Automatically Extracted Quantitative Biomarkers for Assessing Connective Tissue Disease Using Nailfold Capillaroscopy

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Background/Purpose

Videomicroscopy can capture high-magnification images of nailfold capillaries, allowing non-invasive assessment of microvasculature change indicative of connective tissue disease. Whilst images may be qualitatively graded visually, quantitative biomarkers are required for detailed analysis and tracking disease progression. To overcome the problems of manual measurements (time consuming, subjective), we have developed fully automated software to measure the spatial density, width and tortuosity of capillaries[1]. Our objective was to assess how well these automated biomarkers differentiate between healthy controls (HC), subjects with primary Raynaud's phenomenon (PRP), patients with systemic sclerosis (SSc), and patients with an undifferentiated connective tissue disease (UCTD).

Methods

Our software was used to analyze 577 nailfold images (85 HC; 46 PRP; 402 SSc, 44 UCTD). Analysis is performed in four stages: the software 1) detects all vessels, measuring the orientation and width for each 2) locates the apex of each capillary and determines which belong to the distal row 3) extracts measures that characterize the size and shape of each distal capillary 4) combines these measurements to compute a single value of density, width and tortuosity for each image. For each biomarker one-way ANOVA, followed by Tukey's range test, was used to check for differences between the means of each subject group.

Results

ANOVA tests showed significant group-wise differences for all biomarkers (all p <0.001). The group mean and 95% confidence interval of each biomarker are shown in Table 1, along with the pairs of groups that showed significantly different means under Tukey's test.

Table 1: Group-wise means and confidence intervals for each automatically measured capillaroscopy biomarker. Pairs of groups with significantly different means are listed in the rightmost column.

Biomarker type	Subject group means (95% confidence intervals)				Groups with significantly different means under Tukey's test
	HC (n=85)	PRP (n=46)	SSc (n=402)	UD (n=44)	
Capillary density (per mm)	12.6 (12, 13.3)	13.4 (12.5, 14.2)	9.02 (8.74, 9.3)	11.5 (10.6, 12.3)	HC v SSc (p< 0.001); PR v SSc (p< 0.001); UD v SSc (<0.001 PR v UD (p=0.011);
Mean apical width (mm)	10.5 (11, 10.1)	11.2 (11.9, 10.5)	14.3 (14.7, 14)	12.5 (13.4, 11.7)	HC v SSc (p<0.001); PR v SSc (p<0.001); UD v SSc (p =0.0017); HC v UD (p<0.001);
Mean capillary tortuosity (no units)	4.42 (4.38, 4.46)	4.33 (4.27, 4.39)	4.55 (4.53, 4.57)	4.41 (4.35, 4.47)	HC v SSc (p<0.001); PR vSSc (p<0.001); UD v SSc (p<0.001);

Conclusion

Images from patients with SSc had significantly lower capillary density and higher width and tortuosity than all other subject groups (including UCTD), matching findings from earlier studies using manual or semi-automated analysis[2]. No significant differences were observed between healthy controls and

PRP, again, matching clinical expectations. Images from patients with UCTD generated biomarkers that lay in between healthy controls/PRP and SSc. These highly promising results suggest our software produces clinically useful biomarkers of connective tissue disease. Automatic analysis is potentially a major step forward, enabling large datasets of images to be assessed quickly and efficiently, and obviating the inherent subjectivity of manual assessment.

1. Berks, An Automated System for Detecting and Measuring Nailfold Capillaries, MICCAI, to appear November 2014

2. Murray, Non-invasive Imaging Techniques in the Assessment of Schleroderma Spectrum Disorders, Arthritis Care and Research, 61(8), 2009