CHAPTER 13

Imaging photoplethysmography and its applications

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13.1 Introduction: Fundamentals of imaging photoplethysmography

Photoplethysmography (PPG) is a technique in which light is shone onto a tissue containing blood vessels and then either the reflected or transmitted light is measured by a photosensitive element. Since the absorption of light that interacts with tissue is determined by blood volume, a waveform measured in vivo turns out to be modulated in time with the heart rate. Therefore, this technique is mainly used to assess the variations in blood volume that occur with each heartbeat. A PPG device requires only a light source for tissue illumination and a photodetector to measure the small variations in the light power (Allen, 2007). It is a simple, noninvasive, inexpensive, and easy-to-use tool. The low-cost and simplicity of this optical technology can provide significant benefits to healthcare. However, the changes in PPG signal due to variations in blood volume are quite small and are sensitive to artifacts. For this reason, the classical contact PPG device, which consists of a light source and photodetector, operates in contact with the tissue to prevent or minimize influence of motion artifacts (Hertzman, 1938). Classical PPG devices have widespread clinical application with the technology utilized in commercially available medical devices, for example in pulse oximeters, vascular diagnostics, and digital beat-to-beat blood pressure measurement systems (Allen, 2007).

Several studies have been undertaken to prove the ability of the PPG system on assessing pulse rate variability, pulse arrival time, vascular tone, tissue perfusion, and sympathetic activity, etc. (Nitzan et al., 1998; Lima et al., 2002; Khanokh et al., 2004; Reisner et al., 2008; Abay and Kyriacou, 2015). However, despite intensive investigations over a long time and for a wide range of applications, the physiological model of PPG waveform formation remains a subject of continuing debate. The conventional model of the PPG waveform generation assumes that the main reason of the light-intensity modulation registered by the photodetector

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is variations of the blood volume in the tissue (Hertzman, 1938; Roberts, 1982; Reisner et al., 2008). This modulation mechanism is easy to understand in the transmitting-mode PPG operating at the near infrared: an increase of blood volume absorbs more photons resulting in decrease of light intensity measured by the photodetector and vice versa. However, several research groups reported that the largest heartbeat-related AC/DC modulation was observed at the green light (Cui et al., 1990; Verkruysse et al., 2008; Kamshilin et al., 2011; Maeda et al., 2011). The conventional PPG-model fails to explain these observations because of the inability of green light to interact directly with pulsatile blood vessels, as usually green light does not penetrate human skin deeper than 0.5 mm (Anderson and Parrish, 1981). There are no pulsating arteries and arterioles at this depth (Gray, 2008), whereas the pulsatile capillary pressure (Williams et al., 1988) and varying in time velocity profile of red blood cells (RBC) (Volkov et al., 2017) are unlikely to exert a true blood volume modulation in a single capillary due to the inextensible nature of these vessels (Fung et al., 1966). To resolve this contradiction, our group proposed an alternative PPG model (Kamshilin et al., 2015; Kamshilin and Margaryants, 2017). According to this model, it is the pulsatile transmural pressure of the arteries, which compresses/decompresses the density of capillaries in the dermis, thus modulating the blood volume in the capillary bed, which effectively absorbs green light. Due to the dermis compression by transmural pressure at the locality of the measurement, both absorption and scattering coefficients are increased (Chan et al., 1996) that lead to corresponding changes in the measured light power.

Both conventional and alternative PPG models agree that the reason for the modulation of light are the changes in absorption due to changes in the volume of blood with which it interacts. The difference is where exactly in tissue do these changes in blood volume occur. While the conventional PPG model does not indicate the source of blood pulsations, arguing that it is most likely the arteries and arterioles, then an alternative model pays special attention to the change in blood volume in the superficial capillary layer (Kamshilin et al., 2015). Deeper studies into the basic aspects of light interaction with live tissue are extremely important for both correct interpretation of the experimental data and development of new noninvasive and contactless diagnostic instruments.

Imaging photoplethysmography (IPPG) differs from the classical PPG apparatus only in that a digital camera is used as a photodetector. Obviously, the use of a camera transforms the measuring system from contact to contactless. The positive effect of this transformation is that the contactless technology provides unobtrusive, unconstrained (and thus more reliable) blood-volume-pulse measurements for cardiovascular and microvascular monitoring. However, the very small light-power modulation at heart rate is hardly detectable against the strong background of motion artifacts in the video frames recorded by a digital camera in IPPG systems. Nevertheless, recent advances in computer video, signal processing, and machine learning have improved the performances of IPPG techniques significantly (Hassan et al., 2017). Today, this method allows the extraction of reliable physiological

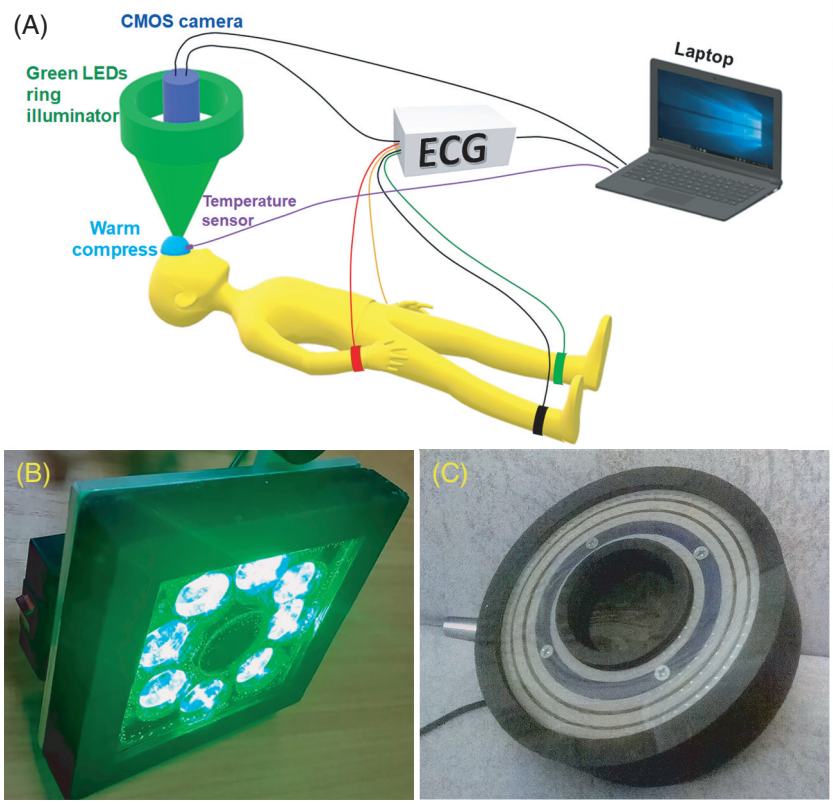

Figure 13.1
Layout of the experimental setup with IPPG system (A) used to study the effect of temperature on facial microcirculation. Photographs of the two versions of IPPG modules containing 0 camera, ring LED illuminators, and polarizing filters are shown in panels (B) and (C).

information even in the presence of significant movement of the body segment and tissue under study.

Instrumental implementation of an IPPG system can be quite straightforward: only a video camera with illumination of the tissue are required. An example of an IPPG system arrangement for studying the reaction of the microcirculation to temperature changes (Volynsky et al., 2019) is shown in Fig. 13.1(A). In order to increase the accuracy of blood pulsation measurements and to obtain reliable physiological results video frames of the skin were recorded synchronously with an electrocardiogram (ECG) which served as a cardiac timing reference. Panels (B) and (C) in Fig. 13.1 show two recent versions of the IPPG module that contain the digital camera and ring LED illuminator, and polarizing filters.

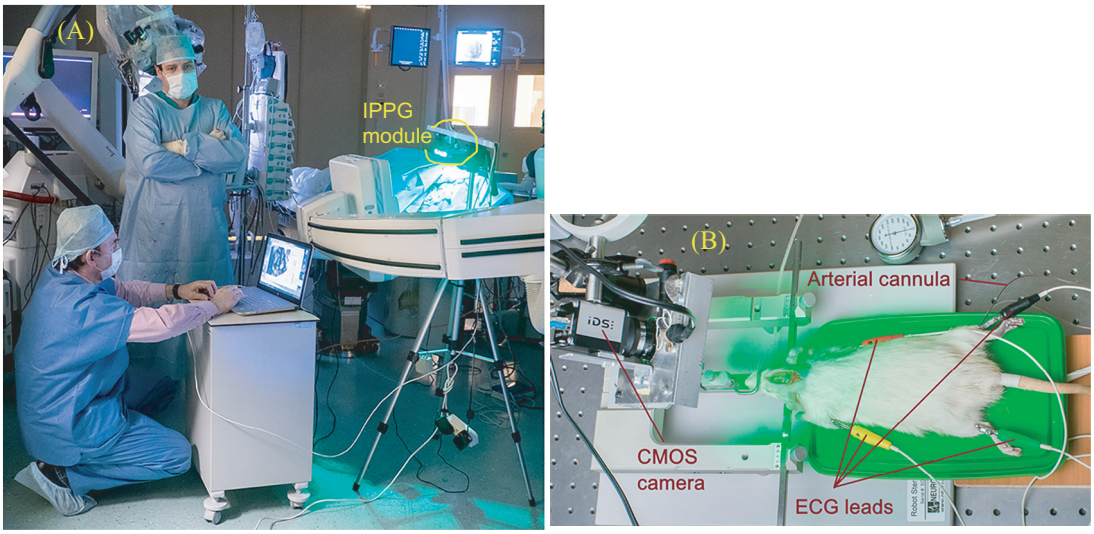

Figure 13.2
Examples of IPPG-system applications. (A) Testing the feasibility of the IPPG method for intraoperative monitoring of cortical blood perfusion during neurosurgical intervention. (B) Monitoring the response of the cortical blood flow to various stimuli in animals.

Since the IPPG module is a user-friendly apparatus which has low weight and small dimensions, it has great potential for application in a wide range of clinical settings, as well as for carrying out sophisticated biomedical studies. Fig. 13.2 shows two examples of the use of the IPPG system in a clinical setting and in an experimental animal study. The photograph in Fig. 13.2(A) was taken during an intraoperative study aimed to assess eligibility to use the contactless IPPG system for remote visualization and quantitative evaluation of cortical microcirculation in patients with various brain pathologies (Mamontov et al., 2020b). A photograph of the experimental setup for measuring cerebral hemodynamic and its response to both physiological and pharmacological stimulation of animals (Lyubashina et al., 2019; Mamontov et al., 2020a) is shown in Fig. 13.2(B).

However, there are a number of factors that still hinder the widespread introduction of the IPPG method into clinical and research practice. First, there is still the lack of a commonly accepted theoretical model of light interaction with biological tissue containing functioning blood vessels. Second, IPPG allows assessment of several blood-flow parameters that were previously impossible to measure. Third, there is a lack of established (gold standard) methods which can hinder the standardization of a new method. Fourth, obtaining highly reliable physiological information is possible only with simultaneous synchronous recording of video frames and the ECG, which is a technical problem that has yet to be solved.

Nevertheless, the main advantages of IPPG are noncontact measurements, which make it possible to assess blood flow in vivo with the possibility of assessing both temporal and spatial characteristics of the microcirculation made simultaneously over large tissue areas. Due to the simplicity and low cost of the equipment required to implement IPPG, the number of research groups in this area and new proposals for applications of this technology is growing rapidly. However, because of difficulties in signal recovery and the lack of a well-established physiological model of PPG, the application of this technology in real clinical practice is currently limited. Nevertheless, advances in data processing have led to a number of studies in recent years which have demonstrated the enormous potential of the IPPG technology in various fields of medicine.

In this chapter, we will focus on those IPPG applications that have emerged as a result of the recently discovered fundamental features of the light interaction with functioning blood vessels. The most attention will be given to the applications that open up exciting new opportunities in clinical diagnostics. We will present what we consider to be the most meaningful and promising directions of the IPPG application for practical medical purposes.

13.2 Heart rate and heart-rate-variability monitoring

It is well known that the ECG is the worldwide gold standard for noninvasive monitoring of heart rate, which is one of the most important vital signs. However, this method requires contact electrodes, which can interfere with patient movement. Another important noninvasive measurement method for heart rate is the pulse oximeter (Wukitsch et al., 1988), which uses photoplethysmography to obtain pulse waveforms resulting from changes in the color intensity and optical properties of a selected area of the skin with each heart beat. Due to the abovementioned problems, geriatric patients (especially those with dementia or in a delirious state) or newborns, do not always accept traditional contact-based monitoring. In this regard, the monitoring of the vital signs for such patients by using IPPG system could offer a very suitable solution since it can be done in a contactless and unobtrusive way. Its basic measurement principle corresponds to that of a conventional PPG in reflectance mode: light enters the skin, is back scattered and detected using a camera (Wu et al., 2000). However, the uncontrolled movement of the subject in respect to the camera (i.e., motion artifacts) seriously affects the correct extraction of information about the subtle modulation of light at the heart rate. Yu et al. (2020) demonstrated the feasibility of measuring both heart rate (HR) and heart-rate-variability (HRV) in geriatric patients using IPPG technique. Considering that for these patients, unobtrusiveness and patient comfort are of particular importance, the measurements were carried out by using a near-infrared (NIR) camera. Similarly, an IPPG system operating with NIR is particularly relevant for patient monitoring in high-acute settings in hospitals that require long-term continuous monitoring such as in intensive care units (Yeung et al., 2019) or neonatal intensive care units (Cobos-Torres et al., 2018). In addition, NIR-IPPG

allows monitoring of vital signs during sleep (Vogels et al., 2018; Wang et al., 2020), which is important for the diagnosis of sleep disorders that could be linked with chronic disease, including those associated with the risk of atherosclerosis.

13.3 Evaluation of neurogenic reactivity and fractional blood flow of the musculocutaneous vessels

Neurogenic regulation of vascular tone plays an essential role in maintaining hemodynamic parameters. Since vascular reactivity can be reduced in some diseases (e.g., with the development of diabetic autonomic neuropathy or in patients with primary autonomic failure), measuring the blood-flow reaction in response to sympathicotonic stimuli is of great diagnostic value. Volumetric blood flow in the extremities can be assessed by monitoring changes in volume or circumference of the extremities during venous occlusion, referred to as a method of occlusive plethysmography. This method is the only direct noninvasive method for assessing vascular reactivity that, unlike neurography, can be used in clinical trials. The change in the volume of the extremities is caused by the blood inflow through the arterial vessels in the conditions of the cessation of the outflow through the veins in response to the action of the occlusive cuff, in which pressure is above the venous pressure, but below the arterial pressure. An increase in the volume or circumference of the extremity at the initial moment of occlusion is proportional to the volumetric blood flow and inversely proportional to the peripheral vascular resistance. The change in size of the extremity is quite small and is usually measured by either strain-gauge plethysmography (which assesses a limb's circumference) (Wilkinson and Webb, 2001) or air plethysmography (APG, which monitors pressure changes in an airbag cuff on the limb segment of interest which can be mapped to a calibrated volume change) (Bays et al., 1994). Both of these techniques, like many of the currently used methods, are contact based, which in itself can impact on the vascular processes one is trying to study.

An alternative noninvasive method for assessing vascular parameters in extremities, which is successfully used to diagnose lymphovenous insufficiency, is the conventional PPG sensor allowing the blood refilling time to be estimated immediately following physical exercising of the study limb (Sam et al., 2006). However, this technique is also of the contact type. Moreover, this type of PPG sensor approach only assesses the venous blood vessels only. Contact PPG sensors cannot measure the response of arterial blood flow in a functional test that takes a long time to complete because it demonstrates the rate of increase in light absorption in the absence of an obstructive effect on the veins. In contrast, the IPPG technique has the advantage of offering contactless measurements of the blood-flow parameters which greatly simplifies the measurement procedure and allows one to estimate the vascular system response without any additional influence from the measuring system. The application of IPPG for monitoring peripheral blood flow during venous occlusion was first demonstrated in our group in 2017 (Kamshilin et al., 2017). In this technique, the venous occlusion challenge

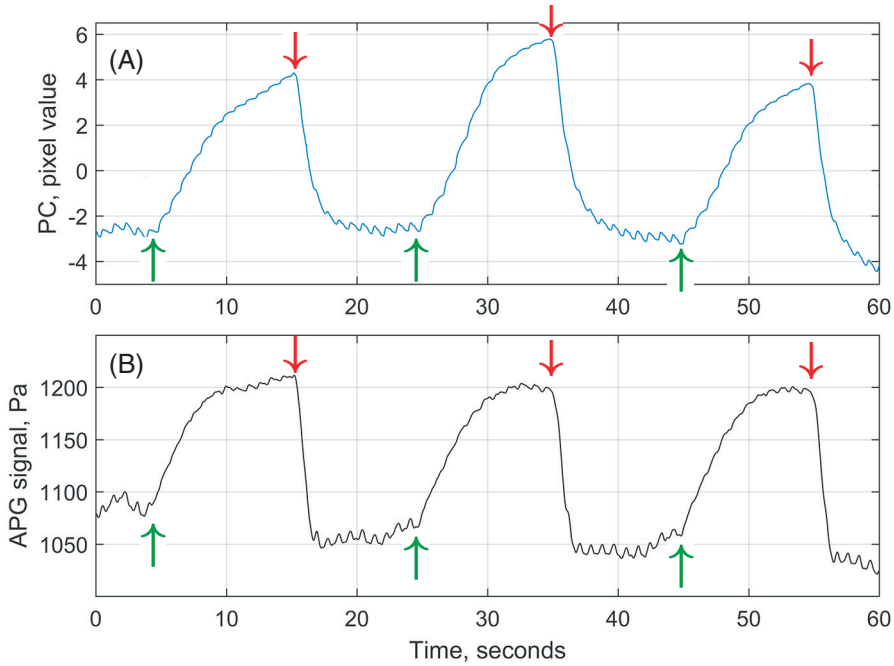

Figure 13.3
Simultaneous recording of triple venous occlusions by green-light IPPG and air plethysmography (APG). (A) PPG waveform (blue curve), (B) APG waveform (black curve). While green arrows show the beginning of each occlusion, the red arrows indicate the moments of occlusion cuff deflation.

is monitored by using a conventional video recording of a limb under green illumination. It is noteworthy that this new approach was a consequence of an alternative theoretical model of PPG-signal formation, also developed by our group a few years previously (Kamshilin et al., 2015). The essence of this model is that the coefficient of both absorption and scattering of light in the capillary bed between skin and veins is changing due to its compression under the effect of increasing pressure in the veins during their occlusion by the cuff. The feasibility of green-light IPPG to assess blood flow reactivity in the forearm was confirmed by the simultaneous monitoring of venous occlusion by imaging photoplethysmography and APG (Zaytsev et al., 2018a). A typical evolution of the PPG signal during multiple repeated venous occlusions is shown in Fig. 13.3, where the green and red arrows indicate the beginning and end of each venous occlusion, respectively. As seen in Fig. 13.3A, the PPG signal rises linearly immediately after the fast cuff inflation and sharply returns to the initial baseline level following cuff deflation. This waveform is very similar to the simultaneously recorded, APG signal shown in Fig. 13.3B, the beginning and end of each occlusion event are well synchronized.

In fact, venous occlusion leads to an increase in limb venous pressure, which increases the pressure in the APG measuring cuff while leading to an increase in the inverted PPG waveform. Since the filling of the venous bed is due to the inflow of arterial blood, the value of which is determined by arterial vessel tone, the use of various stimuli for the sympathetic nervous system can change the blood flow. Therefore, the speed of venous filling will reflect the state of neurogenic regulation of the peripheral vessels, which is the vascular component of neurogenic reactivity. An increase in vascular tone can be caused by hypothermia created by applying a cold mass to the chest area or by immersing one hand in cold water. A pilot study of the cold stimulus influence on vascular reactivity was carried out with simultaneous monitoring of the blood flow response by air plethysmography and contactless IPPG (Zaytsev et al., 2018b). It was shown that the rate of changes in signals measured by both methods decreases during global hypothermia by a comparable amount: $-39.6 \pm 16.6\%$ for IPPG and $-35.7 \pm 12.4\%$ for APG (see Fig. 13.4). Moreover, the data obtained by both methods correlated well with each other: $r = 0.82$, $P = .023$ (Spearman rank correlation). Considering that IPPG is noninvasive, contactless, and can be easy to implement, these studies have demonstrated good promise for this method as applied to the experimental assessment of neurogenic reactivity in a clinical setting.

Another area of applications of the occlusive plethysmography technique enhanced by IPPG can be for measurements of fractional reserve of blood flow in patients with venous occlusive disease of the lower extremities. Currently, this kind of measurement is performed on the lower extremities using strain-gauge plethysmography or APG (Meneses et al., 2018). Nonetheless, recent experimental demonstrations of the effective use of green-light IPPG for measuring blood-flow reactivity of the lower extremities (Zaytsev et al., 2019) has shown the promise of using this technique for studying the functional state of the leg vessels in a wide range of diseases. Assessment of the fractional blood-flow reserve, based on measuring the response of blood flow to an ischemic test or vasoactive drugs, can create the basis for the choice of tactics and control of the treatment adequacy of occlusive lesions of the leg vessels.

13.4 Objective early diagnosis of Raynaud's phenomenon assessing vascular response to cold exposure by IPPG

The "cold-sensitivity" condition Raynaud's phenomenon (RP) belongs to the group of vasospastic conditions of unclear etiology; it can be primary or secondary to an underlying medical condition. RP is not uncommon, affecting from 5 to 15% of individuals in the general population (Cutolo, 2010). In women, this condition can occur 5 times more often than in men. The pathogenesis of the disease is associated with an increase in vascular reactivity in response to various stimuli, primarily to cold, which provokes a painful vasospasm.

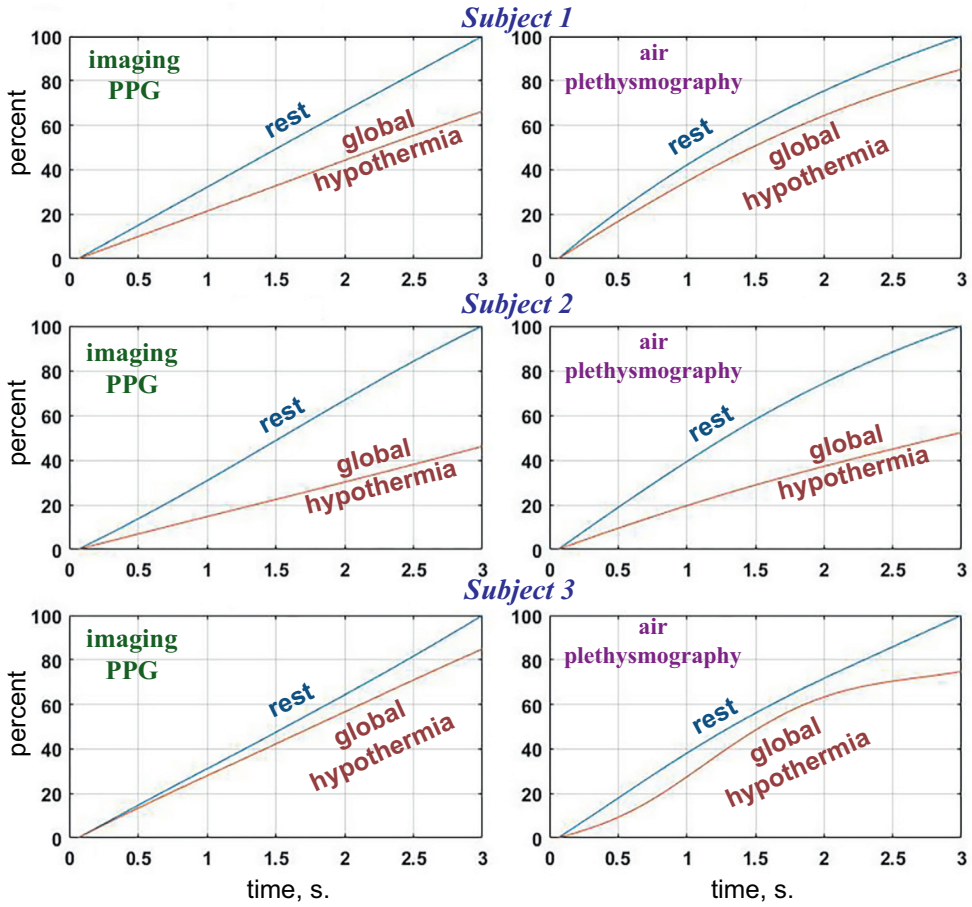

Figure 13.4
Initial parts of the signal variations during the venous occlusion. The panels in the left column show the waveforms measured by the IPPG system whereas signals obtained with the reference air plethysmography (APG) technique are shown in the right column.

In the overwhelming majority, the diagnosis of RP is based on the identification of characteristic clinical signs: changes in the skin color and pain appearance in response to contact of the limb skin with cold exposure. Sometimes it is possible to detect characteristic changes in small vessels by using capillaroscopy and carrying out immunological studies in patients with rheumatological disease, abnormalities here would point to an underlying connective tissue disease such as systemic sclerosis (Cutolo, 2010; Allen and Howell, 2014). Studies with laser Doppler flowmetry and laser speckle imaging, thermography and ultrasound Doppler have been reported (Herrick et al., 2020). However, these approaches can each have their limitations, even in the case of carrying out functional testing. Nevertheless, a change in vascular reactivity is not a qualitative condition, but a process that involves a step-by-step change in

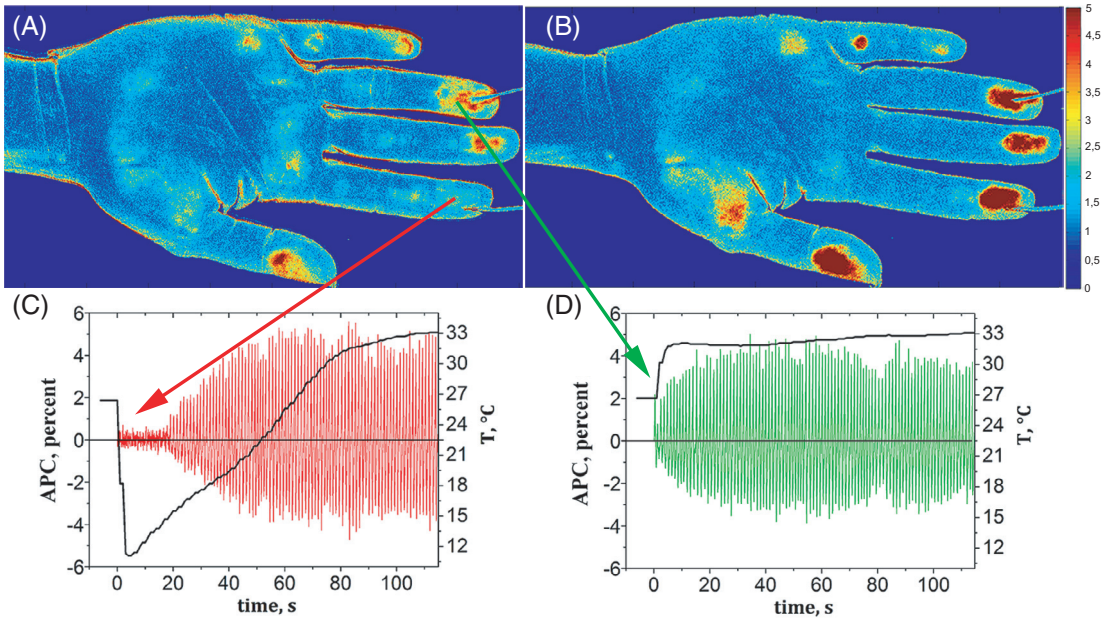

Figure 13.5

Distribution of the amplitude of the pulsatile component (APC) of the PPG waveform measured just after finger cooling (A), and 2 minutes later (B). APC dynamics measured in the preliminary cooled finger are shown in panel (C) whereas that of the noncooled finger are shown in panel (D). The black curves in the graphs (C) and (D) show evolution of the skin temperature in respective fingers. The color scale on the right of the maps shows the APC as measured in percent.

reactivity, an increase in which characterizes the natural course of the condition whereas a decrease shows a regression in the course of effective treatment. Besides the pronounced clinical forms of Raynaud's, there are also subclinical stages of the disease, the identification of which is most promising for their early diagnosis and treatment.

An objective assessment of the severity of vasospasm can be investigated using IPPG. It has been shown that this technology allows us to quantitatively measure the reactivity of cutaneous blood flow to a temperature challenge (Kamshilin et al., 2016). The protocol used in this study was as follows: At the initial stage, a distal phalanx of a subject's index finger was cooled by immersing in a mixture of ice and water at the temperature of 5°C for 60 ± 2 seconds (remainder of the hand not cooled). Then the palm, including the cooled finger, was in contact with a glass plate at a room temperature of 23°C, and a video recording of the whole palm began simultaneously with recording the skin temperature of the fingers. As seen in Fig. 13.5, blood pulsations, assessed by the amplitude of the pulsating component of the PPG waveform (APC), were significantly reduced on the cooled finger, followed by microcirculatory recovery after a certain delay.

Blood flow recovery after cold vasospasm is observed by the clear increase in APC. The recovery time can range from 6 to 25 seconds and is well reproduced upon several repeated measurements. Clearly, a small deviation in the delay time of blood flow recovery can be easily determined even in the case of its slight extension, which is expected in patients with primary or secondary Raynaud's. Moreover, the dynamics of the blood flow recovery in the cold finger could also be accurately assessed, as seen in Fig. 13.5C. The simplicity of the functional test arrangement using IPPG and good repeatability of measurements (Kamshilin et al., 2016; Belaventseva et al., 2019) can enable this method to support an objective assessment even in patients with subclinical variants of RP.

It is worth noting that a recent study on healthy volunteers and Raynaud's patients affirms the association of IPPG signals to cutaneous perfusion (Rasche et al., 2020). Local amplitude of pulsations measured by IPPG was significantly increased by the cutaneous vasomotor response to thermal impact (Volynsky et al., 2019). A comparative study of IPPG with laser Doppler perfusion imaging while simultaneously monitoring local vasodilation caused by topical application of a liniment or local heating has revealed a strong relationship between tissue perfusion that is registered by both methods (Marcinkevics et al., 2016).

13.5 IPPG to assess endothelial function during heat exposure

Endothelial function has an important prognostic value in patients at high cardiometabolic risk, including those with arterial hypertension (Konukoglu and Uzun, 2016), atherosclerosis (Gimbrone and Garcia-Cardena, 2016), heart failure (Zuchi et al., 2020), diabetes mellitus, and chronic obstructive pulmonary disease. This indicator is associated with increased risk of hypertension progression, development of cardiovascular complications, and heart failure. Evaluation of endothelial function is currently carried out by examining both biomarkers and blood vessel responses to reactive hyperemia or drug exposure. As is known, the endothelium plays a crucial role in the regulation of vascular tone by releasing a number of vasodilator mediators. In the case of local tissue heating, its effect on blood flow is realized through the activation of the transient receptor potential (TRP) channels of endothelial cells and a subsequent increase in the concentration of intracellular calcium, leading to the release of vasoactive agents, in which nitric oxide plays a leading role (Zhang and Gutterman, 2011). Therefore, unlike other markers, evaluation of the vascular response to heat exposure is the most physiological way to assess vasodilator endothelial function. In this case, a measure of the vasodilation response to thermal exposure can be such parameter as APC, the value of which is defined by the tone of small arteries and arterioles (Lyubashina et al., 2019).

Recent studies using green-light camera-based PPG (Volynsky et al., 2019) showed that the application of a small transparent bag with warm water (4–7°! warmer than the skin) to the

forehead results in a local increase in APC, while this indicator remains unchanged outside of the heated area (see Fig. 13.6).

As can be seen, the heating of the local area of skin to 38–39°C leads to a significant increase in the APC, which persisted for several minutes after the termination of heat exposure. This observation indirectly indicates the mediatory nature of the causes of vasodilation. The fact that the increased in APC persisted for more than 3 minutes after termination of the heat exposure, most likely indicates the presence of continued release of biologically active substances in response to activation of TRP channels, followed by activation of endothelial cells. Obviously, an impairment of endothelial function will be accompanied by a decrease in reactivity in response to skin heating and will result in a reduction in the time it takes for the APC to return to its initial value. Therefore, IPPG can be used to design a simple method for assessing the most physiological component of the endothelial function for the microvascular response to TRP channels activation by means of a local hyperthermia test.

13.6 Revealing microcirculation parameters in scleroderma skin lesions

Assessment of changes in the skin (both for own skin lesions and as a result of other diseases with secondary involvement of the skin) is based on evaluation of clinical signs associated with the appearance of typical elements (macula, papules, bulla, petechiae, etc.) and specific signs, such as "mechanic's hand" or Gotron's sign in dermatomyositis (Sontheimer and Kovalchick, 1998; Okiyama and Fujimoto, 2019). At the same time, objectification of the lesions, especially for subclinical cases or for an atypical clinical picture, encounter difficulties in verification, and are often not taken into account. One of the pathologies in which skin damage is an important component, but there are no perfect methods of objectification, is the autoimmune condition systemic sclerosis (SSc). Currently, a key method of instrumental verification of the disease is capillaroscopy (van den Hoogen et al., 2013), but the images can take considerable skill to interpret—-especially for early disease cases. IPPG also has the potential to detect capillary-bed lesions in the skin as these would be accompanied by a change in blood-flow parameters in the superficial dermis, with the advantage of IPPG being that it can assess the skin microcirculation across a wide range of body sites, that is, from head to foot. IPPG should be evaluated for the diffuse cutaneous and limited cutaneous variants of SSc from a range of proximal and distal site assessments. One of the proximal regions that is easily accessible for noncontact measurements of cutaneous blood flow using an IPPG camera is the face (Takano and Ohta, 2007).

Recent comparative studies of the spatiotemporal dynamics of facial microcirculation using IPPG revealed several indicators that statistically significantly differ in the group of patients with SSc compared with the healthy control group (Mamontov et al., 2020a). It was shown that with comparable mean values of APC and arrival time of the blood pressure wave (PAT),

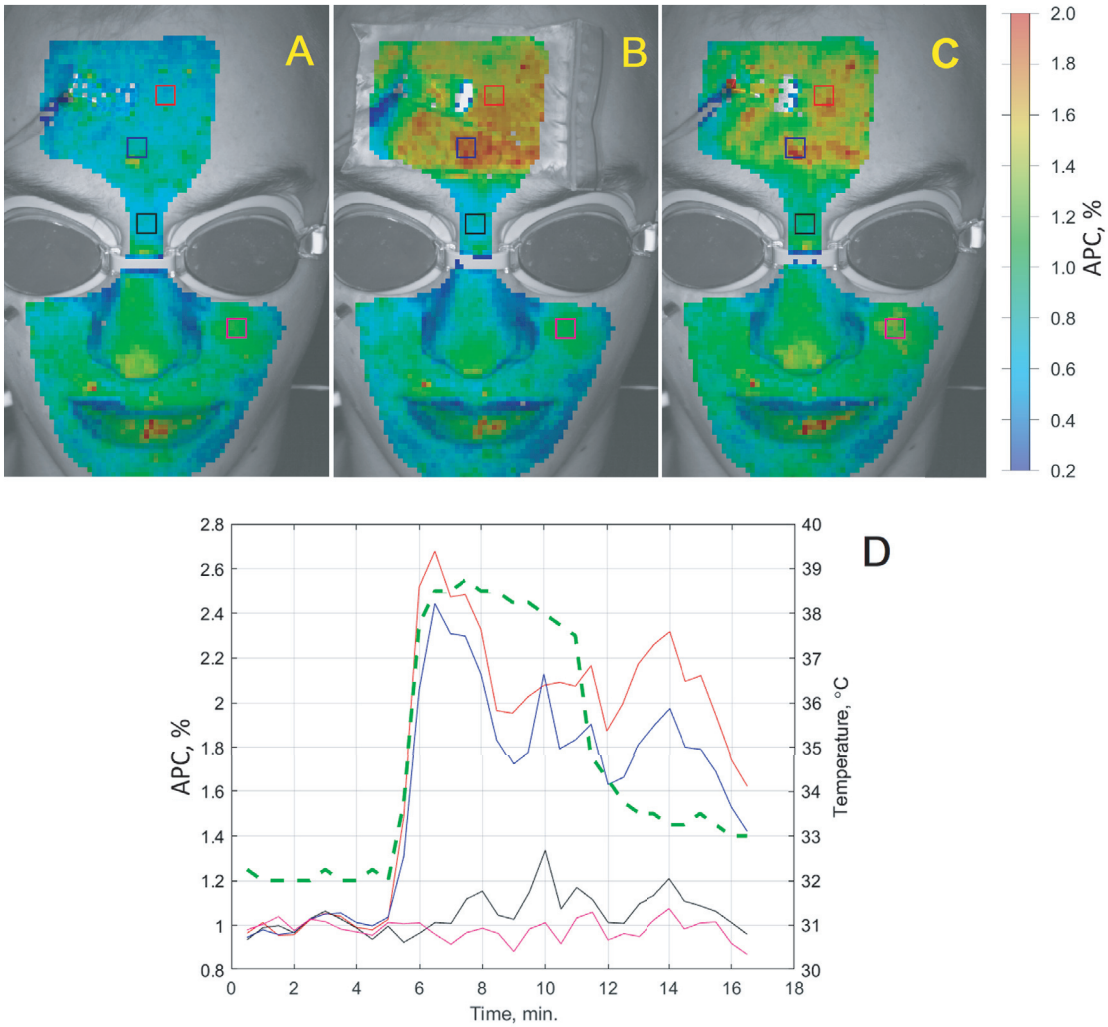

Figure 13.6

APC mapping (in pseudo-color) overlaid with a subject's face image before (A), during (B), and after (C) applying a warm bag to the forehead. The APC color-coding shown on the right is common to all three panels. Panel (D) shows the evolution of APC (solid color curves with a scale on the left) along with skin temperature (a dashed green line with a scale on the right). The dynamics of APC in the area of heat exposure is shown by the red and blue curves calculated in ROIs of the corresponding color, whose location is indicated on the upper panels. The black and magenta curves in panel (D) show APC dynamics assessed in ROIs of the same color located on the nose and cheek, respectively. A warm transparent bag was applied at the 5th minute and removed at the 11th minute.

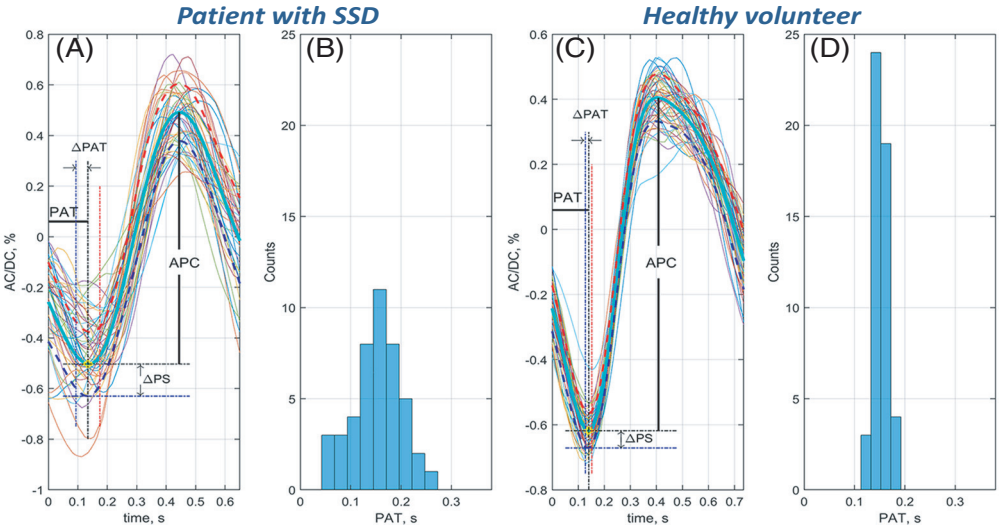

Figure 13.7

Instability of PPG pulses in time and definition of PPG-waveform parameters. Panel (A) shows PPG pulses of 43 consecutive cardiac cycles (thin-colored lines) synchronized with R-peaks of ECG for a patient with SSc. A PAT histogram for the pulses is shown in panel (B). For comparison, PPG pulses of 48 consecutive cardiac cycles in length are shown in the panel for a healthy subject (C) with the respective histogram in panel (D). The thick green lines in (A) and (C) show the mean PPG pulses obtained after averaging of particular waveforms for the patient with SSc and healthy control subject, respectively. The thick dashed red and blue lines in (A) and (C) are plotted as the mean ± standard deviation (in percent) of the pulses in each time point.

the patients with SSc had a significant increase in the variability of these parameters. The variability of the PPG waveform shape (ΔPS) and of the pulse-wave arrival time (ΔPAT) in patients with scleroderma was almost twice as high compared to controls: 0.13 ± 0.07 vs. $0.09 \pm 0.02\%$ ($P < .001$) and 52 ± 47 vs. 24 ± 13 milliseconds ($P = .01$), respectively (see also Fig. 13.7). These markers can characterize the stability of the PPG waveform.

It should be noted that for the patients included in the study (Mamontov et al., 2020a), no specific signs of facial scleroderma skin lesions were revealed in most cases. This means that this method is able to identify abnormalities in capillary blood flow independently from appearance of visible clinical signs of SSc that is impossible to do with the existing routine examination. Probably, an increase in the variability of the pulse waveform (both in time and in space) in scleroderma could be attributed to a decrease in the number of functioning capillaries and changes in the properties of connective tissue, which affect its optical parameters. Therefore, the indicators relate to the statistical characteristics of PPG waveforms offering potential in making instrumental diagnosis of SSc. The application of the IPPG is also promising for the

early diagnosis of other skin diseases, for example, in inflammatory processes in patients with systemic lupus erythematosus and other rheumatological pathologies, in psoriasis, as well as in vascular alopecia.

13.7 Assessment of vascular reactivity in response to topical capsaicin application and other pharmacological impact

Both local effects on various receptors that provide regulatory functions, and systemic effects associated with the direct impact of vasoactive substances on the circulatory system and neurohumoral mechanisms of regulation effect may appear in response to pharmacological impact on skin vessels. Goals and objectives of the research can be different, as well as the groups of pharmacological substances that can change the musculocutaneous blood flow. An example of one of the medical problems solved by IPPG when studying the pharmacological effects on skin vessels is a capsaicin test in patients with migraine (Kamshilin et al., 2018).

Objective diagnosis of migraine is currently the subject of experimental development, far from clinical use. Diagnosis of the disease is established on the basis of clinical criteria in accordance with the recommendations of the International Classification of Headache Disorders (Headache Classification Committee of the International Headache Society, 2018). However, according to modern concepts of the pathogenesis of this disease, an important role is played by genetic factors in migraine patients. These factors determine the state of transient vanilloid type 1 receptors (TRPV1), in response to the activation of which there is a release of calcitonin gene-related peptide (CGRP), which plays the most important role in the pathogenesis of migraine (Schou et al., 2017). TRPV1 activation is accompanied by a change in local blood flow due to pronounced vasodilation, caused by both the action of CGRP on the endothelium and endothelial-independent vasodilation of small vessels (de Hoon et al., 2003). Capsaicin is one of substances that activate TRPV1 and provokes vasodilation due to the release of CGRP. It has been shown that in patients with migraine, this reaction is significantly higher than in people without this disease (You et al., 2018).

Changes in local blood flow are most often assessed visually by measuring the size of the focus of hyperemia. The advantage of IPPG is the ability of this method to objectively measure the dynamics of local microcirculation in a contactless manner, revealing not only changes in vascular filling caused by local hyperemia, but also a decrease in the tone of the supplying arteries and arterioles (Kamshilin et al., 2018). It has been shown that CGRP, by decreasing local peripheral vascular resistance, leads to decrease in the DC-component of the PPG waveform by $8.7 \pm 4.1\%$ after the application of the capsaicin patch. Such a decrease corresponds to the appearance of hyperemia, the visual expression of which is sometimes barely noticeable. In response to CGRP release, simultaneously with the hyperemia, an increase in the APC of PPG waveform is observed due to a decrease in the tone of small arteries. It is worth

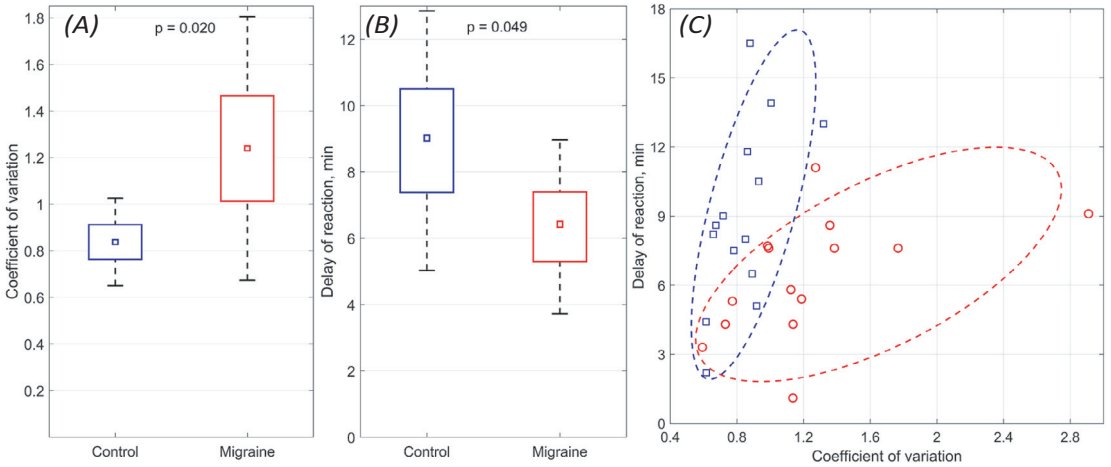

Figure 13.8

Parameters of capsaicin-induced blood perfusion in control and migraine groups. (A) Coefficient of variation (CV) and (B) delay time (DT) of capsaicin reaction in migraine patients and control group. Data presented as the mean (small squares), error of mean (boxes), and standard deviation (whiskers). (C) Two-dimensional distribution for CV and DT in the healthy control and migraine groups. Red circles are for migraine patients, and blue squares are for controls. The dashed red line shows the region of the predominant distribution of the parameters for migraine group, whereas the dashed blue line is for the control group.

noting that changes in APC cannot be visualized with the naked eye. Nevertheless, capsaicin application resulted in significantly larger changes in this indicator: 231 ± 110% and 215 ± 100% in the migraine and control groups, respectively.

Moreover, IPPG allows one to assess specific features of APC dynamics, such as its spatial variability and delayed blood flow response to capsaicin application (Kamshilin et al., 2018). These parameters can only be determined by means of IPPG and they showed a significant increase. That is, they turned out to be pathognomonic for migraine (see Fig. 13.8).

Therefore, IPPG is a significantly more sensitive way to assess the blood-flow response to topical capsaicin application than the commonly used visual assessment of skin redness. The main result of the study (Kamshilin et al., 2018) cited here as an example is the verification of instrumental biomarkers of migraine. These markers represent an increase in both spatial variability and delay in the response of microcirculation to topical capsaicin application. In fact, they are quantitative indicators of vascular reactivity, which is associated with the features of the CGRP release in migraine. Obviously, apart from the response assessment of microcirculation to capsaicin, IPPG can be used to study the response of other vasoactive substances in other diseases for various purposes, including diagnosis and selection of pathogenetic therapy.

13.8 Intraoperative monitoring of cortical blood flow parameters

Evaluation of cerebral blood flow during brain surgery is of great practical importance. Besides the tasks of monitoring the viability of brain tissue, the assessment of cerebral blood flow is important for specifying the value of the functional reserve during neurosurgery, as well as assessing the results of revascularization performed. At the same time, a correction of surgical tactics in the case of inadequate restoration of cerebral blood flow and its functional reserve directly depends on the assessment results. Various methods of intraoperative assessment of cortical-blood-flow parameters are currently being tested. However, all of them experience significant difficulties due to the necessity of impractical and expensive equipment to be used in the operating room. For example, computed tomographic angiography, in addition to being expensive and bulky, requires the mandatory injection of a radiopaque contrast agent, whereas application of either ultrasound or laser Doppler perfusion imaging are significantly limited due to their low accuracy and difficulty in rapidly assessing the perfusion of large areas.

Alternatively, the utilization of IPPG with its main characteristics (noninvasive, contactless easy to use, and capability of providing high information content) opens up great opportunities for intraoperative assessment of cortical blood flow. In a recent pilot study, the high potential of the IPPG method in open surgery for both tumor removal and revascularization of the middle cerebral artery basin was demonstrated (Mamontov et al., 2020b). This study has demonstrated feasibility to visualize both amplitude and temporal characteristics of cortical blood flow with high spatial and temporal resolution simultaneously in the area of the entire visible cortex. Moreover, changes in cerebral blood supply caused by surgical intervention were clearly revealed. As an example, spatial distributions of APC (a parameter related to the tone of arterial vessels) and PAT (time of the blood-pressure-pulse arrival) before and after tumor resection is shown in Fig. 13.9.

As seen in Fig. 13.8(e), in the area of the cerebral cortex incision, a pronounced diminution of perfusion is observed after the surgery in which a sharp decrease in APC was noted. This is most likely due to damage to vessels of the convex surface of the cerebral cortex. It is worth also noting that a significant increase in the average APC outside the dissection area was observed: $2.38 \pm 1.01\%$ presurgery vs. $3.48 \pm 1.05\%$ postsurgery, $P < 0.01$.

In another case of neurosurgery, an anastomosis of the middle cerebral artery with a branch of the external carotid artery was established in a patient with internal carotid artery occlusion (Mamontov et al., 2020a). Spatial distributions of APC and PAT for this patient are shown in Fig. 13.10. Comparing the maps of panels (B) and (E) in Fig. 13.10, it can be seen that the anastomosis application led to a significant decrease in APC: $2.13 \pm 0.50\%$ and $0.80 \pm 0.07\%$ ($P < 0.01$) before and after the surgery, respectively. At the same time, PAT also significantly decreased from 407 ± 137 to 147 ± 117 milliseconds, $P < 0.001$ (see

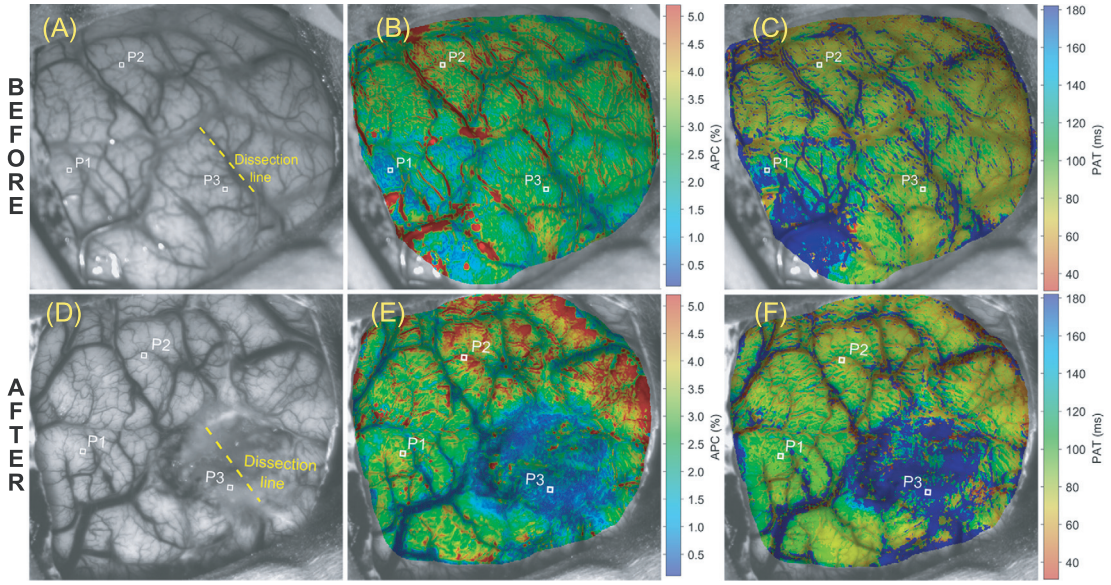

Figure 13.9

Mapping the blood pulsations parameters in the brain cortex for a patient with tumor: The upper and lower rows are images of an open brain obtained before and after tumor resection, respectively. Photographs of the open brain with the dissection region indicated by dashed yellow line are shown in panels (A) and (D). Spatial distributions of amplitude of pulsatile component (APC) and pulse arrival time (PAT) overlaid with still images of the open brain cortex are shown in (B), (E) and (C), (F), respectively. The color scales on the right of the maps show APC in percent and PAT in milliseconds.

panels (C) and (F) in Fig. 13.10). It is assumed that this was due to the normalization of blood flow in the anastomosis basin, the imposition of which was accompanied by an increase in the volumetric blood flow velocity in the perfusion zone and a corresponding reflex increase in arteriolar tone.

It is worth noting that the shape of the PPG waveform was restored after anastomosis application in all parts of the revascularized region (see Fig. 13.11). Before surgery, in conditions of blood flow deficit, significant variability of PPG waveforms in space and time (as well as the prolonged PAT) was most likely caused by the blood supply to the occlusal basin through collaterals from neighboring regions. It should be emphasized that the spread of pulse arrival time and the spatiotemporal variability of pulse shape are very sensitive markers of brain circulatory disturbances. The capability of the IPPG system to assess these informative markers is an important advantage of this technique.

Results of our pilot experiments (Mamontov et al., 2020b) suggest that after anastomosis application, more efficient blood supply to previously hypoperfused areas triggers the compensatory mechanism that increases the tone of arterial vessels, thus increasing regional vascular

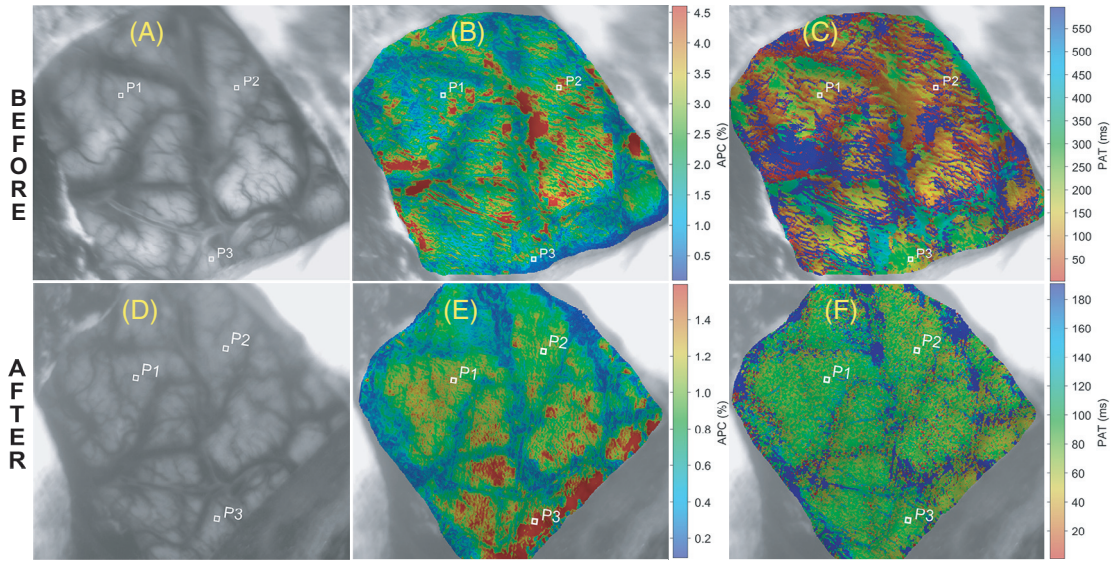

Figure 13.10
Change of cortical blood flow parameters before (upper row) and after (lower row) anastomosis application: The maps of the APC and PAT in panels (B), (C) and (E), (F) are overlaid with still images shown in photographs (A) and (D) of the cortex before and after surgery, respectively. The color scales on the right of the maps show APC in percent and PAT in milliseconds. Note the difference in both scales before and after surgery.

resistance. Accordingly, the amplitude of arterial lumen oscillations decreases, leading to a drop in APC. The observed increase in the arteriolar tone is associated with the normal reactivity of the cerebrovascular reflex, which ensures the constancy of the parameters of cerebral hemodynamics, when arteriolar tone changes depending on the perfusion pressure. Therefore, the amplitude of the pulsatile component of the PPG waveform, APC, can be considered as a measure of the tone of small local arteries.

The latter statement was confirmed in a recent animal study (Lyubashina et al., 2019), where it was shown that APC of cerebral vessels changed in inverse proportion to either spontaneous or reflex systemic-blood-pressure variations in response to somatic or visceral stimuli (see Fig. 13.12). In most rats, a counter-phase change in APC and systemic blood pressure was observed in response to visceral or somatic pain stimuli. Only in two of eleven rats with abnormally low or abnormally high blood pressure did the relative dynamics of APC and pressure deviate from this pattern. Therefore, it was shown that the APC parameter is a measure of vascular tone, an increase in which leads to a decrease in blood pulsation, and a decrease, on the contrary, to its increase that can be used to quantitatively assess cerebral blood flow and its physiological parameters.

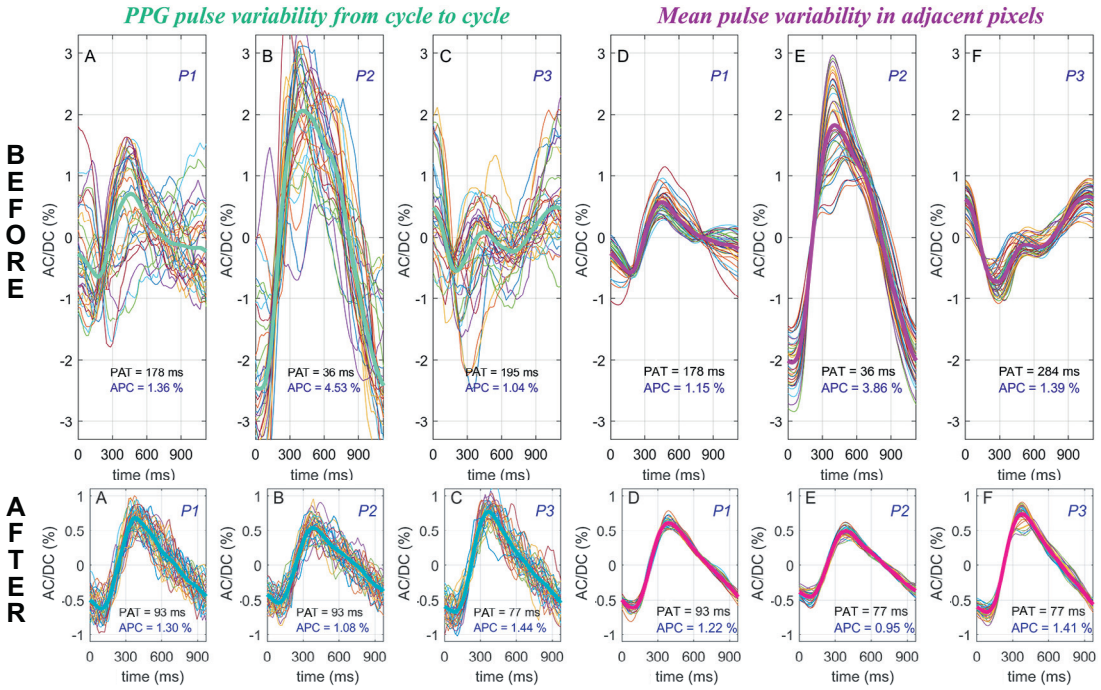

Figure 13.11

Variations of PPG-pulse shape in time and space in the case of carotid artery revascularization: The thin color lines in (A–C) show PPG pulses of 35 consecutive cardiac cycles calculated in the central pixel of ROIs marked by P1, P2, and P3, respectively. The positions of these ROIs in the cortex are shown in Fig. 13.10. The thick green lines in these graphs are PPG pulses averaged over the cardiac cycles. The thin color lines in graphs (D–F) show the mean PPG pulses calculated in each of 49 neighboring pixels within respective ROIs marked by P1, P2, or P3. The thick pink lines in these graphs are the waveforms averaged over all pixels within the ROI. The upper and lower rows show the graphs before and after surgery, respectively.

One of physiological parameters is the functional reserve, the state of which is of great practical importance and is a marker for determining the tactics of treatment of patients with severe cerebral atherosclerosis. Currently, the gold standard for assessing functional reserve is paired measurement of cerebral blood flow by magnetic resonance tomography (MRT) using a pharmacological test with a carbonic anhydrase inhibitor. However, this method is available only at the stage of surgery preparation and it is unfeasible during the operation. In contrast, IPPG allows intraoperative assessment of the functional reserve of blood flow, which is extremely important for rapid assessment of the results of revascularization at a time when the defect in surgical treatment is easy to correct. In a recent study in animal models (Mamontov et al., 2020c), it was shown that the administration of a carbonic anhydrase inhibitor, dorzolamide,

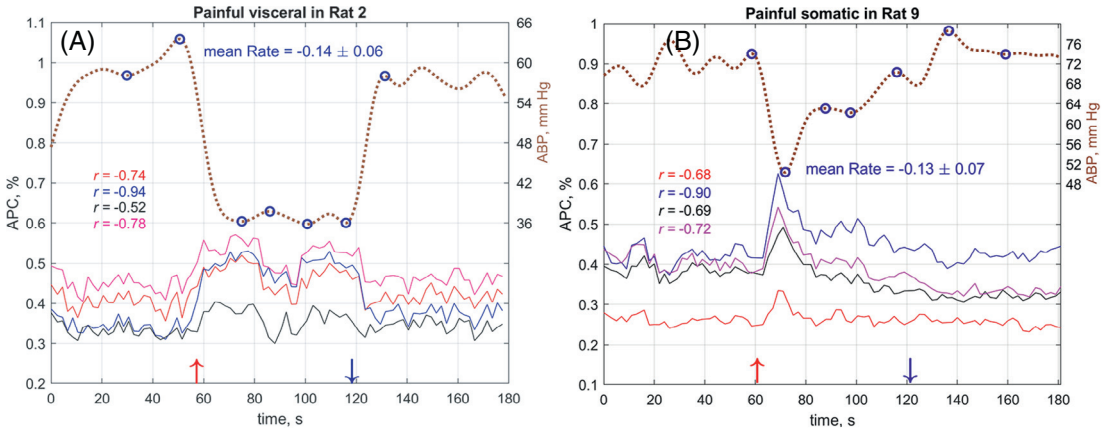

Figure 13.12
Typical dynamics of the systemic blood pressure and amplitude of pulsatile component in cerebral arteries of exemplary rats during visceral (A) and somatic (B) stimulation. Dashed brown curves show dynamics of the mean arterial blood pressure with the labels on the right. Solid colored lines show APC measured in big ROIs selected in different areas of the cortex. Red and blue arrows nearby the X-axes show moments of the beginning and end of stimulation, respectively.

leads to an increase in APC by an average of almost 50% at the third minute after injection (see Fig. 13.13).

As seen, the dynamics of APC is well correlated with the dynamics of CO_2 in exhaled air, while it does not depend on changes in systemic blood pressure. Therefore, in this experiment, injection of the dorzolamide (drug test) led to respiratory acidosis and contributed to a rapid decrease in cerebral vascular tone in healthy rats, which was successfully recorded by means of IPPG. The simplicity and the contactless nature of the measurements provided by IPPG make it possible to carry out studies of this type directly under the conditions of surgical intervention, and to clarify the functional reserve before vessels revascularization, including the recording of the dynamics of its changes after surgery.

13.9 Identification of functioning skin capillaries

Capillaroscopy is a noninvasive method for real-time visualization of soft tissue capillaries in vivo. Currently, the visualization of capillaries in a clinical setting is possible in three main regions: nail folds, gums, and retina. At present most microvascular studies are accomplished combining a microscope with video camera thus providing evaluation of static and dynamic states of the capillaries (Erikkson et al., 2014). Information revealed from capillary imaging regarding their density, size, and shape is of important diagnostic and prognostic value in various diseases, including rheumatologic pathology, arterial hypertension, and diabetes

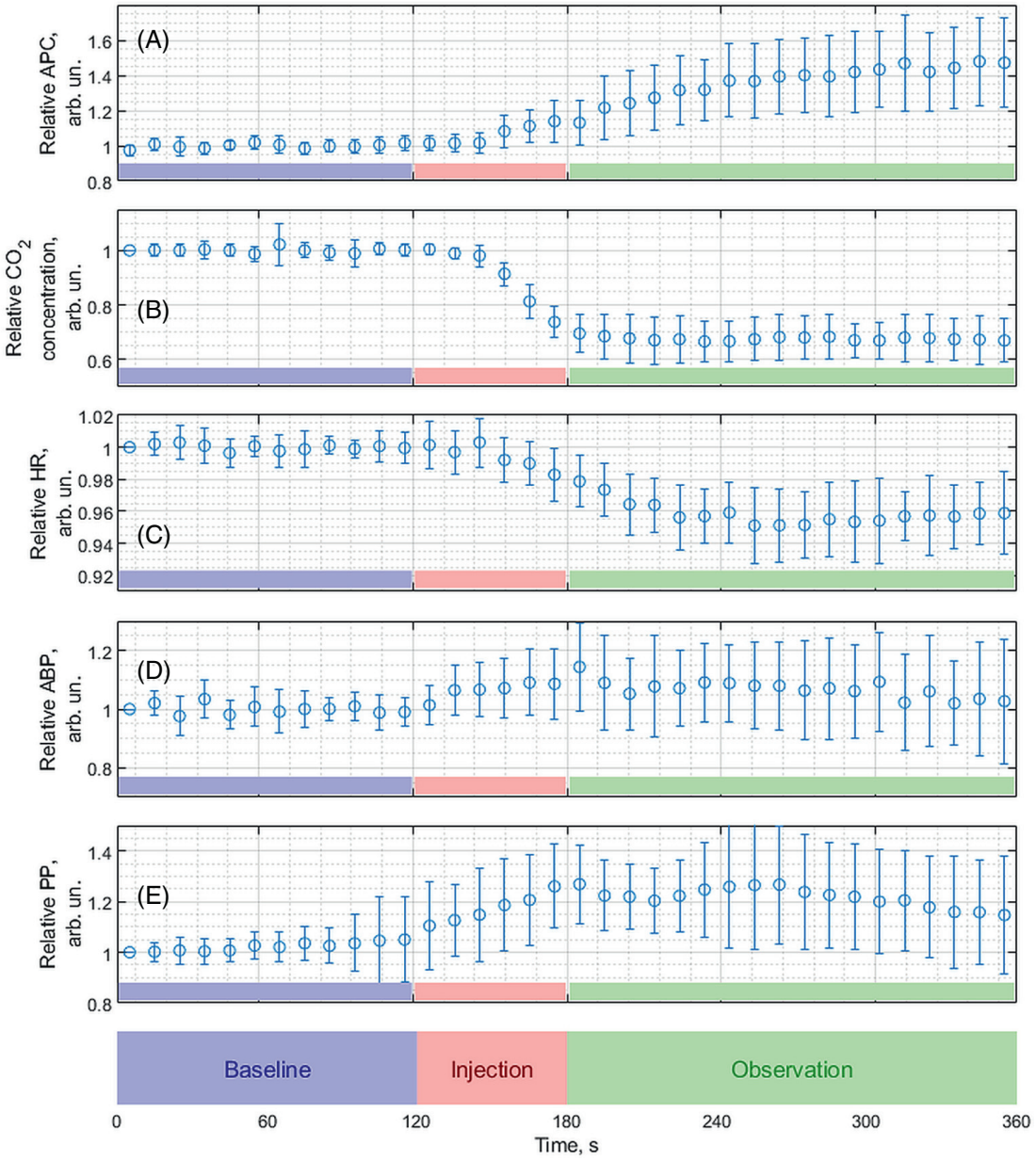

Figure 13.13

Typical dynamics of the systemic blood pressure and amplitude of pulsatile component in cerebral arteries of exemplary rats during visceral (A) and somatic (B) stimulation. Dashed brown curves show dynamics of the mean arterial blood pressure with the labels on the right. Solid colored lines show APC measured in big ROIs selected in different areas of the cortex. Red and blue arrows nearby the X-axes show moments of the beginning and end of stimulation, respectively.

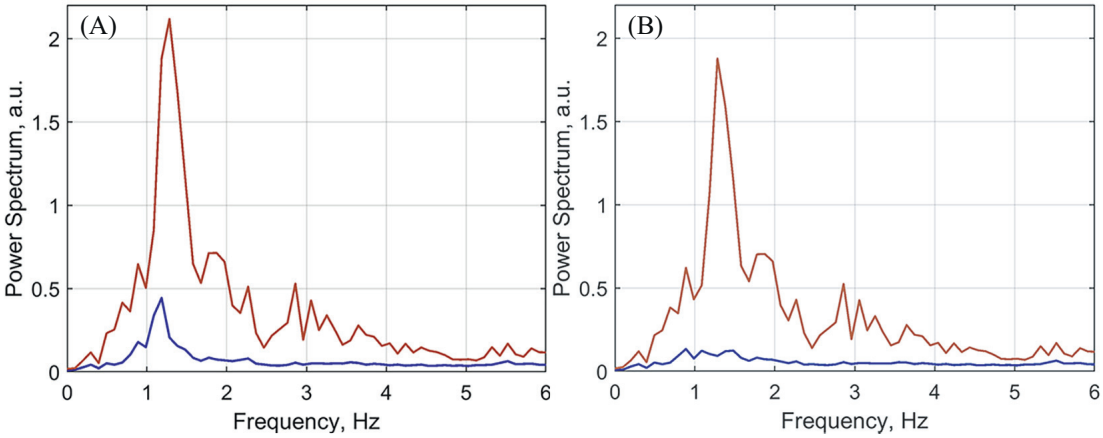

Figure 13.14
Mean power spectra of PPG waveforms. (A) Averaging over 50 randomly chosen ROIs localized in the areas with moving RBCs (brown curve) and over other 50 ROIs localized in the areas without moving RBC (dark blue curve). (B) Similar graphs as in the panel (A) but the spectra from the same ROIs were averaged after suppression of the heart-related modulation.

mellitus (Ciaffi et al., 2020). However, due to the few regions where capillary studies can be carried out, this can significantly limit its diagnostic value in some conditions. At the same time, in a number of diseases (e.g., in scleroderma, vasculitis, and diabetes mellitus), damage to capillaries is often observed outside the areas currently available for capillaroscopy.

Recently, in a pilot study using a microscope in combination with IPPG technique, functioning cutaneous capillaries were visualized outside the three traditional areas, where their in vivo imaging was not previously available (Margaryants et al., 2019). Identification and visualization of the microvessels was achieved due to significant differences in the PPG waveform characteristics measured at the capillary itself and the area outside of capillaries. Capillaries were visualized due to difference in spectral parameters of the green light after its interaction with unevenly moving RBCs in capillaries compared to those parameters of interstitial tissues. One can see in Fig. 13.14 that the power spectrum of re-emitted light from moving RBCs in capillaries covers much wider spectral band than in the area of the interstitial tissue.

This feature formed the basis of spectrally transformed IPPG, which allowed to separate (enhance) images of cutaneous capillaries with moving RBCs from the number of other small details usually observed in skin images under a microscope. Mapping differential PPG waveforms (a spectral characteristic of the waveform) overlaid with an initial image of the skin allowed us to visualize the skin capillaries in various areas of the forearm and face in all eleven subjects examined (Margaryants et al., 2019). An example of such a visualization is shown in Fig. 13.15.

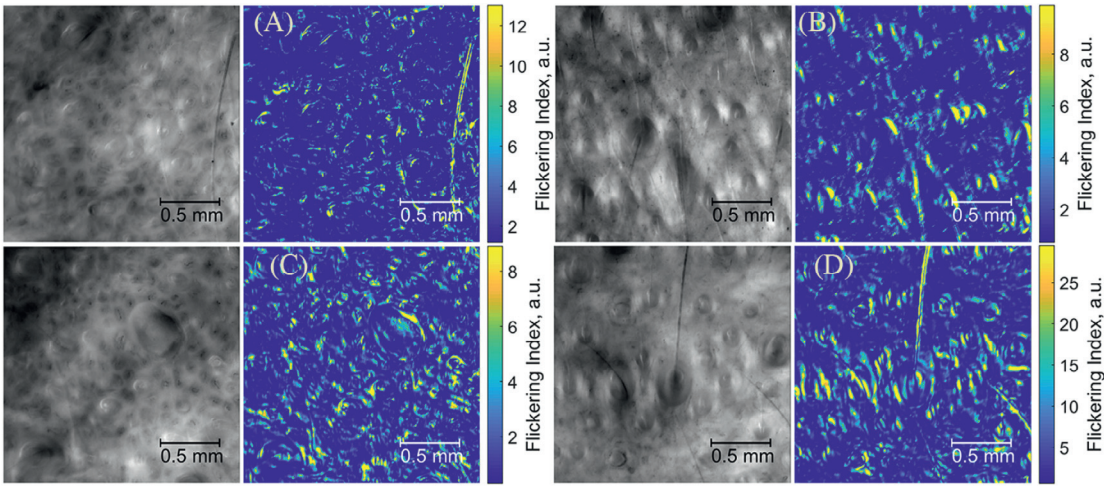

Figure 13.15
Microscopic images of the skin in the facial area (upper row—-areas of the cheeks, lower row—-areas of the forehead) and corresponding distribution of capillaries with moving RBCs evaluated for two subjects as examples: (A) and (C) panels—-for one subject, while (B) and (D) panels—-for another.

Mapping of the spectrally related parameter of PPG waveforms allows not only to identify skin capillaries in previously inaccessible areas, but also to estimate their density and size with high accuracy. Moreover, in some cases the shape of the capillaries could also be assessed. It is worth noting that these capillary parameters could be assessed in almost any region of the skin. In a practical sense, in addition to diagnosing diseases leading to the degradation of capillary blood flow, this technique has an important perspective for assessing the restoration of blood supply during wound healing or after reconstructive surgery. In addition, micro-IPPG allows assessing the dynamics of the capillary-bed status during a physiological test that can change the tone of the sympathetic nervous system. Consequently, this technique has the potential to detect autonomic vasomotor dysfunction associated with damage of peripheral sympathetic nerve fibers, for example, in patients with diabetic foot complications.

13.10 Summary

Imaging PPG appears to be an advantageous method because it is reliable, noninvasive and noncontact, safe, easy to do, cost effective, and suitable for long-term physiological monitoring. One of the most impressive features of the technique is its ability to assess the vasomotor activity and vascular status. This is one of the main conclusions from our recent experimental findings that have demonstrated the feasibility to estimate quantitatively microcirculation's dynamics using IPPG technology. However, the main challenge of the method is still the limited knowledge of the theoretical model behind the technology. A deeper understanding of

the physiological features of in vivo light interaction with biological tissue containing blood vessels will significantly expand the range of applications of the IPPG method in biomedical and clinical environments.

IPPG offers an assessment of both temporal and spatial characteristics of microcirculation simultaneously over large areas, thus revealing vascular information that was previously challenging to measure. However, the lack of established methods (gold standard) for comparing the results obtained hinders the standardization of the IPPG technology. Further work should be focused on a broader study of patient groups for a range of conditions affecting the microcirculation. Only if pathological episodes can be reliably detected and distinguished from artifacts, clinically relevant contributions can be expected.

There is another challenge with IPPG technology that has not yet been addressed. Currently, the majority of IPPG systems operate with uncompressed video data, which occupy a large percentage of computer memory. Further development of new data processing algorithms that could process compressed images while minimizing the negative effect of motion artifacts is a future direction of the research. Ultimately, this will provide the medical doctor with the necessary information about the patient's vascular state in real time, which is very desirable, especially when monitoring surgical interventions.

The future solution of these challenges will significantly increase the prospects of IPPG for a wide range of medical specialties, including cardiology, neurology, endocrinology, rheumatology, neurosurgery, as well as circulatory physiology and experimental medicine. In this chapter, we have demonstrated that IPPG is capable of assessing many aspects of local and systemic hemodynamics that are not available with other diagnostic methods. In addition, through the studies covered in this chapter we have shown that IPPG can improve measurement reliability and utility, and makes it easier to obtain information about the state of microcirculation and blood flow regulation.

Throughout the chapter we have listed several IPPG applications that have emerged because of the development of the opticophysiological model behind the method. For example, when performing neurosurgical intervention, IPPG allows surgeons to assess the spatial distribution of blood flow and monitor the viability of the cerebral cortex, as well as reveal local hemodynamic disturbances in the presence of a cerebrovascular lesion. Also, in the course of a drug test, it is possible to assess the functional reserve of cerebral blood flow quickly, safely, and with a high degree of reliability, which cannot be currently performed by other methods during surgical treatment. Evaluation of the pulse shape using IPPG can be recognized as an instrumental criterion for scleroderma. Assessment of the blood flow recovery after cooling a finger may reveal a subclinical variant of vasospasm in patients with Raynaud's phenomenon. The response of the pulsatile component of the PPG waveform to a slight heating of the skin directly characterizes the vasodilatory function of the endothelium. The microvasculature reaction assessed by IPPG can also be informative when vasoactive drugs are administered.

For example, studies of topical capsaicin application have revealed a qualitatively different response in migraine patients as compared to healthy subjects. Evaluation of the variability of the PPG waveform of the skin under a microscope can allow the visualization of the capillaries in the majority of regions of the skin surface.

The IPPG method can serve to create a fundamentally new medical technology for the diagnosis and monitoring of interventions across a wide range of diseases in which a capillary bed is involved in the pathological process.

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