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Review

Oral microcirculation observed *in vivo* by videocapillaroscopy: a review

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Abstract: Capillaroscopy is a non-invasive diagnostic technique that is fundamental in viewing peripheral circulation and in studying microangiopathies. The morphological study of microcirculation is of fundamental importance, mainly because the microvascular bed is directly involved in the etiopathogenesis of autoimmune disorders and acute and chronic inflammatory pathological conditions. The value of capillaroscopic investigation as a diagnostic means in cases of peripheral microcirculation disorders has been confirmed by numerous studies. Other studies used capillaroscopic investigations to evaluate microcirculation damage not as a complication of disease (diabetes), but as its initial stage, and therefore to make a diagnosis. Capillaroscopy is an interesting method of studying microcirculation, because of the possibility of studying small vessels in vivo by means of a microscope. Today, it has become more reliable, thanks to the development of observation tools (photography, videomicroscopy). This review describes in detail various aspects of the microcirculation of the oral mucosa. (J Oral Sci 51, 1-10, 2009)

Keywords: Oral capillaroscopy; microcirculation.

Introduction

Capillaroscopy is a non-invasive diagnostic technique, fundamental in viewing peripheral circulation and in studying microangiopathies, which are the manifestations of numerous pathologies, in both the diagnostic and monitoring phases of the disease. The alterations in the capillaroscopic picture can represent, in fact, the only documentary evidence of an incipient disease. Capillaroscopy permits timely monitoring of any disease affecting the microcirculation. Literature concerning capillaroscopy has documented how the data concerning position, form, capillary caliber and architectural framework differ at various investigation centres. To our knowledge, a simple, non-invasive method, such as videocapillaroscopy, has never been used to observe the microcirculation characteristics of the human oral mucosa. The morphological study of microcirculation is of fundamental importance, mainly because the microvascular bed is directly involved in the etiopathogenesis of autoimmune pathologies and acute and chronic inflammatory disorders. The value of capillaroscopic investigation as a diagnostic means in cases of peripheral microcirculation damage has been confirmed by numerous studies. Using this method, Halfoun showed that diabetic patients have capillary flow regulation abnormalities (1) and Haak showed that the nervous reflex arcs are impaired in diabetic patients (2). Other studies used capillaroscopic investigations to evaluate microcirculation damage not as a complication of disease (diabetes), but as an initial stage, and therefore to make a diagnosis. The definition of normal or pathological conditions can be dictated by differences in the loop diameter or length, by architectural disorders or by the presence of morphological abnormalities and micro haemorrhages. It is common knowledge that for the defence cells to perform their function, some receptors must be expressed, even in correspondence with the endothelium wall, so that haptotaxis can occur. Since this is the first step of nonspecific defence, it is clear that its alteration involves a greater vulnerability in the subject. The contact of lymphocytes and plasmocytes with the vascular wall

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confirms the trigger role of the vascular factor in damaging the periodontal complex. These morphological data appear extremely relevant, since they would certainly be altered during particular systemic pathologies (systemic sclerosis, autoimmune pathologies, potentially malignant lesions, malignant lesions, inflammatory diseases), and even in the case of exposure to particular risk factors, such as smoking and chewing tobacco (3,4). It follows that capillaroscopy is an interesting way of studying microcirculation because of the possibility of examining small vessels *in vivo* by means of a microscope. Today, it has become more reliable, thanks to the development of observation tools (photography, videomicroscopy). In this review, various aspects of microcirculation of the oral mucosa are discussed.

Oral capillaroscopy: technique and parameters

Oral capillaroscopy is a panoramic technique that uses computerised videomicroscopic techniques and related software (DS Medigroup, Milan, Italy). The optical probe videomicroscope is composed of a main unit, to which an optical probe with video-optical terminal is connected, and a high-resolution colour monitor to view the examined area. The optics has a focal fleck of 1.811 mm. The main unit consists of a cold halogen light source emitted by a 100 W lamp equipped with an electronic device to control light intensity and a processing unit for the high-definition video signal (420,000 pixels) equipped with a colour calibration device. The probe is equipped with a video-optical terminal containing a high-definition video sensor, by which different variable magnification optics from ×10 to ×1,000 can be applied. The video-optical terminal helps to focus directly from the hand piece. Image digitalization allows for the analysis of the fundamental parameters of microcirculation (calibre and length vessel), and the calculation of the number of capillaries per mm^2 of the mucosa examined. The capillaroscopic investigation is performed with the patients in a sitting position, with the same light source, at the same room temperature (23°C), in the morning, usually by the same operator and repeated twice for each examined area. Generally, two independent observers examine all the images. The intraobserver and interobsever variability are assessed with the two observers evaluating the same randomly selected images twice (5,6). The following static parameters are used:

A) Non-parametric data: (Table 1)

a) Capillary loop visibility (marks from 1 to 4): (1) simple focusing – within 30 s from the beginning of the examination; (2) average focusing – over 30 s and within 2 min; (3) difficult focusing – over 2 min; (4) impossible focusing;

b) Orientation to the surface (marks A, B or AB): (A) capillary loop course parallel to the surface; (B) capillary loop course perpendicular to the surface; (AB) both parallel and perpendicular;

c) Microhemorrhages (marks 0 or 1): (0) absence; (1) presence;

d) Characteristics of the capillary loops (marks 0 or 1): (0) absence; (1) presence.

B) Parametric data:

a) Number of visible capillary loops per square millimetre (value obtained from the average of the two observations for examined area);

b) Capillary loop caliber (values obtained from the average of the two observations for each examined area).

c) Tortuosity - number of crossings in the capillary loop (value obtained from the average of the two observations for examined area).

As for the parametric data, it must be emphasised that they originate from the software connected to the videocapillaroscope. The system is specifically calibrated: an exact metric pixel value to every optical magnification corresponds in the digitalised image; therefore, the capillary calibre can be measured with a high degree of precision.

Analysis of the microcirculation in oral mucosa of healthy patients

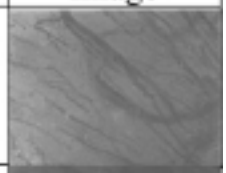
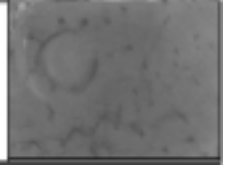
Oral capillaroscopy was used to investigate oral or systemic diseases. For this reason, the first aspect analysed by the videocapillaroscopy was the microcirculation of all the sites of the oral mucosa in healthy patients (7). This study was essential to identify the eventual abnormalities in the sites in presence of pathology. The sites or objects of analysis of oral capillaroscopy are:

a) Lip mucosa: Generally, this is the site with the clearest visibility for easy positioning of the probe and for the clearance of the patients. The capillaries lie parallel to the surface. The presence of the crossing is normal in number. There is no microhemorrhage. A small variation in the inclination of the probe permits good visibility of the capillary loop (Fig. 1).

b) Buccal mucosa: This site is a zone with restricted access and its visibility depends on the mouth opening of the patients. The capillaries lie parallel to the surface. Rarely, it is possible to find an orientation both parallel and perpendicular to the surface. There is no microhemorrhage. The presence of the crossing is normal in number (Fig. 2).

c) Tongue mucosa: This is a very interesting site for observing the arborescent course of the capillary

Table 1 Non-parametric data

Non-parametric data	Mark	Feature	Image
Capillary loop visibility	1	Simple focusing	
	2	Average focusing	
	3	Difficult focusing	
	4	Impossible focusing	
Orientation to the surface	A	Capillary loop course parallel to the surface	
	B	Capillary loop course perpendicular to the surface	
	AB	Both parallel and perpendicular	
Microhemorrhages	0	Absence	
	1	Presence	
Characteristics of the capillary loops	0	Absence	
	1	Presence	

(Fig. 3) and for the visualization of the papillary microcirculation (Fig. 4) (8). The visibility of the microcirculation of the ventral surface of the tongue is good, but it must be rapid, causing lower clearance of the patient. The papillary microvascular complex is not always appreciable.

d) Periodontal mucosa: This is the site mostly used as the object of analysis. Periodontal local microcirculation can be morphologically divided into two areas: the gingival margin and the interdental papilla. In the gingival margin, the capillaries run perpendicular to the surface and the microcirculation morphology can be described as type II of Curri classification; it is possible to observe the apex of the capillary loop, which is shaped like a comma (9). It is not possible to study the loop, or the afferent and efferent loop diameter. On the contrary, in the interdental papilla, the loops mainly run parallel to the surface. The microcirculation architecture of interdental papilla is described as type I of Curri classification (polygonal-meshed capillary net with a pattern parallel to the surface), with some aspects more similar to group B (long capillary loops with even calibre and hairpin shape) than to group A (short, stubby, rather wide loops with a stirrup morphology) (9). Therefore, it is clear that the study of capillary morphology can only be carried out in relation to the papilla; on the other hand, capillary density can be observed at the margin. From the study of capillary microcirculation morphology, the presence of characteristic (“hairpin-shaped”) capillaries can be noticed; the arterial and venous ends with their different diameters can be easily identified; and the presence and number of capillary crossing can

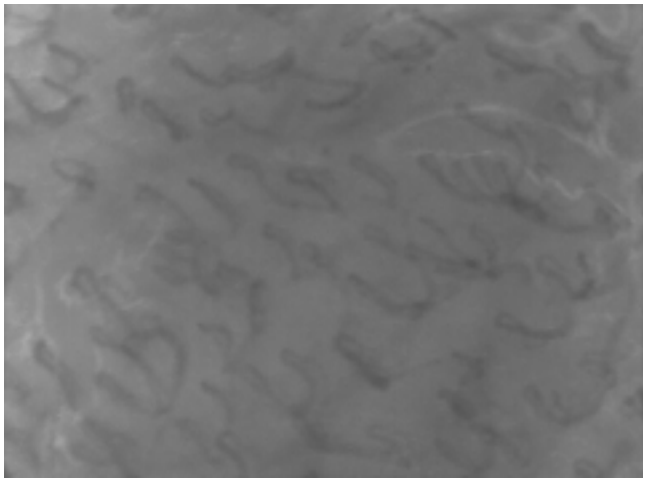


Fig. 1 Oral labial microcirculation (magnification ×200).

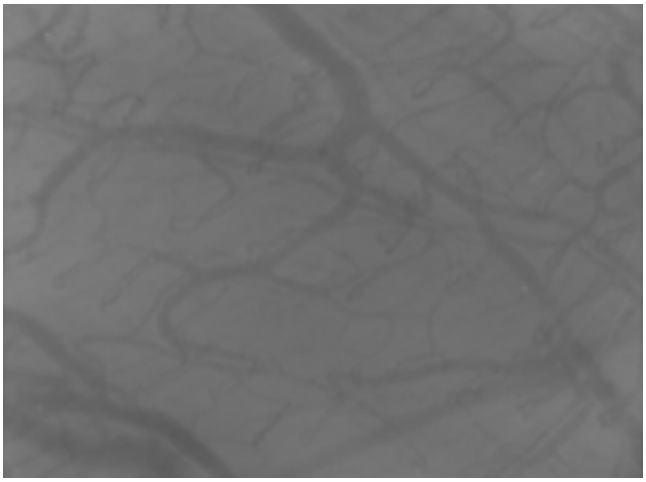


Fig. 3 Lingual microcirculation (magnification ×200).

Fig. 2 Oral buccal microcirculation (magnification ×200).

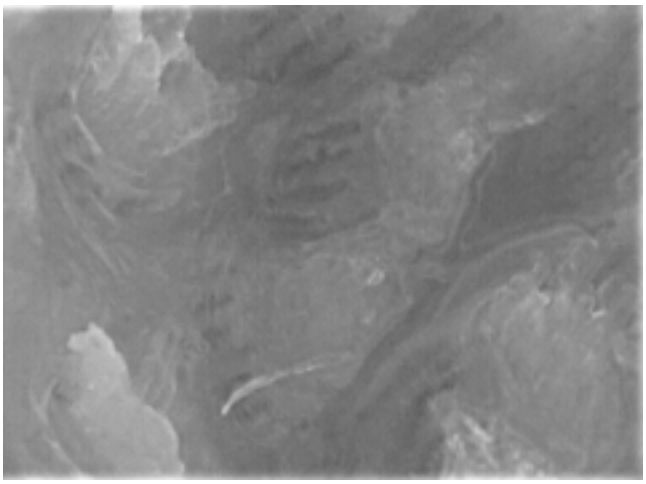


Fig. 4 Papillary lingual microcirculation (magnification ×200).

also be detected. The loops examined showed a variable pattern; beside those with the typical stirrup shape, there were others with a hairpin, comma and corkscrew shape, as well as rare micro haemorrhages in the form of reddish spots, which could be traced back to possible micro traumas. Particularly interesting was the discovery of characteristic (tortuous, branched) loops (10) (Fig. 5).

Oral capillaroscopy and autoimmune pathologies

The oral capillaroscopy was used to investigate many autoimmune pathologies, including:

a) Oral lichen planus (OPL): Lichen planus is a chronic inflammatory pathology with autoimmune etiology (11), which frequently involves the oral mucosa, either with the skin surface, or independently and precociously. It affects about 0.5-2% of the global population (with an incidence varying according to the geographical location), mainly women; it begins on average between the ages of 40 and 50. OLP (12) develops on the buccal mucosa in 60-70% of cases. Particularly interesting is the examination finding of the gingival mucosa, which, although it cannot always be examined in depth because of its frequently excessive keratinisation, proved to be the best site for showing the increase in capillary density, which is the only unequivocal sign linked to angiogenetic activity. The capillaroscopic patterns give us a snapshot of the oral mucosa *in vivo*, showing alterations, either significant or not, especially in parameters such as vessel diameter, capillary density, loop tortuosity and length. A review of previously published studies concluded that the risk of developing squamous cell carcinoma in patients with oral lichen planus was approximately 10 times higher than that in the unaffected general population. The study of the microcirculation in lingual lichen planus (LLP) would be important in the interception of the evolution of LLP (13,14). Capillaroscopy applied to lingual mucosa is a reliable method, useful for study and monitoring of oral lichen planus, if combined with the current conventional methods (15,16). A pathological condition is characterised by an apparent architectural disorder and/or by the presence of morphological anomalies. The capillaroscopic method might also be useful to check the effectiveness of a selected therapeutic protocol (17). It can permit a comparison of the characteristics of pre- and post-treatment local microcirculation, as well as an objectification or parameterization of an aspect of the program, often relying on patient information (symptoms) or on clinician evaluation (16). The capillaroscopic patterns illustrate alterations, either significant or not, in the lingual mucosa in vivo, especially for parameters such as vessel diameter and capillary density. In the final analysis, thanks to videocapillaroscopy, the lingual mucosa could serve as a reliable indicator of the evolutionary condition of inflammatory conditions such as LLP, allowing the oral surgeon to evaluate in vivo the effectiveness of ongoing pharmacological therapies, the patient's state of health, the evolution or regression phases of a certain pathology, and all those microstructure alterations of the vascular system useful for predicting and monitoring the progress of a systemic and/or topical pathological condition based on an angiogenesis process (12) (Fig. 6).

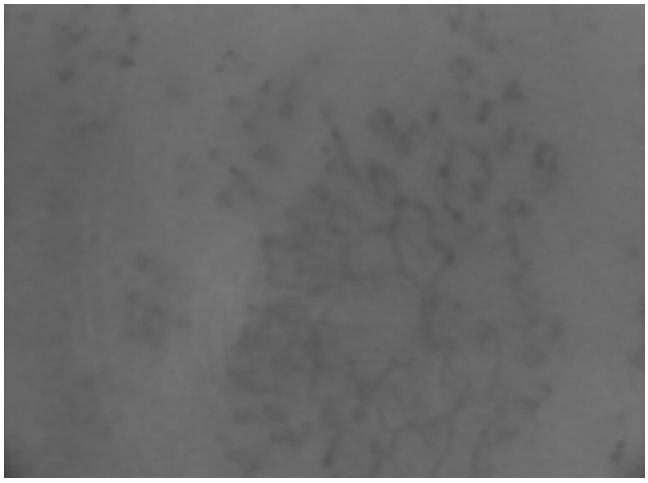


Fig. 5 Periodontal microcirculation (magnification ×200).

b) Hashimoto's thyroiditis: The *in vivo* microvascular characteristics of the labial and lingual mucosa were observed in Hashimoto's thyroiditis patients affected by macroglossia. Capillaroscopic alterations during Hashimoto's thyroiditis affect the oral mucous peripheral circulation. Labial capillaroscopy in patients with Hashimoto's thyroiditis revealed significant microvascular changes compared to the controls (Fig. 7). The lingual capillaroscopic pattern in patients with Hashimoto's thyroiditis is recognisable by direct evaluation and is characterised by:
   - wide architectural disorganisation;
   - loosening of the U shape capillaries with a high degree of heterogeneity in shapes characterised by reduced calibre;
   - reduced capillary density corresponding to lingual microcirculation (18).

c) Rheumatoid arthritis (RA): Recent studies seem to assert the existence of a relationship between periodontal disease and RA (19-27). Some authors even affirm that the two diseases have so much in common that they represent the same disease (28). In recent literature reviews, the lack of a relationship between the two diseases observed in some studies seems to be ascribable to limitations of the studies themselves. In fact, they possibly did not make a careful evaluation of two aspects, which certainly play a fundamental role in the relationship between the two diseases; i.e., the duration of the systemic disease and its greater or lesser intensity. Another aspect which must not be underestimated is represented by the possible therapeutic RA program, which could interfere with the pathogenesis of periodontal disease, making the observation of a relationship between the two diseases more difficult. The existence of a specific capillaroscopic pattern in RA patients is a matter of debate. Schumacher excluded the presence of specific alterations in RA (29). Other authors found aspecific capillaroscopic alterations (30-33). According to these authors, abnormalities consisted of elongated and tiny loops, microhemorrhages, low capillary density, and subpapillary venous plexus visibility alterations. Although they did not seem to be pathognomonic for RA, they do appear to be sufficiently characterised as to differentiate patients with RA from normal controls (34-38). The hypotheses on the pathogenic mechanism of vascular damage involve the auto-antibody and circulating immune complex precipitation in the vessel walls, considered to be the main cause of damage. Endothelial cells and their products participate in the initiation and progression of tissue damage (39,40). The vascular damage is also correlated to the production of osteopretogerin (OPG) by endothelial cells. OPG has been reported to be required for endothelial cell survival and growth. In addition, OPG knock-out mice have been shown to develop microvascular damage, suggesting that vascular endothelial expression of OPG may have a role in vascular homeostasis. Capillaroscopy is a very interesting method for studying microcirculation because of the possibility of studying small vessels *in vivo* by means of a microscope. Today, it has become more reliable, thanks to the development of the observation tools (photography, videomicroscopy). It is demonstrated that the periodontal microcirculation is characteristic in RA patients. The periodontal capillaroscopic pattern is recognizable through direct evaluation and is characterised by reduced caliber and greater length and tortuosity of capillaries (41) (Fig. 8).

d) Sjögren's syndrome (SS): The labial microcirculation of the patients affected by SS has a parallel course

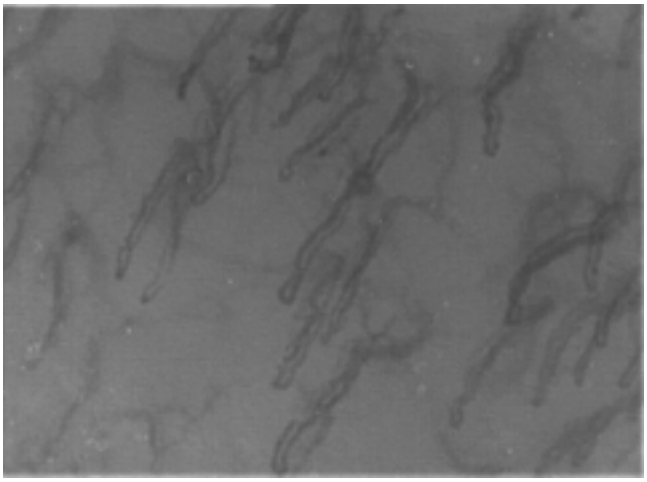


Fig. 6 Oral lichen planus microcirculation (magnification ×200).

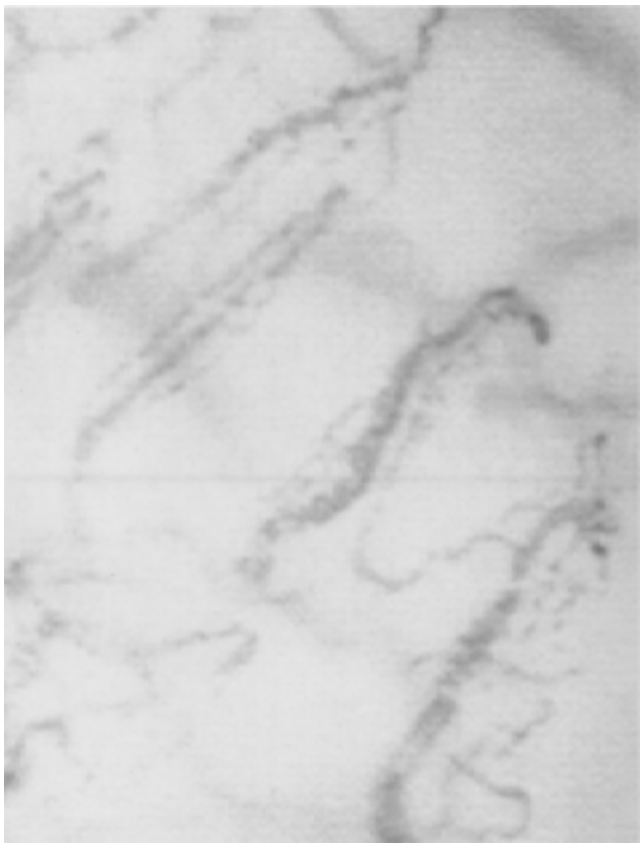


Fig. 7 Hashimoto's thyroiditis oral microcirculation (magnification ×200).

to the surface. Some patients exhibit a smaller quota of capillaries directed perpendicular together with the capillaries having a parallel course. This pattern is a peculiar characteristic of the labial vessels. The SS patients, in fact, present a peculiar morphology of the small capillaries that introduces a similar C shape. In some cases, it is associated with the presence of an abnormal conformation of a whole group of capillaries. This shape has not been recovered so far in any capillaroscopic picture of patients affected by other autoimmune disorders. The collateral microcirculation shows a continuous course that is constituted by capillaries whose limits appear indistinguishable. This peculiar microcirculation assumes a semilunar form or a great C shape that has a notable diameter because its limits do not join (Fig. 9). The presence of small capillaries with C shape and semilunar microcirculation comprise the capillaroscopic pattern of SS.

e) Systemic sclerosis (SSc): Capillary alterations in patients with SSc are not limited to the nailfold bed but also manifest in periodontal mucosa microcirculation. Such evidence could be extremely important in the pathogenesis and treatment of periodontal diseases in patients with SSc (42).

Oral capillaroscopy and burning mouth syndrome (BMS)

The application of capillaroscopy has led to very important diagnostic results regarding the alterations of the local microcirculation in patients with BMS when compared with healthy subjects. The IASP (International Association for the Study of Pain) has defined this condition as a burning sensation of the tongue and/or other mucosa of the oral cavity, where local pathologies and lesions are absent (43). Due to the absence of a clear clinical objective assessment for this disorder and the lack of a definite understanding of its etiopathogenesis, the clinical interpretation and treatment of BMS remains problematic. A local circulatory disturbance of the areas affected by BMS could contribute to the burning sensation described by patients. A disturbed regulation of the mucosal blood circulation plays a part in the symptomatology of BMS; in other words, it seems that BMS results from, or affects, the neurovascular microcirculatory unit (microcirculatory control of the sensory and autonomic innervation). The capillaroscopic examination allowed us to detect a difference between patients with BMS and healthy individuals in the diameters of the capillary and afferent and efferent ansae; in fact, the diameter of the ansae in patients with BMS shows a statistically significant increase when compared with healthy mucosa. The vascular inflammation develops mainly in correspondence with the microcirculation, in the peripheral blood circulation (36). This process can be described as a sequence of the following events: vascular modifications of the microcirculation, in particular variations in the vascular diameter and haematic flow; alterations of the blood-interstitial fluid exchange that leads to formation of exudate; and migration of leucocytes from the blood vessels toward the interstitial space. These vascular modifications during vascular inflammation induce an active hyperaemia, due to the increase in the blood flow in the capillaries causing the typical symptoms, calor and rubor, and a passive hyperaemia, triggered by the blood flow slowing down, subsequently followed by stasis. This condition can be

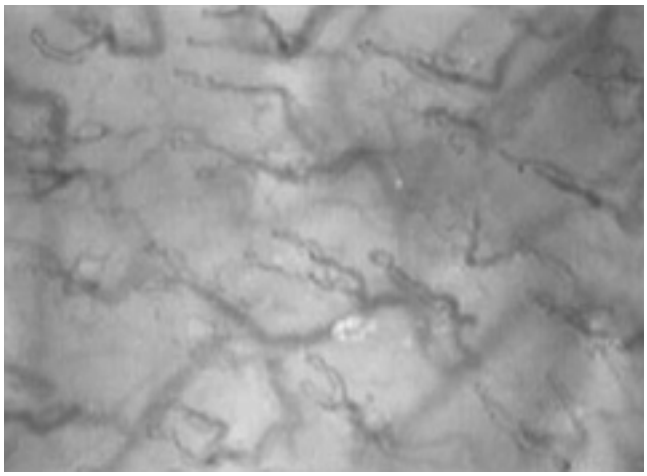


Fig. 8 Rheumatoid arthritis oral microcirculation (magnification ×200).

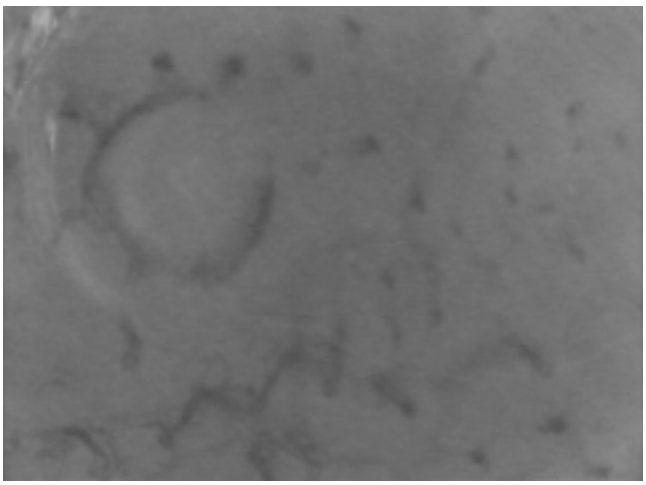


Fig. 9 Sjögren's syndrome oral microcirculation (magnification ×200).

brought on by different factors, such as an increase in the size of the circulatory bed and/or an increase of blood viscosity levels mainly caused by aggregation of the red blood cells, or the margination of the leukocytes that adhere to the endothelial wall; these are attracted through a chemotactic process triggered by chemokines. The biggest question remains whether the alterations herein observed are a mere consequence of the symptoms of BMS, or whether they reflect a possible cause of the disorder. Furthermore, the presence of these alterations can be useful in establishing novel approaches to investigate therapeutic effects of drugs (44-46) (Fig. 10).

New field of study for oral capillaroscopy

a) Peri-implant microcirculation: Characteristics of the peripheral microcirculation *in vivo* can be used to assess whether the vascular pattern of the mucosa at peri-implant sites differs from that around teeth. With respect to the vascular pattern, the oral video-capillaroscopy revealed very interesting findings of peri-implant microcirculation changes in patients with implants compared to control. During the observation time, reconstitution of a vascular pattern that allowed adequate blood supply of the peri-implant tissue was detected in all areas; in particular, the capillaroscopy analysis revealed an increased capillary density in patients bearing implants compared to control patients. This was confirmed by the statistical analysis which indicated a highly significant difference in the parameter indicating the density. The authors demonstrated in vivo what had been previously shown by others – i.e. the vascular pattern of peri-implant tissue is characterised by an increase in the capillary number – and, moreover, in 30% of the cases the vessels are disposed parallel rather than perpendicular to the surface. Therefore, the results indicate that the vascular pattern of peri-implant sites is distinct and different from that of the gingival mucosa around teeth. Thus, another difference can be identified in the peripheral microcirculation that distinguishes the structure of the periodontal ligament from the peri-implant anatomy (47) (Fig.11).

b) Acupuncture: Today, the management of odonto-stomatological patients can make use of more and more innovative methodologies, sometimes supported by other branches of medicine. Examples are videocapillaroscopy and acupuncture. Acupuncture together with videocapillaroscopy can represent a downright innovation characterised by remarkable and numerous advantages. Recently, so-called "alternative medicine" has become more popular as one of the therapeutic algorithms in almost every branch of medicine. The ancient stimulation art of specific energetic centres is an easy and reliable methodology. Acupuncture in odontostomatological patients is a new and interesting methodology that makes use of alteration of patient's perception and tranquillizing effects in order to make diagnostic and sometimes therapeutic management easier. Videocapillaroscopy is not an invasive procedure, thus holding remarkable importance in the diagnostic phase, and also it has an important epidemiological effect. This methodology allows us, in fact, to observe and to study *in vivo* the effects in oral microcirculation of both alternative methodologies like acupuncture and routine dental procedures and to evaluate the effects of topical application of drugs used to manage oral mucosal pathologies and the effects of systemic therapies on

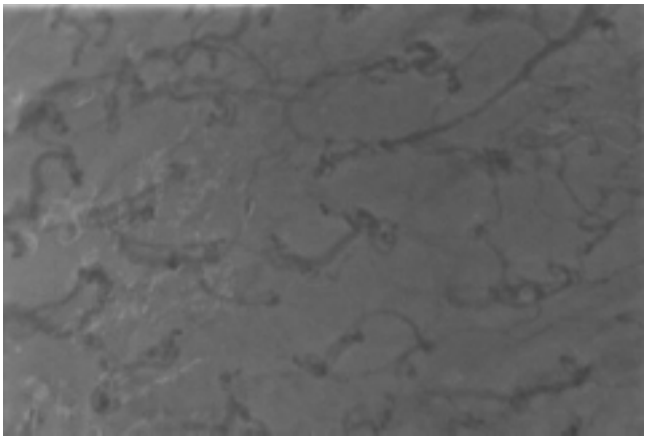


Fig. 10 Burning mouth syndrome microcirculation (magnification ×200).

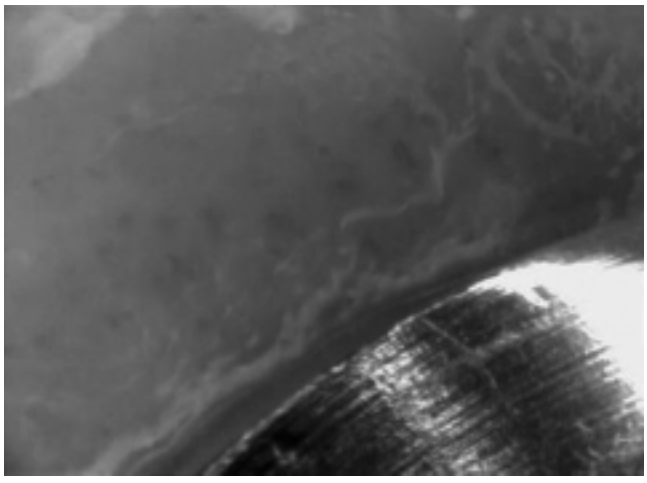


Fig. 11 Periimplant microcirculation (magnification ×200).

oral mucosa. The knowledge of these new methodologies may improve the management of odontostomatogical patients and may expand our understanding of the etiopathogenesis and treatment of oral pathological conditions.

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