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ORIGINAL ARTICLE

Effects of Voluntary Changes in Minute Ventilation on Microvascular Skin Blood Flow

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Abstract

Purpose Performing yoga exercises in addition to basic training helps athletes to improve their results. At the same time, yoga exercises, including Hatha yoga, which involves controlling one's breathing, are integrated into the training process. This work is devoted to study the influence of breathing exercises, with the decrease and increase in the minute volume of breathing with corresponding changes in gas exchange, on peripheral blood flow, spirometry, and gas analysis in anatomically different areas: the skin of the forehead, fingers and toes.

Methods Volunteers performed full breathing exercises, which led to the decrease and increase in the minute volume of breathing with corresponding changes in gas exchange. Blood microcirculation was recorded using laser Doppler flowmetry (LDM) analyzers in the skin of the forehead, fingers and toes. Additionally, spirometry and gas analysis were used.

Results It was found that 5-min practices of full breathing among experienced volunteers led to similar changes in microcirculation parameters, namely, an increase in the skin blood perfusion in all areas, as well as an increase in nutritive blood flow only in the extremities (fingers and toes). Reducing the minute volume of breathing leads to an increase in amplitudes of endothelial and neurogenic oscillations during the recovery period, but increasing the minute volume of breathing leads to an increase in amplitudes of neurogenic oscillations during that same period.

Conclusion The study of the blood microcirculation behavior during breathing exercises and its correlation is useful both for obtaining fundamental knowledge of oxygen delivery to biological tissues in various breathing modes and for evaluating the efficacy of breathing exercises in sports training and rehabilitation. Changes in lung ventilation and the corresponding shifts in gas exchange affect the active mechanisms of blood microcirculation regulation. This stimulation occurs through endothelial mechanisms during reduced minute volume of breathing with hypoxia and hypercapnia, as well as neurogenic mechanisms both in increased and decreased lung ventilation.

Artem Frolov and Yulia Loktionova are co-first authors with equal contributions.

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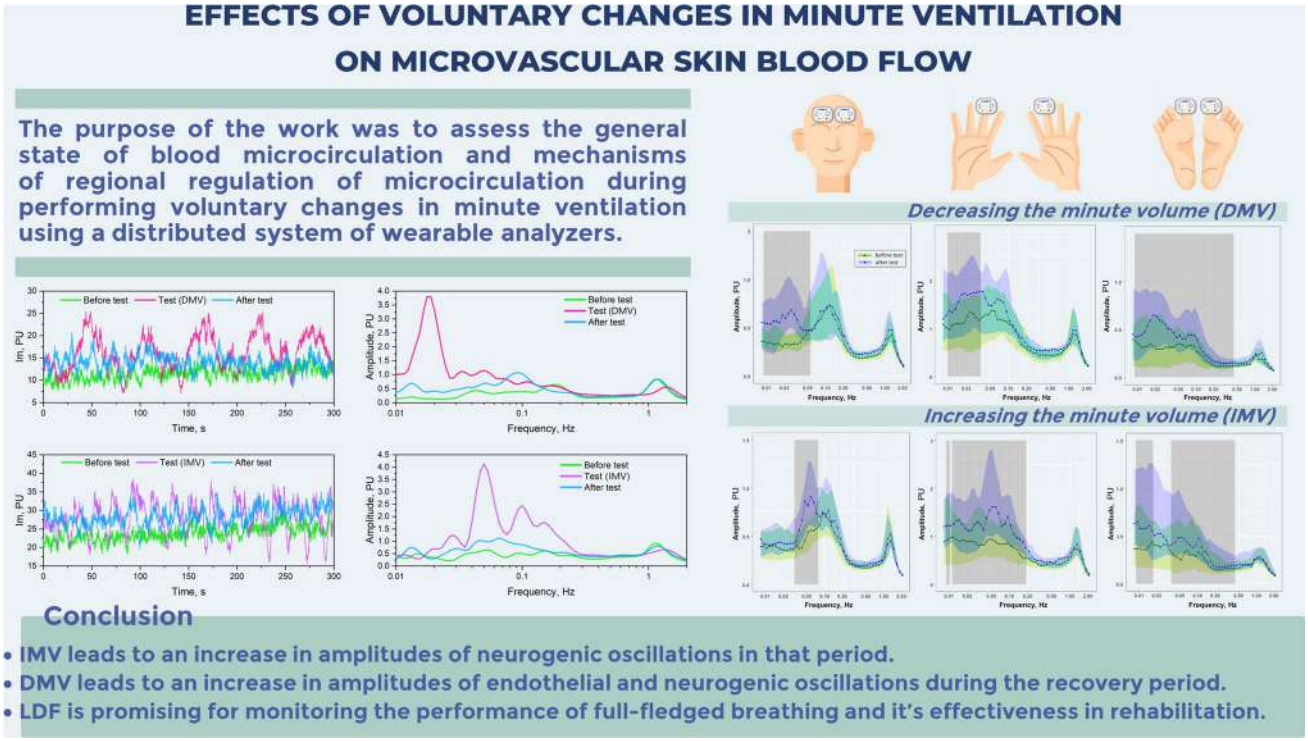
Graphical Abstract



Keywords Breathing exercises · Blood microcirculation · Gas exchange · Spirometry · Laser Doppler flowmetry · Wearable devices

Introduction

An individual approach to physical activity based on a person's physiological parameters makes the training process more effective while concurrently reduces the risk of injury. The ongoing development of wearable electronics and biosensors allows directly monitoring of the an athlete's functional state during the training process [25, 52]. Additionally, including yoga classes such as breathing exercises into the training process is recommended to improve the productivity of athletes [21].

Respiration is a motor behavior that supplies the body with oxygen and removes carbon dioxide. The central nervous system controls breathing through the respiratory center, which is located in the medulla oblongata [12]. Breathing can also be a consciously controlled action with regulated frequency and volume of inhalation and exhalation [6]. Regular performance of breathing exercises (for example, called "pranayama" according to the "hatha-yoga" system) has a broad range of cardiovascular and autonomic physiological effects [30, 31], improving respiratory functions [8], normalizing blood pressure, reducing anxiety and increasing parasympathetic tone [32, 34, 38, 46]. A number of breathing exercises involve an arbitrary change in the minute volume of breathing (MV)—either in the direction of increase (hyperventilation) or decrease (hypoventilation) with corresponding changes in gas exchange. In respiratory techniques, the achievement of decreasing the MV (DMV) is usually achieved by reducing the respiratory rate (RR) while maintaining the maximum tidal volume (TV), as close as possible to the lung vital capacity (VC). Experienced practitioners are able to maintain a state of decreasing the MV for significant periods of time (30–60 min or more).

A limited number of investigations have been devoted to studying DMV exercises and their accompanying gas exchange shifts. Experiments demonstrated the ability to maintain breathing at a frequency of 1 time/min for 60 minutes, resulting in alveolar hypercapnia and hypoxia, as well as respiratory acidosis [28].

Breathing exercises that provide arbitrary maintenance of DMV (as well as alveolar and arterial hypercapnia and hypoxia) can be considered as a form of hypoxic-hypercapnic training, potentially capable of influencing microcirculation, cerebral and peripheral blood circulation. Breathing exercises with increased breathing are presumably capable of increasing the MV (IMV) with the

development of hypocapnia. In practice, these breathing modes are used in short series, followed by compensatory breath retention to prevent the development of IMV).

A limited number of studies have explored the effect of arbitrary respiratory regulation on microcirculation. In the finger pads with well-developed sympathetic vascular innervation, individuals with a predominance of parasympathetic tone exhibited higher amplitudes of respiratory skin blood flow oscillations at a respiratory rate of 0.05 and 0.07 Hz (3 and 4.2 times/min). In the skin of the forearm (where the density of sympathetic innervation density is low compared to finger skin), there were no statistically significant differences in the amplitude of respiratory skin blood flow oscillations between the two groups of subjects [23].

Breathing exercises are a crucial aspect of rehabilitation after COVID-19, because of their positive effect on many respiratory and metabolic parameters. Training inspiratory muscles after COVID-19 has been shown to improve aerobic endurance and decrease shortness of breath and chest symptoms [27]. It is recommended that outpatient post-hospital pulmonary rehabilitation should be available for all patients who have been hospitalized with COVID-19 [49]. Breathing exercises increase breath retention time and alleviate the influence of stress during lockdown periods associated with the COVID-19 pandemic [40].

The effect of COVID-19 on microcirculation processes (including those in the skin and mucous membranes) is a characteristic pathogenetic connection. Skin microcirculation changes among critically ill COVID-19 patients indicate that the infection causes systemic microcirculatory disorders with persistent long-term consequences for microcirculatory function [18, 36].

Altered perfusion of oral mucosal tissues was detected in patients with COVID-19. Sublingual microcirculation is characterized by a decrease in the proportion of perfused vessel and blood flow rate [13]. Known risk factors of COVID-19 (hemorheological parameters, age) correlate with the microvessel reactivity to heating in patients with COVID-19, which was confirmed by the laser Doppler flowmetry (LDM). It is assumed that LDM can be used for noninvasive instrumental assessment of microcirculation disorders in patients with COVID-19 in the future [19].

Despite the active use of full breathing exercises in rehabilitation and physical therapy [51], there are no studies on the reciprocal effect of such breathing on the cardiovascular system and, in particular, the microcirculatory system. The purpose of this study was to assess the overall state of blood microcirculation and mechanisms of regional regulation during voluntary changes in minute ventilation using a distributed system of wearable analyzers.

Materials and methods

The study comprised 22 participants (16 men and 6 women), the average age was 43 ± 8 years. All participants considered themselves healthy and did not take any pharmacological drugs on a permanent basis. All participants had experience of regular breathing exercises, ranging from 2 to 20 years, for at least 15 min 3 times a week. The body mass index (BMI), calculated from weight and height, was 22.8 ± 3.2 kg/m^2. VC was determined by spirometry, with VC = 5.3 ± 1.0 l.

The inclusion criteria involved the volunteer's ability to perform the full breathing technique, performing full breathing several times a week on a regular basis for a minimum of six months. The exclusion criteria encompassed the presence of pathologies of the cardiovascular, respiratory, and endocrine systems of the body, pregnancy, regular use of pharmacological medications, as well as alcohol and nicotine use.

The research methodology was standardized to exclude the influence of environmental factors on the state of microcirculation during the study. Measurements were carried out no earlier than 2 h after the meal and at the same time of day to avoid any influence of circadian rhythms on the blood circulation. The room temperature was maintained at 24 ± 1 °C. In addition, all volunteers underwent adaptation to environmental conditions within 15 min before the study.

All studies were conducted in accordance with the principles of the Declaration of Helsinki of 1975, revised in 2013. Before the measurements, all participants signed an informed consent to participate. The measurements were approved by the local Ethics Committee of the Orel State University named after I.S. Turgenev.

Assessment of gas exchange and respiratory function

The breathing patterns were executed in a sitting position with a straight back on a chair. Nasal breathing was blocked with a clamp, breathing was performed through the mouth into the tube of the device using a certified disposable antiviral filter (“Vitalograph”, Ireland).

All participants performed the following respiratory regimes:

- free breathing for 2 min;
- breathing with a frequency of 3–3.5 times/min (inhale for 8–10 s and exhale for 8–10 s) with the maximum available tidal volume for 5–6 respiratory cycles;
- rest (free breathing) for 5 min;

– breathing with a frequency of 1–1.5 times/min (inhale for 20–30 s and exhale for 20–30 s) with the maximum available tidal volume for 5–6 respiratory cycles.

All participants had prior experience of regularly performing breathing patterns with RR = 1–1.5 times/min for extended durations (15–30 min or more). However, within the framework of this study, taking into account the unique breathing conditions (breathing through the mouth into the mouthpiece of the device with nasal breathing blocked by a clamp), the performance of breathing exercises was limited to 5–6 respiratory cycles.

Measurements were carried out using a spirometer MAC-2C with the function of gas analysis and pulse oximetry ("Belintelmed", Belarus). The setup time for the operating mode was less than 15 min.

The following parameters were determined:

– tidal volume (TV);
– respiratory rate (RR);
– minute ventilation (MV);
– partial pressure of CO_2 in exhaled air at the end of exhalation ($PetCO_2$);
– percentage of O_2 in exhaled air (FeO_2);
– minimum blood oxygen saturation level ($SpO_{2\ min}$)

The measurement channel of the spirometer has the following characteristics:

– duration of continuous measurements—at least 4 h;
– drift of the parameters for a period of up to 4 h during continuous measurements—not exceeding 50 mL;
– resolution (detection threshold) of the recorded flow—not exceeding 35 mL/s;
– lower limit of the flow range ensuring accuracy of ± 3% - not exceeding 100 mL/s;
– air resistance - not exceeding 30 Pa(L/s) across the entire range of measured flows.

Out-of-breath capnometry with continuous gas sampling (sidestream analysis) was used. $PetCO_2$ was determined by optical infrared capnography. In the first phase of exhalation, gasses from the anatomical space of the lungs are exhaled. It does not contain CO_2, since it did not enter the alveoli and did not participate in gas exchange. In the second phase of exhalation, gas begins to flow from the alveolar space, evidenced by the rise in CO_2 levels in the exhaled air. The third phase reflects the flow of alveolar gas, while the CO_2 level reaches a plateau. The $PetCO_2$ value is calculated as the maximum value of the capnogram at the end of exhalation.

Assessment of microcirculation

Laser Doppler flowmetry (LDF) was used to assess the parameters of skin blood perfusion. LDF is a widely used optical noninvasive diagnostic method for assessing the functional state of the microcirculatory bed [11, 17, 54]. The mean skin blood perfusion (I_m) was calculated. It is measured in perfusion units (PU) and proportional to the product of the number and velocity of red blood cells in the diagnosis volume. In a previous study [9], the similarity between the rate of erythrocytes in capillaries obtained by videocapillaroscopy and the skin blood perfusion evaluated by the LDF method was experimentally confirmed. Additional works [7, 26, 43] also show the extensive experience of using the LDF method in scientific and clinical practice.

The LDF method allows to obtain information about several microcirculatory oscillations, reflecting active and passive mechanisms of blood flow regulation. Active mechanisms include endothelial (A_e; 0.0095–0.021 Hz), resulting from the production of vasoactive substances by endothelial cells, neurogenic (A_n; 0.021–0.052 Hz), formed through sympathetic adrenergic effect on smooth muscle walls of arterioles, and myogenic vasomotor (A_m; 0.052–0.145 Hz), associated with muscle tone of precapillary sphincters, regulating the nutritive component of perfusion. Passive mechanisms include respiratory (A_r; 0.145–0.6 Hz), formed by venous pressure dynamics due to hest mechanical activity, and cardiac (A_c; 0.6–2 Hz), associated with changes in red blood cell movement speed during the systolic and diastolic phases of the heart.

The software allows to calculate the average value of nutritive blood flow (M_{nutr}). M_{nutr} is indicative of capillaries blood flow, directly contributing to trophic and oxygenation processes (as opposed to blood flow through arterio-venous anastomoses) [41].

The study was conducted in the sitting position following protocols No. 1 "LDF-Decreasing the MV" (Table 1)

Table 1 Protocol No. 1 "LDF-Decreasing the MV"

Research stage	Stage description	Duration (min)
1	Registration of LDF under free breathing (pre-test)	6
2	Registration of LDF under breathing in "DMV" mode – inhale and exhale for 30 or 20 s–depending on individual capabilities (test)	5
3	Registration of LDF under free breathing (post-test)	6
Total duration		17

Table 2 Protocol No. 2 "LDF-Increasing the MV"

Research stage	Stage description	Duration (min)
1	Registration of LDF under free breathing (pre-test)	6
2	Registration of LDF under breathing in "IMV" mode – inhale and exhale for 10 s (test)	5
3	Registration of LDF under free breathing (post-test)	6
Total duration		17

and No. 2 "LDF-Increasing the MV" (Table 2). Between studies according to these protocols, participants rested for at least 15 min, and sometimes the studies were conducted on different days.

The distributed system consisting of 6 wearable LDM analyzers "LAZMA PF" (LAZMA Ltd, Russia; in EU/UK this device made by Aston Medical Technology Ltd., UK as "FED-1b"), was used to monitor blood microcirculation. The devices have built-in identical channels for recording blood perfusion, as well as a skin thermometer and accelerometer to compensate for temperature and motion artifacts. The devices use a single-mode vertically emitting laser (VCSEL) with a working wavelength of 850 nm and a radiation power of 1 mW. These devices do not have optical fiber, which makes it possible to deliver coherent light directly into the biological tissues. The measurement base (distance between the source and receiver of radiation) of these devices is 1200 µm, and the time for setting the operating mode is 10 min. With a continuous operation time of 4 h, these devices transmit signals to a personal computer via a Bluetooth channel. A wireless communication system allows the integration of up to 8 devices into one distributed system, enabling simultaneous registration of blood microcirculation parameters and comprehensive assessment of the functional state of the microcirculatory system. Currently, these analyzers are actively used in scientific research, various areas of medical fields and functional diagnostics, including the detection of microcirculatory disorders in patients with diabetes mellitus [55], as well as in space medicine [10].

Figure 1 illustrates the arrangement of analyzers. The devices were fixed symmetrically on the right and left sides without any pressure on the study areas: two analyzers were positioned on the palmar surface of the distal phalanges of the third fingers and the plantar surface of distal phalanges of the first toes, and on the forehead at areas of supraorbital arteries (SA).

The recorded LDF signals were divided into sections corresponding to the study stages (Protocols No. 1 and No. 2). To investigate the influence of various controlled ventilation (IMV and DMV) modes on the mechanisms of blood flow regulation, two 6-min segments of the initial LDF signals were analyzed for each participant—before the breathing exercises (stage 1) and after (stage 3) for each protocol. All fragments were not subjected to any pre- or post-processing before analysis. The mean values of I_m and M_{nutr} [41], as well as amplitude-frequency spectra, were calculated using adaptive wavelet transform [45].

Statistical analysis

Statistical analysis of spirometry, gas analysis data, and microcirculation parameters was carried out in the OriginPro 2021 software environment (1991–2020 OriginLab Corporation, USA). The nonparametric Mann–Whitney test was used to assess the significance of the observed differences across various modes of breathing exercises. The nonparametric Wilcoxon paired criterion was used for microcirculation parameters to assess the significance of differences at the stages before and after breathing exercises. Differences in parameters were considered significant at $P < 0.05$. The paired Spearman correlation coefficients were calculated.

Fig.1 Location of "LAZMA PF" analyzers during the research

Table 3 Results of spirometry and gas analysis

Breathing mode	MV (L/min)	TV (L)	$PetCO_2$ (mmHg)	FeO_2 (%)	$SpO_{2\ min}$ (%)
Free breathing (RR = 11.6 times/min)	8.8 ± 1.9	0.8 ± 0.2	37.3 ± 2.9	13.9 ± 0.7	95.5 ± 1.1
DMV (RR = 1–1.5 times/min)	5.2 ± 1.1*	4.4 ± 0.7*	44.0 ± 3.2**	11.0 ± 1.0**	93.1 ± 2.2*
IMV (RR = 3–3.5 times/min)	13.9 ± 2.5*	4.5 ± 0.8*	32.5 ± 2.9**	15.6 ± 0.6**	95.7 ± 1.4

*Statistically significant difference was confirmed by a paired Wilcoxon test, $P < 0.05$

**Statistically significant difference was confirmed by a paired Wilcoxon test, $P < 0.001$

Results

Spirometry and gas analysis

Table 3 provides a summary of the changes in spirometry and gas exchange parameters for the studied breathing modes.

For free breathing spirometry, RR was 11.6 times/min.

For breathing with RR = 3–3.5 times/min (IMV), the MV significantly increased compared to the baseline (free breathing). The decrease in $PetCO_2$ in this case indicates alveolar hypocapnia. An example of the spiro-gas analysis protocol is shown in Fig. 2A–C.

For breathing with RR = 1–1.5 times/min (DMV), the MV significantly decreased compared to the baseline (free breathing). The increase in $PetCO_2$ in this case indicates alveolar hypercapnia. An example of the spiro-gas analysis protocol is shown in Fig. 2D–F. $SpO_{2\ min}$ significantly decreased, reaching borderline values withing the normal range.

Assessment of microcirculation

Examples of the LDF signals and their wavelet spectra for the area of supraorbital arteries are shown in Fig. 3. Performing full breathing resulted in increased chest excursion, which causes the respiratory process to dominate over the mechanisms of microcirculation regulation. As a result, sinusoidal oscillations of the LDF signals were formed (Fig. 3A,C) with the frequency dependent on respiratory rate, which appears as the dominant frequency on the wavelet spectra (Fig. 3B,D).

both DMV mode (RR = 1–1.5 times/min) and IMV mode (RR = 3–3.5 times/min) breathing exercises, I_m increased significantly in all study areas—during and after the test compared to the parameters recorded before the test (Figs. 4 and 5).

After performing breathing exercises, M_{nutr} significantly increased in the fingers and toes, but not in the area of the supraorbital arteries (Figs. 4D, E, F and 5D, E, F). In the toes, there is also a statistically significant increase in the amplitudes of myogenic oscillations associated with the work of vascular smooth muscles, namely precapillary sphincters. An increase in A_m indicates an increase in the number of functioning capillaries [54]. For both areas of the forehead skin (left and right), there is a significant increase in A_n (~ 0.05 Hz) under IMV and in A_e and A_n ranges (0.01–0.05 Hz) for DMV mode. Figure 6 shows the wavelet spectra before and after DMV (Fig. 6 A, B, C) and IMV (Fig. 6D, E, F) breathing modes for the left side. The changes on the right side were similar.

Relationships between respiratory and microcirculatory systems

To study the associations between blood microcirculation parameters in the area of supraorbital arteries and gas analysis parameters, Spearman correlation coefficients were calculated for the free-breathing regime. The results are shown in Fig. 7.

Oscillations at a frequency of 1 Hz result from the propagation of a pulse wave through the vessels, and their amplitudes characterize the inflow of arterial blood into the microvascular bed. The obtained connection between the amplitudes of cardiac oscillations (A_c) with MV and $SpO_{2\ min}$ can characterize the coherence of the respiratory system and the supply of oxygenated blood to cells. This is further supported by a statistically significant correlation of M_{nutr}, reflecting effective perfusion (specifically its capillary component) and amplitudes of myogenic oscillations (A_m), which are associated with the number of functioning capillaries and with TV, representing the volume of inhaled or exhaled air during each breathing cycle. Statistically significant correlations were also found between SpO_{2min} and the amplitudes of neurogenic oscillations (A_n), influencing the vasomotor function (vasoconstriction and vasodilation) of microvessels through their innervation, that is, the neurogenic tone of arterioles depends in some way on blood oxygenation.

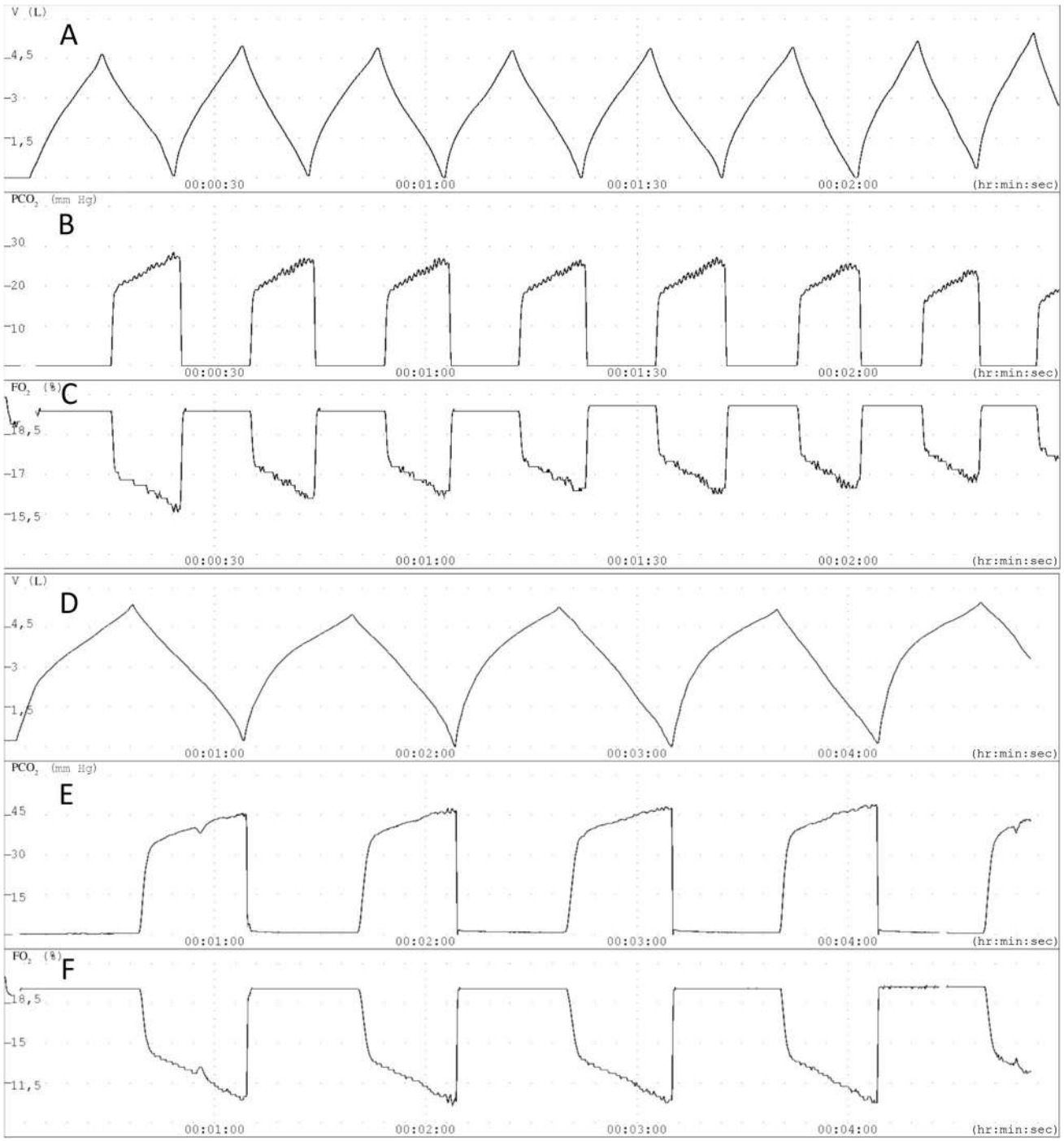


Fig. 2 Examples of the spirometry and gas analysis curves: **A**—spirographic curve at RR = 3 times/min (IMV): the ascending part of the curve is inhaled (10 s), the descending part of the curve is exhaled (10 s); **B**—$PetCO_2$ at RR = 3 times/min (IMV); hypocapnia ($PetCO_2$ less than 30 mm Hg when norm is 35–45 mmHg); **C**—FeO_2 at RR 3 times/min (IMV); **D**—spirographic curve at RR 1 time/min: the ascending part of the curve is inhale (30 s), the descending part of the curve is exhale (30 s); **E**—$PetCO_2$ at RR = 1 time/min (DMV); hypercapnia ($PetCO_2$ = 46.5 mmHg); **F**—FeO_2 at RR = 1 time/min (DMV), alveolar hypoxia

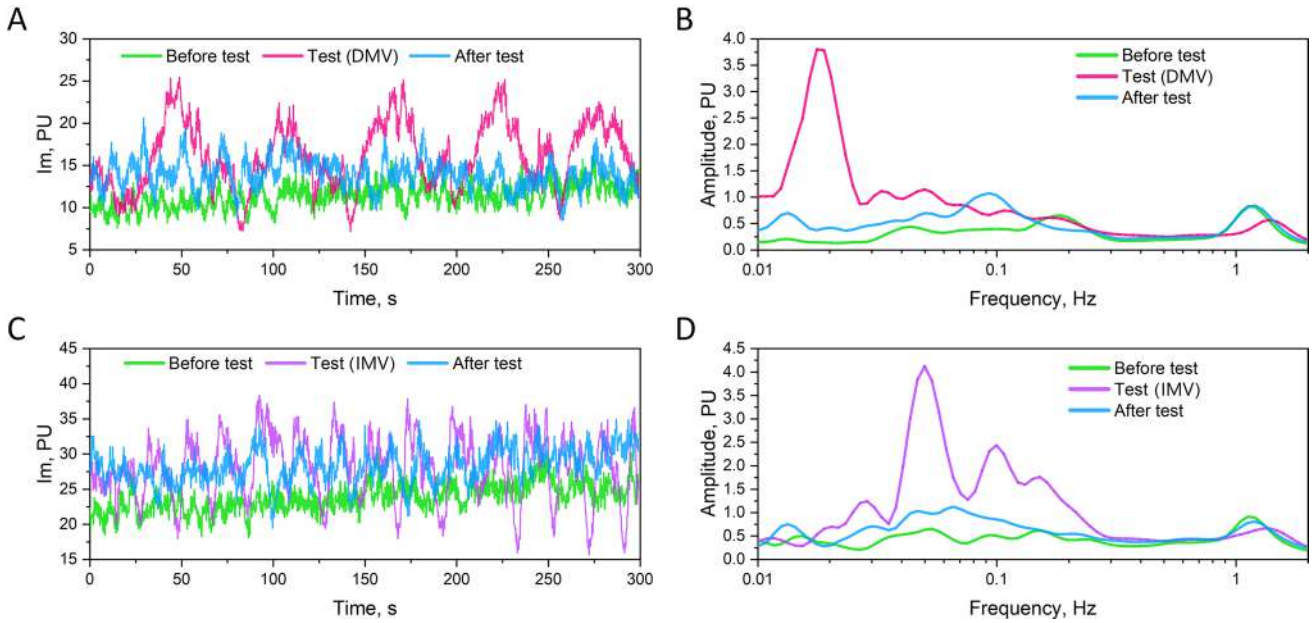


Fig.3 Individual LDF signals of the participant for both breathing modes (**A**, **C**) and its wavelet spectra (**B**, **D**). Colors indicate the following stages and modes: before (green) and after (blue) full breathing, as well as DMV (pink) and IMV (purple) modes

Discussion

The skin microcirculatory bed is highly heterogeneous, stemming from anatomic variances (depending on different regions of the body), as well as functional distinctions (concerning the regulation of various components of the microcirculatory bed across different body parts: arterioles, precapillaries, arterio-venular shunts, etc.).

Supraorbital arteries, being a branch of the internal carotid artery (ICA) and skirting the supraorbital margin in the region of the eponymous notch in the frontal bone, reaches the forehead skin and supplies blood to this area. It can be assumed that blood flow oscillations, corresponding to the regulatory processes, and alterations in blood circulation observed in the SA, may correlate with regulatory processes in the ICA. A number of contemporary scientific papers support this hypothesis [16].

Decreasing the MV

Forehead skin: The I_m significantly increased, but there were no significant changes in the M_{nutr}. A significant increase in the amplitudes of endothelial and neurogenic oscillations was observed.

Fingers: Both I_m and M_{nutr} significantly increased. The frequency ranges for these differences were asymmetrical: on the left, there was an increase in A_e and A_n, on the right side, A_n and A_m increased.

Toes: Both I_m and M_{nutr} significantly increased, as well as the amplitudes across all active regulatory mechanisms (in frequencies from 0.01 to 0.4 Hz) on both sides.

Increasing the MV

Forehead skin: The I_m significantly increased, but there were no significant changes in the M_{nutr}. For the active regulatory mechanisms, significant changes (growth) were only obtained for A_n.

Fingers: Both I_m and M_{nutr} increased significantly. An increase in the amplitudes of endothelial, neurogenic and myogenic oscillations was found (the growth of A_e on the right side did not reach a statistically significant level).

Toes: Both I_m and M_{nutr} increased significantly. Increased values were observed for A_e and A_m on the left side, there was a tendency to increase the amplitudes of vasomotion (A_m) on the right side, although this group did not reach statistically significant levels.

Thus, the reaction of the microcirculatory bed to the shift of tissue homeostasis is different across different skin areas, likely involving different mechanisms.

The respiratory regime with RR = 3–3.5 times/min demonstrated an increase in MV compared to the free breathing (the nature of this regime is associated with an increase in MV because participants used the maximum available respiratory volume during its execution, leading to hyperventilation even at breathing rate significantly lower compared to free breathing). The RR = 1–1.5 times/min at maximum TV

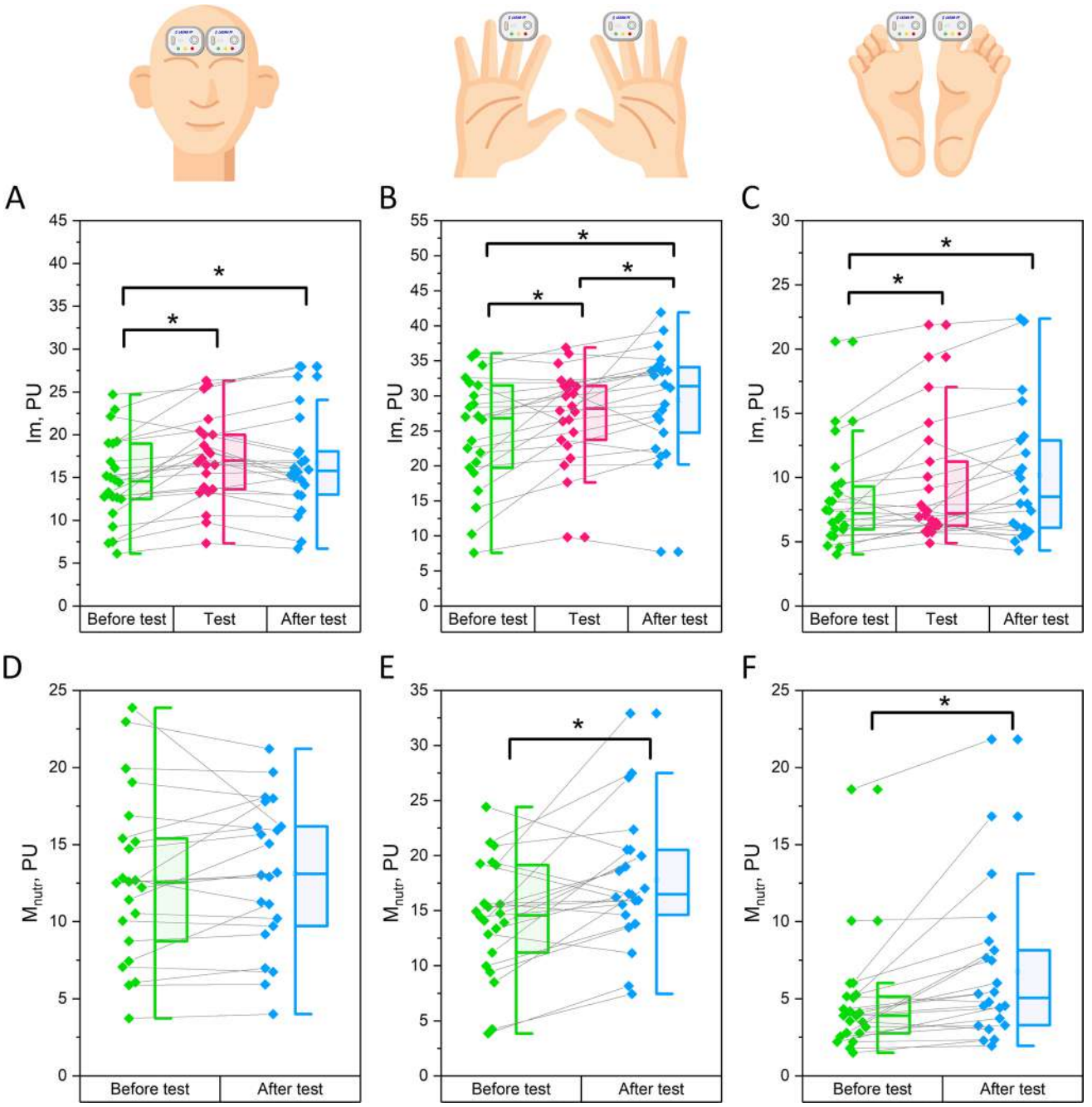


Fig. 4 Changes in the skin blood perfusion (**A**, **B**, **C**) and nutritive blood flow (**D**, **E**, **F**) of all analyzed areas for the DMV mode (RR = 1–1.5 times/min). (*Statistically significant difference confirmed by a paired Wilcoxon test, $P < 0.05$)

demonstrated, on the contrary, a decrease in MV relative to the initial level. Along with these shifts in minute ventilation of lungs, corresponding changes in gas exchange were detected (including hypercapnia and hypoxia in DMV mode, hypocapnia in IMV mode).

Hypercapnia (an increase in the CO_2 content in the blood) leads to the dilation of cerebral arterioles and precapillary sphincters, thereby reducing cerebral vascular resistance and promoting cerebral blood flow. Hypocapnia (an decrease in CO_2 content), on the contrary, causes constriction of resistive vessels of the brain with a decrease in cerebral blood flow [1, 2]. An increase in partial pressure of arterial blood CO_2 ($PetCO_2$) and the subsequent decrease in pH directly affect smooth muscle cells in arterial vessels by acting on the potassium channels of their membranes. This action induces hyperpolarization of the membranes of vascular

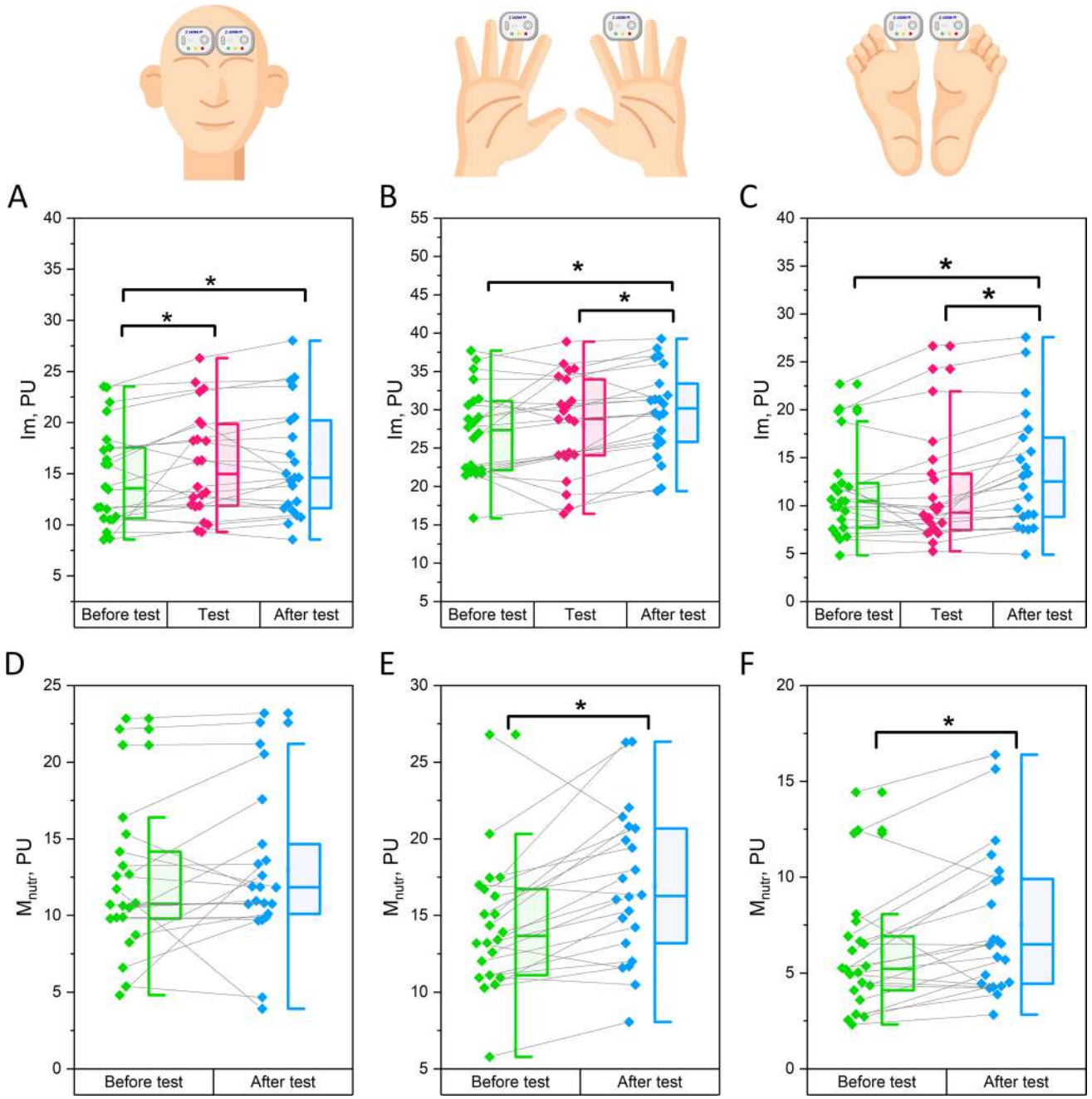


Fig. 5 Changes in skin blood perfusion (**A**, **B**, **C**) and nutritive blood flow (**D**, **E**, **F**) of all analyzed areas for the IMV mode (RR = 3–3.5 times/min). (*Statistically significant difference was confirmed by a paired Wilcoxon test, $P < 0.05$)

wall muscular elements and reduces the activity of calcium channels and intracellular calcium concentration, which ultimately leads to vasodilation [33, 37]. An increase in $PetCO_2$ and a decrease in pH also activate endothelial NO synthase, leading to increased NO concentration and the relaxation of vascular wall myocytes [5, 15].

In many studies, CO_2 is used as an agent capable of influencing the tone of resistive arterioles. Various methods have been used to increase the partial pressure of carbon dioxide ($PetCO_2$), including inhalations of gas mixtures with a high content of CO_2, respiratory retention, as well as the technique of rebreathing and devices for creating an additional volume of functional space [24, 44].

Taking into account the available data on the effect of CO_2 on the resistive vessel tone, it is reasonable to assume that these breathing modes, accompanied by the listed shifts in gas exchange, may have influence on the processes of cerebral and peripheral microcirculation.

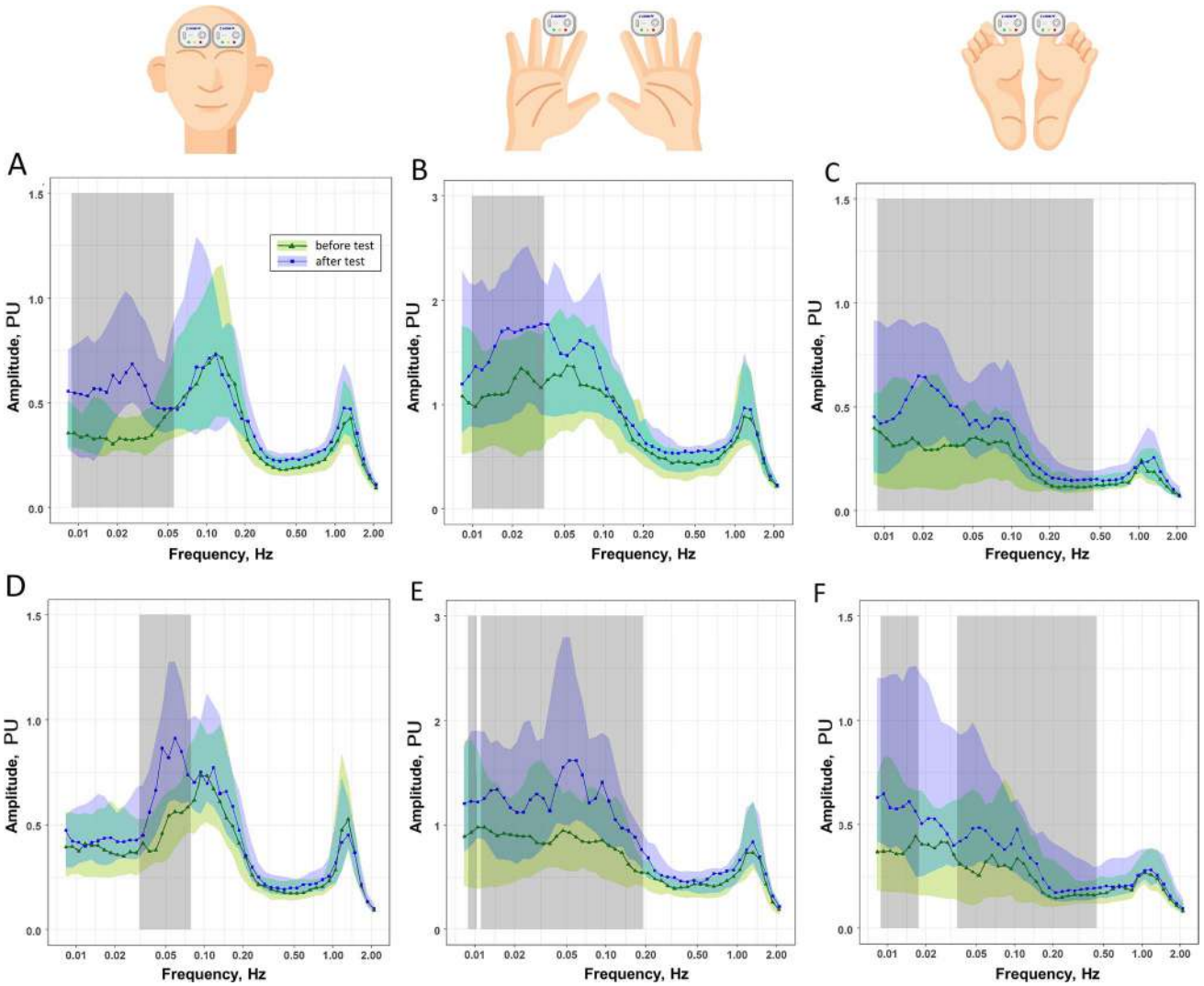


Fig. 6 Amplitude-frequency spectra of blood flow oscillations from the left side before (green) and after (blue) DMV (**A**, **B**, **C**) and IMV modes (**D**, **E**, **F**). The data are presented as medians, with the interquartile range (25% and 75%). The gray area indicates the frequency ranges of significant differences.

Nevertheless, despite the obtained data indicating statistically significant shifts in breathing patterns, there is a significant increase in I_m in all analyzed areas during and after both DMV and IMV. There are no differences between the two different ventilation modes, despite their corresponding multidirectional shifts in gas exchange. It can be assumed that these changes in I_m occur not solely due to the changes in gas exchange, but may be due to other factors, including deep breathing, regardless of its frequency. No significant changes in the nutritive blood flow in the forehead skin were observed in both breathing modes, however, there is a significant increase in M_{nutr} in the arms and legs for both breathing modes (suggesting changes in M_{nutr} both in the limbs and the forehead are independent of gas exchange shifts).

Thus, under deep breathing with the utilization of the maximum respiratory volume, I_m increases significantly across all zones, and M_{nutr} increases in the extremities, regardless of variations in respiratory rate, minute ventilation of the lungs, and shifts in gas exchange. It can be assumed that one of the influencing factors here is the respiration depth (and possibly other factors), rather than changes in gas metabolism. At the same time, there is a reason to assume that the cognitive component of respiratory regulation, which occurs in both (DMV and IMV) respiratory patterns, may have a certain effect along with breathing depth, since the participants of our study simultaneously performed a specific respiratory pattern and a cognitive task in the form of mental counting under metronome. Other studies have shown that mental state has a significant effect on the

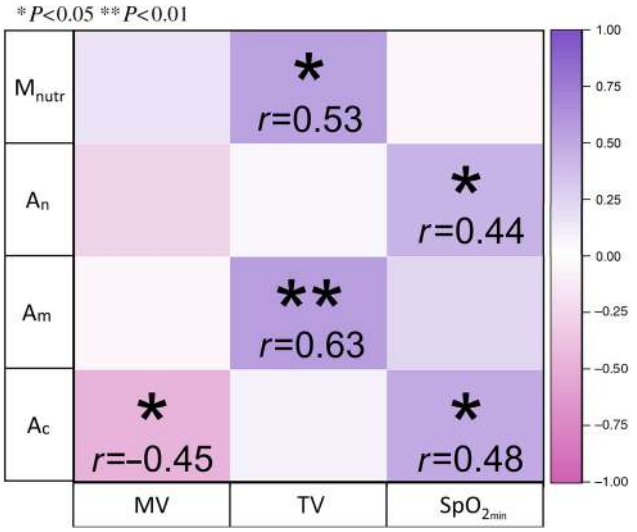


Fig. 7 Correlation map of gas analysis and blood microcirculation parameters in the area of supraorbital arteries for free breathing

spectral structure of oscillations in microvascular skin blood flow [50].

Significant changes in M_{nutr} in the extremities and the absence of changes in the area of supraorbital artery area, except for regional regulatory features, may be due to the adaptation of head vessels to regular hypercapnic-hypoxic training. It is known that the use of interval hypercapnia-hypoxia is accompanied by a decrease in the reactivity of cerebral vessels to hypercapnia—which is an important mechanism for increasing the tolerance of the brain to ischemia. The observed decrease in chemosensitivity to CO_2 resulting fromsystematic hypercapnic training, including exercises involving DMV [28], can be considered as a mechanism that ensures the stability of cerebral circulation under conditions of both DMV and IMV.

Since all the participants in our study had a minimum of 2 years of regular practice in breathing exercises, it can be assumed that regular hypercapnic-hypoxic training led to a decrease in chemosensitivity and an increase in adaptive reserves of the cerebral vascular system—the consequence of which is the absence of significant shifts in M_{nutr} in the area of supraorbital arteries (and possibly ICA). The autoregulation system of cerebral hemodynamics has significant regional features, possessing its own mechanisms and an adaptation rate distinct from peripheral blood circulation in the extremities. This may explain why individuals with a history of systematic hypercapnic-hypoxic training exhibit significant changes in nutritive blood flow in the distal extremities, but not in the forehead skin in the areas of supraorbital arteries when performing breathing exercises with MV shifts.

For both areas of the forehead skin (left and right), there is a significant increase in oscillation amplitudes within the neurogenic rhythm range (~0.05 Hz) for IMV mode, and within the ranges of endothelial and neurogenic rhythms (0.01–0.05 Hz) for DMV mode.

The active mechanisms of regulation and the resulting fluctuations in vessel walls can improve adequate oxygen delivery to all tissues [48]. Flow fluctuations caused by vasomotion can significantly increase tissue oxygenation under hypoxia conditions, with the greatest effect observed when analyzing oscillations at low frequencies associated with endothelial and sympathetic activities [20]. Studies indicate the potential for hypoxic activation of endothelial mechanism of vasomotion: a decrease in hemoglobin saturation leads to activation of endothelial oscillations with a frequency of 0.02 Hz. Moreover, there is discussion about the role of erythrocytes as regulators of endothelial oscillatory activity for stimulating tissue blood flow in hypoxia [14].

The results of our study demonstrate an increase in the amplitudes of endothelial oscillations in the forehead skin as a result of a hypoxic breathing regime. On the one hand, this can be regarded as a confirmation for the association between endothelial mechanisms of blood flow regulation in the forehead skin and tissue oxygen supply in conditions of reduced hemoglobin saturation, manifested by increasede amplitudes of endothelial oscillations [47]. On the other hand, it contradicts the concept suggesting an increase in the number of functioning capillaries (and consequently, enhanced oxygen delivery to the tissues) by increasing the amplitudes of myogenic oscillations. Perhaps these contradictions can be resolved through research on a larger group of participants.

As mentioned earlier, after performing both breathing modes with DMV and IMV, there was a significant increase in the amplitudes of neurogenic oscillations. Based on these observations, shifts in respiratory metabolism beyond physiological values (hypocapnia during IMV, hypoxia and hypercapnia during DMV) appear to cause a sympathetic reaction—at least with the realm of microcirculation regulatory mechanisms.

As for the effect of hypocapnia, the available literature contains contradictory data. Hypocapnia may be an additional factor in the stimulation of the sympathetic nervous system, as shown in studies examing the effects of iso- and hypocapnic hypoxia on sympathetic activity [42]. An increase in cardiac output is associated with the development of IMV on the background of isocapnia, which may also indirectly indicate in favor of sympathetic activation. However, this could be due to the very fact of IMV and possibly an increase in oxygen consumption by respiratory muscles [3]. On the other hand, an acute respiratory alkalosis, with a decrease in $PetCO_2$ from 39.7 to 18.3 mmHg, was shown to lead to a reduction in cardiac output and shock volume

against a decrease in spontaneous postganglionic sympathetic activity in anesthetized dogs [29].

The effect of hypercapnia appears more unequivocal, as it leads to the activation of the sympathetic system by exciting central and peripheral chemoreceptors, which results in an increase in cardiac output [22, 39]. Hypoxia also causes sympathetic activation, increasing plasma norepinephrine levels in humans and animals [35], and increasing postganglionic sympathetic activity [4].

Thus, the activation of the neurogenic sympathotonic regulatory mechanism, observed in this study after performing both protocols (DMV and IMV), may reflect the sympathetic system's response to hypocapnia and hypoxic hypercapnia, respectively. Perhaps, in both cases, sympathetic activation is also influenced by a non-trivial type of breathing characterized by precise regulation of the respiratory cycle duration under the metronome.

The above-mentioned data demonstrate the effect of breathing exercises on microcirculation through various metabolic and hemodynamic mechanisms. The widespread use of breathing exercises and official recommendations for their inclusion in rehabilitation processes [51] necessitate profound studies into their effect on the human body. These findings provide valuable information for further studies on the integration of breathing exercises in the practice of rehabilitation after COVID-19 and other respiratory infections [53], as well as to improve the efficacy of the training regimens in various sports [11], etc.

Conclusion

Both DMV and IMV have an unidirectional effect on the skin blood perfusion in all examined areas (left and right fingers/toes/forehead), resulting in a significant increase in nutritive blood flow, particularly in the extremities. The skin blood perfusion in the areas of the supraorbital arteries bed exhibits distinctive patterns in terms of nutritive blood flow (characterized by the absence of significant reactions), which may be due to the the regional regulatory peculiarities. Changes in lung ventilation and the corresponding shifts in gas exchange affect the active mechanisms of blood microcirculation regulation. This includes the stimulation of endothelial mechanisms in DMV, marked by with hypoxia and hypercapnia, as well as neurogenic mechanisms with both increased and decreased lung ventilation.

Investigating the behavior of blood microcirculation during breathing exercises and examining their correlations serves a dual purpose. Firstly, it contributes to the acquisition of fundamental knowledge concerning oxygen delivery to biological tissues under various breathing modes. Secondly, it aids in evaluating the efficacy of breathing exercises in sports training and rehabilitation.

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Data availability The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest Authors declare no conflict of interest.

Ethical approval The study was approved by the local Ethics Committee of the Orel State University named after I.S. Turgenev (meeting protocol No. 15 of February 21, 2019).

Animal and human rights All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Declaration of Helsinki of 1975, revised in 2013.

Consent to participate Informed consent was obtained from all participants included in the study.

Consent to Publish Not applicable (anonymous data).

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