J Periodontal Implant Sci. 2022 Feb;52(1):65-76
https://doi.org/10.5051/jpis.2101160058
pISSN 2093-2278·eISSN 2093-2286

JPIS
Journal of Periodontal & Implant Science

Research Article
Periodontal Science

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Identification of venular capillary remodelling: a possible link to the development of periodontitis?

David Townsend *

Periodontology Unit, UCL Eastman Dental Institute, UCL, University of London, London, UK

OPEN ACCESS

Received: Feb 3, 2021
Revised: Jul 13, 2021
Accepted: Aug 23, 2021
Published online: Sep 30, 2021

***Correspondence:**
David Townsend
Periodontology Unit, UCL Eastman Dental Institute, UCL, University of London, London, UK.
Email: sejjdmt@ucl.ac.uk
Tel: +44(0)20 34567899
Fax: +44(0)20 79151071

ORCID iDs
David Townsend
https://orcid.org/0000-0001-7354-5106

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Purpose: The present study measured changes in arteriolar and venular capillary flow and structure in the gingival tissues during the development of plaque-induced gingival inflammation by combining dynamic optical coherence tomography (OCT), laser perfusion, and capillaroscopic video imaging.
Methods: Gingival inflammation was induced in 21 healthy volunteers over a 3-week period. Gingival blood flow and capillary morphology were measured by dynamic OCT, laser perfusion imaging, and capillaroscopy, including a baseline assessment of capillary glycocalyx thickness. Venular capillary flow was estimated by analysis of the perfusion images and mean blood velocity/acceleration in the capillaroscopic images. Readings were recorded at baseline and weekly over the 3 weeks of plaque accumulation and 2 weeks after brushing was resumed.
Results: Perfusion imaging demonstrated a significant reduction of gingival blood flow after 1 and 2 weeks of plaque accumulation ($P<0.05$), but by 3 weeks of plaque accumulation there was a more mixed picture, with reduced flow in some participants and increased flow in others. Participants with reduced flux at 3 weeks also demonstrated venular-type flow as determined by perfusion images and evidence of the development of venular capillaries as assessed by the velocity/acceleration ratio in capillaroscopic images. After brushing resumed, these venular capillaries were broken down and replaced by arteriolar capillaries.
Conclusions: After 3 weeks of plaque accumulation, there was wide variation in microvascular reactions between the participants. Reduced capillary flow was associated with the development of venular capillaries in some individuals. This is noteworthy, as an early increase in venous capillaries is a key vascular feature of cardiovascular disease, psoriasis, Sjögren syndrome, and rheumatoid arthritis—diseases with a significant association with the development of severe gingival inflammation, which leads to periodontitis. Future investigations of microvascular changes in gingival inflammation might benefit from accurate capillary flow velocity measurements to assess the development of venular capillaries.

Keywords: Capillaries; Periodontitis; Venules

INTRODUCTION

The vascular reaction to plaque-induced gingivitis has been extensively studied in humans and animals [1-15]. In some people, gingival inflammation leads to tissue destruction with

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the development of periodontitis, whereas in other people no further progression occurs. Microvascular dysfunction in periodontitis includes an increase in venules and venous capillaries [4-7]. This growth of venous capillaries is mediated by increased levels of vascular endothelial growth factor during active periodontitis, and vascular endothelial growth factor levels are also elevated during healing following the successful treatment of periodontitis [8]. Braverman showed that areas with healthy arteriolar capillary flow can be identified by their relative proximity to an underlying ascending arteriole; low-flux areas with a large number of moving red blood cells tend to be predominantly venular [16,17]. Identification of capillaries as arteriolar capillaries or venular capillaries is usually done by biopsy and histology or *in vivo* by assessing morphology; the problem with a morphological assessment is that a dilated arteriolar capillary may look very similar to a venular capillary. It has recently been shown that it is possible to reliably classify a capillary as arteriolar or venular by measuring the flow in the lumen [18]. However, the anatomy of the human gingival vasculature has only recently been fully described in detail with little functional assessment [19]. We have previously shown that capillary loops in tissues affected by periodontal breakdown contain predominantly deoxygenated blood and that these loops have no evidence of an intact glycocalyx, suggesting the presence of venous capillary loops [20,21]. This has increased our knowledge of the disease process, but gives no indication of why some people develop periodontal breakdown whilst others do not progress beyond gingival inflammation. The aim of the present study was to measure changes in arteriolar and venular capillary flow and structure in the gingival tissues during the development of plaque-induced gingival inflammation over a 3-week period by combining dynamic optical coherence tomography (OCT), laser perfusion, and capillaroscopic video imaging.

MATERIALS AND METHODS

Patient selection and experimental design

This study was performed at the Eastman Clinical Investigation Centre, University College London, over a 6-month period between February 2016 and July 2016. Twenty-one healthy volunteers were recruited, aged 18 to 60 (10 men and 11 women, age 44±9 years, Caucasian/non-Caucasian: 12/9). The inclusion criteria were as follows: patients aged over 18 years with a full-mouth plaque score and a full-mouth bleeding on probing score <20% and intact maxillary teeth (13, 12, 11, 21, 22, 23). The clinician confirmed the absence of the exclusion criteria. The following exclusion criteria were applied: active periodontal disease (basic periodontal examination score of 3 or above or furcation involvement in any sextant), gingival pathology, patients with cardiovascular disease, and patients with systemic disease or those taking medication that might affect microvascular function such as calcium channel blockers or immunosuppressive drugs.

Patients were educated on oral hygiene and shown how to brush their teeth using the roll technique and a soft bristle brush. Gingival inflammation was induced in subjects by refraining from all oral hygiene for a period of 21 days; induction of gingival inflammation was limited to the upper right incisor region. Subjects were not allowed to use floss, mouthwash, mouth sprays, or chew gum during the study. Imaging was performed at baseline (week 0) and at weekly intervals for a 5-week period. Brushing was stopped at week 0 and resumed after imaging at week 3. Written informed consent was obtained from all participants. The research protocol for human subjects was reviewed and approved by the University College London ethics review board (No. 16/NS/0012). The study was conducted in accordance with the Helsinki Declaration as revised in 2013.

https://doi.org/10.5051/jpis.2101160058

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Imaging

Laser perfusion imaging was combined with dynamic OCT and capillaroscopy to monitor the microvascular reaction to plaque accumulation.

Dynamic OCT scanning was performed with a VivoSight (VivoSight, Michelson Diagnostics, Maidstone, UK) at a transverse resolution of <10 μm and an axial resolution of <10 μm.

Perfusion imaging was performed using a MoorFLPI-2 Full Field Laser Perfusion Imager (Moor Instruments Ltd., Axminster, UK), with a 785-nm laser. Perfusion was measured in units of flux.

A KK Capiscope was used for gingival imaging and sublingual microvascular images (KK Technology, Honiton UK), with the following settings: image size, 1,280×1,024 pixels; resolution, 0.8 μm/pixel; field of view, 1,037×829 μm; 25 fps.

All imaging was carried out by 1 operator with the subject seated at ambient temperature and subdued lighting. Images were obtained of the buccal gingival tissues in the upper right incisor region. Dynamic OCT and perfusion imaging were carried out at baseline and at week 1, week 2, week 3, week 4 and week 5. A 20-second capillaroscopic video sequence was recorded of the gingival tissues at baseline and at weeks 3 and 5. Presence of plaque accumulation was confirmed visually in all participants at week 3 (Modified Quigley-Heine plaque index, score 3: plaque greater than 1 mm in width and covering up to one-third of the tooth surface) [22].

At week 3, when plaque removal was re-established, some additional capillaroscopic imaging was performed over the first 24 hours of tissue recovery. A 20-second capillaroscopic video sequence of sublingual capillary flow was also made at baseline to allow estimation of the baseline endothelial glycocalyx dimensions in each participant.

Gingival image sampling was limited to the buccal surface of the interdental papilla mesial to the upper right lateral incisor. The same area was used for laser perfusion imaging, dynamic OCT, and capillaroscopy. Laser perfusion imaging flux values were averaged over 6 consecutive scans to remove pulsatile variations. A sample perfusion image is shown in **Figure 1**; perfusion images of the buccal gingival tissues included a histogram of the flux index, from green through red above 425 units. The Moor FLPI-2 obtains images to a depth of 500 μm and can detect flow in ascending arterioles and the accompanying vein supplying a mucosal surface capillary region. The flux value of such an arteriole will be 400 flux units or more, identified

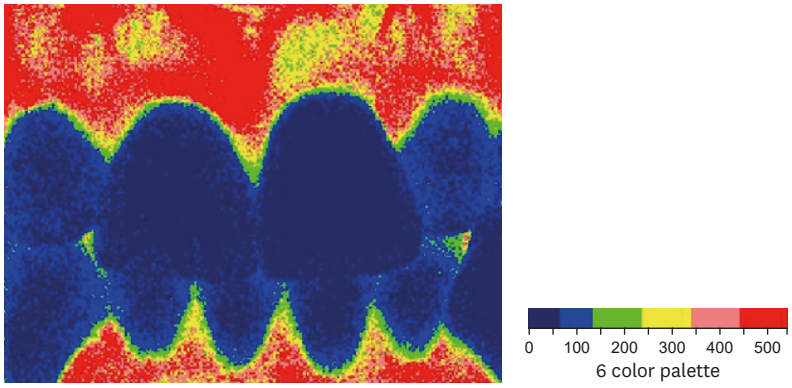

Figure 1. Perfusion image of buccal gingival tissues including a histogram of the flux index, with green representing a flux value between 125 and 225 flux units, yellow above 225 flux units, pink above 325 units, and red above 425 units.

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as pink or red in the flux image. A surface region with good capillary flow will be within 1.5 mm of such an arteriole, and areas with reduced capillary flow or venular flow will generally be more than 1.5 mm from an area with a flux of 400 units. For each image, the mean distance between active flux in the gingival crest/sulcus and an area with flow greater than 400 flux units was measured. The technique has been described in full by Braverman [17].

En-face dynamic OCT imaging was performed at the same sites as laser perfusion imaging. The images generated display hard and soft tissue in greyscale and microvessels in red. The software was used to create en-face scans with the depth set at 300 μm below the surface. Capillaroscopic images were recorded with a KK Capiscope, generating a 20-second video sequence. The software was used for automated assessment of the capillary density, vessel diameter, and capillary flow at baseline, week 3, and week 5. Additional images were obtained in 1 individual at 3 weeks of plaque accumulation and after resuming brushing at 8 and 24 hours; in these images, the software was used to identify venous and arterial capillaries in the tissues by measuring the mean and peak flow rate as described by Buschmann et al. [18]. High maximum shear stress on the microvessel wall helps maintain arteriolar capillaries, meaning that the ratio of maximum red blood cell acceleration to the mean velocity (relative pulse slope index, RPSI) for a given vessel diameter can reliably differentiate a venous capillary from an arterial capillary.

The endothelial glycocalyx was measured in the sublingual tissues at baseline in each participant. The video sequence was adjusted for movement correction and contrast enhancement using the KK Capiscope software and then analysed to estimate the width of the endothelial glycocalyx using the white cell passage method. The method has been thoroughly described elsewhere and involves automated measurement of the width of the red cell column in a microvessel before and after the passage of a white cell. The white cell compresses the endothelial glycocalyx, allowing an estimate of the width of the glycocalyx [23-25]. In each video sequence, 5 capillaries with a diameter between 3 and 7 μm were selected and the width of the flowing erythrocyte column before and after the passage of a leukocyte was determined using a digital calliper. Leukocytes are much more rigid than erythrocytes and temporarily compress the glycocalyx in narrow vessels. In a narrow vessel, the difference between the before and after measurements gives an estimate of the glycocalyx thickness.

RESULTS

All results were tabulated using an Excel (Microsoft Corp., Redmond, WA, USA) spreadsheet. Data analysis was carried out using SPSS version 19 (IBM Corp., Armonk, NY, USA). The paired 2-tailed *t*-test was used to evaluate the significance of differences between means. Visible plaque accumulation was confirmed in all participants at week 3 (plaque greater than 1 mm in width and covering up to one-third of the tooth surface). There was little inter-subject difference in sublingual capillaroscopy glycocalyx measurements with a mean width of 0.65 μm (standard deviation [SD], 0.2 μm). The glycocalyx measurements in the tissues lining the floor of the mouth showed little variation among participants; there is also no current evidence that measurements in the sublingual tissues have any relationship to gingival values. Valid measurements in gingival tissues in the future would require the development of improved imaging techniques.

In the capillaroscopic images, there was no significant difference in the mean diameter of microvessels from the baseline, at 3 weeks of plaque accumulation, or 2 weeks after brushing

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Table 1. Mean flux levels at each week and the mean distance of the measurable flux in the gingival crest/sulcus from an area with arteriolar flow (flow greater than 425 flux units), and mean blood flow velocities measured by capillaroscopy

Week	Mean flux in the interdental papilla (SE)	Sig.	Mean flux in the gingival margin (SE)	Sig.	Mean distance (mm, SD)	Capillaroscopic blood flow velocity (μm/s, SD)
0	476 (38)	-	478 (41)	-	0.88 (0.5)	115 (73)
1	359 (23)	0.003	372 (27)	0.005	0.98 (0.4)	-
2	344 (22)	0.005	330 (30)	0.004	1.0 (0.4)	-
3	408 (34)	0.096	398 (42)	0.047	0.95 (0.4)	25 (44)
4	485 (38)	0.898	425 (47)	0.258	1.83 (0.3)	-
5	410 (25)	0.016	409 (37)	0.006	0.9 (0.3)	97 (45)

SE: standard error, SD: standard deviation.

had resumed (P=0.8 at week 3, P=0.7 at week 5). The mean blood flow velocity measured at baseline, after 3 weeks of plaque accumulation, and at 2 weeks after resumed brushing showed a reduction after 3 weeks of plaque accumulation. In 9 cases, there was no detectable flow in the superficial microvessels after 3 weeks of plaque accumulation. **Table 1** shows the mean and SD of blood flow velocities measured from the capillaroscopic images at baseline, after 3 weeks of plaque accumulation, and at 2 weeks after brushing was resumed. Only vessels with measurable flow were included in the velocity measurements.

Dynamic OCT images were reconstructed and sampled at a depth of 300 μm below the surface. A sample scan is shown in **Figure 2**. The scans were combined to produce an en-face image, which was analysed for the number of microvessels present in each scan. There was no significant change in the number of vessels visible in the area covered by each scan over the experimental period. There was, however, a marked difference between participants after 3 weeks of plaque accumulation, which was not evident during the first 2 weeks. The results are shown graphically in **Figure 3** and in **Table 1**.

In laser perfusion imaging, there was a significant drop in the flux after 1 and 2 weeks of plaque accumulation; at 3 weeks there was a greater diversity of flux indices among different participants, as some participants maintained low flux, but the levels returned to baseline in others. There was a reduced overall mean flux after 3 weeks, but this was not significant (P=0.096). **Figure 4** shows an example of flux images decreasing over the 3 weeks of plaque accumulation and another example of the flux decreasing initially but returning to baseline after 3 weeks of plaque accumulation. **Figure 3** shows a graph of the flux levels with significant drops at 1 and 2 weeks of plaque accumulation (at 1 week of plaque accumulation, P<0.05, at 2 weeks of plaque accumulation, P<0.05).

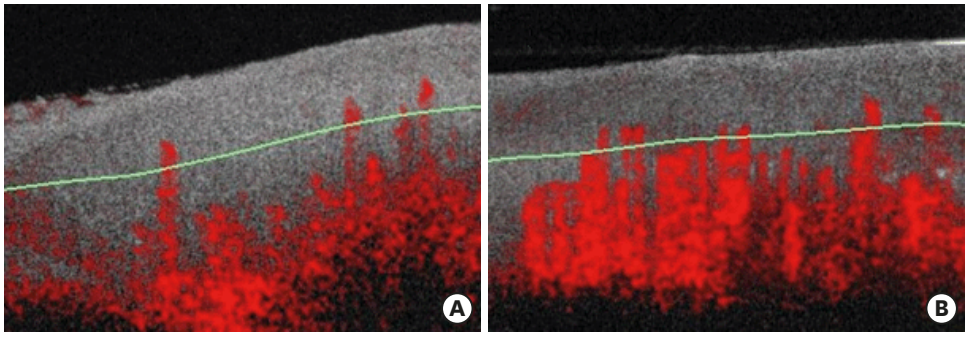

Figure 2. (A) Section of a dynamic OCT scan at baseline showing few microvessels just below the 300-μm depth marker. (B) Section of dynamic OCT scan after 3 weeks of plaque accumulation, showing a slight increase of microvessels above the depth marker but a much greater increase deep to the depth marker.
OCT: optical coherence tomography.

https://doi.org/10.5051/jpis.2101160058

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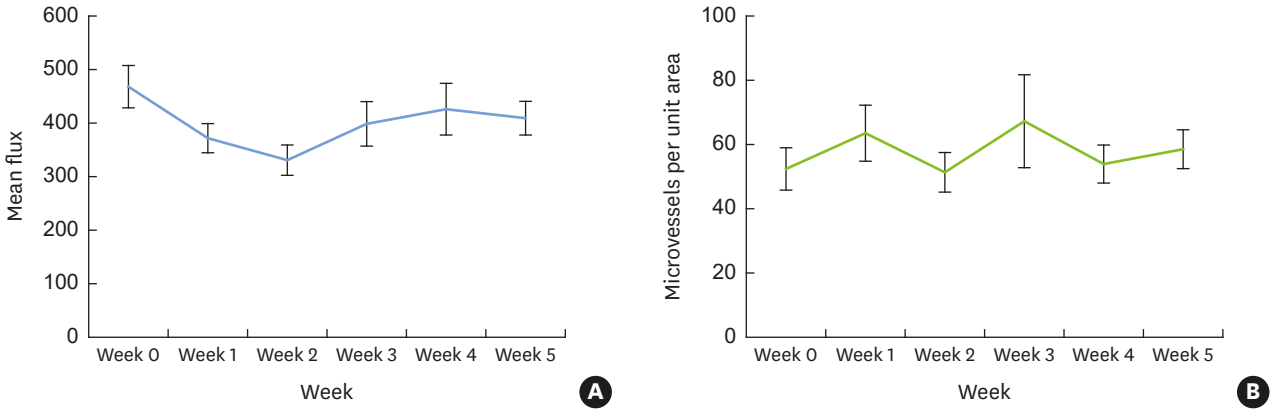

Figure 3. (A) Graph of mean weekly laser perfusion imaging flux measurements. (B) Graph of mean dynamic optical coherence tomography imaging of microvessels per unit area at a 300-μm depth.

Venular capillary flow was assessed by mean measurements of the distance from the gingival crest to an area with arteriolar flow, which showed no overall change during plaque accumulation. However, all participants who showed a continued reduction in flux at 3 weeks also had an increased mean distance, and all participants with an increased flux at 3 weeks had a reduced mean distance. This suggests that flux returning to baseline levels was associated with arterial capillary flow, but reduced flux at 3 weeks was associated with the development of venular capillary flow. **Table 1** gives the mean flux levels at each week and the mean distance of the measurable flux in the gingival tissues from an area with arteriolar flow (flow greater than 400 flux units). A detailed analysis of flux images is not able to reliably differentiate venous capillaries from arterial capillaries, but capillaroscopic imaging in a case with reduced flux after 3 weeks of plaque accumulation initially showed extensive tortuous dilated capillaries; then, over the first 24 hours of resumed brushing, there was a breakdown of these vessels and formation of healthy loop capillaries. An analysis of these video sequences confirmed that the tortuous capillaries observed after 3 weeks of plaque accumulation were all venous capillaries with no arteriolar capillaries, and these were replaced by arteriolar capillaries over the 24-hour period following the resumption of plaque removal. **Figure 5** shows the capillary changes over the first 24 hours after brushing was

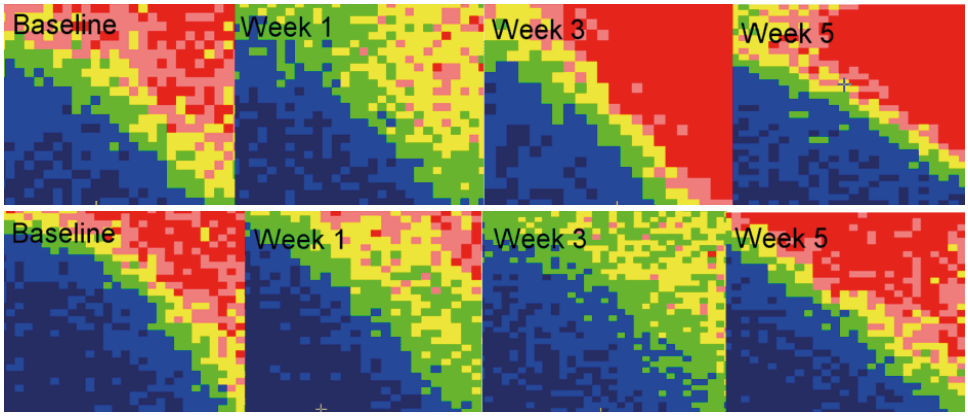

Figure 4. Flux images at baseline, week 1, week 3, and week 5. Top: from an individual with high flux after 3 weeks of plaque accumulation. Bottom: from an individual with low flux after 3 weeks of plaque accumulation.

https://doi.org/10.5051/jpis.2101160058

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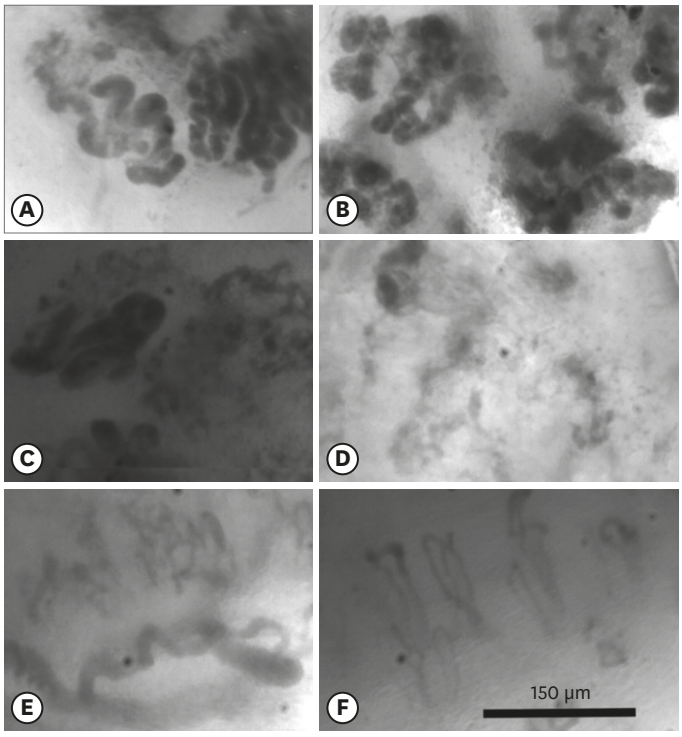

Figure 5. Capillaroscopic images from 2 gingival sites. (A, B) Dilated venous capillaries after 3 weeks of plaque accumulation. (C, D) Eight hours after the resumption of plaque removal, with evidence of extravasated red blood cells suggesting vessel destruction. (E, F) Reappearance of arteriolar capillaries 24 hours after plaque removal was resumed.

resumed, and **Figure 6** presents the measurement of the ratios of vessel diameter, mean flow, and peak flow rate in these microvessels, which give the maximum acceleration/mean velocity ratio, as described by Buschmann et al. [18].

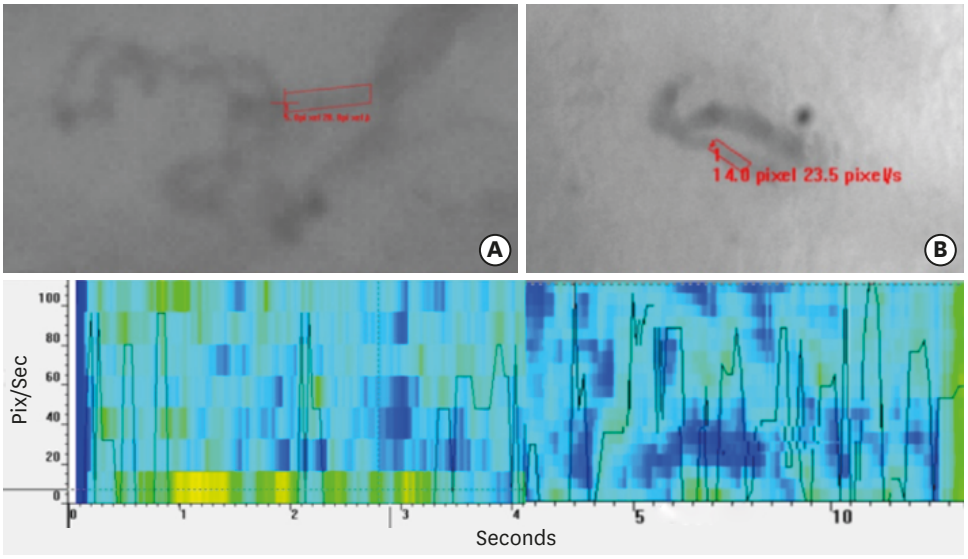

Figure 6. KK Technology software was used to measure peak and mean blood velocity in efferent and afferent capillary loops. (A) High peak acceleration typical of arteriolar flow. (B) Low peak acceleration relative to the mean flow, typical of venous capillaries.

https://doi.org/10.5051/jpis.2101160058

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DISCUSSION

Dynamic OCT, laser speckle contrast imaging, and capillaroscopy all detected wide variation in vascular indices in participants after 3 weeks of plaque accumulation. Capillaroscopic images displayed a significant reduction in flow in microvessels after 3 weeks of plaque accumulation; however, there was no measurable flow in 9 cases, which may have been an artifact due to pressure on the microvessels by the capillaroscope. These values were excluded from the results; but this suggests that the assumption of reduced flow should be accepted with caution. There was only a slight increase in diameter of the gingival vessels, but many loops were imaged end-on making automated measurements unreliable; the software often measured the loop width rather than the vessel diameter. Dynamic OCT showed no mean change in microvessel numbers after 3 weeks of plaque accumulation, but again there was a marked diversity in vascular reactions among participants at 3 weeks.

In the laser perfusion imaging flux images, there was a significant reduction in flux in the first 2 weeks of plaque accumulation. This was expected as capillaries dilate as part of the inflammatory reaction to plaque. By 3 weeks of plaque accumulation, some individuals had continued reduced flux, but others had developed increased capillary flux, suggesting a different reaction to plaque in these individuals. Braverman showed that areas with healthy arteriolar capillary flow can be identified by their relative proximity to an underlying ascending arteriole. Low-flux areas with a large number of moving red blood cells tend to be predominantly venular [16,17]. All participants who showed a continued reduction in flux at 3 weeks also had an increased mean distance, and all participants with an increased flux at 3 weeks had a reduced mean distance. This suggests that flux returning to baseline levels was associated with arterial capillary flow and that reduced flux at 3 weeks was associated with the development of venular capillary flow. It has recently been shown that it is possible to reliably classify a capillary as arteriolar of venular by measuring the flow in the lumen [18]. There was clear evidence of development of venous capillaries in 1 individual after 3 weeks of plaque accumulation. These venous capillaries underwent destruction with reappearance of arterial capillaries when plaque removal was recommenced. Whilst there was clear evidence of breakdown of venous capillaries with extravasated blood, the very short time span until the reappearance of arteriolar capillaries may have been due to a hydrostatic effect as opposed to any growth of new arteriolar capillaries. Local tissue oedema can exert hydrostatic pressure effects on the microcirculation, and this is capable of closing capillary circuits and reducing local flow. The early reappearance of arteriolar capillaries following resumption of brushing may have been due to the reopening of existing capillaries.

The pathophysiology of periodontal breakdown in periodontitis is reasonably well understood; in a published review of current knowledge in 2014, Cekici et al. [26] stated “There is evidence that specific microbes are associated with periodontitis; however, the presence of these microorganisms in individuals with no evidence of disease progression suggests that the disease is the net effect of the immune response and the inflammatory process, not the mere presence of the bacteria”. In 1994, Neymeth et al. [27] showed that in periodontitis there was significant proliferation of the endothelial cell population, but vessel numbers remained at a constant level as the creation of new capillaries and venules was matched by their destruction. *Porphyromonas gingivalis* is believed to play a key role in the development and maintenance of inflammation in periodontal pockets, and a key feature of *P. gingivalis* is its inability to synthesize the proto-porphyrin ring and hence its dependence on a source of haem [28]. A host microvascular reaction that favours the development of fragile capillary venules over more

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robust arteriolar capillaries may support colonisation of the tissues by *P. gingivalis* and hence an increased sussceptibility to periodontal inflammation. Cardiovascular disease is associated with dilation of capillary loops, a change from arterial capillaries to venous capillaries, and loss of the endothelial glycocalyx [29]. Development of venous capillary loops is also one of the first changes that occurs in psoriasis; the endothelial cells divide to lengthen the venous limb of the loop [16,30]. Almost identical changes occur in rheumatoid arthritis, with increased dilation of the efferent and afferent limb of the capillary loop. Patients with greater skin capillary loop changes experience a significantly longer duration of disease and a higher frequency of joint erosions [31]. Identical venous capillary changes occur in patients with Sjögren syndrome [32]. This is interesting as there is a significant association linking periodontitis, cardiovascular disease, Sjögren syndrome, rheumatoid arthritis, and psoriasis; these all have an inflammatory element that is associated with microvascular proliferation, and a significant increase in venous capillaries is a feature of the disease process in all of these conditions [33-36].

The systemic diseases associated with periodontitis all involve the development of venous capillaries as a significant part of the pathological process [16,29-32]. Fragile venous capillaries could be a source of haem for the proliferation of *P. gingivalis* in patients who develop periodontitis [28]. This might also explain why a disease caused by bacteria is associated with systemic diseases not caused by bacteria, whilst at the same time periodontitis is not usually associated with other infective diseases. Thurston studied endothelial proliferation during infection and found that mice strains showing a proliferative vascular response are better able to control and localize infections than strains showing vascular expansion, which were less able to control infections. The initial vascular response in both strains is the same, with vessel enlargement; in C57BL/6 mice, this is followed by the growth of new capillaries and venules. In CH3 mice, the enlargement is followed by conversion into venule-like vessels and a much higher mortality rate [37,38]. Epithelial cell proliferation occurs early in the inflammatory process, reaching a peak in the first 5 days, which occurs before the other tissue changes in response to the infection. This suggests a fundamental difference in the host response mediated through the vascular reaction to bacteria.

This discussion would be incomplete without mentioning the vaso-destructive nature of diabetes and smoking and their contribution to the worsening of periodontal disease. It may be that capillary flow and oxygenation influence microvascular glycocalyx stability and therefore morphology; this would be the reverse concept, with capillary flow being reactive to tissue conditions rather than driving those changes. In this case a single unified hypothesis would concur with the evidence regarding inflammatory disease and explain the microvascular findings.

Our study only investigated the development of gingivitis and any link to periodontitis is purely theoretical; in addition to this, it is important to note that the small number of participants has made it impossible to remove possible confounding factors in the statistical analysis such as age, sex, and ethnicity. However, recent 3-dimensional histochemical analyses and imaging studies of the human gingiva have confirmed the presence of many tortuous dilated capillaries and shown some evidence of the loss of the endothelial glycocalyx and low oxygen saturation in afferent and efferent arms of the capillary loop, also suggesting a shift to venular capillaries [19,20]. The present study has confirmed evidence from previous studies of a disparity in gingival flux in different participants after 3 weeks of plaque accumulation, and we also found evidence of the development of venous capillaries, which are replaced by arteriolar capillaries during tissue recovery.

https://doi.org/10.5051/jpis.2101160058

Future investigations of microvascular changes in gingival and periodontal inflammation in humans might benefit from accurate capillary flow velocity measurements. The validation of the *in vivo* differentiation of venous and arterial capillaries by Buschmann et al. [18] should be a major help in improving our understanding of the growth and destruction of microvessels; however accurate flow measurements are essential for this technique. The transformation of arteriolar capillaries to venular capillaries is an early feature of all diseases associated with periodontal breakdown in humans. Microvascular imaging in gingival tissues can be used to identify the transition to venular capillaries and could help our understanding of why some people develop periodontal breakdown whilst others do not.

ACKNOWLEDGEMENTS

This research forms part of a PhD thesis supported by Health Education England.

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