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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1990

Link to publication in University of Groningen/UMCG research database

Pulmonary Diffusing Capacity Disturbances Are Related to Nailfold Capillary Changes in Patients with Raynaud's Phenomenon with and without an Underlying Connective Tissue Disease

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PURPOSE: The aim of this study was to evaluate whether pulmonary microvascular damage is part of a more generalized involvement of the microvasculature in the spectrum of scleroderma (Scl)-like syndromes.

PATIENTS AND METHODS: We studied four groups of patients, all with Raynaud's phenomenon (RP), distinguished by the extent and nature of their underlying connective tissue disease. Twenty-two patients had primary RP (pRP), another 22 patients had RP and an undifferentiated connective tissue disease (uCTD), 15 patients had Scl, and eight patients had the CREST syndrome (CREST). Pulmonary vascular damage in these groups was assessed by measuring the pulmonary diffusing capacity $(T_{L,CO})$ and its components: the diffusing capacity of the alveolocapillary membrane (Dm) and the pulmonary capillary blood volume (Vc). Results were compared with morphologic abnormalities of the nailfold capillaries, as determined by nailfold capillary microscopy, and related to the presence of antinuclear antibodies.

RESULTS: Vc was below normal in 38% and 43% of patients with pRP and uCTD, respectively (versus 52% in patients with Scl or CREST combined). In contrast, Dm was below normal in only 5% and 26% of patients with pRP and uCTD, respectively (versus 61% in patients with Scl or CREST combined). In patients with Scl and CREST, Dm was significantly decreased as compared with the former groups (p <0.01). Dm was also the pulmonary function parameter that correlated most strongly with both nailfold capillary abnormalities and the presence of antinuclear antibodies, whereas Vc did not.

CONCLUSION: Early pulmonary involvement in Scl syndromes is functionally characterized by a lowered Dm, correlating with morphologic changes of the nailfold capillaries. Decreased Vc is probably a reflection of RP of the pulmonary vasculature.

Raynaud's phenomenon (RP) can be defined as the intermittent symmetric occurrence of pallor, cyanosis, and rubor of the fingers during or after exposure to cold [1]. The clinical significance of RP in any patient includes the possible presence or development of an underlying connective tissue disease. One of the connective tissue diseases most frequently observed in patients with RP is scleroderma (Scl). Fifty percent to 70% of patients with Scl present with RP [2,3], but it is not possible to predict which individual patient with RP will develop Scl. It has been shown, however, that the presence of antinuclear antibodies in a patient with RP is a substantial risk factor for the future development of Scl. More specifically, anticentromere antibodies are considered predictive for limited cutaneous Scl including the CREST syndrome, whereas antibodies against topoisomerase I are predictive for diffuse Scl [4–8]. Characteristic morphologic changes of the nailfold capillaries, as studied by nailfold capillary microscopy, are another early manifestation of connective tissue disease [9–11]. The occurrence of immunologic and vascular abnormalities early in the development of the disease suggests that immunologically mediated vascular damage plays an important role in the pathogenesis of Scl [12–15]. Results of follow-up studies on patients with RP and early connective tissue disease show a slow progression toward definite connective tissue disease in many patients [16,17]. This indicates that studying patients with RP, especially those with antinuclear antibodies and nailfold capillary abnormalities, may enable us to monitor the early progression to Scl and may reveal clues as to the pathophysiologic mechanisms underlying its development.

In Scl, immunologically mediated vascular damage may explain its manifestations in several organ systems, including the lungs [18,19]. Pulmonary involvement in Scl is functionally characterized by impaired carbon monoxide diffusing capacity $(T_{L,CO})$ and restrictive lung function abnormalities. It has been reported to occur in up to 85% of patients with Scl [20], and it is becoming the most important cause of death in patients with Scl as the management of renal involvement is improving [21]. Vascular damage to the lungs may eventually result in pulmonary fibrosis through a perivascular interstitial inflammatory response accompanied by excessive formation and deposition of collagen [13]. An assessment of pulmonary vascular and interstitial changes can be obtained by measuring $T_{L,CO}$ and its two components, the diffusing capacity of the alveolocapillary membrane (Dm) and the pulmonary capillary blood volume (Vc). Dm reflects the physical component of diffusion through all

membranes and tissue layers between the alveolar air and the hemoglobin in the red blood cells in the pulmonary capillaries. Vc is determined by the reaction rate of carbon monoxide with hemoglobin and by the hemoglobin concentration, and therefore represents the volume of blood in the pulmonary capillaries.

In the current study, we investigated whether pulmonary microvascular damage is part of a more generalized involvement of the microvasculature in the spectrum of Scl-like connective tissue syndromes. We studied four groups of patients, distinguished by the nature and extent of their underlying connective tissue disease (primary RP, RP and undifferentiated connective tissue disease [uCTD] [22], RP and Scl, and RP and the CREST syndrome). These groups may represent stages of one disease spectrum, ranging from RP without any other signs of a connective tissue disease, through RP accompanied by symptoms of a connective tissue disease, to Scl and its variant, the CREST syndrome. To evaluate whether pulmonary involvement is an expression of a more generalized immunologically mediated vasculopathy, we related the components of $T_{1,CO}$ to the capillary pattern observed by nailfold capillary microscopy and to the presence and specificity of antinuclear antibodies.

PATIENTS AND METHODS

Patients

All patients with RP seen at the division of Vascular Diseases are involved in ongoing studies on the early detection of a connective tissue disease [4,11,15,23]. During 1987 and 1988, 67 consecutive patients with RP with or without a connective tissue disorder (41 women and 26 men, mean age 46.9 years, range 23 to 77), were studied. Exclusion criteria were: (1) use of drugs known to induce RP; (2) large vessel obstructive arterial disease; and (3) a history of trauma to the vessels. In each patient, a careful history was obtained and physical examination was performed with special emphasis on the presence of signs and symptoms of a connective tissue disease. In addition, the following studies were carried out: pulmonary function testing, nailfold capillary microscopy, radionuclide transit studies of the esophagus, and chest roentgenography. Chest roentgenograms were judged independently by two observers, who were uninformed of the clinical findings, for the presence of bilateral reticulonodular patterns. Laboratory studies included standard analysis of blood and urine and serologic immunologic tests. The results of these tests were used to classify the patients into the diagnostic groups.

Diagnostic Criteria

Diagnosis of RP was based on a typical history of triphasic or biphasic symmetric episodes of discoloration of the fingers and/or toes after exposure to cold or emotional stimuli. Plethysmographic patterns during cold provocation and/or recovery [24] were used as an additional diagnostic tool. Patients with RP without any other sign of an underlying connective tissue disease were diagnosed as having primary RP (pRP). Patients with RP and other signs of a possibly underlying connective tissue disease who did not fulfill the criteria for a specific connective tissue disease were diagnosed as having an uCTD (e.g., patients having one minor criterion for Scl). The CREST syndrome was considered present if the patient had at least four of

the five signs characterizing the syndrome (i.e., subcutaneous calcinosis, RP, esophageal hypomotility, sclerodactyly, and telangiectases), always including calcinosis. All patients diagnosed as having Scl fulfilled the preliminary 1980 criteria of the American Rheumatism Association for Scl [25].

Pulmonary Function Testing

Lung volumes were obtained by helium dilution according to standardized techniques. Predicted values according to Tammeling [26] were applied. Slow inspiratory vital capacity (IVC) was measured with a standard water-sealed spirometer. Values of IVC and total lung capacity (TLC) were expressed in liters BTPS (body temperature, pressure, saturated). $T_{1,CO}$ and its components, Dm and Vc, were determined from triplicate measurements of $T_{1,CO}$ at high (88%) and low (19.2%) inspiratory oxygen concentrations, using the single-breath technique of Krogh, as modified by Ogilvie et al [27] and Cotes [28]. The $T_{1,CO}$ values, breathing air, were corrected for hemoglobin concentrations according to Cotes [28] to obtain $T_{1,CO}$ values under standard conditions. The calculation of Dm and Vc follows the equation originally devised by Roughton and Forster [29]:

$$1/T_{1,CO} = 1/Dm + 1/\theta \, [Hb]Vc,$$

where θ is the reaction rate of carbon monoxide with oxyhemoglobin at the average normal hemoglobin concentration of 14.6 g/100 mL; and [Hb] is the measured hemoglobin concentration as a fraction of normal. $T_{1,CO}$ and Dm were expressed in mmol/kPa/minute, and Vc was expressed in mL. Predicted values were taken from Cotes [28]. All pulmonary function tests were performed at room temperature, with the patient in a steady-state condition. Pulmonary function parameters were considered abnormal when below 80% of the predicted value.

Nailfold Capillary Microscopy

Nailfold capillary microscopy was performed as previously described [11]. In short, the following procedure was performed. After the hands were warmed between heating pads (40°C) for 15 minutes, we clamped the fingers of the subject to be examined in a holder under an Olympus stereozoom microscope (Olympus Optical, Tokyo, Japan) in a temperature-controlled room (24°C). The nailfolds of the left and right third and fourth fingers were examined after immersion oil had been applied to the finger to increase skin transparency. The nailfolds were then photographed with a camera attached to the microscope (**Figure 1**).

A standard protocol was used to describe capillary patterns on the photograph, qualitatively and quantitatively, for both the entire nailfold and a representative area of 5 mm. For this study, we used the number of capillary loops/5 mm, the number of enlarged loops/5 mm, and the number of giant loops/5 mm (**Figure 2**). These items have been shown to be the most relevant parameters from this protocol for distinguishing between primary and (possibly) secondary RP [11]. The photographs were judged blindly and independently by two observers. Average values of the left and right fourth fingers (or the value of the remaining finger if one of the photographs was missing or could not be evaluated) were used for the statistical analyses.
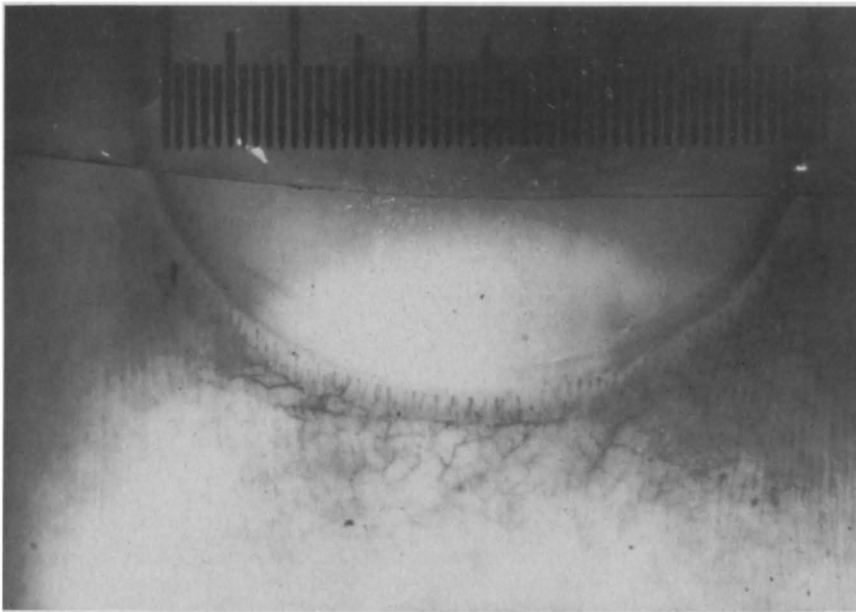
Figure 1. Photomicrograph of a nailfold of a healthy person illustrating the normal nailfold capillary pattern. Space between two small lines on the measuring bar represents 0.2 mm.
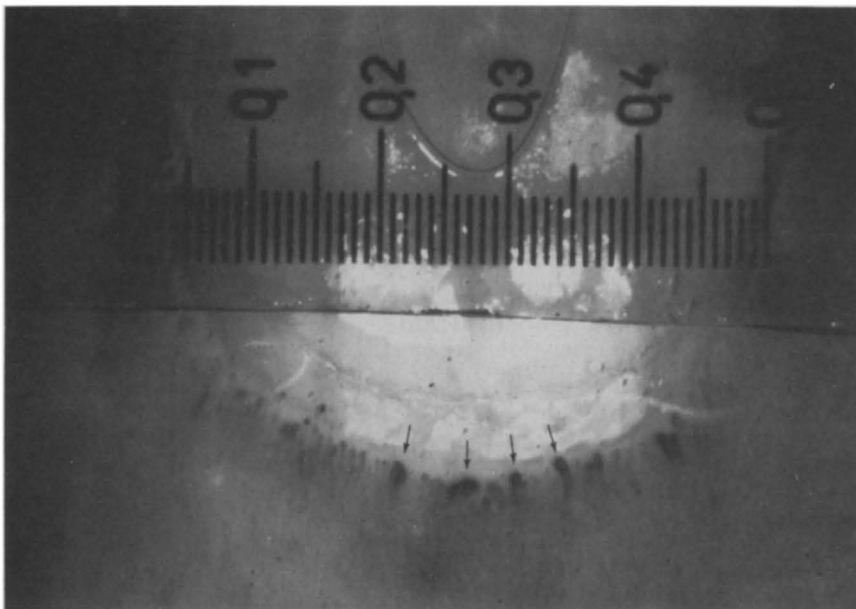

Figure 2. Photomicrograph of a typical patient with uCTD showing enlarged and giant capillary loops (**arrows**). Space between two small lines on the measuring bar represents 0.2 mm.

Immunologic Studies

Antinuclear antibodies were detected with an indirect immunofluorescence technique using human fetal fibroblast monolayers as a substrate. When a titer of 1:40 or more was present, the test was considered positive [30].

The specificities of antinuclear antibodies were determined by the immunoblotting technique as previously described [4]. Anticentromere antibodies (anti-CR-19 protein) and antibodies against topoisomerase I (Scl-70/-86) and the U1-RNP, Sm, and SS-B antigens were determined with a nuclear protein fraction from HeLa S_3 cells as a substrate. Antibodies against the SS-A and Jo-1 antigens were detected with protein blots containing cytoplasmic HeLa proteins.

Data Analysis

All data are presented as mean ± SEM unless otherwise indicated. Statistical analyses were performed us-ing the SPSS/PC+ Statistical Package. For between-group comparisons of continuous variables, one-way analysis of variance, followed by Duncan's multiple range test [31], was performed, and, when appropriate, Student's t-test or the Mann-Whitney U-test was used. For non-parametric variables, chi-square analysis was applied. Linear regression was used to calculate correlations between variables. Differences were considered significant when the null hypothesis had a probability less than 0.05. Pulmonary function values were expressed as percentages of predicted values. When required, exponential variables were transformed to a linear scale by taking the logarithmic values.

RESULTS

Patient Population

Based on the nature and extent of the underlying disease, we formed four groups of patients. Twenty-

TABLE I

Demographic, Clinical, and Laboratory Data of All Groups of Patients with RP

	pRP	uCTD	Scl	CREST	Total
Number of patients	21	23	15	8	67
Age (years)					
Mean	45.7	50.4	48.9	58.0	49.5
Range	29–75	24–68	23–76	40–77	29–75
Male/female	7/14	12/11	7/8	0/8	26/51
Positive test for ANA (number [%])	3 (14)	4 (17)	8 (53)	7 (89)	22 (33)
Esophageal hypomotility* (number [%])	0	13 (57)	11 (73)	4 (50)	32 (48)
Sclerodactyly (number [%])	0	3 (13)	12 (80)	5 (63)	14 (21)
Calcinosis of the skin (number [%])	0	0	2 (13)	8 (100)	10 (15)
Digital pitting scars (number [%])	0	5 (22)	13 (87)	5 (63)	22 (33)
Tuft resorption on hand roentgenogram (number [%])	0	2 (9)	4 (27)	2 (25)	8 (12)
Bilateral reticulonodular patterns on chest roentgenogram (number [%])	0	4 (17)	5 (33)	0	9 (13)

ANA = antinuclear antibodies.
* Abnormalities on radionuclide transit study.

one patients were diagnosed as having pRP. The second group was comprised of 23 patients diagnosed as having uCTD. Fifteen patients with Scl constituted the third group, and the fourth group was comprised of eight patients with the CREST syndrome. **Table I** shows additional demographic and laboratory data.

Pulmonary Function—Prevalence of Abnormalities of Dm and Vc

Mean pulmonary function values for all patient groups are listed in **Table II**. IVC, TLC, and $T_{1,CO}$ values were normal in all patients with pRP. In the group of patients with uCTD, abnormal values were rare, although the mean IVC value was significantly lower than in the former group. Patients with Scl had significantly lower mean scores for IVC, TLC, and $T_{1,CO}$ than patients with pRP. As compared with patients with uCTD, patients with Scl had significantly lower values of IVC and $T_{1,CO}$. CREST patients had a significantly lower mean IVC value than patients with pRP, but the mean values of IVC, TLC, and $T_{1,CO}$ did not differ from those of patients with uCTD or Scl.

Concerning the components of $T_{1,CO}$, i.e., Dm and Vc, there were no significant differences in mean values between the groups of patients with pRP and uCTD, nor between the groups of patients with Scl and CREST. Patients with Scl had lower mean Dm values than patients with uCTD, and lower mean Dm and Vc values than patients with pRP. Patients with CREST had lower mean Dm values than patients with pRP or uCTD.

We also evaluated the prevalence of abnormal pulmonary function values (below 80% of predicted values) in the diagnostic groups (**Figure 3**). A marked difference between Vc and Dm was noted. The prevalence of abnormal Dm values increased markedly from the group with pRP (5%) to the group with uCTD (26%) and again to the group with Scl and CREST combined (61%). IVC (0%, 13%, and 26%, respectively) and $T_{1,CO}$ (0%, 17%, and 48%, respectively) showed similar patterns. Vc, however, was abnormal in 38% of patients with pRP and showed only a slight increase in prevalence in the consecutive groups (43%, 52%).

Nailfold Capillary Microscopy

Nailfold capillary microscopy was performed in 65 patients. In seven of these patients, photomicrographs were not evaluable. This concerned mostly patients

with Scl and CREST, probably due to severe trophic disturbances in the fingers. Nailfold capillary microscopic scores for all patient groups are presented in **Table III**. The number of capillary loops was significantly decreased in patients with Scl and in patients with CREST as compared with patients with pRP and uCTD (p <0.01). Patients with Scl had significantly more giant loops than any of the other groups (p = 0.05), and also significantly more enlarged loops than patients with pRP and uCTD (p <0.05).

We performed linear regression analysis between nailfold capillary microscopic findings and pulmonary function values. The results of this analysis, for all patients combined, are shown in **Table IV**. IVC and Dm proved to be the parameters most strongly correlated with nailfold capillary microscopic scores of the number of loops (p <0.0005 and p <0.005, respectively), indicating an association between decreased IVC and Dm values and decreased numbers of capillaries. The numbers of enlarged and giant loops were negatively correlated with IVC and Dm (p <0.005 in all analyses), indicating an association between decreased IVC and Dm values and high numbers of abnormal capillary loops. Within diagnostic groups, there were significant correlations in the group of patients with Scl. IVC was correlated negatively with the number of giant loops (r = −0.73, p = 0.01), whereas Dm was correlated negatively with the number of enlarged loops (r = −0.69, p <0.05). Unlike Dm, no correlations were found between Vc and any of the nailfold capillary microscopic findings.

TABLE II

Mean Pulmonary Function Values of All Groups of Patients with RP*

	pRP (n = 21)	uCTD (n = 23)	Scl (n = 15)	CREST (n = 8)
IVC	105.8 ± 2.4	96.8 ± 3.7†	84.0 ± 3.1†‡	93.1 ± 2.9†
TLC	104.2 ± 2.8	100.5 ± 3.4	91.6 ± 3.8†	98.7 ± 5.5
$T_{1,CO}$	106.1 ± 3.0	100.8 ± 4.7	82.3 ± 5.4†‡	91.1 ± 7.3
Dm	103.2 ± 2.9	106.2 ± 7.3	75.9 ± 5.8†‡	74.8 ± 7.2†‡
Vc	91.6 ± 4.2	82.4 ± 5.0	76.8 ± 6.3†	92.3 ± 9.4

* Pulmonary function values expressed as percentages of predicted standard values ± standard error of the mean.
† Significantly different from pRP (p <0.05).
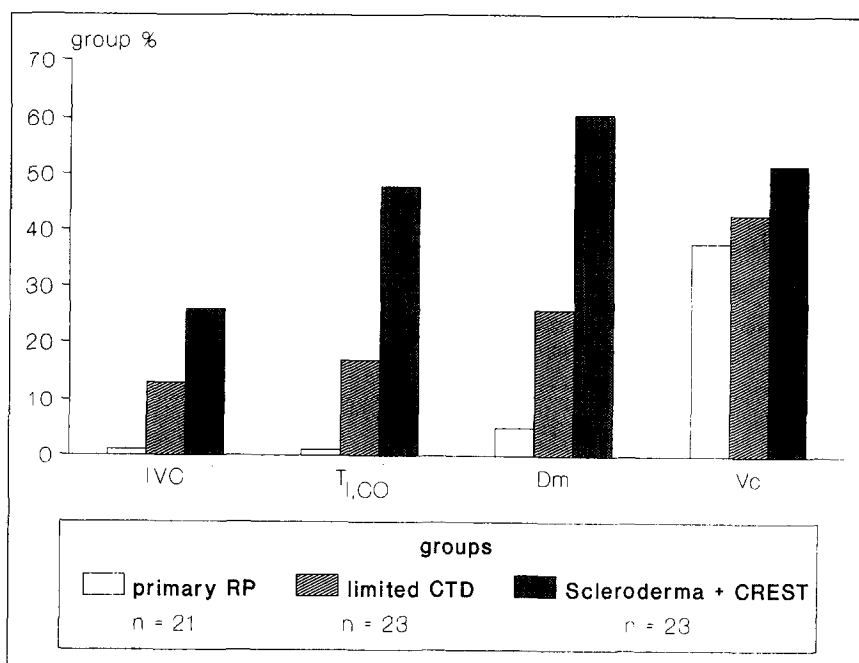‡ Significantly different from uCTD (p <0.05).

Figure 3. Prevalence of abnormal pulmonary function values in groups of patients with RP, distinguished by the nature and extent of the underlying connective tissue disease. (Y-axis: percentage of patients with abnormal pulmonary function values [lung function parameter less than 80% of predicted]; X-axis: pulmonary function parameter).

TABLE III

Nailfold Capillary Microscopic Results of All Groups of Patients with RP

	pRP (n = 20)	uCTD (n = 23)	Scl (n = 11)	CREST (n = 5)
Number of loops	43.0 ± 0.9	40.6 ± 1.8	30.1 ± 2.9†	25.4 ± 5.2†
Giant loops	0.05 ± 0.05	0.09 ± 0.05	1.10 ± 0.4‡	0.10 ± 0.10
Enlarged loops	0.40 ± 0.16	1.09 ± 0.31	3.10 ± 0.84*	1.50 ± 0.82

* Significantly different from pRP and uCTD (p <0.01).
† Significantly different from pRP (p <0.01).
‡ Significantly different from all other groups (p = 0.05).

TABLE IV

R Values of Correlations between Pulmonary Function and Nailfold Capillary Microscopy (NCM) Findings of 59 of the 67 Patients with Valid NCM and Pulmonary Function Data

	IVC	$T_{I,CO}$	Dm	Vc
Number of loops	0.46‡	0.30*	0.38†	0.01
Giant loops	−0.39†	−0.28*	−0.40†	−0.07
Enlarged loops	−0.46‡	−0.38†	−0.45‡	−0.02

Significance of R values: * p <0.05; † p <0.005; ‡ p <0.0005. See Table III for relationships between NCM findings and disease stage.

TABLE V

Specificities of Antinuclear Antibodies Determined by the Immunoblotting Techniques

	pRP (n = 21)	uCTD (n = 23)	Scl (n = 14)	CREST (n = 8)
Anti-topoisomerase	0	2	7	0
Anticentromere	0	3	1	5
Anti-U1-RNP	0	0	1	0
Anti-Jo-1	0	0	1	0
Negative	21	18	4	3

Immunologic Studies—Results and Correlations with Pulmonary Function and Nailfold Capillary Microscopy

Of all patients, 22 had a positive test for antinuclear antibodies as detected by indirect immunofluorescence. As might be expected, the prevalence of antinuclear antibodies showed a steady increase from the group of patients with pRP to the groups of patients with Scl and CREST (Table I). The distribution of the defined specificities of antinuclear antibodies is shown in **Table V**. No patient had antibodies against SS-A, SS-B, or Sm antigens. Anti-U1-RNP and Jo-1 antibodies were each present in one patient with Scl.

Because of the small number of patients with positive tests for antinuclear antibodies within the diagnostic groups, statistical analysis was restricted to comparisons between patients with and without positive tests for all groups combined (**Table VI**). The group of patients with a positive indirect immunofluorescence test for antinuclear antibodies had significantly lower mean values of IVC, $T_{1,CO}$, and Dm than patients without antinuclear antibodies. Similar differences were seen when comparing patients with an immunoblot test positive for any of the defined specificities and patients without a positive immunoblot result. Within the diagnostic groups, there was a tendency toward similar differences in pulmonary function, but these were only significant for Dm in patients with Scl and patients with CREST. Comparing patients with antibodies against topoisomerase I with patients with antibodies against CR-19, we found that the presence of anti-topoisomerase I antibodies was associated with significantly decreased IVC and TLC values, whereas the presence of CR-19 antibodies was not. Unlike Dm, no significant differences in Vc values were found in any of these comparisons.

In addition, the number of capillary loops was decreased and the numbers of enlarged and giant loops were increased in patients with a positive indirect immunofluorescent test for antinuclear antibodies as compared with patients without antinuclear antibodies (p <0.05). Accordingly, in patients with an immun-

TABLE VI

Pulmonary Function in Patients with RP with and without Antinuclear Antibodies (ANA) Determined by Indirect Immunofluorescence (IIF) and Immunoblotting

		IVC	TLC	$T_{I,CO}$	Dm
ANA (IIF)	Positive (n = 22)	90.8 ± 3.1	88.4 ± 4.3	88.4 ± 4.3	77.9 ± 4.4
	Negative (n = 45)	99.0 ± 2.4‡	101.4 ± 3.1‡	101.4 ± 3.1‡	103.0 ± 4.2*
Immunoblot	Positive (n = 20)	88.4 ± 3.6	94.4 ± 3.6	82.5 ± 4.3	71.0 ± 4.5
	Negative (n = 46)	99.7 ± 2.2†	101.0 ± 2.1	103.3 ± 2.8‡	104.6 ± 3.8*
Anti-Scl-86	Positive (n = 9)	79.7 ± 4.5	84.3 ± 2.2	80.8 ± 6.8	76.5 ± 8.6
	Negative (n = 46)	99.7 ± 2.2*	101.0 ± 3.8†	103.0 ± 2.9†	104.5 ± 3.8†
Anti-CR-19	Positive (n = 9)	96.2 ± 4.4	104.5 ± 4.3	90.2 ± 6.8	70.5 ± 6.1
	Negative (n = 46)	99.7 ± 2.2	101.0 ± 2.2	103.0 ± 2.8‡	104.6 ± 3.8*

Anti-Scl-86 = anti-topoisomerase determined by immunoblot; anti-CR-19 = anticentromere antibody determined by immunoblot.
* $p < 0.0005$.
† $p < 0.01$.
‡ $p < 0.05$.

oblot test positive for any of the defined specificities, the number of nailfold capillary loops was decreased (27.7 ± 3.0 versus 41.1 ± 1.1) and the numbers of enlarged loops (3.0 ± 0.7 versus 0.8 ± 0.2) and giant loops (1.0 ± 0.3 versus 0.05 ± 0.03; p <0.001 in all analyses) were increased as compared with patients without a positive immunoblot test for specific antibodies.

Chest Roentgenographic Examination—Correlation with Pulmonary Function and Nailfold Capillary Microscopy

Bilateral reticulonodular patterns on chest roentgenographs were present in nine of 65 (13%) patients (Table I). The presence of these abnormalities was associated with decreased mean IVC (p <0.05), $T_{1,CO}$ (p <0.01), and Vc (p <0.05) values, as well as with an increased number of enlarged nailfold capillary loops (p <0.01).

COMMENTS

In the current report, we assessed the association between the presence of impaired $T_{1,CO}$ and nailfold capillary abnormalities in patients with RP with and without a connective tissue disease. Four groups of patients were tested for pulmonary and extrapulmonary (nailfold) vascular changes. The groups, distinguished by the nature and extent of the underlying connective tissue disease, may represent stages in one disease spectrum, ranging from primary RP to RP as part of Scl or the CREST syndrome. Previous studies by our group [4,32,33] have demonstrated a temporal relationship between the several disease stages in patients with RP. These studies indicate that, indeed, transitions from one stage to the other frequently occur during follow-up of patients with RP, supporting the concept of a continuous spectrum of disease in these patients.

As a measure of pulmonary vascular changes, we used the two components of $T_{1,CO}$, i.e., Dm and Vc. As a measure of extrapulmonary vasculopathy, we used nailfold capillary microscopy. Data on alterations in Dm and Vc in patients with connective tissue disease are limited, since Dm and Vc are rarely mentioned in reports on pulmonary involvement in connective tissue disease. Emmanuel et al [34] reported seasonal fluctuations in the components of the diffusing capacity in patients with Scl. Recently, Barr and Fahey [35] measured Vc and Dm after cold challenge in patients with primary and secondary RP. They found that Vc

decreased in patients responding to cold challenge to the hands with an episode of RP, whereas Dm remained unchanged, suggesting a vasospastic reaction of the pulmonary vasculature.

We found that Vc was decreased in a high percentage of patients with pRP and uCTD (Figure 3). In addition, the prevalence of decreased Vc in these groups did not differ from that in the groups with Scl and CREST. Taking into account the findings of Barr and Fahey [35], lowered Vc values in patients with primary or secondary RP may, at least in part, be due to a vasospastic reaction of the lung vasculature at the time of investigation caused by cold challenge or emotional stress. Such a spasm, when occurring at the level of the small arteries (as in the fingers), would affect Vc without changing Dm.

Unlike Vc, Dm was altered in 5% of patients with pRP, in 26% of patients with possible connective tissue disease, and in 61% of patients with Scl and CREST combined. The increasing prevalence of an altered Dm in the successive groups may reflect an increasing extent of damage to the tissues constituting the alveolocapillary membrane. This may involve interstitial changes as well as thickening of the vascular wall. Decreased Dm, therefore, will only be accompanied by a decrease of Vc in cases in which there is extensive damage to the vascular endothelium leading to partial luminal occlusion or in cases in which there is simultaneous vasospasm. Accordingly, patients with uCTD and lowered Dm values, possibly representing an early stage of Scl or CREST, did not have significantly lower Vc values than did patients with uCTD and normal Dm values.

Another aspect should also be taken into account. Follow-up studies, as performed in our laboratory [36], on patients with testicular carcinoma treated with bleomycin, a drug that induces pulmonary vascular damage, have shown that both Vc and Dm return to normal values 2 years after treatment, Vc reaching even higher values than before treatment. The latter may indicate that recruitment of capillaries takes place, possibly in addition to actual repair of damaged capillaries. The changes in Dm after bleomycin treatment, both in terms of decrease and of recovery, are slower than those in Vc. In our patients, immunologically mediated vascular damage, unlike bleomycin damage, is likely to occur repetitively. Consecutive repair and, possibly, recruitment, will blur the pattern of reaction and may also explain in part why Vc is not progressively altered from pRP to Scl and CREST.

blur the pattern of reaction and may also explain in part why Vc is not progressively altered from pRP to Scl and CREST.

We also compared functionally defined vascular changes in the lung with morphologically defined vascular changes in the nailfold. Previous studies have shown that nailfold capillary microscopic findings in pRP are normal in most cases (high numbers of capillary loops, no enlarged or giant loops) [11], whereas abnormal findings in patients with pRP or uCTD are predictive of subsequent development of a connective tissue disease [15,16]. Pulmonary function findings in our patients with pRP were normal, except for a high prevalence of decreased Vc values. We did not find an association between decreased Vc values and decreased numbers of nailfold capillaries or any other nailfold capillary microscopic variable. On the contrary, such abnormalities were clearly associated with decreased Dm values. Assuming that vascular abnormalities, similar to those visible in the nailfolds, occur in the lungs, our data show that Dm, the physical resistance to gas exchange and therefore a reflection of the thickness of the membrane at the capillary level, is the parameter most directly correlated with changes at the same level in the nailfold. Decreased Vc values, on the other hand, can be caused by functional changes upstream of the capillaries affecting blood flow, e.g., spasm due to cold exposure or emotional stimuli.

A decrease in IVC values was also correlated with nailfold capillary microscopic abnormalities in our patient population. In patients without obstructive pulmonary disease, decreased IVC values can be a reflection of decreased pulmonary compliance due to a certain degree of pulmonary fibrosis. The strong correlation of IVC with nailfold capillary abnormalities suggests that these early fibrotic changes are caused by pulmonary vascular abnormalities. The fact that both pulmonary functional and nailfold capillary microscopic abnormalities are associated with the presence of antinuclear antibodies is compatible with a common immunologic background for these two phenomena.

The presence of bilateral reticulonodular patterns on chest roentgenograms was an infrequent finding except in the group of patients with Scl, where it was one of the diagnostic criteria. Overall, roentgenologic abnormalities were less frequent than pulmonary function alterations and were weakly yet significantly correlated. Therefore, the chest roentgenogram seems less sensitive for assessing interstitial lung involvement in connective tissue disease than pulmonary function testing, a finding corresponding with earlier studies [37,38].

The results of antinuclear antibodiy testing in this study are in accordance with previous reports [6,7]. Anticentromere (CR-19) antibodies were found to predominate in patients with limited forms of Scl and the CREST syndrome, whereas anti-topoisomerase I was found mainly in patients with more extensive disease with skin and internal organ involvement. In addition to this, we found that different specificities of antinuclear antibodies were associated with different patterns of pulmonary functional impairment. In our patients, the presence of anticentromere antibodies was associated with an isolated decrease in $T_{1,CO}$ and Dm, whereas a more general pattern of restrictive pulmo-

nary function was seen in patients with antibodies against topoisomerase I. These differences may be a reflection of the predominance of structural vascular changes (i.e., pulmonary hypertension) in the CREST syndrome as opposed to the fibrotic lesions in Scl [39].

In summary, we conclude that pulmonary involvement in Scl syndromes is functionally characterized by lowered Dm values. These alveolocapillary membrane changes are correlated with morphologic changes of the nailfold capillaries. Decreased pulmonary capillary blood volume is probably a reflection of RP of the pulmonary vasculature.

ACKNOWLEDGMENT

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