ISSN 1062-8738, Bulletin of the Russian Academy of Sciences: Physics, 2026, Vol. 90, No. 4, pp. 626–633. © Pleiades Publishing, Ltd., 2026.

# Autoimmune Disease Screening (by an Example of Systemic Lupus Erythematosus) Using Imaging Photoplethysmography

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Received December 5, 2025; revised December 12, 2025; accepted December 24, 2025

**Abstract**—For the first time, imaging photoplethysmography synchronized with an electrocardiogram was used to study and diagnose systemic lupus erythematosus. It was found that patients experience significant changes in the photoplethysmographic characteristics of the microvasculature of the facial skin in the cheeks compared with the control. Therefore, the proposed technique can pretend to be an objective instrumental criterion of the disease.

**Keywords:** imaging photoplethysmography, blood flow, microcirculation, amplitude and phase of pulse wave, systemic lupus erythematosus, autoimmune diseases

**DOI:** 10.1134/S1062873826700206

## INTRODUCTION

Autoimmune diseases are a group of diseases that occur due to dysregulation of the immune system. They are characterized by systemic damage to connective tissue, blood vessels and internal organs, polymorphism of the clinical picture and a progressive nature of the disease [1]. Currently, many diseases are known with systemic autoimmune damage to connective tissue, and one of the most common is systemic lupus erythematosus (SLE). Connective tissue pathologies are characterized by the following common features: systemic lesions, stages of development, dynamism of clinical manifestations, a tendency to progression and a tendency to form clinical crossovers [2]. Diseases of this group are being actively studied; however, early and differential diagnosis of these pathologies currently faces several difficulties. Thus, an objective examination of the skin can reveal changes, the nature of which may not be specific enough, especially in the early stages of the disease, which reduces the diagnostic value of the method. This can be partially compensated by performing a laboratory examination, in particular by identifying specific antibodies in the blood or by biopsy [3]. However, this disease is difficult to diagnose because specific diagnostic antibodies may not be detected even in the presence of an obvious disease or may be detected in various types of pathology, that is, in some cases, existing methods do not have sufficient sensitivity and specificity.

An important diagnostic criterion for SLE is skin lesions; however, these manifestations do not always appear at the onset of the disease. Changes in the skin on the face in SLE also often do not fit into the typical clinical picture of “discoid rash” and “butterfly wings”, representing many transitional forms of acute and chronic lesions. The basis of the disease, as a rule, is damage to the vascular network and therefore identifying disorders of the skin circulation in the early stages can facilitate the diagnosis of the disease. To date, there are several methods for assessing cutaneous blood flow that are used to diagnose SLE at its onset and during therapy.

Capillaroscopy of the nail bed has been used in clinical practice since 1823 and is one of the widely used methods for examining superficial microvessels [4, 5]. The method is based on visualization of the vascular structure of the superficial papillary layer of the dermis using a microscope. The capillary loops in the area of the nail bed are located almost parallel to the surface of the skin, which allows one to assess their density, architecture, size, shape and structure, and determine changes in the microcirculatory pattern in the case of the disease. A serious disadvantage of this technology is the ability to assess the condition of cap-

illaries only in the area of the nail bed [6]. However, vascular disorders that are characteristic of SLE, as a rule, are systemic in nature.

Power Doppler ultrasound is also used to study blood flow in a network of small vessels in different areas of the skin. Power Doppler ultrasound is a technique that encodes the power in the Doppler signal in color. This method is based on the analysis of the spectral power of the Doppler signal reflecting the density of red blood cells (RBC) in a volume under study [7] with further encoding of the integral power of the Doppler signals into a pseudo-color image. However, it is impossible to differentiate arterial and venous flows using such an image, therefore the diagnostic value of this method lies mainly in assessing the vascularization of tissues and pathological areas. Consequently, this technique does not quantify the parameters of blood flow.

Another non-invasive optical method for diagnosing vascular pathologies is raster-scanning optoacoustic mesoscopy [8]. This relatively new optoacoustic imaging technique produces three-dimensional images of vessels up to 1–2 mm beneath the skin by reconstructing optoacoustic waves generated in tissue in response to pulsed laser illumination. The disadvantages of the method include the long scanning time of the study area, which increases the risk of motion artifacts.

Two-dimensional mapping of two blood flow parameters simultaneously in different parts of the human body can be performed using the technology of imaging photoplethysmography (IPPG) under green illumination developed by our research team [9]. The blood-flow parameters assessed by the IPPG system synchronized with an electrocardiogram (ECG) are the spatial distributions of the amplitude of the pulsatile component (APC) of the IPPG waveform and the pulse arrival time (PAT) [10]. In our early work, we have already shown that the IPPG method can be successfully used to study disturbances in the blood flow of the extremities in patients with risk factors for cardiovascular diseases [11] and to assess the blood flow of the facial area in patients with migraine and localized scleroderma [12, 13]. In this work, peculiarities of facial blood flow in patients with SLE were studied. We assume that analysis of facial skin perfusion parameters in various areas will reveal specific signs of this disease associated with characteristic microcirculation disorders, which could be potentially useful for the early diagnosis of SLE. The undoubted advantage of the proposed approach is the low cost of installation, simplicity and speed of the study, its non-invasiveness and high resolution, which allows the use of the IPPG technique for screening patients who are suspected of having SLE disease.

**Table 1.** Anthropometric data of the subjects

| | | SLE | Control |
|---|---|---|---|
| Age, years | | 47.6 ± 10.4 | 46.8 ± 14.0 |
| Body mass index, kg/m$^2$ | | 26.2 ± 5.7 | 24.0 ± 3.8 |
| Blood pressure, mmHg | Systolic | 117.7 ± 17.5 | 118.2 ± 6.0 |
| | Diastolic | 68.5 ± 5.6 | 77.4 ± 6.9 |

## PATIENTS AND CONTROL GROUP

The study involved 11 females diagnosed with SLE. As a control group, 13 apparently healthy volunteers of comparable age were examined (Table 1).

The average duration of the disease was about 6–7 years, 70% of patients received conventional therapy. The disease activity of the patients was predominantly moderate and was assessed using the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index), which was 6 [5.5; 8.5]. All patients showed no signs of a typical discoid rash in the facial area. Exclusion criteria were concomitant severe somatic pathology (oncological diseases, patients with cardiovascular, respiratory, hepatic and renal failure), women during pregnancy and lactation. persons with indications of constant consumption of alcohol and drugs, which may adversely affect the patient's compliance with the study procedures, age under 18 years, and patient refusal to participate in the study.

## MEASURING SYSTEM

The study was carried out in a darkened room with appropriate sanitary conditions at an air temperature of 23 ± 1°C. The period of adaptation of the subject to the experimental conditions was at least 15 min. During the study, the subject was lying on his back in a relaxed state, avoiding movements, the subject's head was fixed with a headrest, and his eyes were protected with special glasses. Sensors for recording ECG in the first Eithoven lead were installed on the patient's limb. The measurement setup is illustrated in Fig. 1. For visualization and subsequent assessment of perfusion parameters in the facial area, we used IPPG module, which consisted of a digital monochrome camera (UI3060CP-M-GL, Imaging Development Systems, Germany) with an M1214-MP2 lens (Computar, Tokyo, Japan) in combination with an illuminator that includes 250 light-emitting diodes (LEDs) operating at a wavelength of $\lambda = 525 \pm 25$ nm (green light) and arranged in four concentric rings around the camera lens. This arrangement of LEDs ensured uniform illumination of the skin of the subject's face. The LEDs and the camera lens were covered with crossed polarizing filters to reduce the influence of radiation reflected from the skin surface and motion artifacts on the recorded signal [14]. The IPPG module was installed as frontally as possible to the area under study, and the distance between the camera lens and

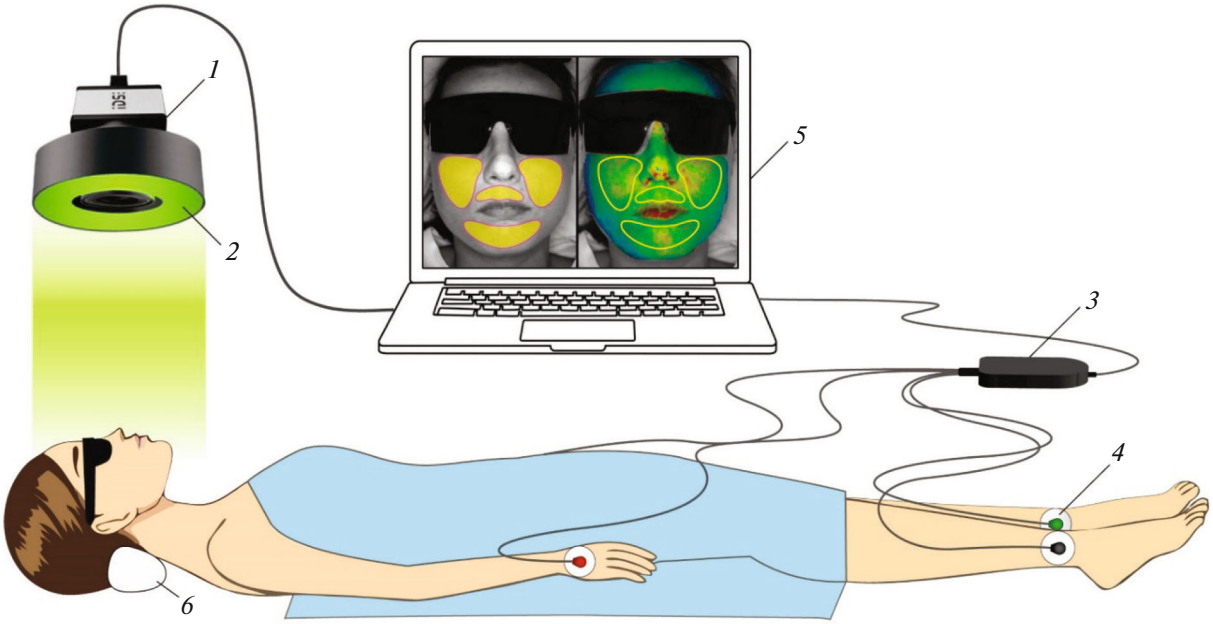


**Fig. 1.** Graphical diagram of the experimental setup for evaluation of the parameters of facial blood supply in patients with SLE and the control group. Digital monochrome video camera (*1*); LED illuminator (*2*); electrocardiograph (*3*); ECG sensors (*4*); personal computer (*5*); fixing headrest (*6*).

the subject's face was approximately 40 cm. The video recording of the subject's face was carried out at a rate of 30 frames per second with a resolution of 1800 × 850 pixels for 120 s synchronously with the ECG recording using a digital electrocardiograph "Kardiotechnika-EKG-8" (Incart Ltd., St. Petersburg, Russia). The video and ECG synchronization error did not exceed 1 ms. All data was recorded in the memory of a personal computer for further processing using custom-made software implemented in MATLAB® platform (version R2020a, The MathWorks, United States).

## METHOD

Erythematous rash in the form of "butterfly wings" on the patient's face, which is caused by inflammation of the upper layers of the dermis with concomitant changes in the microvasculature, is a specific early manifestation of SLE. The hemodynamic parameters of the subjects' facial skin were assessed using an algorithm described in detail in [13] and improved in this study to increase the signal-to-noise ratio. We hypothesized that the main causes of the modulation of the recorded video signal are changes in blood volume interacting with light and tissue motions that inevitably occur during respiration and random movements of the subject when performing in vivo measurements. It is known that living tissue is very heterogeneous and any displacement relative to the incident luminous flux can lead to a more significant change in the intensity of reflected light than the desired modulation caused by a change in pulse blood pressure, which greatly reduces the sensitivity of the method. Therefore, to minimize the impact of motion artifacts, the first stage of image processing was digital stabilization using an optical flow algorithm. Unlike our previous studies, here we calculated the intensity gradients in the image segments within each cardiac cycle. The remaining noise component of the signal was suppressed using a low-pass filter (9 Hz) implemented by the filtfilt function in MATLAB®.

As is known, the registered IPPG waveform consists of an alternating component (AC), mainly modulated at the heart rate, and a slowly varying component (DC) [10, 15]. Modulation of light intensity at the heart rate, AC, is associated with the arrival of a pulse wave in the study area, while DC changes are caused by periodic muscle activity and/or changes in lymphatic pressure, which can also affect the compression of the capillary bed. Therefore, at the second stage of signal processing, to reduce the influence of these factors, we compensated the trend of DC components of the IPPG signal within each cardiac cycle. Next, we normalized the obtained waveform to the average DC value to compensate for the uneven tissue illumination. The signal obtained in this way and then inverted has a shape as close as possible to the true shape of the peripheral blood pressure wave.

At the third stage, the APC parameter was calculated as the difference between the maximum and minimum values of the normalized IPPG waveform,

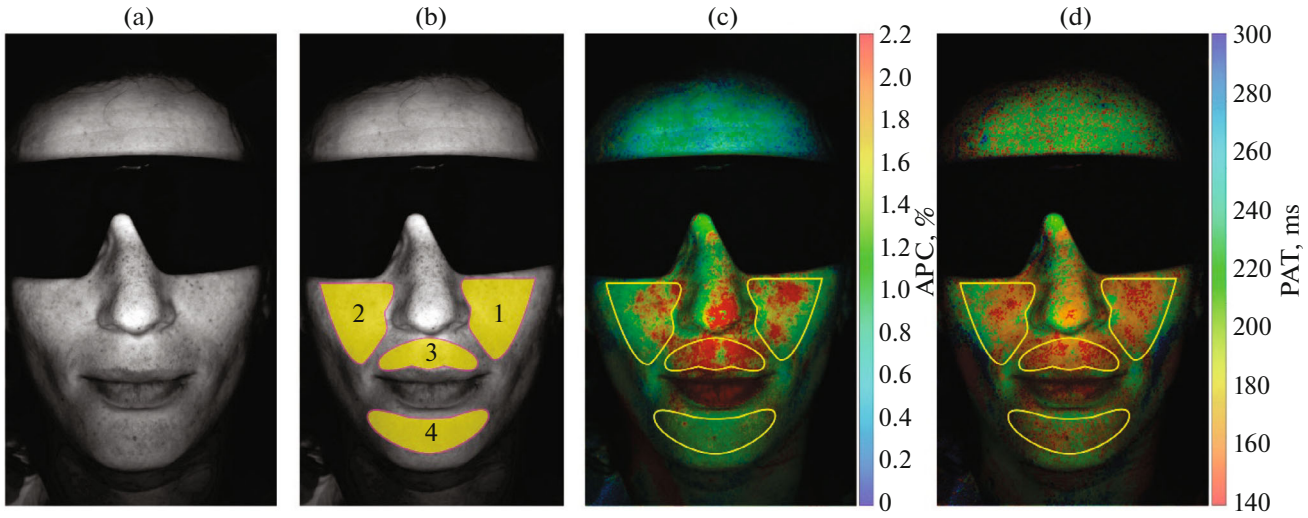


**Fig. 2.** Assessment of facial-blood-supply parameters in patients with SLE and the control group. The original image of the subject's face (a); an example of the location of regions of interest (ROI-1 to ROI-4) on the original image (b); spatial distribution of the APC (c) and PAT (d) parameters of the subject's facial blood supply with the boundaries of the selected ROIs.

with the boundaries of each cycle determined by the R-peaks of the synchronously recorded ECG. This parameter is a quantitative measure of blood flow perfusion, and maps of the spatial distribution of this parameter in pseudo-colors reflect the distribution of the amplitude value of perfusion in area under study. The PAT parameter was calculated as the time difference between the R-peak of the ECG and the minimum of the average IPPG signal corresponding to the beginning of the systolic phase of the cardiac cycle. Two-dimensional mapping of this parameter gives an idea of the arrival time of the pulse wave in different regions of the patient's face.

Quantitative assessment of the APC and PAT parameters was carried out throughout the entire observation time (120 s). To minimize the influence of artifacts associated with random movement of the patient, as well as possible fluctuations in heart rate, the evolution of the cardiac cycle duration and averaged APC and PAT values over the entire observation time were visualized. Then the most stable interval of 20 s was selected, according to which the median value of the specified parameters was calculated. To do this, four regions of interest (ROI) were identified on the APC map: the left (ROI 1) and right (ROI 2) cheeks, the skin area above the upper lip (ROI 3) and the chin (ROI 4) in a shape that does not touch the nose and the lip border. Areas with a 50% percentile of the maximum values of APC were selected for analysis. The ROIs selected on the APC map were automatically transferred to the PAT map. Thereafter, the data obtained in different regions of the patient's face were compared with each other. An example of choosing ROI positions is shown in Fig. 2.

## STATISTICAL ANALYSIS

All analyzed data were checked by a test for normality of distribution (Kolmogorov-Smirnov test). The spatial distribution of APC and PAT parameters in all selected ROIs turned out to be close to Gaussian. The test for normality of distribution of parameters in groups of subjects showed a negative result. Therefore, nonparametric statistical methods were used in the study of intergroup differences. The Mann–Whitney test and the Kruskal–Wallis rank criterion (for multiple comparisons) were used to reliably verify the difference between the parameter values. The significance level of all statistical indicators is $p < 0.05$. Statistical data analysis was also performed using MATLAB®.

## RESULTS AND DISCUSSION

Based on a comparative analysis of APC and PAT, it was revealed that the average value of these indicators for all regions did not differ in patients with SLE and in the control group: 0.92 [0.79; 1.37]% and 0.89 [0.68; 1.42]%. $p = 0.69$ for APC and 194 [175; 211] ms and 193 [176; 211] ms, $p = 0.79$ for PAT, respectively. However, an analysis of the peculiarities of the distribution of IPPG signal indicators in the groups of interest (initial data for analysis is given in Table 2) revealed significant differences.

During comparison using the Kruskal–Wallis test in the control group, APC indicators were comparable in all areas: left cheek 1.04 [0.81; 1.47]%, right cheek 0.96 [0.77; 1.34]%, region above the upper lip 0.83 [0.53; 1.11]%, and chin 0.86 [0.56; 1.15]%, $p > 0.05$ (Fig. 3a). The same was true for PAT: 191 [179; 194] ms, 196 [179; 210] ms, 201 [165; 225] ms, and 206

**Table 2.** IPPG parameters in different areas of interest in patients with SLE and in the control group

| | Subject no. | APC, % | | | | PAT, ms | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | ROI-1 | ROI-2 | ROI-3 | ROI-4 | ROI-1 | ROI-2 | ROI-3 | ROI-4 |
| SLE | 1 | 0.99 ± 0.17 | 1.29 ± 0.17 | 1.12 ± 0.11 | 0.84 ± 0.12 | 209 ± 16 | 178 ± 14 | 199 ± 17 | 179 ± 25 |
| | 2 | 1.13 ± 0.26 | 1.58 ± 0.21 | 0.78 ± 0.14 | 0.69 ± 0.12 | 171 ± 14 | 153 ± 18 | 203 ± 15 | 211 ± 13 |
| | 3 | 1.72 ± 0.16 | 1.70 ± 0.19 | 0.92 ± 0.16 | 0.82 ± 0.11 | 143 ± 12 | 128 ± 17 | 187 ± 25 | 190 ± 19 |
| | 4 | 1.60 ± 0.29 | 1.66 ± 0.28 | 0.83 ± 0.14 | 0.96 ± 0.23 | 177 ± 16 | 174 ± 16 | 217 ± 17 | 202 ± 18 |
| | 5 | 1.48 ± 0.25 | 1.46 ± 0.21 | 0.53 ± 0.90 | 0.65 ± 0.11 | 170 ± 20 | 174 ± 16 | 218 ± 19 | 204 ± 15 |
| | 6 | 0.80 ± 0.11 | 1.21 ± 0.14 | 0.80 ± 0.12 | 0.89 ± 0.10 | 184 ± 17 | 175 ± 17 | 210 ± 16 | 200 ± 19 |
| | 7 | 0.91 ± 0.12 | 0.88 ± 0.23 | 0.88 ± 0.14 | 0.72 ± 0.17 | 195 ± 12 | 206 ± 18 | 222 ± 11 | 222 ± 19 |
| | 8 | 1.45 ± 0.26 | 1.94 ± 0.17 | 0.96 ± 0.13 | 1.26 ± 0.11 | 149 ± 14 | 146 ± 15 | 188 ± 21 | 178 ± 17 |
| | 9 | 1.72 ± 0.27 | 1.89 ± 0.39 | 1.16 ± 0.22 | 1.03 ± 0.39 | 192 ± 17 | 162 ± 19 | 220 ± 24 | 247 ± 46 |
| | 10 | 0.42 ± 0.09 | 0.42 ± 0.10 | 0.30 ± 0.08 | 0.32 ± 0.10 | 249 ± 35 | 211 ± 20 | 273 ± 49 | 260 ± 49 |
| | 11 | 0.85 ± 0.14 | 0.90 ± 0.13 | 0.21 ± 0.06 | 0.50 ± 0.26 | 179 ± 15 | 166 ± 17 | 231 ± 54 | 210 ± 23 |
| Control | 1 | 0.73 ± 0.10 | 0.96 ± 0.12 | 0.83 ± 0.20 | 1.73 ± 0.11 | 192 ± 19 | 193 ± 17 | 207 ± 17 | 203 ± 16 |
| | 2 | 0.83 ± 0.11 | 0.68 ± 0.12 | 0.46 ± 0.09 | 0.39 ± 0.09 | 183 ± 24 | 188 ± 18 | 197 ± 18 | 184 ± 21 |
| | 3 | 1.50 ± 0.20 | 1.29 ± 0.20 | 1.97 ± 0.14 | 1.60 ± 0.19 | 89 ± 14 | 116 ± 10 | 134 ± 18 | 121 ± 23 |
| | 4 | 0.61 ± 0.09 | 0.59 ± 0.12 | 0.46 ± 0.13 | 0.57 ± 0.16 | 184 ± 28 | 165 ± 43 | 166 ± 40 | 206 ± 29 |
| | 5 | 0.72 ± 0.11 | 0.54 ± 0.10 | 0.39 ± 0.08 | 0.30 ± 0.06 | 191 ± 18 | 183 ± 26 | 233 ± 26 | 234 ± 32 |
| | 6 | 1.04 ± 0.13 | 0.81 ± 0.10 | 0.61 ± 0.13 | 0.53 ± 0.8 | 180 ± 15 | 208 ± 17 | 222 ± 22 | 234 ± 19 |
| | 7 | 1.44 ± 0.29 | 1.22 ± 0.28 | 1.87 ± 0.23 | 1.42 ± 0.21 | 172 ± 18 | 190 ± 23 | 154 ± 17 | 166 ± 16 |
| | 8 | 2.07 ± 0.44 | 1.63 ± 0.22 | 1.48 ± 0.33 | 1.47 ± 0.22 | 186 ± 20 | 210 ± 19 | 190 ± 20 | 194 ± 17 |
| | 9 | 0.85 ± 0.14 | 0.81 ± 0.11 | 0.55 ± 0.10 | 0.92 ± 0.23 | 285 ± 34 | 227 ± 19 | 248 ± 28 | 219 ± 24 |
| | 10 | 0.85 ± 0.24 | 0.84 ± 0.11 | 0.69 ± 0.11 | 0.81 ± 0.15 | 193 ± 24 | 211 ± 18 | 179 ± 19 | 181 ± 19 |
| | 11 | 1.46 ± 0.18 | 1.29 ± 0.30 | 0.97 ± 0.12 | 0.86 ± 0.16 | 152 ± 13 | 137 ± 61 | 163 ± 20 | 166 ± 36 |
| | 12 | 1.43 ± 0.19 | 1.48 ± 0.22 | 1.29 ± 0.15 | 1.03 ± 0.11 | 192 ± 19 | 199 ± 13 | 201 ± 14 | 211 ± 18 |
| | 13 | 1.54 ± 0.20 | 1.51 ± 0.33 | 1.05 ± 0.13 | 1.06 ± 0.15 | 195 ± 19 | 196 ± 21 | 202 ± 24 | 193 ± 54 |

[177; 223] ms, respectively, $p > 0.05$ (Fig. 3c), which indicated the relative symmetry of photoplethysmographic characteristics of facial blood flow in this group.

However, in contrast to the control group, the distribution of IPPG parameters in patients with SLE turned out to be different. Thus, in the course of a multiple comparison of the APC, it was found that there are significant differences in this parameter: left cheek 1.13 [0.86; 1.57]%, right cheek 1.46 [0.98; 1.69]%, region above the upper lip 0.83 [0.59; 0.95]%, and chin 0.82 [0.66; 0.94]%, $p < 0.01$ (Fig. 3b). The maximum APC values were observed in the cheek area. Besides, it was found that patients with SLE have not only APC asymmetry, but also PAT. The Kruskal-Wallis test also revealed a significant difference in this parameter in various corresponding areas of the face: 179 [170; 195] ms, 174 [155;177] ms, 217 [201; 221] ms, and 204 [193; 219] ms, $p < 0.001$ (Fig. 3d). However, unlike the amplitude characteristics of the IPPG waveforms, the PAT value in the cheek area turned out to be minimal.

To check the non-randomness of the detected differences in IPPG parameters in different regions of the face, the next step was to combine the areas of the left and right cheeks and compare them with other areas. In the control group, in the cheek area, APC = 0.99 [0.81; 1.46]% and PAT = 192 [181; 209] ms, while in the combined lip and chin area, APC = 0.84 [0.55; 1.06]% and PAT = 203 [167;222] ms. In contrast, in patients with SLE in the cheeks, APC =1.37 [0.90; 1.66] % and PAT = 175 [162; 193] ms, and in the combined lip and chin area, APC = 0.82 [0.65; 0.96]% and PAT = 210 [200; 222] ms. In the control group, the Mann–Whitney test revealed no differences in both APC and PAT values between the combined regions: $p = 0.08$ and $p = 0.34$ for APC and PAT, respectively (Figs. 4a, 4c). On the contrary, in patients with SLE, APC was significantly higher in the cheek area, $p < 0.01$ (Fig. 4b), while PAT in these regions was significantly lower, $p < 0.01$ (Fig. 4d). Moreover, it was found that APC in the cheek area in patients with SLE was higher than in the control group ($p < 0.01$), whereas in the rest of the face in both groups the indicators did not differ.

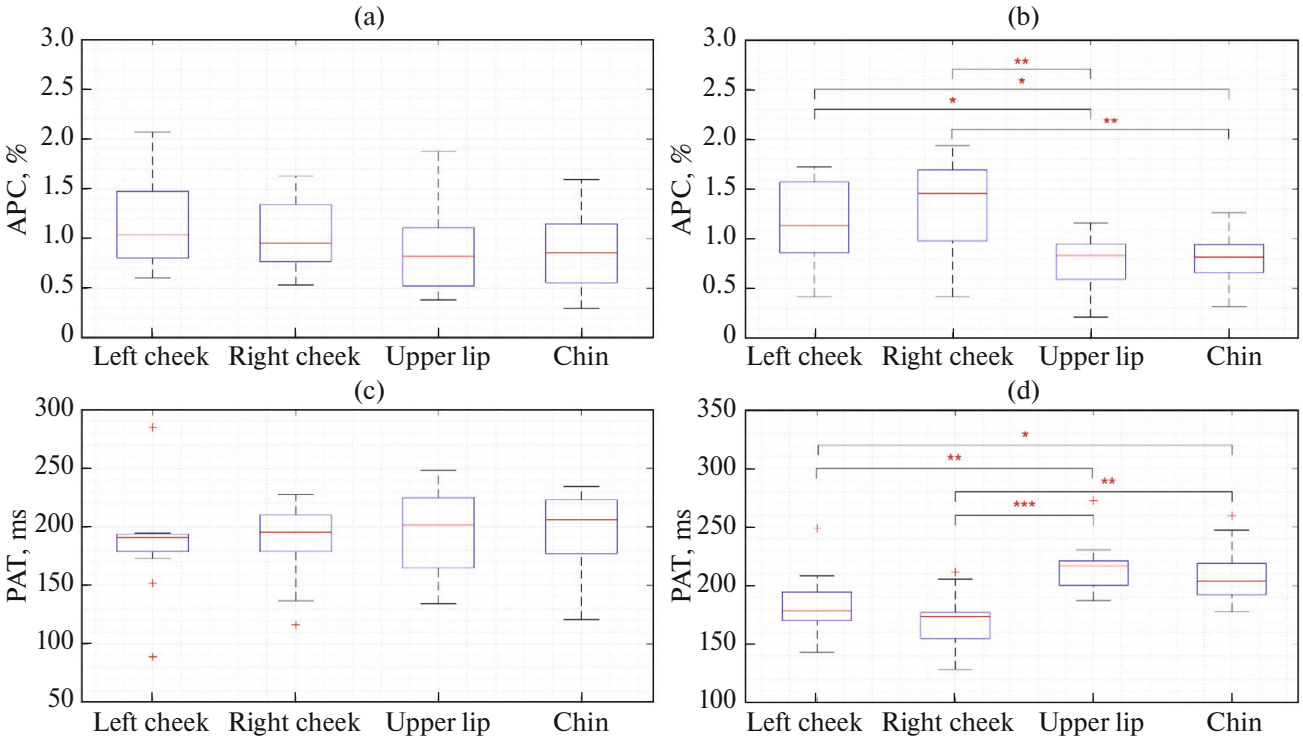


**Fig. 3.** IPPG parameters in the control group and in patients with SLE in various areas of the face. Indices of APC (a) and PAT (b) in the control group; Indices of APC (c) and PAT (d) in the group of patients with SLE. The data is presented in the format (Me [Q1; Q3]). The red line in the box center indicates the median value of the parameter. Outliers are indicated by a separate "+". The level of statistical significance of the differences: * $p \le 0.05$; ** $p \le 0.01$; *** $p \le 0.001$. The identified differences between the regions were obtained using the Mann–Whitney test.

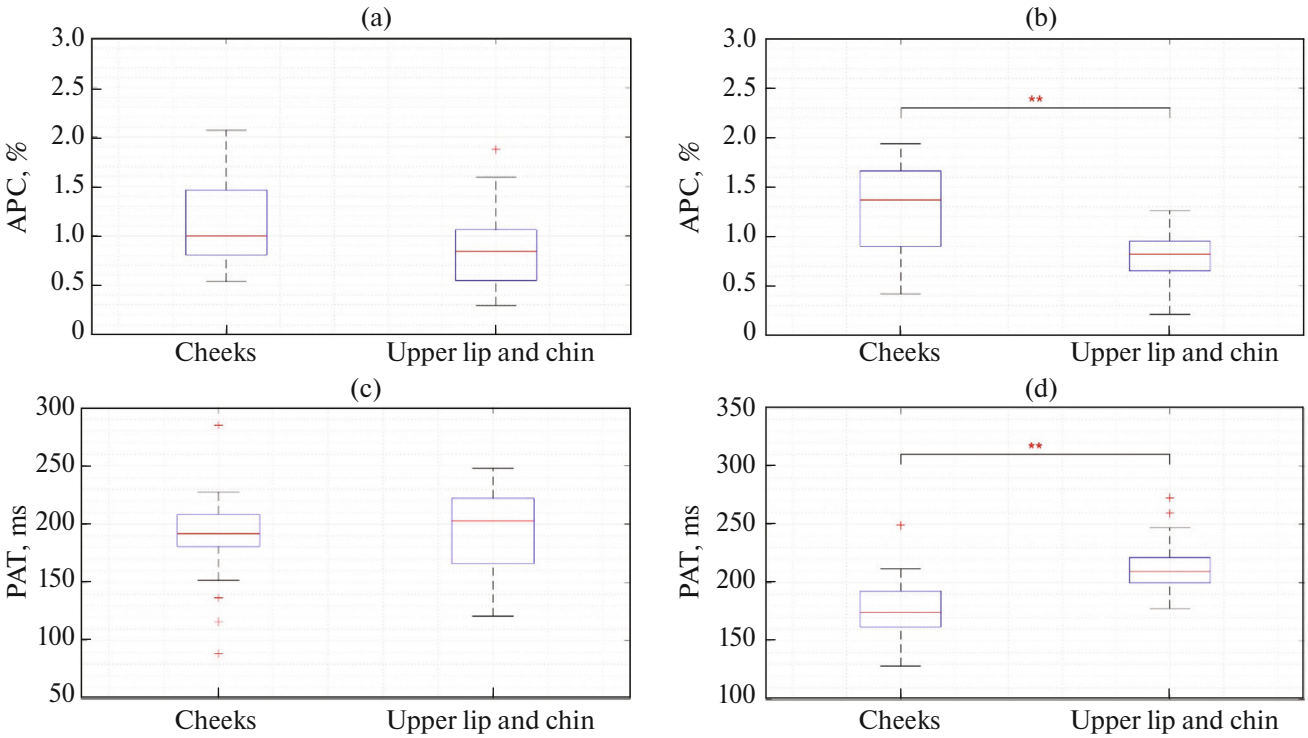


**Fig. 4.** IPPG parameters in the control group and in patients with SLE in the combined areas of interest. Indices of APC (a) and PAT (b) in the control group; values of APC (c) and PAT (d) in the group of patients with SLE.

Therefore, it has been established that in patients with SLE there is a significant change in the IPPG parameters of the microvasculature of the facial skin in the cheek area, which can be used for objective instrumental diagnosis of the disease.

Systemic lupus erythematosus is one of the most common connective tissue diseases, with an estimated incidence of 5.14 (from 1.4 to 15.13) per 100000 people per year [16]. Diagnosis of the disease is often difficult due to the atypical course of the disease. Most patients have clinical criteria associated with damage to the skin and mucous membranes [17]. The most striking manifestations are caused by acute and subacute facial lesions. The most specific area of the lesion is the skin in the cheeks in the form of butterfly wings. However, the occurrence of typical manifestations of skin lesions, which also include discoid rash, is just about a quarter of cases [18]. In this regard, objectification and increasing the sensitivity of diagnostic methods for skin lesions is an urgent problem.

Visible changes on the skin are a consequence of inflammation of the upper layers of the dermis, which is accompanied by changes in the microcirculatory bed [19]. The technology of IPPG synchronized with ECG is an efficient method for assessing blood supply to superficial tissues. The effectiveness and promise of optical technology in the diagnosis of vascular diseases is primarily due to the possibility of non-contact measurement of blood flow parameters in vivo, since visible light has minimal impact on biological tissues. In the studies carried out by our group, the high sensitivity of this method to changes in blood supply to the tissue has been demonstrated, which makes it possible to predict the course of the disease, not only in the skin area, but also in the cerebral cortex, as well as in abdominal organs [20, 21].

## CONCLUSIONS

A detailed study of APC and PAT in different regions of the face, as well as changes in the shape of the IPPG waveform, was carried out by us earlier in [13] for patients with systemic scleroderma, which showed significant differences in IPPG characteristics that allowed us to reveal equivalents of proximal scleroderma, the criterion most specific for this disease. This pilot study showed the characteristic features of the distribution of the amplitude and time of arrival of the IPPG waveform in the cheek area compared to other parts of the face. It is noteworthy that these changes were observed exactly in the cheek area, the location of skin changes in patients with classical manifestations of systemic lupus erythematosus [22]. Thus, the IPPG method made it possible to detect early pathological changes in microcirculation that are inaccessible to visual assessment, which is used for the clinical diagnosis of the disease. Therefore, the tested technique can claim to be an objective instrumental criterion of the disease. The most valuable is the fact that this criterion is independent of the visible changes in the skin and allows one to identify hidden changes in the microcirculatory system.

## FUNDING

The study was carried out with the financial support of the Russian Science Foundation (grant no. 25-15-00400) in terms of experimental setup and software development; within the framework of state assignment of the Institute of Automation and Control Processes, Far East Branch, Russian Academy of Sciences (state registration no. 125020301282-0) in terms of the implementation of the experimental study; and within the framework of state assignment no. FSER-2025-0020 as a part of the national project "Science and Universities" in terms of software development, data processing and analysis.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was performed in accordance with the ethical standards presented in the 2013 Declaration of Helsinki and approved by the Interdisciplinary Ethics Committee of the Primorskii Regional Clinical Hospital no. 1 (Protocol no. 1 of April 21, 2023). All subjects signed a written informed consent to participate in the study. The study was carried out in the Primorskii Regional Clinical Hospital no. 1 (Vladivostok, Russia) and in the Institute of Automation and Control Processes, Far Eastern Branch, Russian Academy of Sciences (Vladivostok, Russia).

## CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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