ground glass" image is an expression of alveolitis while a reticular image is associated with fibrosis (14, 15, 23-25). HRCT can reveal the perivascular fibrosis of small caliber vessels, although it cannot provide information on the microvasculature or on the presence of regional vasoconstrictive phenomena in the pulmonary vasculature, which has been hypothesized but never clearly demonstrated.

**Frequency of cardiological problems related to survival**

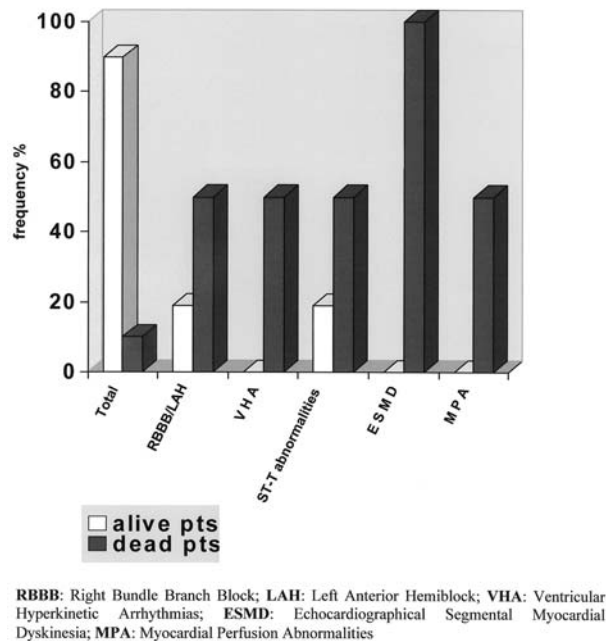


Figure 2. Frequency of abnormal cardiac instrumental findings in relation to survival. The statistical significance of the occurrence of segmental dyskinesias is indicated.

On the other hand, the use of lung perfusion magnetic resonance currently provides an accurate evaluation of the pulmonary microvasculature, because scans are performed in basic conditions and after paramagnetic contrast agent administration, with exclusion of the large vessels.

The aim of our study was to evaluate the role of non-invasive diagnostic methods in the early detection of pulmonary and cardiac involvement in SSc with the purpose of defining the underlying mechanisms of organ damage and identifying clinical and/or laboratory parameters of prognostic value.

## Patients and Methods

Twenty female patients, with an age ranging between 23 and 77 years (mean age 54.7 years; S.D. 13.7 years), affected by SSc diagnosed according to the criteria of the American College of Rheumatology (21), were enrolled in our study. Eight patients were affected by diffuse cutaneous SSc and 12 by limited cutaneous SSc. With the exception of two ex-smokers, none of the patients were smokers. The period of onset of the disease was defined by the occurrence of the first symptom clearly referable to SSc. The duration of the disease ranged between 2 and 46 years (mean 12.0 years; S.D. 10.7 years).

Renal involvement was evaluated through the measurement of blood creatinine and urea nitrogen, plasma electrolytes and routine urine examination.

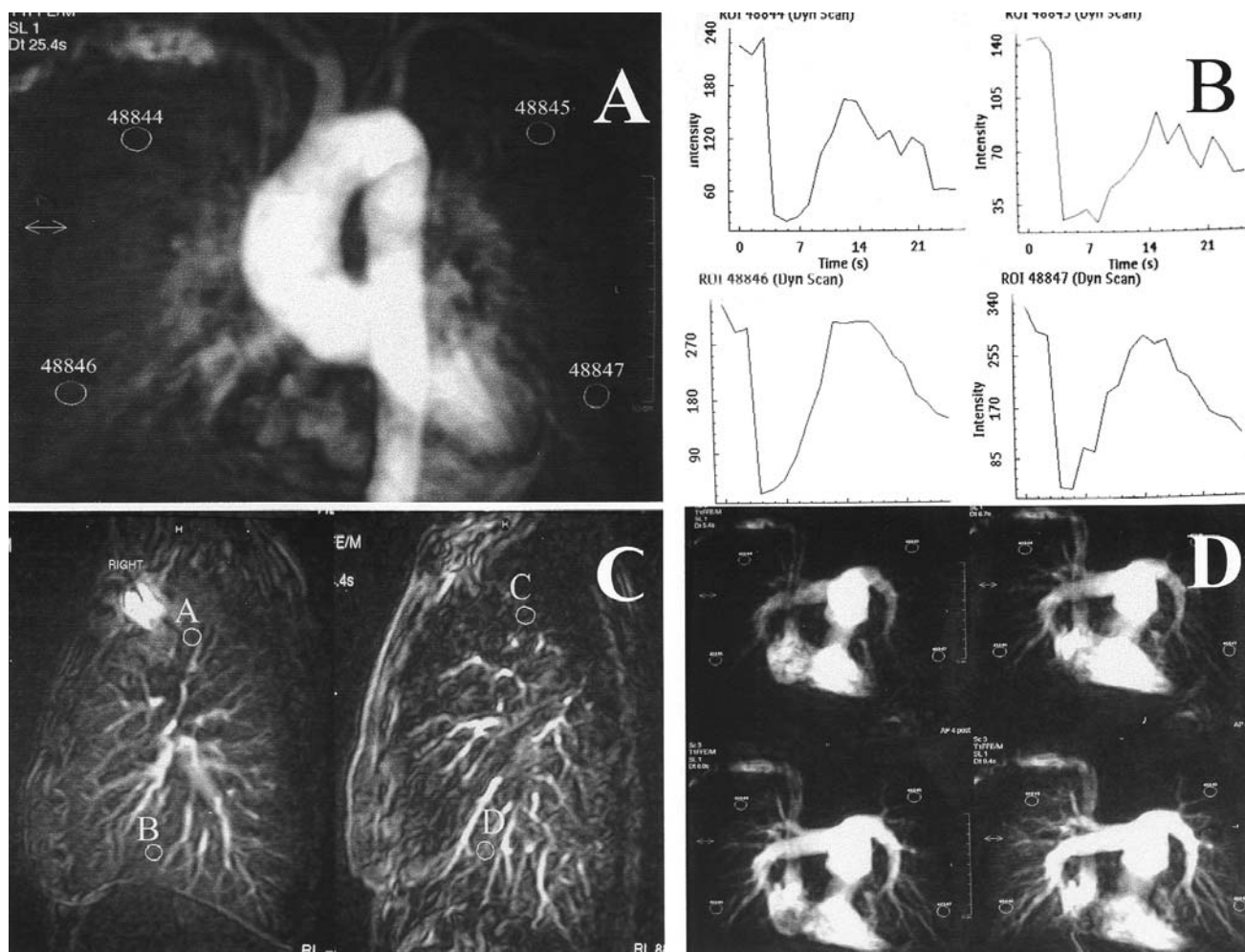


Figure 3. Lung perfusion MRI study in a sclerodermic patient.

A) A single dynamic study acquisition showing an inhomogeneous enhancement pattern of the pulmonary lobes and the relative hypoperfusion of both of the left lobes.

B) Intensity/time curves showing a semi-quantitative evaluation of lung perfusion: ROI 48844, 48845, 48846, 48847 are positioned respectively in the right superior, left superior, right inferior and left inferior lobe.

C) Right and left sagittal views of a single dynamic study acquisition at 24 sec, showing ROI A, B, C, D positioned in the superior and inferior lobes, respectively.

D) Dynamic study acquisitions at 5.4 sec, 6.7 sec, 8 sec and 9.4 sec after contrast media bolus administration showing a hypoperfusion in the left superior lobe.

Cardiac involvement was assessed through both conventional electrocardiogram (ECG) and 24-hour ambulatory ECG-Holter recordings, color-Doppler echocardiography and myocardial perfusion scintigraphy in case of angina, even when atypical. Systolic pulmonary artery pressure (sPAP) was evaluated with Doppler echocardiography and was considered high when it exceeded 30 mmHg.

Pulmonary evaluation included pulmonary function tests with DL<sub>CO</sub> (1), standard chest X-ray, HRCT and lung perfusion magnetic resonance. Chest HRCT was performed with a GE Medical Systems (Milwaukee, CA, USA) apparatus, thin layer scans (1 mm), short acquisition time (1 sec), 10 mm distance between each scan and three-dimensional high resolution image

reconstruction. Lung perfusion MR was performed using a Gyroscan 1.5 T (Philips, Best, Holland) apparatus with sagittal and coronal scans in basic conditions and after paramagnetic contrast media administration (Gadolinium-DTPA).

**Statistical analysis.** The sensitivity of chest X-ray, chest HRCT and lung perfusion MR was determined and the Chi-square test was used to evaluate the presence of significant differences between methods (Figure 1). Furthermore, the frequency of abnormal cardiac findings in relation to mortality (Figure 2) was determined using Fisher's exact test for the comparison of proportions. Differences with  $p < 0.05$  were considered significant.



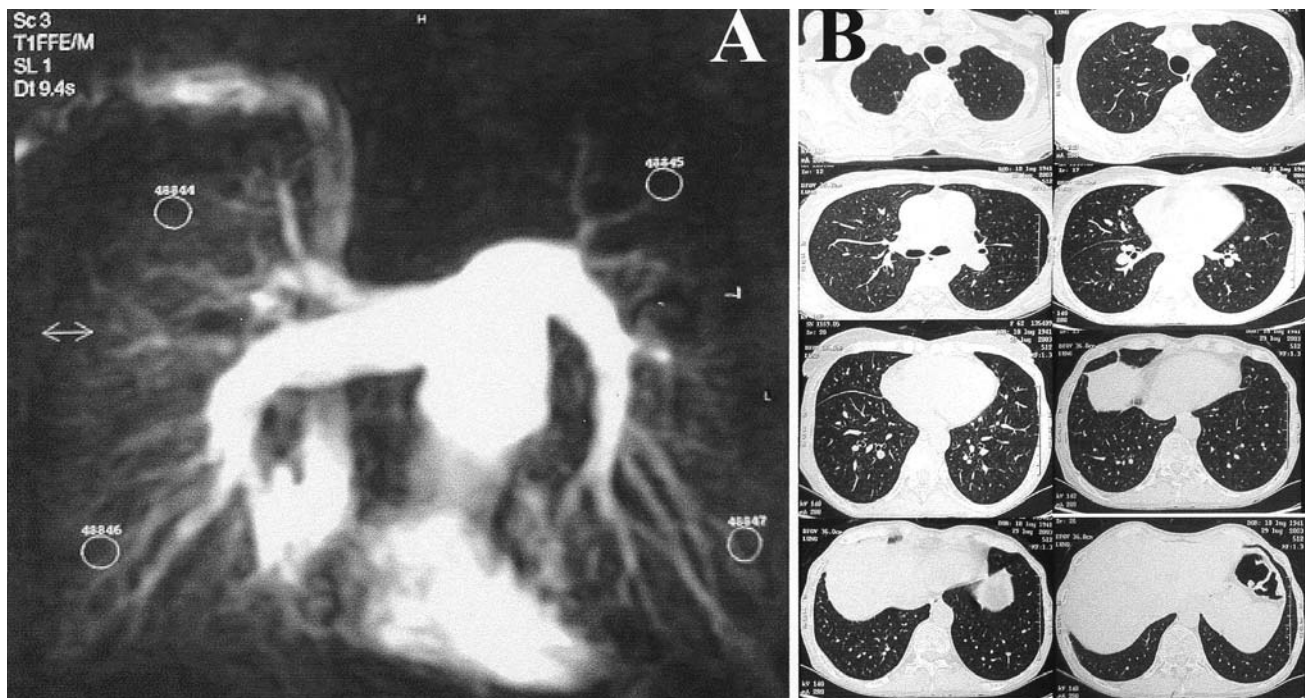


Figure 4. Morphological comparison between lung perfusion MRI and high resolution computed tomography (HRCT).

A) Lung perfusion MRI: a single dynamic study acquisition showing an inhomogeneous enhancement of the pulmonary lobes, a marked hypoperfusion of the left superior lobe and a mild hypoperfusion of the ventral portion of the inferior lobe.

B) HRCT: wide redistribution with severe reduction of the vascularization in the superior lobe and in the anterior portion of the lower lobe suggesting a sclerodermic vasculitis. Ground glass HRCT finding and diffuse hypertrophic pattern of the contralateral and homolateral residual vascularization confirming the MR findings of a districtal hyperemia, common in alveolitis.

## Results

Among the 20 SSc patients of our study group, three did not complete the study protocol. In 19 patients ANA positivity was found, with a centromeric pattern in 10 and a nucleolar pattern in 4 patients. Seven patients had an anti-Scl-70 positivity, associated in one case with ANA negativity. Sclerodermic pattern was observed in the nail folds by wide-field microscopy in 11 patients, while aspecific microvascular abnormalities were present in 7.

All 18 patients studied with respiratory function tests showed a significant reduction of  $DL_{CO}$  associated with a restrictive pattern in 2 patients and with a moderate obstructive pattern in 8 patients. Standard chest X-ray showed findings within the normal range in 9 patients, interstitial reticular changes in 5 patients and emphysematous changes in 4 patients.

Chest HRCT revealed ground glass opacity in one patient, interstitial pulmonary fibrosis in 6 patients, fibrotic striae and bilateral basal bullous emphysema in 1 patient, apical fibrotic sequelae in 2 patients and normal findings in the remaining patients. The subset of patients with abnormal HRCT

findings included 6 diffuse and 4 limited cutaneous SSc patients. No significant difference regarding the duration of disease was found between patients with abnormal and normal HRCT findings ( $10.2 \pm 8.4$  years vs.  $16.5 \pm 14.5$  years, respectively).

Lung perfusion MR revealed normal findings in 15 patients. Abnormal results were found only in 3 patients, and were:

- 1) A diffuse reduction of perfusion in a patient with normal HRCT and standard chest X-ray findings (Figure 3).
- 2) A hypoperfusion of the left upper lobe demonstrated in another patient with diffuse interstitial densitometric irregularities observed by HRCT and an accentuation of the interstitial texture observed by chest X-ray (Figure 4).
- 3) An increase of perfusion in the right inferior lobe corresponding to the ground glass alteration observed with HRCT in 1 patient.

The respiratory functional study and imaging protocol was not carried out in two patients and the HRCT exam in one patient. The first two patients had relevant ECG findings revealing severe myocardial ischemia in one and left anterior fascicular block (LAFB) and right bundle branch block

(RBBB) associated to ventricular tachyarrhythmias in the other; both had severe regional wall motion abnormalities detected by echocardiography as segmental dyskinesia and died suddenly a few months after the initial observation.

In the remaining 18 patients, the resting ECG was normal in 7 patients, showed LAFB in 1 patient, RBBB in 2 patients, left atrial enlargement in 3 patients, right atrial enlargement in 4 patients and ventricular repolarization changes in 3 patients. Furthermore, none of these patients showed relevant modifications on the 24-hour ECG-Holter recordings. The echocardiography showed a grade I diastolic dysfunction in 11 patients (9 had arterial hypertension) and an increased wall thickness of the left ventricle in 3 patients (2 had arterial hypertension).

In 4 patients, Doppler echocardiography revealed a sPAP greater than 30 mmHg. In the eldest patient a 38 mmHg sPAP was associated with moderate mitral valve regurgitation and left atrial enlargement without MR lung perfusion modifications. Another two patients, with a sPAP ranging between 35 and 33 mmHg, had interstitial pulmonary fibrosis and had received, also due to severe Raynaud's phenomenon with digital ulcers, an intermittent venous infusion therapy with prostaglandins. In this subgroup perfusion MR did not reveal regional perfusion defects. Only one patient had diabetes, 8 had hypercholesterolemia and 6 had hypertriglyceridemia.

## Discussion

These results indicate that a pulmonary involvement occurs both in limited and in diffuse cutaneous SSc patients and develops, in 83% of the cases, without any regional lung perfusion abnormality, while a cardiac involvement is detected in 65% of the cases.

The results of the pulmonary studies confirm the reduction of the  $DL_{CO}$ , which is always present, as the most sensitive and common abnormality among lung function tests in SSc. It is known that the reduction of  $DL_{CO}$  may precede the beginning of symptoms (8, 13), but it may also correlate with the presence of dyspnea and with the extent of diffuse interstitial fibrosis in post-mortem studies. Only two patients showed the characteristic restrictive pattern (18) suggesting a natural history of progressive pulmonary volume loss associated with superimposed infectious and emphysematous structural modifications, in accordance with functional respiratory tests and conventional radiographic findings.

This development is likewise confirmed by HRCT, which in our study yielded findings within the range of normality in 7 patients. In our patients with reduced  $DL_{CO}$ , HRCT proved to be useful both in the early detection of interstitial disease and in the evaluation of active pulmonary disease.

The detection of alveolitis using HRCT, although sensitive, does not retain a high specificity. In SSc patients

with evidence of ground glass opacity a bronchoalveolar lavage (5, 14), that can demonstrate the presence of an increased percentage of polymorphonucleates (>3%) and/or eosinophils (>2.2%) in the lavage fluid, or a pulmonary biopsy is therefore recommended.

In the patient with exertional dyspnea and declining  $DL_{CO}$ , HRCT showed an increase of pulmonary parenchymal density that was more evident in the basal portions of the inferior lobes due to thickening of the intralobular and interlobular interstitium with an associated ground glass alteration. Perfusion MRI showed a significant correlation with the latter, with an increase of the perfusion of the right inferior lobe documented by the relative intensity / time curve, indicating regional hyperemia (Figure 3B).

The association of these findings may provide strong support for the non-invasive diagnosis of an active inflammatory disease and contribute to the early institution of a therapy aiming at the stabilization or prevention of the deterioration of the respiratory function and of the fibrosis with its progressive sequelae (17, 26).

Our lung perfusion MR results are consistent possibly with a lack of detection, or with the absence, of regional vasoconstrictive phenomena in the pulmonary vasculature. These data need to be interpreted with caution for two reasons. First of all, SSc lung involvement might consist of a generalized disease process resulting in diffusely and uniformly reduced regional blood flow. More remarkably, the pulmonary vascular capacity can accommodate normal resting blood flow despite abnormal vascular tone and remodeling through the recruitment of vessels that are normally closed when at rest, at least until the recognized excess capacity of the vascular bed is lost due to the advancing disease process. As a matter of fact, the hypoperfusion of the left inferior lobe associated with interstitial densitometric irregularities suggested the presence of organic alterations of the vasculature in one case and a condition of diffuse reduction of lung perfusion in another. The latter was correlated with normal HRCT and chest X-ray findings, and was observed in a patient with hypertensive and diabetic cardiopathy with a diastolic dysfunction of the left ventricle. Overall, in 82% of the patients no regional lung perfusion abnormality was observed. However all these 15 SSc patients were symptomatic for digital Raynaud's phenomenon, had microvascular abnormalities in the nail folds documented by wide-field microscopy, had a reduction of  $DL_{CO}$ , 4 of them had a sPAP greater than 30 mmHg found by Doppler echocardiography and, most remarkably, 8 of them had abnormal HRCT findings.

These data argue against the primary pathogenic role of the hypothesized vasospasm, a potentially reversible mechanism which is the target of the most current therapy for pulmonary hypertension (3, 8). Previous authors have

described the favorable effects of an aggressive treatment of pulmonary hypertension secondary to connective tissue diseases using intravenous steroids or cyclophosphamide; other authors randomized patients with systemic lupus erythematosus with sPAP greater than 30 mmHg to cyclophosphamide or enalapril and found significant hemodynamic and symptomatic improvement among those receiving cyclophosphamide but no benefit with enalapril, suggesting that active inflammation is the target for the management of pulmonary hypertension in systemic lupus erythematosus and diffuse cutaneous SSc (2, 6, 8, 10, 17). These observations indicate an ancillary role of the vasospasm while suggest inflammatory mediators, persistent endothelial dysfunction and growth factors dysregulation as the origin of pulmonary vascular remodeling which, according to our data, seem to occur early in the scleroderma spectrum of diseases (8).

Our study had some limitations. No invasive diagnostic test was performed for the definition of both cardiac and pulmonary damage, and the administration of drugs that were considered to be necessary for the patients was continued regardless of the schedule of the diagnostic exams.

Although such limitations exist, our results confirm that chest HRCT (15) is considerably more sensitive than traditional chest radiography (59% versus 28%) (Figure 1) for the detection of SSc lung involvement, while lung perfusion MR should be considered as a complementary method which should be employed just for specific questions. In our study, the hypothesis of an active inflammatory alveolitis with a ground glass appearance on HRCT found confirmation in the MR finding of a regional hyperemia (Figure 4B). Furthermore, the extremely rare observation of a segmental hypoperfusion does not support the hypothesis of a frequent occurrence of regional vasoconstrictive phenomena in the pulmonary vasculature. The segmental defect we observed was probably correlated to structural vascular modifications occurring in the context of an interstitial pulmonary disease in an elderly patient with a long history of SSc (Figure 3D).

A range of noxious events including myocardial ischemia, fibrosis and pressure overload may be responsible for a cardiac involvement detected in 65 % of the cases and clinically overt for ventricular dysfunction and arrhythmias.

In a recent study, Nakajima *et al.* (12) evaluated the diastolic function of SSc patients as a sign of subclinical myocardial fibrosis. These Authors described the presence of diastolic dysfunction in the absence of ischemic myocardial damage in more than half of the patients. Our results are concordant and demonstrate a diastolic dysfunction in 55% of the patients. Since in 82% of the cases this functional alteration was present in patients with systemic arterial hypertension, this anomaly cannot be considered as an indicator of cardiac structural modification caused by the

main disease. Diastolic dysfunction can thereby be considered a sign of fibrotic remodeling of the left ventricle, a subclinical expression of SSc, in only 18% of the patients.

It is worth highlighting the critical significance of some clinical and laboratory markers of cardiac involvement. The presence of angina pectoris with electrocardiographic and scintigraphic ischemic changes, the presence of severe regional wall motion abnormalities and the occurrence of complex arrhythmias seem to be associated with poor prognosis.

Although limited by the small size of the study group, our results suggest the usefulness of the above mentioned techniques and parameters in order to assess the severity of the organ damage, and then choose treatment for SSc patients.

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