ORIGINAL ARTICLE

# Microcirculation disorders of the oral cavity in patients with primary Raynaud phenomenon

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**KEY WORDS**

microcirculation dysfunction, oral cavity lesions, Raynaud phenomenon

**ABSTRACT**

**INTRODUCTION** Raynaud phenomenon is a medical condition in which the spasm of the arteries causes episodes of reduced blood flow. Potential disorders in the microcirculation of the oral mucosa may promote the occurrence of lesions.

**OBJECTIVES** The aim of the study was to investigate the association of the frequency of oral cavity lesions with oral microcirculatory dysfunction in patients with primary Raynaud phenomenon (PRP) in comparison with healthy control group.

**PATIENTS AND METHODS** Measurements of oral capillary flow were performed using laser doppler flowmetry (LDF) in 61 patients with PRP. In a group of 31 of 61 patients (group 1), the measurements were made during a Raynaud phenomenon (RP) attack. The RP attack was caused by stress initiated by the examination or the first visit itself. The RP attack was not deliberately caused by a cold test, vibration40w56 or any stress test. After 10 to 14 days, the measurements were repeated in all 61 patients and in the control group, and a dental examination was performed. Follow-up visits were conducted every 3 months for a period of 12 months to monitor oral mucosa.

**RESULTS** Differences in LDF were found between various anatomical points in both the PRP and control groups. On the first visit, the LDF flow in group 1 was significantly lower at all examined points in comparison with those in the control group. On the second visit, differences were observed in the LDF of the teeth and oral mucosa temperature in all patients with PRP in comparison with controls. Oral cavity lesions reported in the past and at follow-up were significantly more common in patients with PRP.

**CONCLUSIONS** Patients with PRP have dysfunction in the microcirculation of the oral mucosa and they more often have lesions in the oral cavity.

**INTRODUCTION** Primary Raynaud phenomenon (PRP) is the paroxysmal reversible vasoconstrictive reaction of the small vessel arteries and arterioles in response to stress or low temperatures, which cause limited pallor and subsequently cyanosis, as well as redness of the fingers and toes.[1] It can also affect the lips, auricles, nose, and tongue.[2-4] An RP attack may occur at irregular frequencies and lengths, from a single annual episode to multiple times a day, lasting a few minutes to a couple of hours.[5] Primary independent Raynaud phenomenon is not accompanied by an underlying disease, being the direct cause of paroxysmal vasospasm. Between attacks in patients with PRP, physical examination is usually within the normal limits. The incidence of PRP varies from 3.0% to 9.6%, depending on sex, country, and occupational exposure to cold, vibration, and stress.[6-10] Capillaroscopy and laboratory tests allow the differentiation and exclusion of secondary Raynaud symptoms, most commonly found in connective tissue diseases.[2] Moreover, noninvasive measurement of capillary flow using the laser Doppler flowmetry (LDF) method is helpful in assessing microcirculation and differentiation of primary and secondary Raynaud phenomenon.[11] Potential dysfunction in the microcirculation of the oral mucosa may promote the occurrence of lesions. For this reason, examination of microvascular circulation is one of the best methods for the diagnosis of pathological changes, since there are no clinical parameters available that would

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**TABLE 1** Demographics and basic characteristics of the examined groups

| Parameter | Group 1 (n = 31) | Group 2 (n = 30) | Control (n = 50) | *P* value |
|---|---|---|---|---|
| Age, y, median (IQR) | 24 (20–27) | 23 (20–28) | 22.5 (20–26) | NS |
| Sex, female/male | 22/9 | 20/10 | 35/15 | NS |
| Thyroid function | Normal | Normal | Normal | – |
| RF | Negative | Negative | Negative | – |
| ANA | Negative | Negative | Negative | – |
| Smoker | No | No | No | – |
| Mean PRP duration, mo | 48 (8) | 51 (7) | – | NS |
| Mean RP attack frequency, per mo | 2 (1.5) | 3 (1.2) | – | NS |
| Vasoactive drugs | No | No | No | – |

Abbreviations: ANA, antinuclear antibodies; IQR, interquartile range; NS, nonsignificant; PRP, primary Raynaud phenomenon; RF, rheumatoid factor; RP, Raynaud phenomenon

**TABLE 2** Study timeline

| Visit 1 (enrollment) | Visit 2 (check-up) 10–14 days later | Follow-up |
|---|---|---|
| Capillary flow measurement LDF, oral mucosa temperature | Capillary flow measurement LDF, oral mucosa temperature, dental examination | Telephone call every 3 months for 12 months: an interview about the presence of trophic lesions |

Abbreviations: LDF, laser Doppler flowmetry

**TABLE 3** Study inclusion and exclusion criteria

| |
|---|
| **Inclusion criteria** |
| Symptoms of PRP as defined by LeRoy and Medsger criteria |
| Aged 18 to 35 years old |
| Informed consent for participation in the study |
| **Exclusion criteria** |
| Autoimmune diseases |
| Thyroid disorders |
| Diabetes mellitus |
| Immunosuppressive treatment within the previous 6 months |
| Dental defects potentially harming oral cavity mucosa during dental exam |
| Bleaching within the previous 3 months[17] |
| Use of orthodontic appliances within the previous 6 months |
| Movable denture use |
| Declaration of failure to brush teeth at least twice a day |
| Current smoking |
| Hypertension and the use of antihypertensive drugs; use of vasoactive or other medications that could influence blood circulation |
| Pronounced gag reflex |
| Nailfold capillary morphological abnormalities on capillaroscopy |

Abbreviations: see TABLE 1

be sufficiently reliable. Changes in microvessels usually occur prior to clinical manifestation and can be successfully used as predictors of future disease development, playing an important role in prevention, since dysfunctions in microcirculation can be detected at a very early stage of the disease.[12] In dentistry, LDF can be used to diagnose vascular flow changes in the connective tissue of mucosae.[13-16] LDF measurements within the oral cavity differ depending on the anatomical site.[13] Microcirculation of the oral mucosa has not been previously studied in patients with PRP. In the present study, we investigated the association of the frequency of oral cavity lesions with oral microcirculatory dysfunction in patients with PRP in comparison with a healthy control group.

**PATIENTS AND METHODS** Patients enrolled in the present study were admitted for the first time to the microvascular disorder clinic at an angiology center, presenting with symptoms of PRP as defined by the LeRoy and Medsger criteria.[1] A total of 61 patients met the study criteria: 42 women and 19 men at a median age of 24 years (interquartile range [IQR, 20–27], and capillary flow was measured using LDF on the oral mucosa, teeth, and lower lip vermilion (TABLE 1).[1,17] At the same time, the temperature of the oral mucosa was measured. In 31 of the 61 patients (group 1), the measurements were performed during an unprovoked RP attack caused by the stress of their first-time visit and examination. In the remaining 30 patients, no vasospastic attack was observed (group 2). The same measurements were performed in a control group consisting of 50 healthy volunteers (35 women, 15 men) at a median age of 22.95 years (IQR, 20–26). After 10 to 14 days, during the second visit, repeated measurements of capillary flow (LDF) and oral mucosa temperature, as well as a dental examination, were performed in all 61 patients and controls. During this visit, no RP attacks were recorded either in group 1 or 2. A follow-up telephone interview was performed every 3 months for a period of 12 months to enquire about the presence of lesions in the oral cavity (TABLE 2). Moreover, thyroid function was assessed, rheumatoid factor and antinuclear antibody titers were measured, and capillaroscopic examination of nailfold capillaries was performed to exclude secondary Raynaud phenomenon.[18] All inclusion and exclusion criteria are presented in TABLE 3. All participants were asked to refrain from the consumption of any caffeinated or alcoholic beverages prior to the LDF examination.

**Measurements** Each examination was carried out in a quiet room with increased sound absorption at a temperature of 21°C to 23°C. The oral mucosa temperature was measured using the ELLAB ctd 85 system (Copenhagen, Denmark) with the ELLA PRC A probe, and expressed in °C. The probe was positioned in the mouth's vestibule at the level of the upper incisors. LDF measurements were performed using the Periflux4001 Master apparatus (Perimed AB, Jarfalla, Sweden) with the Capy Flow software package

**TABLE 4** Median laser Doppler flowmetry (periflux unit [PU]) and oral mucosa temperature (M_tmp) on visits 1 and 2 in group 1 (n = 31)

| | Visit 1 | Visit 2 | *P* value[a] |
|---|---|---|---|
| Palate | 6.9 (6.1–8.1) | 29.3 (26.9–34.7) | <0.001 |
| Gingiva | 10.7 (9.1–12.2) | 37.1 (31.1–40.1) | <0.001 |
| Buccal mucosa | 8.1 (6.5–10.9) | 33.7 (28.9–39.9) | <0.001 |
| Lip | 9.6 (7.7–11.8) | 33.8 (27.2–36.8) | <0.001 |
| Tooth 1 | 14.4 (12.8–16.6) | 15.5 (13.8–18.1) | 0.004 |
| Tooth 2 | 11.9 (10.9–13.3) | 12.9 (11.1–16.1) | 0.07 |
| M_tmp | 34.1 (33.5–34.5) | 36.2 (36–36.7) | <0.001 |

a Visit 1 vs visit 2

Data were compared using the Wilcoxon test.

Abbreviations: M_tmp, oral mucosa temperature

for registration and analysis of results. The apparatus was equipped with a probe of standard fiber separation (0.25 mm) and a 780-nm wavelength laser with a measuring depth of 0.5 to 1.2 mm. The probe was stabilized by acrylic mass on the: 1) teeth – 1/3 gingival crown of the maxillary anterior incisors; 2) palatal mucosa (Schroeder area), as previously described;[19] 3) gingiva over the maxillary anterior incisor; 4) lower lip vermilion;[20,21] and 5) internal buccal surface.

The baseline microvascular blood flow was subsequently measured for a duration of 1 minute. LDF measurements were expressed in arbitrary perfusion units (periflux unit [PU]). The degree of adhesion of the probe to the oral mucosa, teeth, and vermilion was controlled by the flowmeter sensor. Previously untreated teeth, and oral mucosae and lips without macroscopic changes were chosen for LDF measurement, which was performed by 2 angiologists with many years of experience. The intra- and interobserver reliability was calculated using the reliability statistics of intraclass correlation. The reliability was excellent for all measured parameters. No measurements were rejected for technical reasons. There were no systematic differences between the first and second measurement or between observers.

**Dental examination** During the second visit, dental examinations were performed by a certified dentist, which included the inspection and palpation of the oral cavity vestibule mucosa, main oral cavity, gingiva, lip angles, and lips. The type and topography of lesions were described and noted. Aphte were rated according to the classification into minor, major, and herpetiform lesions. In addition, the state of dentition was assessed to check for potential abnormalities that would exclude the patient from further participation in the study. Dentition state was evaluated using a dental probe and dental mirror following the procedures of a standard physical examination. Based on that exam, all patients with active dental caries, incorrect tooth fillings, or fillings that irritate mucose membrane were excluded from the study. No specific indices were used for the evaluation of dental health.

**Questionnaire** Each participant was given a questionnaire with the following questions enquiring about the frequency of RP attacks and the occurrence and type of lesions in the oral cavity in the past and their annual frequency: 1) the frequency of RP attacks: everyday; >1 × a week but not on the daily basis, 1 × in few weeks, occasionally; 2) the type of oral cavity lesions: erosion (small 2–5 mm, large >10 mm, the size of pinhead, confluence); vesicle; angle of the mouth redness or crack; other; 3) the frequency of occurrence of oral cavity lesions: reoccuring within a short period of time – seem to persist continuously; every 1 to 4 months; less frequent.

**Ethics** The study protocol was approved by Jagiellonian University Medical College Bioethics Committee. Written informed consent was provided by each participant prior to inclusion in the study. The present study was conducted in accordance with the 1963 Declaration of Helsinki and its later amendments.

**Statistical analysis** Gaussian distribution estimation of variables was performed using the Kolmogorov–Smirnov and Shapiro–Wilk normality tests. For descriptive analysis, quantitative variables are represented as the median and IQR, since they exhibited non–Gaussian distributions. Categorical variables are represented as a simple frequency and percentage. Categorical variables were estimated using the Fisher exact test. For comparison of the medians of independent variables with nonparametric distribution, the Mann–Whitney test was used, and for medians of dependent variables with nonparametric distribution, the same was applied. Correlations were tested using the Spearman rank test. For comparison of the medians of numeric variables with more than 2 categorized groups, the Kruskal–Wallis analysis of variance was used followed by the post-hoc Dunn's multiple comparison test to assess measurements between groups, and the Dunnett's test for comparison with the control when the general tests were significant.

## RESULTS

All results of LDF and temperature measurements in group 1 at visit 1 were significantly lower in comparison with those at visit 2 when a paroxysmal capillary spasm was not present and LDF flow and temperature normalization occurred (TABLE 4). At visits 1 and 2, we compared the medians of LDF measured on the palate, gingiva, lip, buccal mucosa, and teeth, as well as the oral mucosa temperature in groups 1 and 2 versus healthy controls. During the first visit, all the above measurements were significantly lower in group 1 as compared with the control (palate, 6.9 [IQR, 6.10–8.10] vs 30.80 [IQR, 25.90–38.40); gingiva,

**TABLE 5** Median capillary laser Doppler flowmetry, periflux unit, and oral mucosa temperature at visit 1 and 2

| | Group 1 (n = 31) | Group 2 (n = 30) | Control (n = 50) | *P* value |
|---|---|---|---|---|
| Visit 1 | | | | |
| Palate | 6.9 (6.1–8.1)[a] | 29.00 (26.90–33.30)[b] | 30.80 (25.90–38.40) | <0.001[a]<br>NS[b] |
| Gingiva | 10.7 (9.1–12.2)[a] | 35.55 (27.90–39.70)[b] | 38.60 (26.20–42.80) | <0.001[a]<br>NS[b] |
| Buccal mucosa | 8.1 (6.5–10.9)[a] | 39.8 (31.2–43.8)[b] | 37.75 (29.8–40.2) | <0.001[a]<br>NS[b] |
| Lip | 9.6 (7.7–11.8)[a] | 30.40 (27.20–32.90)[b] | 28.50 (21.90–34.80) | <0.001[a]<br>NS[b] |
| Tooth 1 | 14.4 (12.8–16.6)[a] | 15.15 (10.9–19.6)[b] | 21.9 (18.9–26.2) | <0.001[a]<br>NS[b] |
| Tooth 2 | 11.9 (10.9–13.3)[a] | 14.8 (11.7–20.6)[b] | 22.3 (17.9–29.8) | <0.001[a]<br>NS[b] |
| M_tmp | 34.1 (33.5–34.5)[a] | 36.55 (36.20–36.80)[b] | 36.75(36.50–36.90) | <0.001[a]<br>NS[b] |
| Visit 2 | | | | |
| Palate | 29.3 (26.90–34.70) | 31.00 (28.60–32.80) | 30.55 (26.80–36.10) | 0.7[a]<br>0.6[b] |
| Gingiva | 37.1 (31.10–39.90) | 34.80 (29.90–40.80) | 39.40 (32.20–45.50) | 0.3[a]<br>0.09[b] |
| Buccal mucosa | 33.7 (29.6–40.6) | 37.85 (29.3–50.4) | 39.25 (33.9–43.2) | 0.08[a]<br>0.1[b] |
| Lip | 33.80 (27.2–36.80) | 32.35 (27.90–37.10) | 36.20 (28.40–38.70) | 0.4[a]<br>0.3[b] |
| Tooth 1 | 15.5 (13.8–18.1)[a] | 15.85 (13.3–18.9)[b] | 25.8 (19.6–30.8) | <0.001[a]<br><0.001[b] |
| Tooth 2 | 12.9 (11.1–16.1)[a] | 15.5 (12.8–20.1)[b] | 22.3 (19.9–33.8) | <0.001[a]<br><0.001[b] |
| M_tmp | 36.40 (36.00–36.70)[a] | 36.60 (36.40–36.70)[b] | 36.70 (36.60–36.90)[a,b] | <0.001[a]<br><0.001[b] |

Data were compared using the Kruskal–Wallis analysis of variance and post-hoc Dunnett's test.

**a** Group 1 vs control

**b** Group 2 vs control

Abbreviations: see **TABLE 4**

10.7 [9.1–12.2] vs 38.60 [26.20–42.80]; buccal mucosa, 8.1 [6.5–10.9] vs 37.75 [29.8–40.2]; lip, 9.60 [7.7–11.8] vs 28.50 [21.90–34.80]; teeth 1, 14.4 [12.8–16.6] vs 21.9 [18.9–26.2]; teeth 2, 11.9 [10.9–13.3] vs 23.3 [17.9–29.8]) (**TABLE 5**, **FIGURE 1**). At these visits, LDF values were also significantly lower in group 1 than in group 2 (Supplementary material, *Table S1*) In group 2, at the first visit, no significant differences were observed in comparison with controls (**TABLE 5**); however, at the second visit, significant differences were seen in the LDF of the teeth and mucosa temperature in both PRP groups in comparison with controls (**TABLE 5**, **FIGURE 2**). At visit 2, when no RP attack was observed, we compared the LDF among different anatomical points in both RP groups and the healthy control group. Significant differences were found, with the lowest values being observed on the teeth, which has not been mentioned previously[19] (Supplementary material, *Figure S1*). During the dental examination at visit 2, 24 patients with PRP and 12 individuals from the control group had superficial lesions in the oral mucosa: minor aphtha, herpes labialis, and angular cheilitis. Oral cavity lesions confirmed at the dental visit were significantly more common in patients with PRP as compared with control individuals (**TABLE 6**). We found no direct correlation between the frequency of lesions and the frequency of vasospastic paroxysms reported by patients; however, lesions found at the dental visit were more common in group 1 as compared with group 2 (16 of 31 [51.6%] and 8 of 30 [26.66%]; $P = 0.04$) and the control group (12 of 50 [24%]; $P = 0.01$). Interestingly, oral cavity lesions reported by patients in the past as well as at follow-up visits were significantly more common in both RP groups in comparison

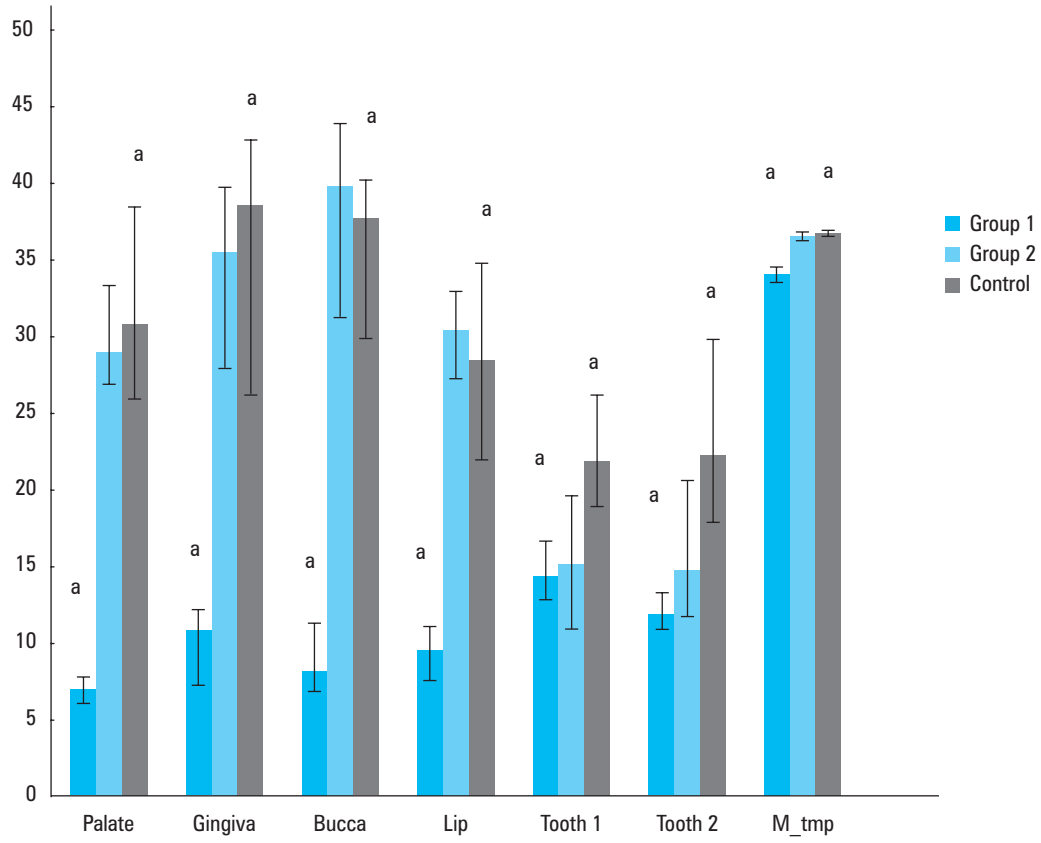


**FIGURE 1** Enrollment visit (visit 1); laser Doppler flowmetry and oral mucosa temperature (m_tmp) in groups 1, 2, and controls
**a** Significant differences

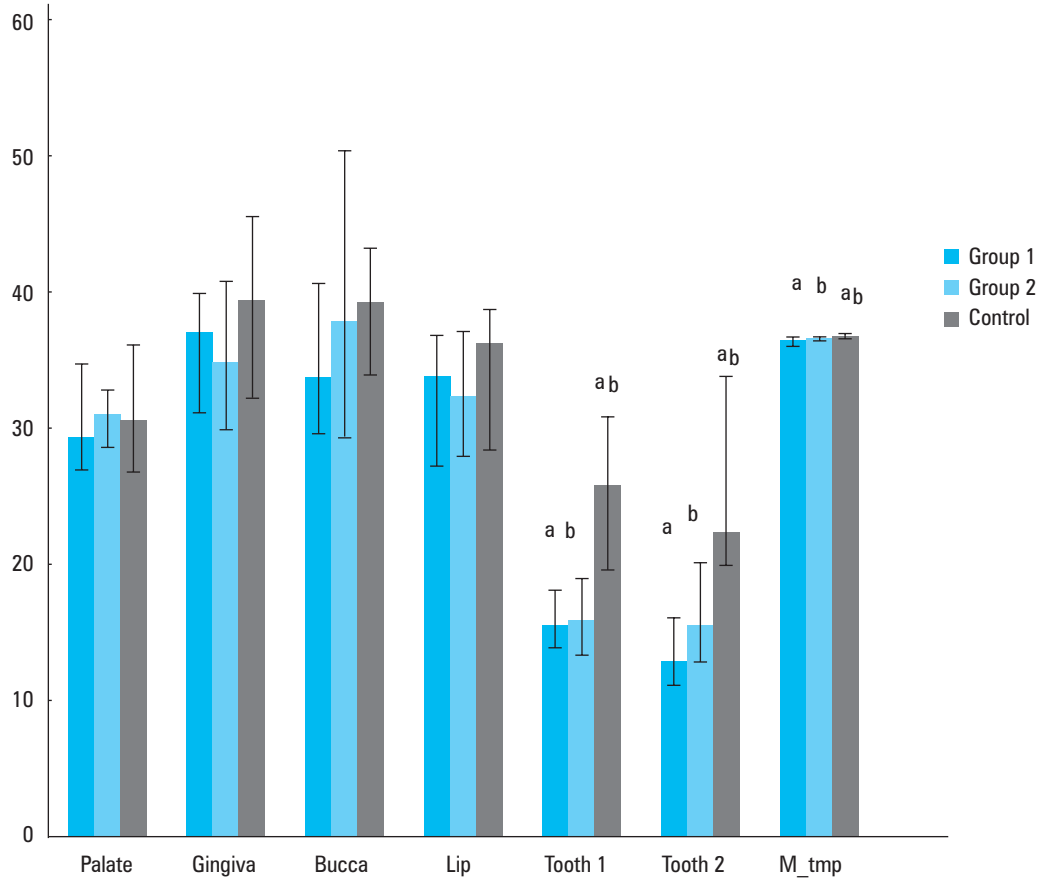


**FIGURE 2** Control visit (visit 2); laser Doppler flowmetry and oral mucosa temperature (m_tmp) in groups 1, 2, and controls
**a** Significant differences: group 1 vs control
**b** Significant differences: group 2 vs control

with the control group (TABLE 6; Supplementary material, *Figure S2*). No significant correlations between RP attack frequency reported by patients in the questionnaire and LDF flow or mucosa temperature were shown.

**DISCUSSION** Measurement of the microcirculation in the oral cavity has been described as a useful method for the detection of microvessel dysfunction and the diagnosis of palatal mucosal pathologies.[10,16] Here, we focused on microvascular

**TABLE 6** Oral lesions (aphtha, herpes labialis, angular cheilitis) (R8) reported by patients in the past (data from questionnaire) and confirmed on dental examination at visit 2 and during follow-up in groups 1 and 2 as compared with healthy controls

| | Group 1 (n = 31) | Group 2 (n = 30) | Control (n = 50) | *P* value[a] | *P* value[b] | *P* value[c] |
|---|---|---|---|---|---|---|
| Reported in the past | 19 (61.2) | 18 (60) | 10 (20) | <0.001 | <0.001 | NS |
| At visit 2 | 16 (51.6) | 8 (26.66) | 12 (24) | 0.01 | NS | 0.04 |
| At follow-up visit | 21 (77.4) | 20 (66.66) | 8 (16) | <0.001 | <0.001 | NS |

Data are presented as number (percentage). Fisher exact test was used for comparison.

**a** Group 1 vs controls; **b** Group 2 vs controls; **c** Group 1 vs group 2

Abbreviations: see **TABLE 1**

disturbance in the oral cavity of patients with PRP. On visit 2, we found significant differences in LDF among different oral cavity anatomical points including the teeth, palate, bucca, and gingiva in all patients with PRP and in the healthy control group. The lowest LDF values were observed on the teeth (Supplementary material, *Figure S1*). Le Bars et al[19] and Hirai[22] also showed a significant difference in LDF among the various anatomical areas of the palate in healthy volunteers, with the lowest values being recorded on the median raphe; however, they did not measure the LDF of the teeth.[19,22] Oral microcirculatory flow using LDF has already been evaluated in healthy smokers and nonsmokers, as well as in denture-supporting maxillary mucosa.[19,23] To the best of our knowledge, to date, no such measurements have been performed in patients with PRP, although dental disorders in patients with RP have been previously observed.[24] In the present study, we demonstrated significantly lower LDF results in patients with RP during vasospasm attacks (**TABLE 5**, **FIGURE 2**). At control visit 2, no vasospastic attacks were observed; nevertheless, some differences in mucosa temperature could still be seen (**TABLE 5**, **FIGURE 2**), in addition to a significantly lower dental pulp LDF. Other authors investigating the blood flow in the pulp of the teeth have reported a decrease in flow as a result of cooling, as well as a slow increase in flow under the influence of different thermal stimuli.[25] These studies are in accordance with our results, showing a complicated and individually variable interaction between the local effects of the flow in the dental pulp and that generated by the nervous system during temperature changes.[25] In both groups with PRP, oral cavity lesions were much more frequent as compared with the control group (**TABLE 6**; Supplementary material, *Figure S2*). The etiopathogenesis of oral cavity lesions is usually multifactorial, having for example inflammatory, autoimmune, traumatic, environmental factors or alimentary etiology. Herpes labialis and aphthae might be triggered by emotional stress.[26-34] A wide variety of factors, including nutritional deficiencies, local and systemic factors, and drug side effects, may produce angular cheilitis.[35-37] In PRP, an increase in α-2 adrenergic sensitivity in the small vessels results in the vasoconstrictive response to cold temperatures and emotional stress.[3,38] α-2 adrenergic receptors are present on the distal arterial smooth muscles and are affected by the sympathetic nervous system, causing a perfusion disorder, which may induce other disease processes.[2,39] In this case, paroxysmal ischemia of the oral cavity mucosae and vermillion border might be the predisposing factor to other pathomechanisms in the etiology of oral cavity lesions.

**Conclusions** Patients with PRP present the disorders of the oral cavity's mucosa microcirculation, and oral cavity lesions are more common in this group of patients.

**SUPPLEMENTARY MATERIAL** Supplementary material is available with the article at www.pamw.pl.

**CONTRIBUTION STATEMENT** IGM contributed to the concept of the study, dental examination, and data interpretation. MF contributed to manuscript preparation and editing as well as statistical analysis. PK coordinated patient and control recruitment. PM contributed to laser flow exams and temperature measurement, as well as coordination and review of manuscript drafting. All authors edited and approved the final version of the manuscript.



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