

BRIEF REPORT

## Association Between Nailfold Capillary Density and Pulmonary and Cardiac Involvement in Medium to Longstanding Juvenile Dermatomyositis

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**Objective.** To explore the associations between microvascular abnormalities as assessed by nailfold capillaroscopy (NFC) and pulmonary and cardiac involvement in patients with juvenile dermatomyositis (DM) who are assessed after medium- to long-term follow-up.

**Methods.** Fifty-eight patients with juvenile DM were examined a mean  $\pm$  SD of  $17.0 \pm 10.6$  years after symptom onset. Nailfold capillary density (NCD) and a neovascular pattern (defined as an active or late scleroderma pattern) were analyzed, with blinding to clinical data. Pulmonary involvement was assessed by pulmonary function tests including spirometry, diffusing capacity for carbon monoxide (DLCO), and body plethysmography. High-resolution computed tomography (HRCT) was also performed. Cardiac involvement was assessed by electrocardiography, Holter monitoring (heart rate variability), and echocardiography.

**Results.** Patients with low NCD (<6 capillaries/mm) ( $n = 21$ ), compared to patients with normal NCD ( $\geq 6$  capillaries/mm) ( $n = 37$ ) had lower forced vital capacity (89.7% versus 98.5% predicted), total lung capacity (87.8% versus 94.5% predicted), and more often had low DLCO values (15 [71%] of 21 patients versus 14 [38%] of 37 controls) (all  $P < 0.05$ ). Use of HRCT to assess airway disease was more frequent in the group with low NCD (6 [30%] of 20 patients versus 3 [8%] of 36 patients in the normal NCD group;  $P = 0.034$ ). No associations between NCD and cardiac parameters or between neovascular pattern and pulmonary or cardiac parameters were observed.

**Conclusion.** In patients with juvenile DM, low NCD was associated with lung involvement, which was mostly subclinical. No significant associations with cardiac involvement were observed. These results shed light on possible mechanisms underlying organ involvement, but further and preferably larger studies are needed to identify NCD as a potential biomarker for lung and cardiac involvement in juvenile DM.

### INTRODUCTION

Juvenile dermatomyositis (DM) is a rare autoimmune myopathy with a childhood origin and is characterized primarily by pathognomonic skin rashes and muscle weakness. Juvenile DM

is considered to be a multisystemic vasculopathy in which autoimmune mechanisms target small vessels. Systemic vasculopathy and the consequent microvascular remodeling might play an important role in the involvement of various organs, including the heart and lungs.

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No potential conflicts of interest relevant to this article were reported.

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## SIGNIFICANCE & INNOVATIONS

- In patients with juvenile dermatomyositis (DM) assessed after medium- to long-term follow-up, low nailfold capillary density (NCD) is associated with impaired pulmonary function tests and high-resolution computed tomography-detected airway disease.
- NCD is not significantly associated with cardiac involvement, including systolic and diastolic dysfunction, echocardiographic abnormalities, and heart rate variability.
- These findings shed light on the role of microvascular remodeling for organ involvement, but further and larger studies are needed to assign a possible role of NCD as a biomarker for organ involvement in juvenile DM.

Pulmonary involvement is a relatively infrequent complication in patients with juvenile DM and is associated with a poor prognosis (1). Interstitial lung disease (ILD) and impaired pulmonary function tests (PFTs) are the most frequent findings. Although pulmonary involvement is mostly subclinical, rapidly progressive ILD has been shown to be a major cause of death in Japanese patients with juvenile DM (2). Clinically important cardiac involvement is even more sporadic in patients with juvenile DM; however, abnormal findings assessed by electrocardiography (ECG) and echocardiography have been observed both early (3) and late (4,5) in the disease course. Notably, even if the clinical relevance of these subtle cardiac abnormalities has yet to be determined, cardiac monitoring is recommended for patients with juvenile DM (6).

Nailfold capillaroscopy (NFC) is a simple, noninvasive technique that can be used to evaluate the microvascular architecture. It has been hypothesized that NFC might be a putative biomarker in autoimmune rheumatic diseases; pilot studies in patients with systemic sclerosis (SSc) have shown associations with peripheral vascular and pulmonary involvement (7). Additionally, microvascular changes in the nailfolds are associated with pulmonary involvement (7–9) and might be predictive of future severe organ involvement in SSc (9). Patients with SSc with striking microvascular abnormalities also more frequently presented with cardiac involvement and decreased heart rate variability (HRV), although the findings are conflicting (7). In adults with DM, NFC findings were associated with pulmonary but not cardiac involvement (10,11). Of note, cardiac-related pathologies were uncommon in most of these studies (7,10). Thus, there are data suggesting that NFC may be a useful tool to investigate organ involvement in adults with rheumatic diseases; however, there are no studies addressing this issue in juvenile DM or in other pediatric rheumatic diseases.

Our group has established a cohort of Norwegian patients with juvenile DM. Patients in this cohort (which has been thoroughly described with regard to NFC [12], pulmonary involvement [13], and cardiac involvement [4,5,14]) were clinically examined after medium- to long-term follow-up. Patients showed more abnormal findings in all NFC measures compared to age- and sex-matched controls. Nailfold capillary density (NCD), low NCD (defined as <6 capillaries/mm), and neovascular pattern (defined as an active or late scleroderma pattern) were shown to be the most applicable NFC measures (12). Compared to controls, patients had smaller lung volumes and reduced gas diffusion capacity. In addition, 37% of patients showed abnormalities as assessed by high-resolution computed tomography (HRCT) (13). Moreover, in our cohort, patients had cardiac abnormalities including decreased systolic (4) and diastolic function (5), reduced HRV (14), and more ECG-detected pathologies (5) compared to matched controls.

No studies have investigated the association between NFC findings and pulmonary or cardiac involvement in patients with juvenile DM. Thus, the objective of the current study was to investigate the possible relationship between NFC and pulmonary and cardiac measures in patients with juvenile DM who were examined after medium- to long-term follow-up.

## PATIENTS AND METHODS

**Study design and cohort.** Our established Norwegian juvenile DM inception cohort consists of 60 patients in whom juvenile DM was diagnosed between January 1970 and June 2006 (15). Inclusion criteria included a probable or definitive diagnosis of DM according to the Bohan and Peter criteria, disease onset before age 18 years, ≥24 months from symptom onset to follow-up, and age at follow-up ≥6 years. Informed consent was obtained from all patients (and parents, for patients ages >16 years), and the Regional Ethics Committee approved the study (S-05144).

**Data collection and clinical and laboratory measurements.** Patients were clinically examined after a mean disease duration of 17 years. Disease onset was defined as the time of the first muscle or skin symptom, and disease duration was defined as the time from disease onset to the follow-up examination. We have previously published data on NFC in relation to general disease variables in this cohort (12), as well as data on pulmonary (13) and cardiac outcomes (4,5,14).

**NFC.** A Scalar video microscope (VideoCap; DS MediGroup) was used for NFC examinations (performed by HS) (12). The analyses were performed by ZB, who was blinded to clinical information. VideoCap 8.20 software (VideoCap; DS MediGroup) was used for image analysis. NCD

and neovascular pattern (defined as active or late scleroderma pattern) were assessed, as previously described in detail (12). The cutoff used for low NCD was <6 capillaries/mm (12). In our inception cohort, 1 patient was not examined with NFC, and 1 patient was excluded due to a limited number of available NFC recordings of good quality; thus, data for 58 patients were used for further analyses.

**Pulmonary assessment.** *PFT.* All PFT measurements, including spirometry (forced vital capacity [FVC]), measurements of gas diffusion (diffusing capacity for carbon monoxide [DLco]), and body plethysmography (total lung capacity [TLC]), were performed on a computerized Vmax pulmonary function

unit (Viasys). All spirometry variables were measured in accordance with current guidelines (13). The PFT variables were expressed as percent predicted (13). Low FVC, TLC, and DLco values were defined as less than the 5th percentile of predicted values, and PFT abnormality was defined as low TLC and/or low DLco values.

*HRCT.* HRCT was performed in 56 patients, using a LightSpeed 16 scanner (GE Healthcare). An experienced radiologist (TMA) who was blinded to clinical information read the images and scored the presence of ILD (reticular pattern with or without traction bronchiectasis, and/or ground-glass opacity), and airway diseases (bronchiectasis, and/or air trapping, and/or micronodules) (13).

**Table 1.** Characteristics and pulmonary and cardiac measures in patients with juvenile dermatomyositis, stratified by normal and low NCD\*

	All patients (n = 58)	Normal NCD (n = 37)	Low NCD (n = 21)	P
Patient characteristics				
Female	36 (62)	21 (57)	15 (71)	0.268
Age, mean ± SD years	25.4 ± 12.5	27.9 ± 12.9	19.8 ± 8.8	0.013†
Disease duration, mean ± SD years	17.0 ± 10.6	19.8 ± 10.9	12.1 ± 8.4	0.008‡
NCD, mean ± SD capillaries/mm	6.4 ± 2.1	7.7 ± 0.9	4.2 ± 1.6	NA
PFTs				
FVC, mean ± SD percent predicted	95.3 ± 12.4	98.5 ± 12.3	89.7 ± 10.6	0.008‡
Low FVC	10 (17)	4 (11)	6 (29)	0.085
TLC, mean ± SD percent predicted	92.0 ± 10.4	94.5 ± 10.9	87.8 ± 8.2	0.020†
Low TLC	14 (24)	8 (24)	6 (30)	0.600
DLco, mean ± SD percent predicted	81.6 ± 14.8	84.3 ± 16.2	76.7 ± 10.6	0.059
DLco/VA, mean ± SD percent predicted	96.2 ± 15.4	96.0 ± 17.1	96.7 ± 12.3	0.866
Low DLco	29 (50)	14 (38)	15 (71)	0.014†
PFT abnormality§	33 (57)	17 (50)	16 (80)	0.036†
HRCT				
ILD	8 (14)	5 (14)	3 (15)	0.909
Airway disease	9 (16)	3 (8)	6 (30)	0.034†
Cardiac measures				
LAS, mean ± SD percent	16.6 ± 2.5	16.3 ± 2.7	16.9 ± 2.3	0.383
e', mean ± SD cm/second	11.2 ± 2.7	11.0 ± 3.0	11.6 ± 2.1	0.433
Pathologic ECG	10 (17)	7 (19)	3 (15)	0.710
cSDNN, mean ± SD msec	39.1 ± 16.3	41.3 ± 17.1	36.8 ± 15.1	0.402

\* Values are the number (%) except where indicated otherwise. Normal nailfold capillary density (NCD) was defined as ≥6/mm; low NCD was defined as <6 mm. The following measures were missing in patients with normal and low NCD, respectively: total lung capacity (TLC) in 4 patients (3:1), high-resolution computed tomography (HRCT) in 2 patients (1:1), early diastolic tissue velocity (e') in 1 patient (1:0), electrocardiogram (ECG) in 1 patient (0:1), and standard deviation of all normal-to-normal intervals corrected to the heart rate (cSDNN) in 4 patients (4:0). PFTs = pulmonary function tests; FVC = forced vital capacity; DLco = diffusing capacity for carbon monoxide; VA = alveolar volume; ILD = interstitial lung disease; LAS = long axis strain.

† P < 0.05, normal vs. low NCD.

‡ P < 0.01, normal vs. low NCD.

§ Low TLC and/or low DLco.

**Cardiac assessment.** *Electrocardiography.* Two-dimensional and Doppler echocardiography were performed and analyzed, with the assessors blinded to patient information (4,5). Diastolic function was measured by early diastolic tissue velocity ( $e'$ ), which was recorded in the mitral ring in 2-chamber and 4-chamber views (5). Systolic function was measured by long-axis strain (LAS) (mitral annulus displacement as the percent of end-diastolic left ventricular length) (4). A lower value for early diastolic tissue velocity and LAS suggests poorer diastolic and systolic function, respectively.

**ECG.** A 12-channel ECG and 24-hour ambulatory Holter monitoring were carried out as previously described in detail (5,14). ECGs were analyzed by investigators blinded to clinical information and classified as normal or pathologic. Calculation of HRV (standard deviation of all normal-to-normal intervals corrected to the heart rate) was performed using HolterSoft Ultima version 2.44 software (Novacor) (14).

**Statistical analysis.** Differences between patients and controls were tested using Student's *t*-test for continuous and normally distributed variables and the Mann-Whitney U test for continuous non-normally distributed variables, as appropriate. Chi-square tests were used to test differences between 2 groups for categorical variables. Correlations were determined using Spearman's correlation coefficient ( $r_s$ ).

NCD is known to be dependent on age and possibly disease duration; therefore, multivariate logistic regression analysis was used to age-adjust the associations between low NCD (dependent variable) and cardiac parameters as well as HRCT findings (with age used as an independent variable). PFT variables are presented as the percent predicted; thus, values were already corrected for age.

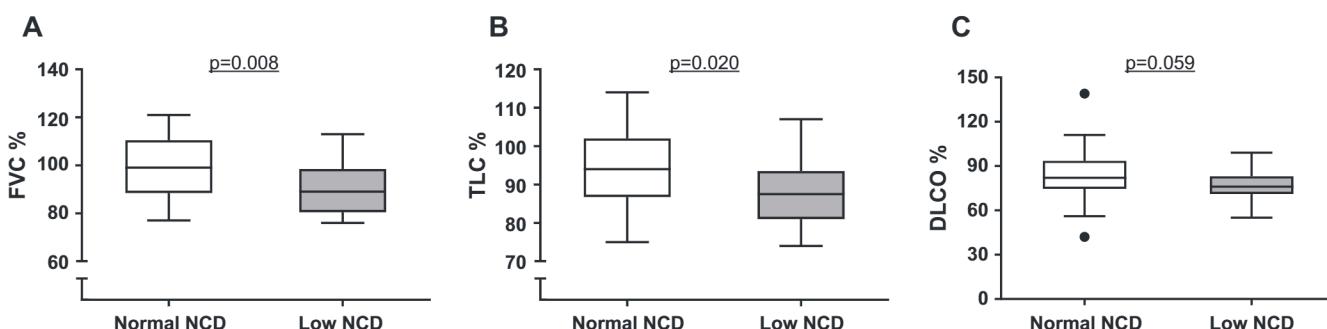
To explore the possible effect of disease duration on the association between PFT variables and NCD and low NCD, respectively, multivariate linear and logistic regression analyses were performed with disease duration and various PFT variables as independent variables. Due to a strong intercor-

relation between age and disease duration ( $r_s = 0.938$ ,  $P < 0.001$ ), both variables could not be included as independent variables in the regression analyses. Two-tailed tests were used for all calculations, and  $P$  values less than 0.05 were considered significant. Statistical analysis was performed using SPSS v.24SA. Due to the explorative nature of the study, we did not adjust  $P$  values for multiple comparisons.

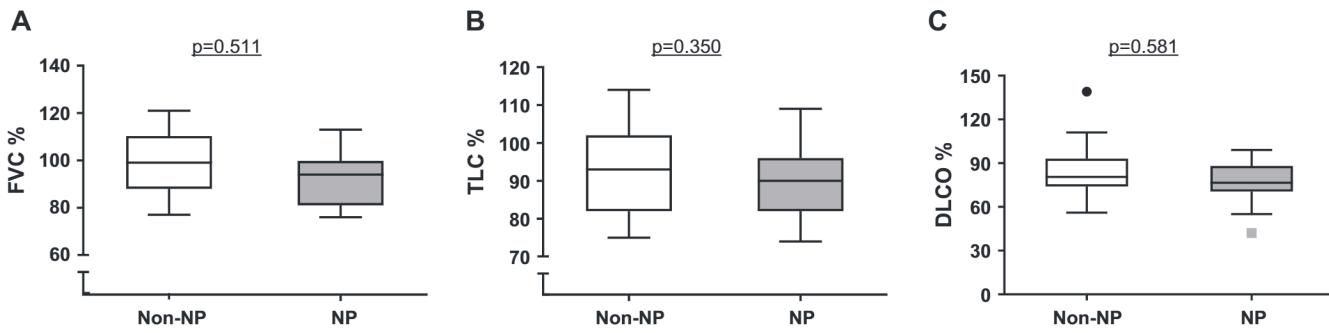
## RESULTS

The characteristics of the patients have previously been described in detail (15), and selected parameters are shown in Table 1 as background information. Of 58 patients, 21 (36%) had low NCD (Table 1), and a neovascular pattern was observed in 24 (41%) of 58 patients (12). Table 1 also shows data for selected pulmonary tests in all patients with juvenile DM patients as well as in patients with normal and low NCD. Low NCD was associated with lower FVC and TLC values (percent predicted) (Figure 1). Moreover, low NCD was associated with low DLco values (percent predicted). Signs of airway disease on HRCT were also more prevalent in the group with low NCD. There were weak-to-moderate correlations between NCD (as a continuous variable) and the following variables: FVC ( $r_s = 0.262$ ,  $P = 0.047$ ) and HRCT-assessed airway disease ( $r_s = -0.359$ ,  $P = 0.007$ ) but not with any of the other PFT or HRCT variables included in Table 1 (data not shown).

When adjusting for the association between NCD/low NCD and all PFT variables (that were already age-adjusted) for disease duration, FVC was no longer significantly associated with NCD (standardized  $\beta = 0.219$ ,  $P = 0.080$ ), but an association between TLC and NCD was observed (standardized  $\beta = 0.295$ ,  $P = 0.018$ ). Both FVC and TLC remained associated with low NCD (odds ratio [OR] 0.936,  $P = 0.18$  and OR 0.931,  $P = 0.006$ , respectively), while low DLco lost significance (data not shown). Additionally, we analyzed the differences in HRCT measures after adjusting for age; airway disease was more frequently observed in the group with low NCD than in the group with normal NCD.



**Figure 1.** Pulmonary function measures, including forced vital capacity (FVC), percent predicted (A), total lung capacity (TLC), percent predicted (B), and diffusing capacity for carbon monoxide (DLco), percent predicted (C), in patients with normal nailfold capillary density (NCD) and patients with low NCD. Data are shown as box plots (using Tukey's method). Each box represents the 25th to 75th percentiles. Lines inside the boxes represent the median. Lines outside the boxes are error bars. Circles indicate outliers.



**Figure 2.** Pulmonary function measures, including forced vital capacity (FVC), percent predicted (A), total lung capacity (TLC), percent predicted (B), and diffusing capacity for carbon monoxide (DLco), percent predicted (C), in patients with non-neovascular pattern (non-NP) and patients with NP. Data are shown as box plots (using Tukey's method). Each box represents the 25th to 75th percentiles. Lines inside the boxes represent the median. Lines outside the boxes are error bars. The circle and shaded box indicate outliers.

Table 1 also shows selected cardiac data for patients with juvenile DM as well as patients with normal NCD and those with low NCD. We observed no significant differences between patients with low NCD and those with normal NCD, including ECG findings, HRV, and systolic or diastolic function as assessed by echocardiography. Also, no significant associations between low NCD and cardiac measures were observed after adjusting for age. No significant correlations between cardiac parameters and NCD (as a continuous variable) were observed (data not shown). Additionally, no associations between neovascular pattern and any pulmonary or cardiac variables were found (selected data are shown in Figure 2; remaining data are not shown).

## DISCUSSION

To our knowledge, this is the first study to investigate the relationship between NFC findings and pulmonary and cardiac involvement in patients with juvenile DM. We observed associations between NFC variables and lung involvement: low NCD was associated with smaller lung volumes, reduced gas diffusion capacity, and HRCT-detected airway disease. No significant associations between NFC and cardiac involvement were detected. The representativeness of our juvenile DM cohort has been described previously (15); we believe it covers the vast majority of patients with juvenile DM diagnosed from 1970 to 2006 in Norway.

Our key finding is the relationship between low NCD and smaller lung volumes (FVC and TLC) and reduced gas diffusion (low DLco) in patients with juvenile DM. A recent study in SSc showed results consistent with our findings (8) when comparing patients with low NCD (<7 capillaries/mm) and those with normal NCD: both FVC values (87% versus 101%) and DLco values (71% versus 86%) were decreased in patients with low NCD. These findings are comparable to our results showing that FVC (percent predicted) was decreased (90% versus 99%) and DLco was bor-

derline decreased (77% versus 84%) in patients with low NCD versus those with normal NCD.

HRCT-assessed airway disease was more prevalent in patients with low NCD than in patients with normal NCD. There was no significant difference in the prevalence of HRCT-detected ILD between the groups. Numerous studies in SSc have shown an association between NFC measures and lung involvement (9); reduced NCD was associated with ILD (8), and SSc patients with lung fibrosis showed decreased NCD and more bushy capillaries compared to patients with idiopathic pulmonary fibrosis (9). Thus, even if a few SSc studies did not demonstrate an association between capillaroscopic variables and lung involvement (9), microvascular changes seem to reflect pulmonary involvement in SSc (7,8). In our cohort, although decreased lung volumes and a higher incidence of HRCT-detected airway disease were observed in patients with low NCD, a considerable proportion of patients with normal NCD also showed lung involvement. Thus, even if microvascular involvement appears to be relevant in the development of pulmonary manifestations, other factors are likely to contribute to the process in juvenile DM.

No significant association between low NCD and cardiac involvement was demonstrated. None of the NFC parameters correlated significantly with systolic or diastolic function or with ECG-detected pathologies or HRV. Although clinically relevant cardiac disease is rare in patients with idiopathic inflammatory myopathies including juvenile DM, we previously showed that subclinical cardiac involvement was present in approximately one-fourth of the patients with juvenile DM (4,5,14). The exact mechanism underlying cardiac involvement is unknown, but atherosclerosis, small vessel vasculopathy, and myocardial as well as systemic inflammation may play a role in the process (16). Because we did not observe any significant association between NCD and parameters of cardiac dysfunction, our data do not support the notion that vasculopathy is an important underlying mechanism for cardiac involvement in juvenile DM. However, our study was limited by a small sample size, which made it challenging to study rare outcomes. Thus, the

study may have been underpowered to demonstrate associations between cardiac involvement and NFC.

There is a known relationship between age and NCD (17), and age, and possibly disease duration, might influence the associations between pulmonary and cardiac variables and NCD. In our study, age and disease duration were strongly intercorrelated ( $r_s = 0.938$ ). Adjustment for these factors did not substantially influence the results; we observed robust associations between lung volumes and NCD. We previously studied NFC findings in the same cohort and compared findings with those in age- and sex-matched controls. Notably, the correlations between NCD and age were comparable in patients ( $r_s = 0.407, P = 0.002$ ) and controls ( $r_s = 0.431, P = 0.003$ ) (12), which supports the idea that this association was mainly an effect of aging and not an effect of disease duration.

In conclusion, patients with juvenile DM with low NCD had impaired pulmonary function and more frequent HRCT-detected abnormalities compared to controls. In contrast, we did not observe significant associations between capillaroscopic variables and cardiac involvement. Our results suggest that systemic microvascular remodeling might be an underlying mechanism for pulmonary involvement in juvenile DM. However, further and preferably larger studies are needed to identify NCD as a potential biomarker for organ involvement.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Sanner had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Barth, Sjaastad, Sanner.

**Acquisition of data.** Aaløkken, Sjaastad, Sanner.

**Analysis and interpretation of data.** Barth, Schwartz, Flato, Aaløkken, Koller, Lund, Sjaastad, Sanner.

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