ISSN 0006-3509, Biophysics, 2022, Vol. 67, No. 6, pp. 1017–1022. © Pleiades Publishing, Inc., 2022.
Russian Text © The Author(s), 2022, published in Biofizika, 2022, Vol. 67, No. 6, pp. 1243–1250.

Development of Medical Sensor Systems in Pulmonology Based on Electrical Impedance Measurement

V. Ju. Mishlanov[a,*], A. L. Zuev[b,c], and Ya. V. Mishlanov[d]

[a]*Perm State Medical University, Perm, 614990 Russia*
[b]*Institute of Continuous Media Mechanics, Ural Branch, Russian Academy of Science, Perm, 614013 Russia*
[c]*Perm National Research Polytechnic University, Perm, 614990 Russia*
[d]*Perm State National Research University, Perm, 614990 Russia*
**e-mail: permmed@hotmail.com*

Received August 11, 2022; revised September 7, 2022; accepted September 14, 2022

Abstract—In order to experimentally confirm the dependence of the bioelectrical impedance on the flow rate of charged aerosol particles and the composition of bronchial secretions in small airways, the electrical impedance of an aerosol of 0.9% NaCl solution in polyethylene tubes of various diameters was studied. The electrical impedance was also measured in cylindrical chambers of various diameters and volumes filled with a 0.9% NaCl solution or a gelatin solution. The studies were carried out at frequencies of alternating electric current from 20 Hz to 150 kHz. It was shown that the electrical current is not recorded in the absence of a flow of aerosol particles, and the impedance decreases with an increase in the flow velocity. The impedance modulus and the phase angle of the electrical impedance has an expressed dependence on the composition of the conductive medium, the impedance modulus increases in the gelatin solution medium, with a decrease in the diameter of the electric current conductor, and decreases with an increase in the frequency of the probing alternating current. The obtained results confirmed the hypothesis about the influence of the speed of salty aerosol particles flow and the composition of bronchial secretions on the results of measuring electrical impedance.

Keywords: bioelectrical impedance, electrical impedance spirometry, aerosol, biological fluids, experimental study

DOI: 10.1134/S000635092206015X

SENSORS IN MODERN MEDICINE

The role of sensory systems in the development of electronic medicine. The issues of development and clinical application of sensors are actively discussed topic today that can change the foundations of modern diagnostics and remote monitoring of patients in the future. Sensors perceive biological signals of a physical, chemical nature, as well as functional, i.e., physiological or pathophysiological origin [1, 2]. However, one signal is not of great diagnostic significance, even if it differs from the norm. The presence of only one signal can only be compared with a risk factor for the development of a disease with a certain clinical significance. Clinical medicine needs numerous studies to answer the questions: for which group of patients or healthy individuals is a particular biosensor intended, what clinical problems does it solve?

The biosensory signal cannot be significant apart from other signs of the disease. Like any objective symptom (sign of illness), it must be associated with other subjective or objective data. For example, in the system of syndromic diagnostics, it should be associated with other signs indicating the same mechanism of the disease [3]. Therefore, the biosensor signal is needed to combine with other sensors or with the patient's responses to the interactive questions of the questionnaire, which together allows us to develop new methods for preliminary diagnosis and remote monitoring of patients. Among the various methods for recording biological signals, the method of measuring bioelectrical impedance deserves great attention.

Electrical impedance sensors for assessing hemodynamics. The physical basis for the application of methods for measuring electrical impedance in cardiology is the presence of vessels containing biological fluids (blood, lymph, etc.), which act as conductors of electric current. In this situation, the magnitude of the electrical impedance is predominantly determined by the active resistance, as well as by the diameter of the blood vessel. The measurement of the electrical impedance of the patient's body should be made along the vessel—the conductor of electric current, but this obvious truth sometimes needs to be clarified for the practitioner, who must correctly apply the electrodes to the patient's body. A change in the vessel diameter under the influence of a pulse wave leads to a change in the electrical impedance for the same length of the measured section. The presented theory is fully suitable for the application of the method of thoracic tetrapolar rheography, proposed to determine the stroke volume of blood and related indicators of cardiac activity [4, 5]. The inaccuracy of the method lies in different schemes of electric current propagation in the chest because there are several parallel vessels that change their diameter: the aorta, other arteries, veins, and even the chambers of the heart. The measurement accuracy becomes much higher if the electrodes are applied directly to the vessel to be examined or to closely spaced points of vessel projections [6]. In 2016–2019, we had carried out experimental studies and numerical calculations that demonstrated the dependence of the electrical impedance on the liquid volume in a chamber with a variable diameter, the liquid flow rate in the tube, as well as the temperature and ionic composition of the electrolyte [7]. Mathematical models have been constructed that describe the change in the volume of the liquid in accordance with the change in the electrical impedance [8, 9]. In addition, equivalent electrical circuits were compiled, allowing the calculation of the volume of biological fluid in accordance with the values of ohmic and capacitive resistance in the circuit. In this case, the variable capacitance often plays the role of an unknown variable in practice, which reduces the accuracy of the method and is due to the influence of the skin, temperature, composition of biological tissues, including the presence of elements of coarse fibrous connective tissue. These interferences were minimal with an increase in the frequency of the probing alternating electric current. The research resulted in the development of a new method for measuring left ventricular end-diastolic volume, mean pulmonary artery pressure, and left ventricular ejection fraction using high-frequency electrical impedance cardiometry [10], as well as a method for early diagnosis of left ventricular failure [11].

Biosensors for assessing ventilation function. The ventilation function of the human respiratory organs is associated, first of all, with the saturation of the body with oxygen, the elimination of carbon dioxide. In detail, this process is divided into the actual ventilation mechanisms: the exchange of gases between the external environment and the alveoli through the respiratory tract, and the diffusion of gases through the alveolar-capillary membrane. Ventilation is the airflow through the airways. This process is characterized by speed, volume, resistance and pressure. The main methods of clinical assessment of these parameters are spirometry and body plethysmography. In 2011, the method of electrical impedance spirometry was proposed [12]. The method is based on bipolar registration of electrical impedance between the electrode located in the mouthpiece of the inhaler and the second electrode located on the patient chest. The measurement is carried out during inhalation of a 0.9% sodium chloride solution. Two theories of the propagation of electric current through the respiratory tract are the subjects to scientific discussion. The first indicates the influence of the flow rate of aerosol particles of sodium chloride, and the second indicates changes in the biochemical composition of the mucus covering the respiratory mucosa.

Biological tissues and fluids have different electrical properties, including different electrical conductivity. The electrical impedance of tissues and liquids is made up of elements of active and reactive resistance, which makes it possible to distinguish between biochemical substances and tissues, as well as to register tissue compartments separated by tissues with high resistivity (usually, coarse fibrous connective tissue). In the case of using electrical impedance spirometry, two main components can be distinguished that affect electrical impedance: the flow of aerosol charged particles and the mucus that covers the epithelium of the respiratory tract. The composition of mucus varies depending on the nosological form of the disease. Mucus consists of two components: gel—a product of the submucosal bronchial glands, containing glycoproteins, peptides, immunoglobulins, biologically active substances, as well as sol—a liquid product of goblet cells of the bronchial mucosa, mainly containing salt solutions (ions). It is known that bronchoobstructive diseases are accompanied by a change in the composition of bronchial secretions with an increase in the proportion of products of submucosal bronchial glands containing mucins and inflammatory proteins. Especially viscous, often vitreous, sometimes in the form of casts of the bronchi, the secret is characteristic of bronchial asthma. Its composition is determined by inflammatory cell products, including eosinophils producing eosinophilic cationic protein, large basic protein, eosinophilic peroxidase, eosinophilic protein X, other enzymes and peptides. In this regard, it should be remembered that it is for patients with bronchial asthma that particularly high electrical impedance values have been established as a result of the use of the electrical impedance spirometry method [13].

The aim of the study was to experimentally confirm the theoretical principles of the use of electrical impedance spirometry in the diagnosis and monitoring of respiratory diseases, the dependence of bioelectrical impedance on the flow rate of charged aerosol particles and the composition of bronchial secretions in small airways.

MATERIALS AND METHODS

Aerodynamics evaluation. The study of aerodynamic factors was carried out in polyethylene tubes

7 cm long and 2 and 1 cm in diameter. These parameters were chosen for simulation the movement of an aerosol in the inhaler mouthpiece between the electrode which was installed in it and the mucous membrane of the respiratory tract in the impedance spirometry method. We studied the electrical conductivity of an aerosol of 0.9% sodium chloride solution, which moved in tubes at different speeds. To create an aerosol and fill the chambers, nebulizer ultrasonic inhalers B.Well WN-116 U and Musson-3 were used. The nebulization performance of the B.Well WN-116 U inhaler was 0.5 mL/min, the average size of aerosol particles was 3.8 μm. The inhaler "Musson-3" had a comparable productivity of 0.4 mL/min, but the aerosol differed in the size of aerosol particles: 10% had a size of up to 100 μm, 90%—less than 10 μm. Two modes of filling the test tube were compared: injection of an aerosol into a tightly closed space (mode 1) and pumping the aerosol through a hollow tube (mode 2). Electrodes 8 × 20 mm in size, made of technical steel, were placed in the same plane inside polyethylene tubes at a distance of 3, 30, and 50 mm from each other.

The electrical impedance was measured using the BIA-lab Spiro software and hardware complex, which consisted of a measuring unit (an alternating electric current generator and a recording device represented by an Acer Aspire One D257 netbook sound card, a Wheatstone bridge, and electrodes). The software and hardware complex was controlled in automatic mode by the computer program "BIA-lab" (Certificate of Rospatent no. 2011611135). The measuring module has been tested on standard resistances and capacitance standards in the ranges from 2 to 100 kΩ and from 2 pF to 1 μF. Maximum current was 0.41 mA, and maximum voltage was 0.38 V.

Study of the influence of the composition of biological fluids on the results of electrical impedance analysis. Biological fluids were prepared using 0.9% sodium chloride solution for infusion in 400-mL glass jars (LLC Krasfarma, Russia) and food gelatin (compliance with TU 9219-03-51021647-11; LLC Promagrotekhnika, Russia).

The following biological fluids were prepared, reflecting the physical, chemical and biological properties of the two components of bronchial secretions (sol and gel): physiological sodium chloride solution and food gelatin solution in physiological sodium chloride solution (10 g/100 mL).

To measure the electrical impedance, a chamber was constructed (Fig. 1), consisting of a fluoroplastic housing and stainless steel electrodes; the chamber volume was 38.151 cm^3.

As follows from Fig. 1, the measuring chamber, consisting of a fluoroplastic tube (*1*), has fluoroplastic caps that are put on both ends for the purpose of sealing (*2* and *3*) with built-in electrical steel electrodes (*4* and *5*), the flat surface of which is on the inside of

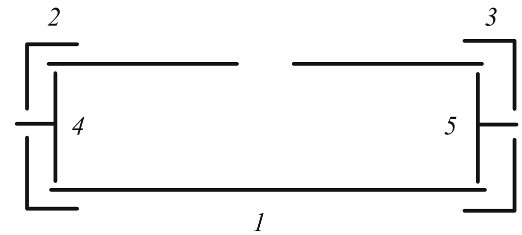

Fig. 1. Scheme of the measuring chamber: (*1*) measuring chamber, (*2*, *3*) caps, and (*4*, *5*) electrodes.

the tube closes it from the end and serves as an electrode. A hole was made in the middle part of the fluoroplastic tube for filling the tube, which was hermetically sealed at the time of the experiment.

The second chamber of a similar device had a smaller diameter, 10 mm, and a correspondingly smaller volume, 8.164 cm^3.

An LCR-78105G high-precision LCR meter (GW-Instek, Taiwan) was used to measure the electrical impedance. Before the measurement, the LCR meter was calibrated. The meter itself was connected to a personal computer via the RS-232 interface; measurements were carried out using a computer program. The computer program set the measurement parameters (discreteness, measured values - impedance modulus and phase angle, voltage level—2 V, frequency—the frequencies of alternating electric current were used 20 and 98 Hz, and 1, 2, 5, 10, 20, 30, 100, and 150 kHz). The indicated frequency ranges were selected taking into account the results of clinical practice using the method of electrical impedance spirometry in patients with bronchial asthma and chronic obstructive pulmonary disease. After that, 30 measurements were performed at each frequency. The results were recorded in files with the .csv extension. Ten series were performed in each experiment. At each frequency, the mean value of the impedance modulus, the standard deviation of the impedance modulus from the mean value, the mean value of the phase angle, and the standard deviation of the phase angle from the mean value were calculated.

Statistical data processing was performed using the Statistica 8.0 software package. Signs that have an incorrect distribution are presented as *Me*, 25%, 75%, σ. In the case of the study of hemodynamic parameters, the results of measuring the modulus value and the phase angle of the electrical impedance had the correct distribution and are presented as $M \pm \sigma$. The significance of differences between samples of independent features was determined using the Mann–Whitney test (in case of incorrect distribution of features) and the *t*-test (in case of correct distribution of parameters). Correlation analysis was performed with the calculation of Spearman's *R*-test.

Table 1. Results of measuring the impedance parameters of cell 1 filled with gelatin solution

Frequency, Hz	Z, Ohm	σ, Ohm	φ, deg	σ, deg
20	134.2	0.80	−42.94	0.064
98	84.9	0.65	−37.36	0.530
1000	55.0	<0.01	−9.93	0.024
2000	53.4	<0.01	−5.76	0.006
5000	52.5	<0.01	−2.79	0.001
10000	52.1	<0.01	−1.61	<0.001
20000	51.9	<0.01	−0.91	<0.001
30000	51.8	<0.01	−0.63	<0.001
100000	51.7	<0.01	−0.09	<0.001
150000	51.7	<0.01	−0.07	<0.001

$n = 10$; σ is the standard deviation, Z is the impedance modulus, φ is the phase angle.

RESULTS

Experimental studies performed with two types of inhalers showed that the probing alternating electric current used by us does not penetrate through the aerosol of a 0.9% sodium chloride solution in the absence of a flow of aerosol particles. The movement of aerosol particles makes it possible to register an electric current and a sufficiently high resistance, which is inversely proportional to the current strength in the flow of aerosol particles. At a fixed spraying performance of the inhaler (Musson-3, productivity is 0.4 mL/min) and a decrease in the cross-sectional area of the tube that passes aerosol particles from 6.28 to 1.57 cm^2, an increase in the velocity of aerosol particles led to a decrease in the electrical impedance (87.42 kΩ (85.24, 90.10) vs. 112.73 kΩ (107.65, 122.44) at 20 kHz). The use of a tube with a diameter of 2 cm was accompanied by a decrease in the electrical impedance to 51.34 kΩ (50.97, 52.10).

The use of two types of inhalers, differing in the parameters of aerosol particles, demonstrated the effect of the size of aerosol particles on the electrical conductivity of the aerosol and the decrease in electrical impedance is inversely proportional to the size of the aerosol particles. When using the ultrasonic inhaler B.Well WN-116 U, which creates an aerosol with an average particle diameter of 3.8 μm, the value of the modulus of the impedance Z was 158.24 kOhm (134.12, 178.67). The aerosol produced by the Musson-3 inhaler, 10% of whose particles are up to 100 μm in size, and 90% are no larger than 10 μm, was characterized by a Z value of 114.94 kOhm (112.92, 116.99). The maximum interelectrode distance at which an electrical signal is recorded for the Musson-3 inhaler was more than 50 mm.

When the cells were filled with physiological sodium chloride solution, the electrical impedance modulus turned out to be close to zero. The impedance of cells filled with gelatin solution was measured. The measurement results in cell 1 are presented in Table 1, in Fig. 2 (modulus of impedance Z) and Fig. 3 (phase angle φ); the measurement results in cell 2 are, respectively, in Table 2 and in Figs. 4 and 5.

DISCUSSION

Experimental data indicate the possibility of using the method of electrical impedance spirometry, provided that there is a coarse fraction of sodium chloride aerosol, which ensures the closure of the electrical circuit between the electrode installed in the mouthpiece of the inhaler and the mucous membrane of the respiratory tract. In the experiment, the allowable distance for registering the electrical signal was 5 cm, which allows us to expect that this path of propagation of the electric current is significant in the segment of the cir-

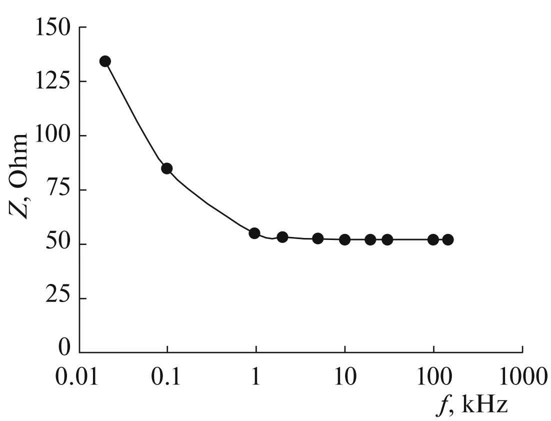

Fig. 2. Graph of the dependence of the impedance modulus of cell 1 containing a solution of gelatin in physiological sodium chloride solution on the frequency of the electric current.

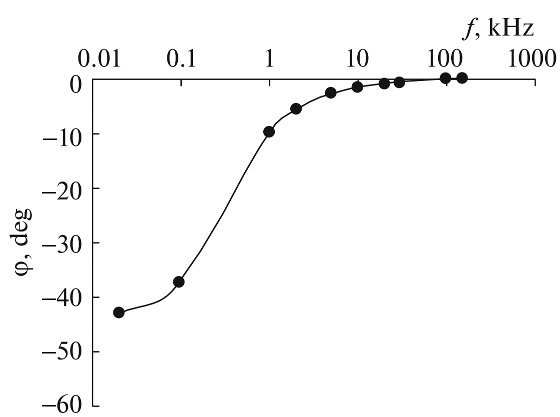

Fig. 3. Graph of the phase angle for cell 1, containing a solution of gelatin in physiological sodium chloride solution, as a function of the frequency of the electric current.

cuit from the inhaler mouthpiece to the mucosa of the trachea and main bronchi. The change in the speed of movement of aerosol particles in a given segment of the electrical circuit is due, on the one hand, to the power of the inhaler, on the other hand, to the strength of the respiratory muscles. Therefore, the increase in electrical impedance in various diseases may depend on the airflow velocity at the level of the upper respiratory tract. Decreased airflow rate is a typical sign of ventilation disorders in bronchial asthma, as well as diseases of the lung parenchyma [14].

An experiment to study the influence of the composition of a biological fluid on the results of measuring the electrical impedance showed that the value of the electrical impedance of a solution of a complex biological compound. An experiment to study the effect of the composition of a biological fluid on the results of measuring electrical impedance showed that the magnitude of the electrical impedance of a solution of a complex biological compound (gelatin) containing proteins, peptides, glycoproteins, other complex carbohydrates and minerals differs from the mineral solvent - physiological sodium chloride solution and decreases in proportion to the increase in the frequency of the probing alternating current. The data obtained correspond to the known electrical properties of biological fluids and tissues, including those described by us earlier in the study of solutions of salts, glucose, albumin, and human immunoglobulins [15–17]. In contrast to the previous data, saline solutions in the large diameter tubes used in this experiment did not show the properties of electrical resistance, which proves the maximum influence of the diameter of the electric current conductor containing biological fluids. This position was demonstrated by us using two chambers of different diameters. The results obtained confirm the hypothesis about the influence of the composition of bronchial secretions on the results of electrical impedance spirometry, but show the dominant influence of the diameter of the airways. This circumstance is especially important for small airways, less than 2 mm in diameter, as well as paths filled with bronchial secretions, where the movement of the gas mixture becomes slow and the diffusion of gases is determined by the properties of bronchial secretions. It can be argued that the method of electrical impedance spirometry has a maximum dependence on two components – the speed of air flow in large airways and the composition of the bronchial secretion of small airways.

Table 2. Results of measuring the impedance parameters of cell 2 filled with gelatin solution

Frequency, Hz	Z, Ohm	σ, Ohm	φ, deg	σ, deg
20	1183.9	1.69	–20.47	0.074
98	1022.0	0.12	–10.20	0.050
1000	949.4	0.01	–1.89	0.005
2000	945.2	0.01	–1.07	0.001
5000	942.5	0.01	–0.51	0.001
10000	941.6	0.01	–0.30	<0.001
20000	941.0	0.01	–0.19	<0.001
30000	940.8	0.01	–0.15	<0.001
100000	940.5	0.01	–0.14	<0.001
150000	940.3	0.01	–0.17	0.005

$n = 10$; σ is the standard deviation, Z is the impedance modulus, φ is the phase angle.

CONCLUSION

As a result of the study, the hypothesis was confirmed that the main factors affecting the results of electrical impedance spirometry are: the speed of the air flow in the large airways and the composition of the

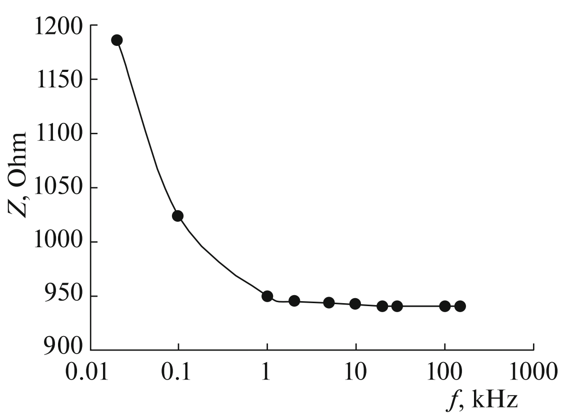

Fig. 4. Graph of the dependence of the impedance modulus of cell 2 containing a solution of gelatin in physiological sodium chloride solution on the frequency of the electric current.

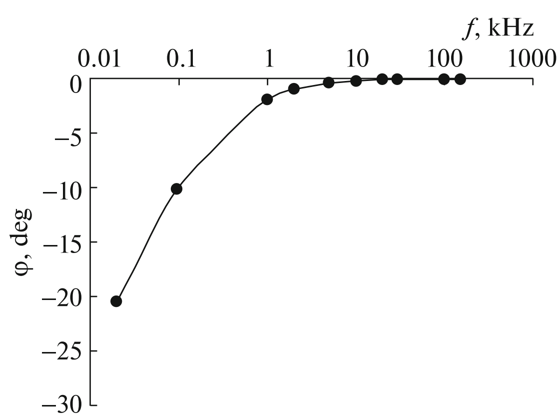

Fig. 5. Graph of the phase angle for cell 2, containing a solution of gelatin in physiological sodium chloride solution, as a function of the frequency of the electric current.

bronchial secretion of the small airways. At the same time, the introduction of a new method into clinical practice will be more effective if remote monitoring of patients with respiratory diseases is implemented. A large number of sensors under development require clinical trials and certification as medical devices. Actual issues of introducing new sensor systems are the accuracy of registration of biological parameters, reproducibility of the result, convenience, feasibility, applicability of the technique, the availability of engineering technical support from the manufacturer during medical operation, and inclusion in clinical recommendations [18]. An equally important issue affecting the effectiveness of clinical trials and the practical use of new technologies, in our opinion, is ensuring the availability of clinical information for the doctor. The ideology of many sensor manufacturers is aimed at the end user—the patient, who is the analyzer of the received medical information, which is contrary to the principles of medical care. The unresolved tasks are: the security of the transmission of electronic information to the doctor's office in real time, as well as the formation of a medical report, taking into account new parameters for assessing human health.

FUNDING

The study was supported by the Russian Foundation for Basic Research (grant r_SEC_Permsky Krai no. 20-415-596008 "The concept of rehabilitation of patients who have had Covid-19 infection by inhalation therapy using a natural mineral complex of deposits in the Perm Territory in the composition of salts of cerium, manganese, zinc and silver and development of principles for monitoring patients using a system of interactive surveys").

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest. V.Ju. Mishlanov has a patent of the Russian Federation no. 2487662 (2013) "Method of Diagnosing Respiratory Function by Means of Impedance Spirography and Computer Appliance "Bia-lab Spiro" for Its Realisation."

Statement of the welfare of humans or animals. The article does not contain any studies involving humans or animals in experiments performed by any of the authors.

REFERENCES

1. C. B. Wilson, BMJ **319** (7220), 1288 (1999).
2. N. Bhalla, P. Jolly, N. Formisano, and P. Estrela, Essays Biochem. **60**, 1 (2016).
3. A. G. Chuchalin, V. A. Chereshnev, V. Yu. Mishlanov, et al., *Bioethics, Artificial Intelligence and Medical Diagnostics* (Permsk. Gos. Med. Univ., Perm, 2019) [in Russian].
4. M. A. Zubarev, A. A. Dumler, and V. A. Rusov, SU Patent No. 1671263 (1991).
5. V. A. Shutov, M. A. Zubarev, A. A. Dumler, and A. A. Krylov, RF Patent No. 2145792 (2000).
6. *National Guidelines for the Management of Patients with Vascular Arterial Pathology (Russian Consensus Document)* (2010) [in Russian].
7. A. L. Zuev, V. Ju. Mishlanov, N. V. Shakirov, and A. I. Sudakov, J. Phys.: Conf. Ser. **1945**, 012065 (2021).
8. A. L. Zuev, V. Yu. Mishlanov, A. I. Sudakov, and N. V. Shakirov, Russ. J. Biomech. **14**, 64 (2010).
9. A. L. Zuev, V. Yu. Mishlanov, N. V. Shakirov, et al., Russ. J. Biomech. **16**, 98 (2012).
10. V. Yu. Mishlanov, RF Patent No. 2547961 (2015).
11. V. Yu. Mishlanov, I. V. Mishlanova, and Ya. V. Mishlanov, RF Patent No. 2499553 (2013).
12. V. Yu. Mishlanov, Vestn. Sovrem. Klin. Med. **4** (4), 24 (2011).
13. V. Yu. Mishlanov, A. L. Zuev, T. L. Ust'yantseva, et al., Ross. Fiziol. Zh. im. I.M. Sechenova **99**, 1425 (2013).
14. *Functional Diagnostics in Pulmonology: a Practical Guide*, Ed. by A. G. Chuchalin (Atmosfera, Moscow, 2009) [in Russian].
15. A. L. Zuev, V. Ju. Mishlanov, N. V. Shakirov, and A. I. Sudakov, J. Phys.: Conf. Ser. **1945**, 012066 (2021).
16. V. Yu. Mishlanov, A. L. Zuev, Ya. V. Mishlanov, et al., in *XIX Winter School on Continuum Mechanics* (2015), vol. 212 [in Russian].
17. V. Yu. Mishlanov, I. V. Mishlanova, Ya. V. Mishlanov, and S. L. Mishlanova, RF Patent No. 2548778 (2015).
18. https://sps.honeywell.com/us/en/support/blog/siot/complete-guide-to-medical-sensors-benefits-and-applications.