Nailfold Capillary Density is Associated with the Presence and Severity of Pulmonary Arterial Hypertension in Systemic Sclerosis

Herman M.A. Hofstee, Anton Vonk Noordegraaf, Alexandre E. Voskuyl, Ben A.C. Dijkmans, Piet E. Postmus, Yvo M. Smulders, Erik H. Serné

ABSTRACT

Objective: The aim of this study was to investigate whether there are differences in capillary nailfold changes in SSc patients with and without pulmonary arterial hypertension (PAH), and whether these changes are associated with PAH severity and disease specificity.

Methods: Capillary density and loop dimensions were studied in 21 healthy controls, 20 patients with IPAH, and 40 patients with SSc. Of the 40 SSc patients, 19 had no PAH (SSc-nonPAH) and 21 had PAH (SScPAH), of whom 8 had PAH during exercise.

Results: Capillary density was lower in SScPAH compared to SSc-nonPAH patients (4.33/mm vs. 6.56/mm respectively, p=0.001), but loop dimensions were equal. In comparison with IPAH, SScPAH patients had reduced capillary density (4.33/mm vs 7.86/mm, p<0.001) and larger loop dimensions (total width 101.05µm vs. 44.43µm, p<0.001). Capillary density in healthy controls (9.87/mm) was significantly higher when compared to SSc-nonPAH (6.56/mm), SScPAH (4.33/mm), and to IPAH (7.86/mm). No differences in capillary dimensions were present between healthy controls and IPAH. Capillary density correlated with mean pulmonary arterial pressure (PAP) at rest in SScPAH at rest (r = -0.58, p = 0.039) and IPAH (r = -0.67, p = 0.001).

Conclusion: Reduction of nailfold capillary density, but not capillary loop dimensions is associated with PAH, and correlates with the severity of PAH in both SSc and IPAH. This suggests that either systemic microvascular changes play a role in the development of PAH, or that PAH itself contributes to systemic microvascular changes.
INTRODUCTION

Systemic sclerosis (SSc) represents the main connective tissue disease (CTD) associated with pulmonary arterial hypertension (PAH).\(^1\) PAH complicates an estimated 12% of SSc patients, and is a leading cause of death in patients with SSc.\(^2\) Microvascular dysfunction is considered to be a key element in the pathogenesis of SSc and its complications.\(^3\)\(^-\)\(^5\)

The majority of SSc patients display characteristic structural changes of the capillaries in the nailfold, consisting of reduction in the number of capillaries (capillary density), and widening of capillary loops.\(^6\)\(^-\)\(^8\) A number of studies suggest an association between systemic microvascular changes and organ involvement in SSc\(^9\)\(^-\)\(^11\); nevertheless, it is not clear whether systemic microvascular changes in SSc are associated with the presence and severity of PAH.

Better knowledge of the association between nailfold capillary characteristics and PAH in SSc could be useful both for better understanding of the pathophysiology of SSc associated PAH, as well as for stratification of SSc patients in terms of PAH risk. Recent developments, including computer based nailfold video capillaroscopy systems, have improved quantitative assessment of microcirculatory changes such as capillary density and loop dimensions.\(^6\)

The aim of this study was to test the hypothesis that there are differences in capillary density and capillary dimensions between SScPAH and SSc-nonPAH patients, and that these changes are quantitatively correlated with pulmonary haemodynamic parameters. To test the hypothesis that these changes are SSc specific, a group of IPAH patients, as well as
healthy controls were investigated. Computer based panorama mosaic video capillaroscopy was used to display the nailfold capillaries.

**MATERIALS AND METHODS**

**Subjects**

Between September 2006 and July 2007 consecutive eligible SSc and IPAH patients were recruited from the Rheumatology and Pulmonology departments of this hospital. The healthy controls were mainly staff members of the hospital who volunteered to participate in the study. Because of female preponderance in patients with SSc, only female controls were recruited. All SSc patients fulfilled the ACR criteria for SSc and were subsequently divided into a limited (LcSSc) and a diffuse (DcSSc) cutaneous SSc group according to LeRoy.\textsuperscript{12} IPAH patients did not have the symptoms and signs of CTD and were tested negative for anti-nuclear antigen (ANA).

PAH was diagnosed according to the clinical classification of Venice 2003\textsuperscript{13}, with PAH defined as a mean pulmonary artery pressure (PAP) of > 25 mmHg at rest or > 30 mmHg during exercise as determined by right heart catheterisation. Exclusion criteria for PAH in SSc patients were: a) SSc patients with New York Heart Association (NYHA) class I dyspnoea, and no signs of PAH at echocardiography and exercise testing; and b) SSc patients with NYHA class II dyspnoea with normal pressures as determined by right heart catheterisation at rest and during exercise. All SSc patients had to have a total lung capacity (TLC) of >70% of predicted, and a pO\textsubscript{2} of >60 mmHg at rest. Study protocols were approved by the local ethics committee.
Exercise testing and right heart catheterisation

Prior to right heart catheterization, maximal exercise tolerance and peak oxygen uptake (VO₂,max) were assessed by an exercise test on a cycle ergometer. Pulmonary artery pressures (PAP) were taken during right heart catheterisation. Cardiac output (CO) was determined and pulmonary vascular resistance (PVR) was calculated as the ratio of mean PAP to CO. Cardiac index (CI) is defined as the CO divided by the body surface area. Haemodynamic measurements were obtained at baseline and, if baseline mean PAP was less than 25 mmHg, while cycling (see the appendix for further details).

Capillaroscopy

Capillaroscopy and computerised mosaic of the nailfold was obtained as described previously. For this study, only images from digit 4 of the non-dominant hand were used. Image quality was scored as ‘good’ or ‘moderate’. Cases in which only ‘poor’ quality images were available, precluding identification of capillary architecture, were excluded from this study (see the appendix for further details). The investigator was blinded to patient diagnosis and laboratory results; all images were coded. Capillary density (number of loops per mm) was calculated by computer from the manually marked loops in the terminal row. Mean apex, arterial, venous and total capillary widths of the 3-5 widest capillaries were measured. In the case of irregular dilatated capillaries, maximal width was measured.

Statistical analysis

Capillary density and dimensions showed a normal distribution in all categories and are presented as means and standard deviations (SD). Data on the duration of Raynaud’s phenomenon (RP) and the duration of SSc were positively skewed and are presented as
geometric means and 95% confidence interval (CI) of the back-transformed data after log transformation was performed. Numerical means of two or more independent categories were analysed using the Student’s t-test or one-way ANOVA, respectively. Differences between the groups with respect to capillary density and loop dimensions, were analysed using analysis of variance with and without adjustment for age and multiple comparisons (Bonferroni). Categorical variables were analysed using the Chi-squared or Fisher’s Exact Test when appropriate. Correlation between density and pulmonary haemodynamic parameters were described using Pearson’s correlation coefficient. Statistical significance was set at $p < 0.05$. Results were calculated using computer software (SPSS, version 15.0 for Windows; SPSS; Chicago, IL).

RESULTS

Characteristics of subjects

In 1 SScPAH and 1 IPAH patient, image quality was poor and these patients were excluded from the analyses. Characteristics of the included 21 healthy controls, 20 IPAH, 19 SSc-nonPAH and 21 SScPAH patients are shown in table 1. Of the 19 SSc-nonPAH patients, 16 had NYHA class I and no signs of PAH at echocardiography and exercise testing, and 3 had NYHA class II with normal PAP. Of the 21 SScPAH patients, 13 had SScPAH at rest, and 8 had SScPAH during exercise. In 93% (75/81) of the cases it was possible to study digit 4 of the non-dominant hand, digit 3 and 5 were examined in the remaining 2 and 4 cases, respectively. The healthy controls were significantly younger than the IPAH and SSc patients. Raynaud’s phenomenon was present in 95% (38/40) of the SSc patients. One IPAH patient
was considered to have longstanding primary Raynaud’s phenomenon, since ANA was negative and there were no other clinical symptoms and signs of a CTD.
### Table 1. Characteristics of controls, patients with IPAH, SSc without PAH (SSc-nonPAH), and SSc with PAH (SScPAH)

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=21)</th>
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<td>PAH rest (n=13)</td>
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<td></td>
<td>PAH exercise (n=8)</td>
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<tr>
<td>Age, yr (SD)</td>
<td>37.7 (10.7)</td>
<td>46.4 (12.0)</td>
<td>56.0 (10.7)</td>
<td>63.1 (15.6)</td>
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<td>62.7 (15.6)*</td>
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<tr>
<td>Female (%)</td>
<td>21 (100)</td>
<td>19 (86)</td>
<td>18 (95)</td>
<td>13 (100)</td>
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<td></td>
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<td></td>
<td></td>
<td>7 (88)†</td>
</tr>
<tr>
<td>RP (%)</td>
<td>0</td>
<td>1 (5)</td>
<td>17 (90)</td>
<td>13 (100)</td>
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<td></td>
<td></td>
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<td></td>
<td>8 (100)‡</td>
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<tr>
<td>Duration of RP, yr (95% CI)</td>
<td>NA</td>
<td>27 (NA)</td>
<td>6.3 (4.0 – 11.9)</td>
<td>15.3 (10.9 – 21.3)</td>
</tr>
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<td></td>
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<td>6.6 (2.7 – 16.3)§</td>
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<td>20/1</td>
<td>19/1</td>
<td>15/4</td>
<td>12/1</td>
</tr>
</tbody>
</table>

NA= Not applicable

* differences significant (p<0.05) between categories
† differences not significant between categories
‡ difference not significant between SSc-non PAH and SScPAH
§ difference significant (p<0.05) between SScPAH rest and SSc-non PAH; difference not significant between SScPAH rest and SScPAH exercise
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<tr>
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<td>1 (5)</td>
<td>17 (90)</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Duration of RP, yr (95% CI)</td>
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* differences significant (p<0.05) between categories
† differences not significant between categories
‡ difference not significant between SSc-nonPAH and SScPAH
§ difference significant (p<0.05) between SScPAH rest and SSc-nonPAH; difference not significant between SScPAH rest and SScPAH exercise

Four patients with IPAH, 3 with SScPAH at rest, and all patients with SScPAH during exercise were without medical treatment for PAH. The other patients with SScPAH at rest and IPAH used monotherapy or combinations of prostaglandin/prostacyclin analogous, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors. No differences in capillary density were present between treated and non treated patients with SScPAH (4.5 vs. 3.9/mm, p=0.61) and IPAH (7.2 vs. 7.9/mm, p=0.38), and did not differ between treatment modalities, although some treatment categories were small.

There were no striking differences between the SSc-nonPAH and SScPAH patients in time since clinical diagnosis of SSc, type of SSc (LcSSc or DcSSc), or antibody testing (table 2).
Compared to SScPAH patients, SSc-nonPAH patients were less likely to have any sign of pulmonary fibrosis in the dorsobasal fields on a high resolution CT scan \( (p = 0.002) \), or a diffusing capacity for CO of less than 70% of predicted \( (p = 0.009) \). None of the IPAH patients had signs of pulmonary fibrosis on a CT scan.

**Capillary density and dimensions in healthy controls, patients with IPAH and SSc subgroups**

The main findings on capillary microscopy are reported in table 3. In comparison with healthy controls, SSc patients had reduced capillary density (5.36 vs. 9.87/mm, \( p<0.001 \)) and larger loop dimensions (total width 101.05 µm vs. 43.20 µm, \( p<0.001 \)). Capillary density was lower in SScPAH patients compared to SSc-nonPAH (4.33 vs. 6.56/mm respectively, \( p=0.001 \)), but no difference in capillary density between SScPAH at rest or SScPAH during exercise could be detected. Loop dimensions were equal in SSc-nonPAH, SScPAH at rest, and SScPAH during exercise. A reduction in capillary density was also observed in IPAH patients compared to healthy controls (7.86 vs. 9.87 respectively, \( p=0.009 \)), but no differences in loop dimensions were present between IPAH patients and healthy controls. In comparison with SScPAH patients, IPAH patients had a higher capillary density (7.86 vs. 4.33/mm, \( p<0.001 \)) and smaller loop dimensions (44.43 µm vs. 109.24 µm, \( p<0.001 \)). Age was significantly different between controls, patients with IPAH, and patients with SSc, but capillary density and loop dimensions were not age related \( (r = 0.097, p = 0.68 \) for capillary density and age). Analysis of differences in capillary density and loop dimensions between groups with and without adjustment for age yielded similar results.
Compared to SSc-PAH patients, SSc-nonPAH patients were less likely to have any sign of pulmonary fibrosis in the dorsobasal fields on a high resolution CT scan (p = 0.002), or a diffusing capacity for CO of less than 70% of predicted (p = 0.009). None of the IPAH patients had signs of pulmonary fibrosis on a CT scan.

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Age was significantly different between controls, patients with IPAH, and patients with SSc, but capillary density and loop dimensions were not age related (r = 0.097, p = 0.68 for capillary density and age).

Analysis of differences in capillary density and loop dimensions between groups with and without adjustment for age yielded similar results.

Table 3. Mean capillary density and dimensions. All between group comparisons for differences adjusted for age and multiple comparisons

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=21)</th>
<th>IPAH (n=20)</th>
<th>SSc-nonPAH (n=19)</th>
<th>SScPAH (n=21)</th>
<th>Controls vs. SSc-nonPAH</th>
<th>SSc-nonPAH vs. SScPAH</th>
<th>SScPAH exercise vs. SScPAH rest</th>
<th>Controls vs. IPAH</th>
<th>IPAH vs. SScPAH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAH rest (n=13)</td>
<td>PAH exercise (n=8)</td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td>Loops/mm, mean (SD)</td>
<td>9.87 (1.38)</td>
<td>7.86 (1.11)</td>
<td>6.56 (2.78)</td>
<td>4.23 (1.77)</td>
<td>4.49 (1.24)</td>
<td>&lt; 0.001</td>
<td>0.001</td>
<td>0.966</td>
<td>0.009</td>
</tr>
<tr>
<td>Apex width, mean (SD)</td>
<td>17.03 (3.73)</td>
<td>19.98 (6.92)</td>
<td>40.62 (25.50)</td>
<td>39.46 (18.34)</td>
<td>42.83 (18.50)</td>
<td>0.001</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Arterial width, mean (SD)</td>
<td>13.21 (2.32)</td>
<td>13.04 (3.34)</td>
<td>28.62 (16.53)</td>
<td>27.56 (10.62)</td>
<td>30.39 (14.35)</td>
<td>&lt; 0.001</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Venous width, mean (SD)</td>
<td>15.32 (2.96)</td>
<td>16.01 (4.66)</td>
<td>35.80 (20.52)</td>
<td>38.25 (18.46)</td>
<td>44.23 (19.25)</td>
<td>&lt; 0.001</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Total width, mean (SD)</td>
<td>43.20 (5.90)</td>
<td>44.43 (9.02)</td>
<td>93.68 (48.77)</td>
<td>103.36 (35.15)</td>
<td>114.53 (43.69)</td>
<td>&lt; 0.001</td>
<td>0.662</td>
<td>1.000</td>
<td>1.000</td>
</tr>
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</table>
Exercise testing and pulmonary haemodynamic parameters

Exercise performances and haemodynamic parameters of patients with IPAH and SScPAH at rest were, as expected, worse than those of patients with SScPAH during exercise as measured by CI, mean PAP, PVR, 6 minute-walking-test (6MWD), VO₂ max, and maximal exercise tolerance (table 4). Exercise performances between IPAH and SSC patients were not different. In comparison with SScPAH at rest, IPAH patients had a higher mean PAP (51.3 vs. 39.2 mmHg, p=0.006), but no other differences in haemodynamic parameters were present. Capillaroscopy was performed after a median of 5.8 months (range 3-48 months) after right heart catheterisation. Time separation was shorter than 18 months in 90% of the patients.

Table 4. Cardiopulmonary findings in 41 PAH patients

<table>
<thead>
<tr>
<th></th>
<th>IPAH (n=20)</th>
<th>SScPAH (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAH rest (n=13)</td>
<td>PAH exercise (n=8)</td>
</tr>
<tr>
<td>CI in l/min/m², mean (SD) at rest during exercise</td>
<td>2.9 (0.8)</td>
<td>2.9 (0.7)</td>
</tr>
<tr>
<td>Mean PAP in mmHg, mean (SD) at rest during exercise</td>
<td>51.3 (14.4)†</td>
<td>39.2 (9.8)†</td>
</tr>
<tr>
<td>Pulmonary vascular resistance at rest in dyne.sec/cm⁵, mean (SD)</td>
<td>737.7 (321.9)</td>
<td>567.2 (261.3)</td>
</tr>
<tr>
<td>6 MWD % of predicted, mean (SD)</td>
<td>77.0 (18.7)</td>
<td>73.6 (29.1)</td>
</tr>
<tr>
<td>VO₂max in ml/kg/min, mean (SD)</td>
<td>13.5 (3.2)</td>
<td>10.7 (6.5)</td>
</tr>
<tr>
<td>Max. exercise tolerance % of predicted, mean (SD)</td>
<td>49.6 (17.0)</td>
<td>41.5 (17.9)</td>
</tr>
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</table>

* differences significant (p<0.05) between IPAH vs. SScPAH exercise and between SScPAH rest vs. SScPAH exercise
† differences significant (p<0.05) between IPAH vs. SScPAH rest
‡ differences not significant between categories (ANOVA)
Correlation of capillary density with NYHA class and haemodynamic parameters

A lower capillary density was associated with a higher NYHA class in SSc patients (p=0.042 by ANOVA). Capillary density correlated with meanPAP at rest in SScPAH at rest (r = -0.58, p = 0.039) (figure 1), SScPAH during exercise (r = -0.82, p = 0.013), and IPAH (r = -0.67, p = 0.001) (figure 2). Capillary density also correlated with PVR at rest in IPAH (r = -0.60, p = 0.005), and, although not significantly, in SScPAH at rest (r = -0.50, p = 0.08), but not in SScPAH during exercise (r = -0.18, p = 0.69). No correlation between capillary density and CI or systemic vascular resistance was observed in the PAH groups.
DISCUSSION

Structural changes in the systemic microcirculation, consisting of reduction of capillary density and widening of capillary dimensions, are a hallmark of SSc. A novel finding of this study is that capillary density, but not capillary dimensions, differs between SScPAH and SSc-nonPAH, and correlates with pulmonary haemodynamic parameters. Interestingly, when compared to healthy controls, the same is true for patients with IPAH, a condition not known to be characterised by systemic microvascular changes. Our data suggests that widening of capillaries and capillary density reduction represent two different aspects of systemic microvascular involvement, i.e. widening of capillaries is SSc specific, whereas reduction in capillary density is a marker of the presence and severity of PAH.

Few studies have investigated nailfold capillary patterns in patients with SScPAH, with only one study including patients with IPAH. Two studies used echocardiography and/or right
heart catheterisation to confirm the diagnosis of PAH. One of these found a significant reduction of capillary density in 8 SSc patients with PAH in comparison with 12 SSc patients without PAH.\textsuperscript{14} No pulmonary haemodynamic parameters were reported in this study. The other study, using capillary density and qualitative scoring of nailfold patterns, found no differences in capillary patterns between 8 SSc-nonPAH and 7 SScPAH patients, but capillary density in these groups was not reported.\textsuperscript{15} A third study, using only right heart catheterisation to diagnose and exclude the diagnosis of PAH, showed a significant difference in semi-quantitative scoring of nailfold patterns between SSC-nonPAH and SScPAH but, again, capillary density was not assessed in this study.\textsuperscript{16} Only one of these studies included IPAH patients and reported no differences in capillary density and capillary patterns between 13 healthy controls and 37 IPAH patients.\textsuperscript{15}

In the present study, a reduction of capillary density was observed in both SSc-PAH and, albeit to a milder extent, in IPAH. However, the explanation for capillary density reduction may not be the same for both disorders. For SSc, it is generally presumed that structural changes in the systemic (micro-)circulation precede changes in the pulmonary circulation, since systemic microvascular changes may precede SSc development by many years.\textsuperscript{15} Hence, nailfold capillary abnormalities might well reflect what is going on in the pulmonary circulation. This may not be true for all capillary abnormalities, because most SSc patients demonstrate nailfold capillary abnormalities, whereas only a minority develop PAH. The present study suggests that only capillary density is associated with the presence of PAH and is a marker of disease severity in SSc. In IPAH, disturbed structure or function of the systemic (micro-)circulation is not considered to be a central feature. However, relatively mild abnormalities of systemic endothelial function (i.e. brachial artery flow mediated
vasodilation) have recently been observed in IPAH\textsuperscript{17}, suggesting that IPAH may not be strictly limited to the pulmonary vascular bed. If indeed the systemic circulation is mildly affected in IPAH, this might explain the relatively mild degree of capillary density reduction seen in our patients. Therefore, another explanation for the more pronounced capillary reduction in SScPAH could be that PAH itself amplifies the already present reduction of capillary density in SSc. Finally, it is conceivable that, both in SSc-PAH and in IPAH, neurohumoral activation due to compromised cardiac function causes systemic microvascular dysfunction. However, this would be at odds with recent observations showing increased rather than decreased nailfold capillary density in patients with heart failure.\textsuperscript{18} In addition, we found no association between capillary density and CI or systemic vascular resistance in our PAH patients.

A computer based panorama mosaic video capillaroscopy was used in this study to display a detailed image of a large part of the nailfold, that allows precise measurements of capillary density and loop dimensions. Furthermore, a diagnosis of PAH was confirmed by right heart catheterisation. However, although we feel that in SSc patients with NYHA class I, and no signs of PAH at echocardiography and exercise testing, a diagnosis of PAH was reasonably excluded, right heart catheterisation remains the gold standard. Therefore, some subclinically PAH could not be fully excluded in this group. In addition, the group of patients with SScPAH during exercise was quite small.

From a pathophysiological viewpoint, our study sheds more light on the involvement of the microcirculation in SScPAH and IPAH, although subsequent research is needed to delineate whether the disturbances in the microcirculation are causal or consequential to PAH. From a
clinical viewpoint, it is interesting to note that a simple, non-invasive tool such as nailfold capillary microscopy is potentially capable of identifying patients with PAH.

ACKNOWLEDGEMENTS

The software to create the panorama mosaic images was received as a license agreement from the University of Manchester (UK). We would like to thank A.L. Herrick, MD, PhD (University of Manchester, Hope Hospital, Salford, UK), T. Moore (Hope Hospital, Salford, UK), and P.D. Allen, PhD (University of Manchester, UK) for their kind support.
REFERENCE LIST


