Predictive value of serum III procollagen for diagnosis of pulmonary involvement in patients with scleroderma


ABSTRACT: High resolution computed tomography (HRCT) was recently demonstrated to be as good as open lung biopsy for the diagnosis of pulmonary involvement in patients with scleroderma. Nevertheless, in view of its price and related irradiation, HRCT cannot be recommended as a screening test. Serum III procollagen (sPIIINP) is an aminopropeptide of type III collagen, which is released during conversion into collagen by specific proteases. Increased levels of sPIIINP have been observed in patients with scleroderma. The aim of the present study was to assess the relationship between sPIIINP measurement and pulmonary involvement defined according to HRCT and pulmonary function tests (PFT) with single-breath carbon monoxide transfer capacity (TL,CO) in 28 patients suffering from scleroderma.

Patients were divided into two groups for analysis, Group A comprising 16 patients without pulmonary scleroderma and Group B comprising 12 patients with pulmonary scleroderma. All patients had stable cutaneous disease and normal renal and hepatic function. The level of sPIIINP was determined by radioimmunoassay (RIA-gnost P-III-P, Prod. Nr. OD MT; Behring, Marburg, Germany).

Mean±SD sPIIINP level in Group A was 0.85±0.21 U·mL⁻¹. Individual values ranged 0.6–1.3 U·mL⁻¹. Mean±SD sPIIINP value was 1.30±0.40 U·mL⁻¹ in Group B and individual values ranged 0.7–1.9 U·mL⁻¹. The difference in mean sPIIINP level between Group A and Group B was significant. Using a cut-off at 1.1 U·mL⁻¹, sensitivity of sPIIINP was 0.66, specificity 0.94, positive predictive value 0.89, negative predictive value 0.79, false positive rate 0.06, and false negative rate 0.33. The value of sPIIINP correlated with HRCT score but not with PFT.

This study confirms the relationship between sPIIINP and scleroderma with interstitial lung disease. We suggest that sPIIINP could be measured in patients with scleroderma to screen those patients requiring HRCT. Further studies are necessary to determine the value of sPIIINP in terms of prognosis and follow-up of patients under treatment.


Lung parenchymal involvement occurs in 70% [1] to 100% [2] of patients suffering from scleroderma. It constitutes a worsening factor of the disease. Early detection is essential, so that patients can then be protected from tobacco and aeroccontaminants and immunosuppressive treatment considered [3]. Open lung biopsy has long been the “gold standard” technique for assessment of pulmonary involvement in scleroderma. High resolution computed tomography (HRCT), which is clearly superior to chest radiography for detection of minimal parenchymal disease [4], was recently demonstrated to be as good as open lung biopsy, with the advantage of imaging the whole of the lungs [5]. Moreover, HRCT data was shown to have a prognostic value both in patients with cryptogenic and scleroderma fibrosing related alveolitis [6, 7]. Single-breath carbon monoxide transfer capacity (TL,CO) is also a sensitive and non-invasive test for detecting interstitial injury [8].

HRCT and pulmonary function tests (PFT), including TL,CO, could therefore be proposed as reference tests for assessment of pulmonary involvement in every scleroderma patient. Nevertheless, the cost of HRCT, and the related irradiation of patients [9] would be a disadvantage. A cheaper test without potential side-effects is necessary to screen patients in whom HRCT is necessary. Nuclear medicine techniques, such as gallium scintigraphy [10], diethylene triamine penta-acetate (DTPA) scintigraphy [11] or J001X scintigraphy [12], cannot be considered as screening tests because they are based on administration of gamma-emitters. Histologically, pulmonary lesions of scleroderma are characterized by alveolar and interstitial injury followed by collagen infiltration [13]. Serum III procollagen (sPIIINP) is an aminoproppeptide of type III collagen, which is released during conversion into collagen by specific proteases [14]. Increased levels of sPIIINP have been observed in patients with scleroderma [15]. The increase in sPIIINP seems to be correlated with disease activity assessed by skin

*Service de Médecine Intérente, **Département des Maladies Respiratoires, Unité d’Evaluation Clinique, *Service de Médecine Nucléaire, **Service de Radiologie, CHU Bretonneau, Tours, France.

Correspondence: E. Diot

Service de Médecine Intérente

CHU Bretonneau

2 bis Boulevard Tonnellé

37044 Tours cedex

France

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involvement or deterioration of internal organs [14, 16]. The aim of the present study was to assess the relationship between sPIIINP measurement and pulmonary involvement, defined by association of HRCT and PFT abnormalities, in 28 patients suffering from scleroderma.

Methods

Study population

Twenty-eight patients suffering from scleroderma, admitted consecutively to our institution with or without clinical respiratory signs were included in this study between October 1990 and March 1993. Scleroderma was defined according to the American Rheumatism Association criteria [17]. Ages ranged 31–81 yrs (mean 54 yrs). Time from diagnosis to beginning of the study ranged 1 month to 37 years (mean 12 yrs). Twenty-six patients were nonsmokers and one patient had stopped smoking 3 years previously. One patient was a current smoker (8 pack-yrs). None of the patients had a recent past history or signs of respiratory infection at the time of the study. Three patients (Nos. 17–19) with known pulmonary fibrosis required continuous oxygen therapy. The extent of cutaneous disease was classified according to König et al. [18]: acroscleroderma (17 patients), and proximal ascending scleroderma (11 patients). All patients had stable cutaneous disease and normal renal and hepatic function. Treatment included: corticosteroids (2); nonsteroidal anti-inflammatory drugs (2); calcium channel blockers (25); Factor XIII (15); and/or normal

Pulmonary function tests (PFT). Forced inspiratory and expiratory flow volume curves and absolute lung volumes were measured in a constant pressure volume plethysmograph Sensor Medics 28000 (USA). A 10 s single-breath carbon monoxide transfer (TLCO) test Morgan (UK) was carried out. Results of forced expiratory volume in one second (FEV1), vital capacity (VC), total lung capacity (TLC) and TLCO were expressed as percentage of normal value [19, 20], and considered to be decreased, as in a previous study [12], when they were less than 85% of normal values.

Computed tomographic (CT) scanning. All patients underwent posteroanterior and lateral chest radiography and all patients except one underwent HRCT scan with a Somatom HIQ CT scanner; patient No. 18 was unable to maintain apnoea and could not undergo HRCT. Two millimetre thick slices performed at the end of inspiration were obtained from apex to base at intervals of 100 mm on a 512 × 512 matrix. Prone sections were obtained when false positive results were suspected on supine sections due to gravity-dependent perfusion. Images were reconstructed with a high resolution algorithm and were viewed with a window level set for optimal imaging of the lung (level 400–500, width 1,600 Hounsfield units (HU)). Chest radiography and HRCT were read by two independent radiologists blind to the results of other tests. Interstitial involvement was assessed on chest radiography based on appearance of a reticulon pattern and/or honeycombing [4]. On HRCT, the presence and extent of honeycombing, subpleural cysts, septal or subpleural lines, irregular pleural margins and ground-glass appearance were considered, to assess interstitial lung disease according to previous studies [7, 21]. A HRCT score from 0 to 30, according to the severity and extent of the disease, was determined for each patient as described previously [21]. The scores defined by the two radiologists, and compared by linear regression analysis, were well correlated (y=0.96 x ± 0.69; r=0.97). In nine cases, there was minimal disagreement between the readers corresponding to 1 point in four cases, 2 points in two cases, and 3 points in three cases. Agreement was obtained after a third common reading, and these final results were used for further analysis.

Serum III procollagen (sPIIINP). Patients’ sera were assayed with a commercially available radioimmunoassay kit (RIA-gnost P-III-P, Prod. Nr. ODMT; Behring, Marburg, Germany) based on the method described by Rhode et al. [22]. This is an immunoradiometric assay (IRMA), which measures the N-terminal propeptide formed in the same proportion as procollagen III. The IRMA technique uses two monoclonal antibodies, highly specific for procollagen III peptide Col I–3, that do not display any cross-reactions with other collagen types. This assay can be performed reliably and rapidly in two steps. In step 1 (2 h) the procollagen III peptide Col 1–3 is specifically bound by the antibody coated on the tubes; and in step 2 (3 h) the tracer antibody is attached to the bound procollagen III peptide. The coated tube technique permits clean and rapid separation of the bound from the nonbound phase.

The precision profile was determined from 220 standards assayed in duplicate. Intra- and interassay coefficients of variation ranged 1–7%. The detection limit of the method was 0.1 U·mL–1. Reference values established in the laboratory ranged 0.3–1 U·mL–1 according to Behring specifications. Levels of sPIIINP were measured in a control group, including 38 subjects submitted to screening tests as part of an occupational medicine survey (13 males aged 30–65 yrs, and 25 females aged 26–65 yrs). Levels of sPIIINP ranged 0.5–1.0 U·mL–1 (0.8±0.1 U·mL–1, mean±sd).

Values > 1.1 U·mL–1 were considered to be abnormal in our patients, who were assayed in duplicate. Reproducibility of the results was assessed by repeating measurements in six patients over a 1 year period.

Analysis of results

Patients were considered to have pulmonary scleroderma when they had at least two positive signs on HRCT associated with PFT abnormalities, i.e. decrease in TLCO and/or decrease in TLC, without any event other than scleroderma in their medical history. In contrast, patients were considered to have no pulmonary scleroderma involvement when they had no sign on HRCT and/or normal TLCO with normal TLC.
Patients were divided into two groups for analysis, Group A comprising patients without pulmonary scleroderma, and Group B comprising patients with pulmonary scleroderma. Results of sPIIINP values were available for all patients in both groups. To assess the normal value of sPIIINP, we reproduced the method used by Pohl et al. [23] based on a receiver operating characteristic (ROC) curve. A decision matrix was constructed to determine predictive value of sPIIINP measurement in pulmonary involvement: sensitivity, specificity, positive and negative predictive values, false positive and false negative rates were calculated. Mean values and standard deviation of sPIIINP were also calculated according to the two stages of cutaneous extent of scleroderma. Comparisons between these two stages were made using one-way analysis of variance (ANOVA). Mean value and standard deviation of sPIIINP measurement was determined in each group. Groups A and B were compared in terms of sPIIINP using Kruskal-Wallis test. To assess correlation between sPIIINP and reference tests, sPIIINP results were correlated with HRCT score and with PFT (FEV1, VC, TLC and TLCO) in the whole study group using Spearman rank test.

**Results**

In Group A there were 16 patients (Nos. 1–16) without pulmonary scleroderma (table 1), and in Group B 12 patients (Nos. 17–28) with pulmonary scleroderma (table 2). There was no significant difference between the two

### Table 1. – Patients Nos. 1–16 with no pulmonary involvement (Group A)

<table>
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<tr>
<th>Patient No.</th>
<th>Cutaneous extension</th>
<th>HRCT abnormalities</th>
<th>HRCT score</th>
<th>sPIIINP U/mL¹</th>
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<td>Proximal sclerosis</td>
<td>Irregular pleural margins</td>
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<td>Septal lines</td>
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<tr>
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<td>Irregular pleural margins</td>
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</tr>
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</tr>
<tr>
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<td>Septal lines</td>
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</tr>
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</table>

sPIIINP: serum III procollagen; HRCT: high resolution compared tomography.

### Table 2. – Patients Nos. 17–28 with pulmonary involvement (Group B)

<table>
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<tr>
<th>Patient No.</th>
<th>Cutaneous extension</th>
<th>PFT</th>
<th>HRCT abnormalities</th>
<th>HRCT score</th>
<th>sPIIINP U/mL¹</th>
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<td>Decrease in TLCO</td>
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<td>Irregular pleural margins, ground-glass appearance, septal lines</td>
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<td>Decrease in TLCO</td>
<td>Subpleural lines, septal lines</td>
<td>8</td>
<td>1.3</td>
</tr>
<tr>
<td>21</td>
<td>Acroscleroderma</td>
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<td>Honeycombing, septal lines, irregular pleural margins</td>
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<td>Decrease in TLCO</td>
<td>Honeycombing, ground-glass appearance, subpleural lines</td>
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<td>1.6</td>
</tr>
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<td>Decrease in TLCO</td>
<td>Septal lines, ground-glass appearance</td>
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<td>1.4</td>
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<td>Irregular pleural margins, ground-glass appearance, septal lines</td>
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PFT: pulmonary function tests; TLCO: single-breath carbon monoxide transfer test. For further abbreviations see legend to table 1.
groups regarding age, treatment and tobacco consumption. Chest radiography was normal in all patients in Group A and revealed interstitial involvement in 7 of the 12 patients in Group B (Nos. 17–19, 21, 22, 24, 26). Levels of sPIIINP are presented in figure 1. The level of sPIIINP was 0.85±0.21 U·mL⁻¹ (mean±sd) in Group A. Individual values ranged 0.6–1.3 U·mL⁻¹. Fourteen

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<th>VC L</th>
<th>% pred</th>
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<th>% pred</th>
<th>TLC L</th>
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<th>mL·min⁻¹·mmHg⁻¹</th>
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Table 3. – Pulmonary function results

FEV\(_1\): forced expiratory volume in one second; TL\(_{CO}\): single-breath carbon monoxide transfer test; VC: vital capacity; TLC: total lung capacity; % pred: percentage of predicted value.
SPIIINP: serum III procollagen.

Results and Discussion

Sensitivity and specificity of sPIIINP were calculated for various limits of sPIIINP (U·mL⁻¹) in the range 0.7–1.25 step 0.05. Best limit is given by the curve point from which the false positive rate increases more than sensitivity, i.e., 1.1 U·mL⁻¹. ROC: receiver operating characteristic; sPIIINP: serum III procollagen.

 confirming that this value corresponds to the best sensitivity and specificity ratio. Using this 1.1 U·mL⁻¹ limit for sPIIINP normal value, sensitivity was 0.66, specificity was 0.94, positive predictive value 0.89, negative predictive value 0.79, false positive rate 0.06 and false negative rate 0.33.

Discussion

This study demonstrates a relationship between sPIIINP levels and pulmonary involvement in patients suffering from scleroderma.

Diagnosis of pulmonary involvement was established on HRCT and PFT criteria. The superiority of HRCT over chest radiograph for detection of minimal parenchymal disease, as previously reported [4], was confirmed in our study: five patients of Group B had normal chest radiograph. The diagnostic [5] and prognostic [6, 7] values of HRCT have recently been demonstrated for the assessment of pulmonary scleroderma, and HRCT is the method of choice for assessing lung damage in scleroderma [24]. It would, therefore, have been ethically questionable to submit these patients to open lung biopsy. Nevertheless, the specificity of some HRCT signs, such as septal thickening and subpleural linear opacity, is controversial when they are isolated. Scleroderma is known to induce vascular damage, which can itself induce reduction of TlCO which is, therefore, not specific of parenchymal involvement, when isolated. Therefore, association of at least two positive signs on HRCT and PFT, i.e., decrease in TlCO and/or a restrictive syndrome, without any pulmonary event other than scleroderma in the medical history, was required to specifically define pulmonary involvement. Among the three patients with clinically obvious and severe pulmonary involvement characterized by dyspnoea, crackles and severe hypoxaemia, patient No. 18 was unable to maintain apnoea and could not undergo HRCT. All other patients had, by definition, both HRCT and PFT abnormalities.

Collagen is synthesized in a precursor form as procollagen during fibrotic processes. After secretion of the molecule into the extracellular space, the N- and C-terminal procollagen peptides are cleaved off. They then act as feedback inhibitors [25]. Serum III procollagen is a precursor of type III collagen and its serum measurement has been shown to increase during fibrosis of various tissues and diseases, e.g., chronic active hepatitis and liver cirrhosis [26, 27]. Renal failure has also been reported as a possible aetiology of increased sPIIINP [28]. Several radioimmunoassays derived from the first technique described by Rhode et al. [22] are available commercially to assess the predictive value of sPIIINP for pulmonary involvement in patients with systemic scleroderma. The RIA-procollagen-III-peptide (FAB) assay system measures only the N-terminal fragment of sPIIINP, representing a small fraction of the total pool of this metabolite, using polyclonal antisera specific for amino-terminal type III procollagen raised in rabbits [29]. Its level in the blood depends on the rates both of entry and removal. The IRMA technique that we employed in our study (RIA-gnost-PIIIP) uses specific monoclonal antisera recognizing only the N-terminal propeptide Col 1–3 formed in equimolar proportion to collagen type III. This procollagen III peptide Col 1–3 can be broken down by proteolysis into Col 1 fractions, which are not detected in the serum with this technique. On the other hand, the FAB assay system recognizes both the N-terminal propeptide Col 1–3 and Col 1. The RIA-gnost-PIIIP technique is, therefore, considered to be the most specific to assess sPIIINP value.

The increase in sPIIINP during scleroderma correlates with the cutaneous course of the disease and is also suspected of being associated with pulmonary involvement [14–16]. However, this relationship with lung disease has not been demonstrated. Indeed, previous studies [14–16] focused on cutaneous disease and did not include HRCT imaging of the lungs. Histologically, the occurrence of pulmonary fibrosis is associated with an increase in collagen III in the extracellular matrix [30], mainly during its early phase [31]. Procollagen III, as precursor of type III collagen, is produced by pulmonary fibroblasts and is, thus, potentially a marker of fibroblast activity [28]. Increased levels of type III N-terminal propeptide have been observed in the sera of patients with pulmonary fibrosis [32] and sarcoidosis [23]. Our patients had stable cutaneous disease and there was no difference in mean values of sPIIINP between patients belonging to the two cutaneous stages, i.e., acroscleroderma and proximal ascending scleroderma. All patients had normal liver and renal function.

We aimed to assess the predictive value of sPIIINP for detection of pulmonary scleroderma in patients under their current treatment, which included corticosteroids in two cases and colchicine in four cases. Steroids can depress collagen synthesis [33]. Of the two patients treated with corticosteroids, one belonged to Group A (patient No. 8) and had a normal sPIIINP level (1.0 U·mL⁻¹) and one belonged to Group B (patient No. 17), and had an increase in sPIIINP (1.7 U·mL⁻¹). There have not yet been studies demonstrating an effect of colchicine on
procollagen metabolism. Two of the patients treated with colchicine belonged to Group B (patients Nos. 17 and 20) and had high levels of sPIIINP (1.7 and 1.3 U·mL$^{-1}$, respectively). The two remaining patients (patients Nos. 5 and 7) belonged to Group A and were among those patients with the highest sPIIINP levels (1.1 and 0.9 U·mL$^{-1}$, respectively). We believe that there was no bias in our study and, by comparing our groups of patients with and without pulmonary involvement, we demonstrated the effect of pulmonary involvement on sPIIINP. The sPIIINP value was significantly greater in the group of patients with pulmonary scleroderma than in the group of patients without pulmonary involvement ($p<0.0001$). Both positive predictive value and specificity were high in relation to the reference values that had been established from a ROC curve. The level of sPIIINP correlated with HRCT score but with none of the FFT parameters (FEV$_1$, VC, TLC and TLCO). This discrepancy supports the hypothesis of a predictive value of sPIIINP to detect early lung parenchymal abnormalities in scleroderma.

Several recent studies have demonstrated the value of HRCT to assess the diagnosis and prognosis of pulmonary involvement during scleroderma [5, 7]. Nevertheless, in view of its financial cost and related irradiation, HRCT cannot be considered as a screening test. We suggest that sPIIINP should be measured in patients with scleroderma to screen those patients requiring HRCT. Further studies are necessary to determine the value of sPIIINP in terms of prognosis and follow-up of patients under treatment.

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**References**


