



Plethysmographic assessment of vasomotor response in patients with congestive heart failure before and after heart transplantation

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Abstract: Sympathetic vasomotor response is the most important part of the autonomic regulation of circulation, which determines the quality of life. It is disrupted in a number of diseases, particularly in patients with congestive heart failure (CHF). However, experimental evaluation of reflex vasoconstriction is still a non-trivial task due to the limited set of available technologies. The aim of this study is to assess the dynamics of vasomotor response of forearm vessels due to both the deactivation of cardiopulmonary baroreceptors and cold stress using a newly designed imaging plethysmograph (IPG) and compare its performance with classical air plethysmograph (APG). In both vasoconstriction tests, vasomotor response was assessed as a change in the blood flow rate due to venous occlusion compared to that at rest. Both tests were carried out in 45 CHF patients both before and after heart transplantation, as well as in 11 age-matched healthy volunteers. Prior to transplantation, both APG and IPG showed a significant decrease in vasomotor response in CHF patients due to both tests as compared to the control group. After heart transplantation, an increase in vasomotor reactivity was revealed in both vasoconstriction tests. We have found that both plethysmographic techniques provide correlated assessment of changes in the vasomotor response. In addition, we have found that IPG is more resistant to artifacts than APG. The new IPG method has the advantage of measuring blood flow in a contactless manner, making it very promising for experimental evaluation of vasomotor response in clinical conditions.

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1. Introduction

Autonomic regulation of blood circulation is accomplished by neurogenic reactions affecting both the heart rate and vascular tone [1]. Notably, the sympathetic part of the autonomic nervous system affects vascular tone to a greater extent than the heart rate to maintain adequate arterial blood pressure (ABP) in dynamically changing conditions [2]. There are several different approaches to assessing the neurogenic regulation of blood vessels based on different principles. This includes either assessing the dynamics and variability of blood pressure at rest and during various tests [3], or evaluating the blood flow dynamics using ultrasound Dopplerography [4], laser Doppler flowmetry [5,6], and magnetic resonance imaging [7]. However, all these methods cannot be considered sufficiently specific to assess neurogenic regulation, and the parameters measured by these methods are not a quantitative physiological value, allowing only a qualitative assessment of the vasomotor response. Quantitative assessment of the sympathetic tone and, consequently, vasomotor response is possible only by measuring a muscle sympathetic nervous

activity (MSNA), which can be obtained using a microneurographic technique [8]. Typically, MSNA is assessed by analyzing compound volleys induced by various stimuli and recorded from peripheral nerves of human subjects with extraneural electrodes carefully inserted in muscle nerves [9,10]. However, the invasive nature of this technique limits its widespread use. In most research protocols, venous occlusion plethysmography can successfully perform the role of a method for assessing peripheral tone and vasomotor response to various physiological stimuli [11]. The technique of occlusion plethysmography has been actively used for assessing vasomotor response up to date [12,13]. This is obviously due to the high informative value of occlusion plethysmography, which allows for evaluation of changes in peripheral resistance in response to various physiological provocations gives a result comparable in information content with the assessment provided measuring MSNA [9,14,15]. The technique of venous occlusion plethysmography combines simplicity and reliability, and consists in recording the blood flow changes in the limb at the moment of cessation of venous outflow. All of the aforesaid points to the continuing relevance and the importance of improving the methods of assessing vasomotor reactions by occlusion plethysmography.

The method of venous occlusion plethysmography combines simplicity and reliability, and consists in recording the blood flow in the limb at the moment of cessation of venous outflow, which occurs when the veins are occluded but arterial blood continues to inflow, increasing the volume of the limb. The method was proposed more than 100 years ago [14] and since then only the techniques for registering blood volume increase after occlusion were altering. The dynamics of peripheral blood flow during venous occlusion is evaluated on the basis of various physical principles. Along with historically previous methods based on the use of a water- or air-plethysmography, in which the registration of blood flow was based on an increase in pressure in a closed cavity by a limb increasing in volume during venous occlusion [16], many studies of this kind are performed assessing the limb's circumference by measuring the electrical resistance of the strain gauge, which did not always, but in most cases demonstrated results comparable to the water- or air-plethysmography [17,18]. Nevertheless, the plethysmography with registering of limb's volume changes using strain-gauge, due to its ease of use, has become more often applied in scientific and clinical study [19–22] both to evaluate the vasomotor response to various tests and to diagnose venous blood flow disorders [23,24]. However, the complexity of the implementation and the contact nature of the sensors inevitably affect the parameters of blood flow, which leads to inaccurate measurements. This probably encourages researchers to look for alternatives containing contactless sensors of blood flow that could simplify diagnostics. However, recent attempt to replace the contact sensor in venous occlusion plethysmography with an optical sensor based on near-infrared spectroscopy was unsuccessful [25]. The indicators obtained during the test with reactive hyperemia using an infrared sensor were only partially consistent with the blood-flow indicators in the lower limb area, and did not correlate at all on the arm. Somewhat earlier studies have shown differences between the parameters recorded using venous occlusion plethysmography and the data obtained from the Doppler method of blood flow assessment during physical exercises of different intensity, which also calls into question the comparability of the methods [26]. Recently, we proposed a novel approach of contactless assessing the dynamics of blood flow in limbs by using imaging photoplethysmography (iPPG) to measure an effect of the veins filling with blood due to venous occlusion [27]. More recently [28], we compared the response of blood flow on venous occlusion of an upper limb with two plethysmographs: classical air plethysmograph (APG) and imaging plethysmograph (IPG), which uses iPPG system for contactless assessment of blood flow changes. A high correlation ($r > 0.93$) between the waveforms measured by both plethysmographs was observed. However, a full-fledged validation of an alternative method involves studying the nature of the vasomotor response in patients with diseases involving varying degrees of disruption of blood flow regulation in response to various physiological stimuli.

At present, methods for assessing musculocutaneous blood flow are most in demand for assessing vasodilatory reactions in response to pharmacological substances, reactive hyperemia and physical load [29]. At the same time, vasoconstrictive reactions caused by such physiological effects as deactivation of cardiopulmonary baroreceptors [30,31] or cold stress [32] are capable to provide much more valuable information about neurogenic reactivity. This stipulates the interest in the method for assessing the autonomous regulation of blood circulation [23,33]. In patients with problems of autonomic regulation and cardiovascular pathology, these reactions are modified, and their recovery against the background of treatment can be considered as a favorable effect of the chosen strategy. Evaluation of the vasomotor response is of interest both from the point of view of studying the physiology of the body and for practical diagnostic purposes in patients with autonomic dysfunction [33], rhythm disorders [23], diabetes mellitus, hypertension and, of course, heart failure. Congestive heart failure (CHF), in which many patients experience a decrease in the cardiopulmonary baroreflex, is one of the pathological conditions leading to a significant decrease in vasomotor response [34]. In this pathology, transformation of other components of neurogenic reactivity was also observed [35,36]. Nevertheless, in patients with heart failure, the effect of cold vasoconstriction and the dynamics of vasomotor reactivity after heart transplantation remain insufficiently studied, whereas the restoration of autonomous regulation of blood circulation in patients with a donor heart is of extremely important physiological importance.

The aim of this study was to validate a new IPG method for assessing vasomotor changes, which differs from its predecessors in measurements of blood flow response to venous occlusion without affecting the measurable flow. We assessed the vasomotor response and its changes after heart transplantation in patients with congestive heart failure during the cold stress test and deactivation of cardiopulmonary baroreflex to measure the reaction of blood flow in upper third of the forearm during venous occlusion using simultaneously by IPG and APG methods.

2. Methods

2.1. *Participants and study design*

The experiments were carried out in the Almazov National Medical Research Center (St. Petersburg, Russia) in accordance with ethical standards presented in the 2013 Declaration of Helsinki. This pilot study enrolled 45 patients with severe CHF. All subjects signed the written Informed Consent Form enclosed in the study protocol approved by the local ethics committee of the Almazov National Medical Research Centre (decision No. 110 of 12.06.2010). The mean age of patients was 47.6 ± 13.2 years. The study of vasomotor response was carried out in 16 patients before and after heart transplantation, in 13 patients only before transplantation, and in 15 patients only in the post-transplantation period. This was due to the severity of the patients' condition, as well as a temporary factor that did not allow a repeat examination to be performed by the time the study was completed. In summary, 29 patients were studied in the presurgical period, and 31 patients were studied in the postoperative period. The average duration of the post-transplant period during the study was 7.1 ± 3.3 months. The control group consisted of 11 volunteers of comparable age to patients (47.0 ± 10.7 years) who at the time of examination had no known diseases of the circulatory system.

Study design of evaluation of neurogenic autonomic regulation of blood vessels included two vasoconstrictive tests that were implemented by activating sympathetic efferent nerves. In one test, a change in blood flow was evaluated in response to a decrease in venous return using a special chamber, which leads to deactivation of cardiopulmonary baroreceptors, whereas nonspecific activation of the sympathetic nervous system in response to cold stress was assessed in the other. During the whole test, the subject was asked to relax, avoid any movement, and keep breathing normally. All measurements were carried out in a medical laboratory at the temperature of 22 ± 2 °C.

2.2. Experimental arrangement

Deactivated cardiopulmonary area was induced by using a lower body negative pressure chamber [37] via creating a sub-hypotensive rarefaction (-10 mmHg). This technique allows to reduce venous return in a subject in a horizontal position by depositing an additional blood volume in the veins of the lower half of the body due to rarefaction. In other cold test, the vasoconstrictive effect was exerted by placing an ice pack on the chest for 2–3 minutes as it was described previously [38].

Changes in peripheral resistance in response to each physiological test (both before and during the test) were evaluated as a reaction of the arm's blood flow to venous occlusion, which was measured simultaneously using classical APG suggested by Dohn et al. [16] and novel IPG recently proposed in our group [27]. Measurements of blood flow dynamics in both physiological tests were performed on the patient's forearm. Diagram illustrating the relative position of the key elements is shown in Fig. 1(A), and the photograph of the setup during the cold test is shown in Fig. 1(B) in which the ice pack is marked with the symbol IV. During the study, the patient was in a comfortable supine position while his palm and elbow were on a soft support keeping the arm at the heart level. Venous occlusion was accomplished by inflating a cuff attached to the lower third of the patient's upper arm indicated by the symbol II in Fig. 1(B). An occlusive pressure of about 60 mmHg was rapidly (in 0.2 sec) increased in the cuff II and maintained for 4 sec, after which the cuff was reset to zero and increased again after 8 sec. A total of four occlusion sessions were implemented both before and during each physiological test.

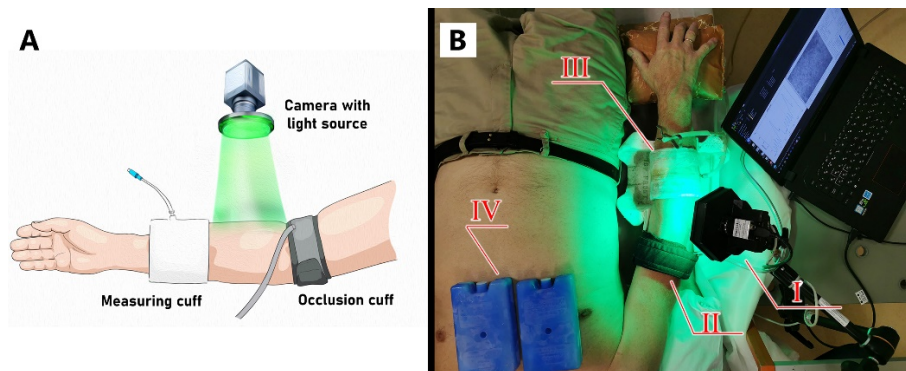


Fig. 1. Setup for simultaneous assessment of vasomotor reactivity using an air plethysmograph (APG) and a contactless imaging plethysmograph (IPG). (A) Graphic representation of the installation. Venous occlusion is performed using an occlusive cuff. Measuring cuff is the main part of the APG, and a digital camera with a built-up illuminator of green light is essential part of IPG. (B) Photograph of the setup during the cold test study. The camera, the occlusive cuff, the measuring cuff, and the ice packs are indicated by symbols I, II, III, and IV, respectively.

Measurements of changes in the size of the forearm during venous occlusion were carried out by another measuring cuff (a part of the air-plethysmograph, which is indicated by the symbol III in Fig. 1(B)) placed on the upper third of the forearm. This cuff was custom-made [28] and consisted of a flexible inner jacket made of thin, elastic rubber and an outer stiff plastic frame. It was filled with air at ambient pressure and connected to the pressure sensor. Venous occlusion leads to increase in the blood volume in the extremity thus increasing the pressure in the measuring cuff [39]. With small changes in blood volume, the pressure increases linearly with time, and these pressure changes are digitalized and recorded in the personal computer. The influx of arterial blood in conditions of cessation of outflow through venous vessels also leads

to compression of the capillary bed, increasing the absorption of light in the upper layer of the dermis [27,28,40], which was simultaneously measured by contactless iPPG system (marked by symbol I in Fig. 1(B)) in a forearm's area between the inflating and measuring cuffs.

As it was shown in our previous study [28], one video camera is enough to correctly assess the rate of blood vessels filling. Therefore, in this study, a configuration with a single camera taking video of the radial side of the forearm was used (see Fig. 1(B)). Digital camera Smartek Vision GC1391MP with Sony ICX267 CCD image sensor and KOWA LM5NCL lens was placed at the distance of 20-25 cm from the patient's forearm. The radial side of the forearm was near uniformly illuminated by two light emitting diodes (LEDs) BL-HP20APGCL-5W STAR type operating at the wavelength of 525 nm (green light) and output power of 5W for each. The incident light was linearly polarized by film polarizers attached to the LEDs, while another cross-polarized film analyzer was attached to the camera lens to increase the signal-to-noise ratio [41,42]. Images of the skin area were recorded at the frame rate of 30 frames per second with a resolution of 696×520 pixels. The frames were saved in the portable network graphics (PNG) format directly into the computer for further processing.

2.3. Data processing

Both APG and IPG data were processed off-line by using custom software implemented in the MATLAB platform. APG signal was sampled at 16 Hz and then filtered by Bessel low-pass filter of 4th order with the cutoff frequency of 4 Hz. The filtering was performed by *filtfilt* function in Matlab providing zero phase shift. This signal was interpolated to obtain new samples at the frequency of 30 Hz to be matched with the frame rate of the images recorded by the iPPG system.

The various stages of IPG signal processing are illustrated in Fig. 2. The IPG signal was calculated as frame-by-frame evolution of the pixel values averaged within a region of interest (ROI) selected on the images of the patient's forearm. Depending on the patient's constitution, the ROI size was varying from 130×35 pixels to 150×70 pixels, which corresponds to the physical size at the forearm of 98×28 and 120×56 mm², respectively. An example of the recorded image frame with selected ROI is shown in Fig. 2(A). As we demonstrated in our previous study, such averaging over a relatively large area provides a sufficiently high signal-to-noise ratio when assessing changes in blood flow by using iPPG system [43]. Figure 2(B) shows the evolution of the mean pixel value during two consecutive venous occlusions, the beginning of which is indicated by blue dotted lines and the end by green dotted lines. As one can see, the blood inflow leads to an increase in the light absorption and, consequently, to a decrease in the pixel value, which is proportional to the reflected light intensity. To achieve positive correlation with changes in the physical size of the forearm, we first inverted the waveform and then subtracted its minimal value. The resulting waveform is shown in Fig. 2(C) and is called an IPG signal. Small oscillations in the IPG waveform with a period of 0.9 s, visible in Fig. 2(C), are associated with heart contractions.

Typical evolution of the IPG signal acquired first at rest and then after applying ice to the patient's chest (cold test) before heart transplantation is shown in Fig. 3 by red curves. As one can see, all occlusion sessions are clearly distinguishable, and immediately after the onset of every occlusion, a linear increase in the IPG signal is observed. It is also seen that both the rate of increase of the IPG signal and the response amplitude is higher at rest (Fig. 3(A)) than under the cold stress (Fig. 3(B)). Waveform of APG, which was simultaneously measured with that of IPG, is shown in Figs. 3(C) and 3(D) by blue curves. Note that the timescale in Fig. 3(D) is a continuation of the scale in Fig. 3(C). Moreover, the timescale in Figs. 3(A) and 3(B) is the same as in Figs. 3(C) and 3(D) due to simultaneous recordings of APG and IPG. Dashed vertical lines in Fig. 3 are drawn at the beginning of each venous occlusion. As seen, the responses to occlusion measured by both plethysmographic methods correlate well with each other ($r = 0.84$, $P = 0.002$).

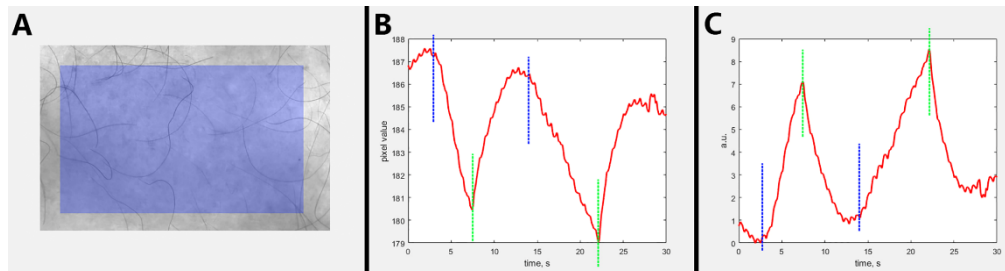


Fig. 2. Illustration of key stages of data processing to calculate the waveform in the imaging plethysmograph (IPG). (A) An example of the image frame with the selected region of interest (ROI), which is highlighted in blue. (B) Evolution of the pixel value averaged within the ROI for first 30 seconds of the recording (initial part of the raw waveform), which includes two events of the venous occlusion. (C) The IPG signal (inverted and shifted raw waveform), the slope of which at the beginning of each occlusion is used to assess vasomotor reactivity. Blue and green dotted lines indicate the beginning and end of each venous occlusion, respectively.

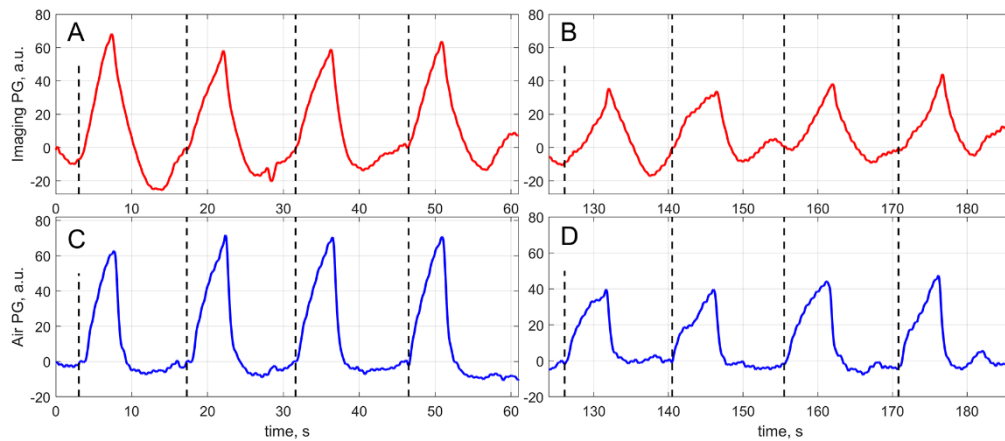


Fig. 3. An example of evolution of plethysmographic signals in response to 8 sequential events of venous occlusion for a patient before heart transplantation. (A) and (C): the responses measured at rest by the IPG and APG system, respectively; (B) and (D): the responses after applying an ice pack to the chest measured by the IPG and APG system, respectively. The timescale is the same for the upper and lower graphs. Dashed vertical lines show the onset of each event of the venous occlusion.

While APG can be calibrated to measure the blood volume changes in absolute values [44], the IPG assesses these changes in the relative units [28]. Nevertheless, when assessing changes in blood flow parameters caused by a functional test, relative changes in indicators provide the required information about neurogenic reactions. Accordingly, the main parameter evaluated in this study is the ratio of the rate of change of the plethysmograph signal in response to venous occlusion, measured before and during the vasoconstrictive test (either cold stress or deactivation of baroreceptors).

Quantitative assessment of vasomotor response was performed in the same way for both IPG and APG systems. To this end, slopes of the response curves to multiple venous occlusions before and after vasoconstriction were measured. In accordance with the commonly used approach [23,45], we defined the vasomotor response as a normalized dynamics of blood flow before and

after the test, which can be represented as following:

$$R_{VM} = \frac{\overline{D_{REST}} - \overline{D_{TEST}}}{\overline{D_{TEST}}}. \quad (1)$$

Here $\overline{D_{REST}}$ and $\overline{D_{TEST}}$ are the signal rise rates calculated in the first two seconds after the start of each venous occlusion and averaged over 4 occlusion events at rest and over other 4 occlusions during one of the vasoconstrictive tests, respectively. Therefore, the effect of cold stress and deactivation of baroreceptors on the dynamics of the blood flow was carried out in a similar way for both tests and both techniques of assessing vasomotor response. Explanations of how we identified heartbeats and defined D_{REST} and D_{TEST} are shown in Fig. 4. As a rule, two-three first heartbeats (depending on the heart rate) were used to estimate the slope of the signal, which is a condition for the correct assessment of changes in blood flow with venous occlusion plethysmography [46]. However, in some cases, when motion artefacts caused by the inflating cuff were severe, we estimate the slope starting from the second heartbeat after the beginning of the inflating of the cuff. Therefore, either an absence or decrease in response R_{VM} to a sympathetic stimulus can be interpreted as an adverse effect of the disease on the state of autonomous regulation associated with negative clinical manifestations and prognosis.

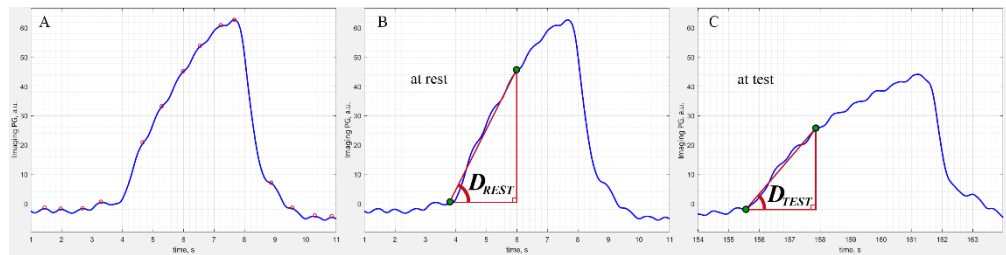


Fig. 4. Defining the vasomotor response. (A) Example of IPG waveform in response to single venous occlusion. Red circles show the moment of local signal maxima corresponding to the heartbeat. (B) an IPG waveform at rest: D_{REST} is a slope of the curve between the start of occlusion and the end of the 3rd cardiac cycle (about 2 s). (C) an IPG waveform during cold test to define D_{TEST} .

Since the blood flow response to venous occlusion was measured simultaneously by both methods, we were able to assess how well the growth rates of the signals of both methods correlate. To this end, we compared two sequences of signal growth rates in both methods, consisting of four responses to venous occlusion at rest plus four responses during sympathectomy test. The total time required to assess vasomotor response did not exceed five minutes, including three minutes for the vasoconstrictive test. During this period, we carefully monitored all parameters that could affect the magnitude of either the IPG or APG signals.

2.4. Statistical analysis

To assess the differences between groups and dynamics of vasomotor response assessed by IPG and APG methods, t-test test for independent and dependent samples with normal distribution was used. The normality of the distribution was evaluated using the Shapiro-Wilk's test providing the output indices W and P . The nonparametric Mann-Whitney criterion and Sign, Wilcoxon Tests were used to assess the relationship between groups of patients, which differ from normal distribution. Pearson correlation was used to compare blood flow responses evaluated by the different methods. To assess differences in the distribution of artifacts when using different estimates, we used Chi-square (χ^2). The level of significance of all of the statistical indicators

was established as $P = 0.05$. The statistical analysis of the measured data was carried out by using the software Statistica 10 (StatSoft, Russia).

3. Results

3.1. Correlation in vasomotor response assessment by APG and IPG

In the course of our study, 150 sessions of simultaneous recording of IPG and APG signals were conducted to assess vasomotor response, including 75 cold tests and 75 baroreceptor deactivation tests. When analyzing the results, 43 paired recordings out of 150 (29%) were found to be corrupted. This was due to the presence of artifacts in three or more responses to occlusion of 8 occlusive session either in IPG or APG signals that did not allow detecting a linear signal increase after the onset of occlusion. We observed three types of the artifacts: (i) very low response to occlusion in patients with low blood flow, which does not allow for confident identification of the pulse peak; (ii) artifacts related to the breathing; (iii) arm displacement due to rapid venous occlusion, which sometime was difficult to minimize. The identification of recordings damaged by artifacts was carried out using an expert assessment by two researchers: in case of discrepancies in the manual evaluation of the blood flow reactivity by more than 10%, the recording was considered corrupted. The corrupted recordings were not taken into account when evaluating synchronicity of the responses to occlusion assessed by IPG and APG. It should be noted that in 36 out of 43 corrupted recordings, artifacts were associated with poor quality of the APG signal. Unsatisfactory quality of the IPG signal was detected only in 19 recordings. Statistical analysis of the frequency of artifacts revealed that they are less frequent ($\chi^2 = 6.43$; $P = 0.011$) when IPG is used to assess blood flow dynamics.

The comparison of APG and IPG responses to the sequence of venous occlusions was carried out without taking into account patients who had three or more artifacts on plethysmographic curves. As a result of the correlation analysis, it was found that the R_{VM} parameter assessed by both methods significantly correlated in 69 out of 107 simultaneous recordings. We speculate that the reasons of unreliable correlation between APG and IPG measurements could be reduced vasomotor response and initially low blood flow in the forearm of some patients.

3.2. Vasomotor response before and after heart transplantation

The Shapiro-Wilk test showed that all indicators of vasomotor reactivity, except for the reaction to the deactivation of cardiopulmonary baroreceptors using the APG method, had a normal distribution ($W > 0.94 - 0.98$; $P > 0.22 - 0.98$). In this regard, the nonparametric Mann-Whitney test was used to assess the reliability of differences in this indicator. Our study revealed that patients with CHF have lower vasomotor response R_{VM} than subjects of the control group as shown in the Table 1. An example of IPG waveforms measured during the hypothermia test for one patient before and after heart transplantation is shown in Fig. 5. As seen, the slope of the response D_{TEST} is diminished after the transplantation that corresponds to an increase in vasomotor response R_{VM} according to Eq. (1).

It is worth noting that statistically significant difference between CHF patients and subjects of the control group was revealed by both IPG and APG methods during both vasoconstrictive tests. It was also revealed that the R_{VM} indicator in the group of patients after heart transplantation significantly increases compared with CHF patients before transplantation, and this increase was observed with vasoconstriction caused by both hypothermia and deactivation of cardiopulmonary baroreceptors (Table 1). The increase in vasomotor response after heart transplantation was also detected by both IPG and APG methods.



Fig. 5. IPG waveforms of a CHF patient during the hypothermia test before the heart transplantation (A) and a month after (B). Both panels show the effect of four venous occlusions.

Table 1. Vasomotor reactivity R_{VM} in the control group and in CHF patients before and after heart transplantation.

Test / Method	Control group, R_{VM} , %	CHF patients before transplantation, R_{VM} , %	CHF patients after transplantation, R_{VM} , %
Cardiopulmonary baroreceptors / APG	28.1 ± 9.6	12.4 ± 14.3^a	17.1 ± 17.7^{ab}
Cardiopulmonary baroreceptors / IPG	26.2 ± 9.9	5.7 ± 20.7^a	15.0 ± 18.5^{ab}
Hypothermia / APG	40.8 ± 18.8	20.3 ± 17.2^a	30.3 ± 17.2^{ab}
Hypothermia / IPG	38.3 ± 16.9	19.8 ± 16.2^a	23.8 ± 20.2^{ab}

^aStatistically significant difference in R_{VM} between groups of control and CHF patients.

^bStatistically significant difference in R_{VM} in CHF patients after heart transplantation compared with the preoperative period. Data are expressed as mean $\pm$ standard deviation.

3.3. Differences in R_{VM} assessment provided by IPG and APG methods

Despite the fact that the main dynamics of changes in vasomotor response was evaluated similarly by both plethysmographic methods, in some cases APG and IPG methods showed different values of R_{VM} . When conducting a paired t-test, it was revealed that APG assesses the vasomotor response index during the test with deactivation of cardiopulmonary baroreceptors in CHF patients before heart transplantation significantly higher than IPG: 12.45 ± 14.34 vs. 5.7 ± 20.7 ; $P = 0.009$. At the same time, after transplantation no significant difference in R_{VM} assessed by each method was found in this test. In opposite, there were no statistically significant difference in R_{VM} during the cold test before heart transplantation, but after it APG showed higher values than IPG: 30.3 ± 17.2 vs. 23.8 ± 20.2 ; $P = 0.01$.

4. Discussion

In this study, we have demonstrated feasibility of assessing vasomotor response in patients with CHF using the IPG technique to measure the response to venous occlusion during vasoconstrictive provocations without any contact with patient's skin. The method of occlusive plethysmography is relatively easy to use and does not require invasive intervention. At the same time, it is quite informative providing the most important information concerning the state of regulation mechanisms that compensate for orthostatic and physical activity, as well as the state of peripheral blood supply and tissue trophic [14,47,48]. Although, the purpose of this study was not to study the relationship between the state of efferent innervation with physiological performance and orthostatic tolerance, but it is these indicators of autonomic regulation that determine the maintenance of adequate hemodynamic. The homeostasis of cardiac output is maintained by compensating for fluctuations in the plasma volume and venous return, which changes is observed under conditions of changing body position, during physical exertion and during thermoregulation [49,50].

Despite the long history of photoplethysmography, the physiological model of photoplethysmographic signal formation remains the subject of ongoing discussions [51,52]. Our first demonstration of the applicability of IPPG to assess changes in blood flow during venous occlusion [27] was the result of an alternative model of photoplethysmographic signal formation proposed in our group [53]. According to this model, the intensity of the light reflected from biological tissue containing living blood vessels is modulated over time due to compression of the capillary bed by a change in transmural pressure in neighboring large vessels. In other words, the capillary bed serves as a natural distributed converter of changes in blood pressure into changes in light intensity. During venous occlusion, blood flow increases the blood pressure in the veins, thereby increasing the forearm's volume, which affects the measuring cuff in the air plethysmograph. The same pressure compresses the capillary bed thus increasing the absorption of light due to reduced distance between the capillaries [40,53]. Moreover, it is this pressure that affects the strain-gauge sensor in a commercial strain-gauge plethysmograph. Therefore, the origin of the plethysmographic signal is the same for all three types of the plethysmographs. The difference in the magnitude of the signal generated by the pressure change is determined by the boundary conditions. If in the case of air- and strain-gauge plethysmographs they are determined by the contact of the measuring module with the skin, then in the imaging plethysmograph the boundary conditions depend only on the skin elasticity.

Since the IPG system measures blood flow without any contact with patient, it obtains several advantages over either air- or strain-gauge plethysmographs. First, any impact on the vascular system in the region of measurements is excluded. Second, there is no need to adjust or even change the measuring module for patients with different limb sizes. Third, the IPG is much more operator-friendly system because its setting requires only pointing the region under study in the field of view of the camera. Fourth, exploitation of the contact plethysmographs requires frequent replacement of the measuring element (cuff or strain-gauge), while the camera in the imaging plethysmograph lasts much longer.

Previously, it was shown that cardiopulmonary baroreflex significantly decreases in patients with CHF [54], whereas in our study it was found that vasoconstriction due to hypothermia also decreases in patients with terminal CHF. The data obtained in this study show that the vasomotor response decreases due to both deactivation of cardiopulmonary zone receptors and cold stress. This observation indicates a violation of efferent sympathetic vascular regulation, probably associated with excessive activation of the sympathetic nervous system in patients of this group at rest [35]. It is reported for the first time that heart transplantation is accompanied by a partial restoration of blood flow regulation, manifested in an increase in vasomotor response to vasoconstriction caused by both cold stress and deactivation of cardiopulmonary baroreceptors. The latter finding is particularly important, since heart transplantation is accompanied by its

denervation. However, the increase in R_{VM} in response to a decrease in venous return due to the application of the lower body negative pressure chamber suggests the restoration of the reflex apparently by a compensatory increase in vasomotor response from other low-pressure area involved in the implementation of cardiopulmonary baroreflex [55].

As a result of the study, the better resistance of IPG technique to artifacts was demonstrated, which makes it possible to obtain reliable results in a larger number of patients. This is especially important for subjects with impaired blood flow due to a decrease of cardiac output and an increase in the effect of respiratory modulation on measurements, as they often complicate non-invasive blood flow measurements in patients with CHF [56]. It should be noted that the assessment of vasomotor response carried out by the IPG method in some cases turned out to be lower than simultaneous assessment by the APG method. One of the reasons for the observed difference in R_{VM} may be the effect of the APG cuff on the measured blood flow, since the cuff inevitably contacts the arm. Elucidation of reasons for the discrepancy between the vasomotor response assessment requires additional in-depth studies.

In conclusions, we have demonstrated that the IPG technique allows detection of changes in blood flow response to venous occlusion in patients with terminal CHF before and after heart transplantation. The assessment of these changes is comparable with that provided by the classical technique of occlusion air plethysmography. These findings allow us to recommend this technique for assessing vascular regulation. Our study revealed for the first time that vasomotor response in patients with CHF is partially restored after heart transplantation. Given the simplicity of registration, non-contact nature and resistance to artifacts of IPG, this method has good prospects for development of new medical equipment based on the principle of imaging photoplethysmography for wider use of vasomotor response evaluation in clinical environment.

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Data availability. Data underlying the results presented in this paper are not publicly available at this time but may be obtained from the authors upon reasonable request.

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