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ELECTRICAL IMPEDANCE MEASUREMENT AS A METHOD FOR EVALUATING MYOCARDIAL PROTECTION IN HEART SURGERIES WITH ARTIFICIAL BLOOD CIRCULATION

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Abstract

Intraoperative myocardial protection methods improvements is one of the most pressing problem of modern "open heart" surgery. To determine the myocardial metabolism condition after cardioplegic ischemia, methods as: assessment of the heart using electro- and echocardiography, assessment of the clinical condition, the need to use inotropic drugs, determining the level of biochemical markers of damage (lactate, myoglobin, troponin, etc.) are used in modern medicine as well as biopsy morphological examination.

Now there is no reliable diagnostic method in clinical practice that can determine the myocardial metabolism condition.

The purpose of the study is to determine the electrical impedance effectiveness as a method for evaluating myocardial protection in various cardioplegic modifications.

The study included 54 patients operated in A.N.Bakulev National Medical Centre of the Russian Academy of medical Sciences in Emergency surgery of acquired heart defects department for valvular heart apparatus defects, including combination with coronary artery pathology. Depending on the method of myocardial protection, patients were divided into 3 groups:

Group 1 - patients who had buckberg cardioplegia as a myocardial protection (n=31); Group 2 - patients operated under pharmacoholodic cardioplegia using Custodiol solution (n=9); Group 3 - patients who used hyperkalic solution No. 3 (n=14) as intraoperative myocardial protection.

The bioelectric impedance of the myocardium was studied in all patients. To assess the myocardial protection adequacy and to compare it with the results of electrical impedance measurement, we also used some common research methods. The study results revealed that electrical impedance measurement is quite good at assessing the state of the myocardium during surgery.

Keywords: *electrical impedance measurement, heart surgery, myocardial protection, heart with artificial blood circulation.*

Introduction

Intraoperative myocardial protection methods improvements is one of the most pressing problem of modern "open heart" surgery. To determine the myocardial metabolism condition after cardioplegic ischemia, methods as: assessment of the heart using ECG and ECHO cardiography, assessment of the clinical condition, the need to use inotropic drugs, determining the level of biochemical markers of damage (lactate, myoglobin, troponin, etc.) are used in modern medicine as well as biopsy morphological examination.

Now there is no reliable diagnostic method in clinical practice that can determine the myocardial metabolism condition.

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Bioimpedance measurements are used in various fields of medicine to assess the cellular homeostasis and extracellular water [*Zhao T, Jacobson B, 1997; Nikolaev D et al., 2003; Cvetkov A, 2010; Barsukov A et al., 2012; Melnikov A et al., 2012; Sindeeva L et al., 2015*]. There are some reports about the possibility of using organs and tissues bioimpedance measurement when they are being probed by currents of different frequencies. This method is used to monitor biological membranes and intercellular space condition [*Nyboer J 1959; Hoffer E et al., 1969; Howie M et al., 2001; Kuznetsov V, Novikov A, 2013; Rudnev S et al., 2014; Sakibaev K, 2015*].

Direct current passage through a biological system causes increasing of electromotive force (EMF) of the opposite direction to the certain limit. This EMF value can be detected by disconnecting the electrodes from the voltage source and quickly attaching them to the galvanometer. Reverse current will be registered that diereses over time. The electricity amount that accumulates in living systems when current flows is due not only to the static capacity, but also to the relatively large polarizing capacity. Regularities electric current passage through biological objects reveal that the resistance of living cells is the total and is determined by the passage of current through the ohmic and capacitive resistances. At alternating current both the ohmic resistance and the capacitance must be taken into account [*Popechitelev E, Filist S, 2011; Zuev A et al., 2012*].

To characterize the living cells and tissues current conductivity equivalent circuits are used: such combinations of ohmic and capacitive resistances that can simulate the electrical parameters of cells and tissues. Thus for a series connection of ohmic resistance and capacitance, the electrical impedance (Z) is equal to

$$Z=(R^2+(\omega c)^{-2})^{1/2}$$

omic component is R, and capacity $-(\omega c)^{-1}$.

With parallel connection the electrical impedance is equal to

$$Z=(R^{-2}+(\omega c)^2)^{-1/2}.$$

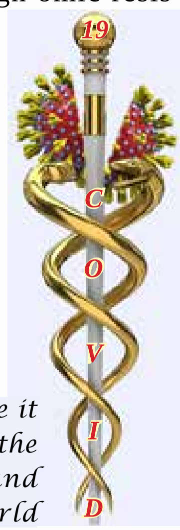
Living cells are characterized by a more complex combination of sequential and parallel elements.

Absolute values of the resistance level are difficult to obtain because this level depends on the study conditions, e.g. the area of the electrodes, the distance between them, the density of the tissue contiguity to the electrodes, the thickness of the object, etc. [*Egorov L, Shvoselskii I, 1969; Tarusov B, Antonov V, 1986*].

In order to assess the physiological state of biological tissue, data describing the steepness electrical conductivity dispersion should be considered. Some of dispersion properties are conveniently expressed by the ratio of the drag value measured at low frequency to the drag value measured at high frequency, assuming that if two resistances are measured at different frequency under the same conditions, the relationship between them is very constant for the normal condition of the tissue [*Egorov L, Shvoselskii I, 1969; Barsukov A et al., 2012*].

After the death of the tissue, the indicated coefficient approximates to one. In normal intact cells and tissues, its magnitude depends on the position of the organism in the evolutionary series. For mammals it is K=2.5-10, for frogs - K=1.5-3. The value of the coefficient also depends on the structure, function and condition of the tissue. In organs with intensive metabolism (liver, spleen) it is higher than, for example, in muscles of the same organism [*Barsukov A et al., 2012; Kuznetsov V, Novikov A, 2013*].

Thus, the following can be concluded. Alternating current at a frequency of less than 40 *kHz* propagates mainly through vessels and intercellular space, encircling the cells whose specific resistance (due to the high omic resistance of the membranes) is much higher than the specific resistance of the liquid media. At frequencies of hundreds and thousands of *kHz*, the capacitive resistance of the membranes already slightly inhibits the penetration of current into the cells and its density outside and within



the cells becomes comparable. At these frequencies current flows easily through both extracellular and intracellular environments. Unlike the low-frequency measurement, the conductivity of the current increases, and the resistance of the tissue (bioimpedance) decreases accordingly.

Aim of the study is to determine the effectiveness of electrical impedance as a method of estimating myocardial protection under different cardiopulpecial modifications.

Material and Methods

The study included 54 patients operated in A.N.Bakulev National Medical Centre of the Russian Academy of medical Sciences in Emergency surgery of acquired heart defects department for valvular heart apparatus defects, including combination with coronary artery pathology. Depending on the method of myocardial protection, patients were divided into 3 groups:

Group 1-patients who had buckbergcardioplegia as a myocardial protection (n=31);

Group 2-patients operated under pharmacoholodiccardioplegia using Custodiol solution (n=9);

Group 3 – patients who used hyperkalic solution No. 3 (n=14) as intraoperative myocardial protection. These patients characteristics are shown in table 1. All patients have been tested for bioelectric myocardial impedance.

The measuring system consists of a sensor, a bioimpedance meter and a computer connected to each other in series.

The sensor were made of two combined myocardial electrodes for a four-pole measurement. The small size and shape of the electrodes provided for its reliable fixation to the myocardium. The body is made of a composite material which provided a hermetically sealed electrode structure. Two rods made of an alloy of precious metals are arranged in the lower part of the housing. The design of one of the electrodes included a thermoelement for measuring myocardium temperature (first tested in A.N. Bakulev National Medical Research Center of Cardiovascular Surgery).

The electrodes were fixed in a way to cover possible the myocardial section under investigation as much as possible, with a distance of about 3 *cm*. All patients were examined the bioimpedance of the anterior wall of the right ventricle.

Table 1

Clinical profile of patients

	Group 1	Group 2	Group 3	Total
Numberofpatients	31	9	14	54
Middleage	45.2 ±5.4	51.2 ±9.6	47.9 ±6.5	46.9 ±3.8
Sex (*m/f*)	22/10	7/2	10/4	39/15
FC 2	2 (6.5%)	1 (11.1%)	-	3
FC 3	13 (41.9%)	5 (55.6%)	6 (42.9%)	24
FC 4	16 (51.6%)	3 (33.3%)	8 (57.1%)	27
Atrialfibrillation	10 (32.3%)	2 (22.2%)	2 (14.3%)	22
Singlevalveprosthesis	24 (80.7%)	6 (66.7%)	11 (85.8%)	41
Two-valveprosthesis	6 (19.3%)	3 (33.3%)	2 (14.2%)	11
OperationRoss	8 (25.8%)	-	-	8
Repeatedoperations	3 (9.6%)	-	-	4 (5.7%)
Duration of aortic compression, mines	127.4 ±14.7	127.2 ±24.4	79 ±9.6	113.4 ±9.5
Duration CPB, min (cardiopulmonary bypass)	196.9 ±20.8	197 ±35.5	132,5 ±17.2	178.9 ±13.5

Note: *The validity of the differences relative to the values of the I-group is p<0.05*

The electrical impedance was measured at two frequencies of 110 *kHz* and 9.4 *kHz*. The received data of high-frequency and low-frequency impedance (Zhf, Zlf) as well as the ratio Zhf/Zlf (DS – dispersion slope) were continuously monitored almost the entire period of the artificial blood circulation. At the same time, the temperature in the myocardial region was monitored. A temperature correction of the impedance curve to 37 °C was performed using a special program. Data was processed and recorded on a computer.

The impedance indicators (Zhf, Zlf and DS) filmed at the following moments of the operation (control points) were the point of particular interest:

√ The start of CPB is the reference values (Zhf-0, Zlf-0, DS -0),
√ Immediately before aortic recalibration (Zhf-1, Zlf-1, DS -1)
√ Immediately before the introduction of cardioplegic solution (Zhf-2, Zlf -2, DS -2),
√ at the end of the cardioplegic solution administration (Zhf-3, Zlf -3, DS -3),
√ Immediately before removal of the aortic clamp (Zhf-4, Zlf -4, DS -4),
√ First minutes of myocardial reperfusion (Zh-5, Zlf -5, DS -5),
√ 20 minutes after recovery of coronary blood (Zhf-6, Zlf -6, DS -6),
√ Impedance reference values recover if it occurred before the end of the CPB (Zhf-7, Zlf -7, DS -7),
√ Initial Zhl decreasing point (Zhf -8).

Results and discussion

All impedance indicators were considered relatively to the reference values, where Zlf, Zhf, Ds values are equal 856.4+6.8, 399.5+4.7 and 2.15+0.03 respectively, which were fixed to the “warm heart” at 36-37°C.

Reference values wide spread of high frequency and low frequency impedance (Zhf, Zlf), where the standard deviation from the average was 14.7 for all patients were due to several factors: the electrical conduction of the tissue, the thickness of the area of myocardium under investigation and the distance between fixed electrodes. Should be noted that for all patients the initial low-frequency to high-frequency impedance (DS – dispersion slope) ratios were on average 2.14 0.03 and did not depend on the volume of the myocardium region studied. So instead of the absolute values of impedance, we payed attention to the changes of the latter relative to the original.

During the material analysis general patterns of electrical impedance of myocardium changes (Fig. 1) were identified.

Before the aortic compression the resistance of the myocardium was almost unchanged, indicating the stability of extracellular and intracellular space. A few seconds after the aortic compression, the impedance increased sharply at the expense of the Zlf, as evidenced by the increase in DS This change is explained by the volumetric discharge of the small blood vessels followed by relative dehydration of the interstitial space (Fig. 1, gap 1-2). This process lasts an average for 1.8 0.1 minutes, after which the electrical resistance of the myocardium stabilizes, unless cardioplegic solution is introduced by that time.

To achieve asystomy the first cardioplegia (induction) was performed averagly in 1.2 ±0.1 minutes after the aortic compression. Immediately after the solution was introduced, impedance rapidly dropped to the initial value, mainly due to Zlf, which indicated that the vascular bed and interstitial space were filled with a cardioplegic solution. A decrease in impedance was observed to a certain value and remained at this level until the end of the infusion (Fig. 1, gap 2-3). After cardioplegia, the impedance value increased again and reached the maximum value (Fig. 1, point 2’), the so-called “dry myocardium impedance” (DMI).

Subsequent cardioplegia (re-infusion) sessions

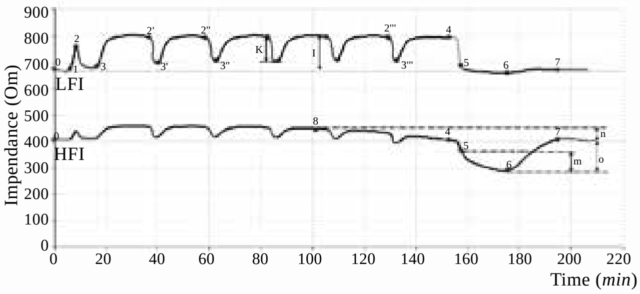


Figure 1. *Schematic myocardial electrical resistance chart*

included similar impedance changes (Fig. 1, gaps 2'-3', 2'-3', etc.).

Table 2 shows the average volumetric velocity of cardioplegic solution administration and Zlf impedance decrease level at antegraden and retrograde path of cardioplegic solution administration.

To delineate colleration between the volumetric rate of injection of a cardioplegic solution and low-frequency impedance decrease, we tried to determine the stage where the values of the two variables are "proportional' to each other. A simple Pearson linear correlation was used to solve this problem (Fig. 2).

The calculations revealed a high correlation coefficient r=0.84 (p<0.001) between the volumetric rate of myocardial perfusion and the decrease level of Zlf during antegradiccardioplegic solution infusion. Antegradiccardioplegia was carried out both in the aortic root and in the estuaries of coronary arteries. As it can be noticed at table 3, a high degree of correlation was observed in both cases.

In the case of retrograde solution injection via the coronary sinus, the data was not correlated. But when analyzing the scattering diagram you can see the heterogeneity of the data whose area is marked with a dotted line (fig. 2, on the right). In such situations a low correlation may result from a split of the data into two groups rather than reflecting a "true" relationship between the two variables. In this case, we tried to calculate the correlations separately for each set by dividing patients from retrograde cardioplanes into two experimental groups A and B.

As shown in figure 2 in group "A", the data is absolutely correlated with r=0.89, where the value level p<0.001. Whereas in the group of patients "B", there was no correlation r=-0.15, which indicates the rigidity of impedance from changes in the volume speeds of retrograde cardioplegia.

I would like to remind you that we have examined the bioimpedance of the anterior wall of the right ventricle - a pool drained mainly by the anterior veins of the heart.

Given the above, it can be assumed that the retrograde group "A" included patients n=27 (61.4%) whose anterior veins of the heart drain into the coronary sinus system. Therefore, in this group of patients retrograde cardioplegia through the coronary sinus provided adequate perfusion of myocardium on the anterior wall of the right ventricle. The retrograde group "B" could be patients with n=17 (38.6%), whose anterior veins of the heart were drained into the right parts of the heart, bypassing the coronary sinus. In these patients, retrograde cardioplegia through the coronary sine did not provide adequate perfusion of the anterior wall of the right ventricle. Therefore, in this group the acceleration of the volumetric speeds of cardioplegia does not

TABLE 2

Average values of myocardium volumetric perfusion rate and low-frequency impedance decrease level during cardioplegia

	Number of observations	Volume tric speed	ΔZ-NH	r	p
Antegradno	55	284 ±10.7	13.3% ±0.5%	0.85	<0.0001
in the root of Ao	18 (32.7%)	304.4 ±22.6	14.1% ±0.8%	0.92	<0.005
in the orifice of the CA	37 (67.3%)	274.1± 10.2	13% ±0.5%	0.8	<0.005
Retrograde	44	223.4 ±11.5	9.6% ±0.7%	0.41	>0.05
group A	27 (61.4%)	220.4 ±14.6	10.8% ±0.8%	0.896	<0.001
internal occlusion	18 (66.7%)	212.2 ±19.7	10.5% ±1%	0.92	<0.005
externalocclusionby	9 (33.3%)	236.7± 15.7	11.4% ±1.1%	0.81	<0.005
group B	17 (38.6%)	228.2 ±18.8	7.8% ±0.3%	-0.15	>0.05
internal occlusion	10 (58.8%)	218± 24.4	7.9% ±0.5%	-0.11	>0.05
External occlusion	7 (41.2%)	242.9± 27.9	7.7% ±0.4%	-0.18	>0.05

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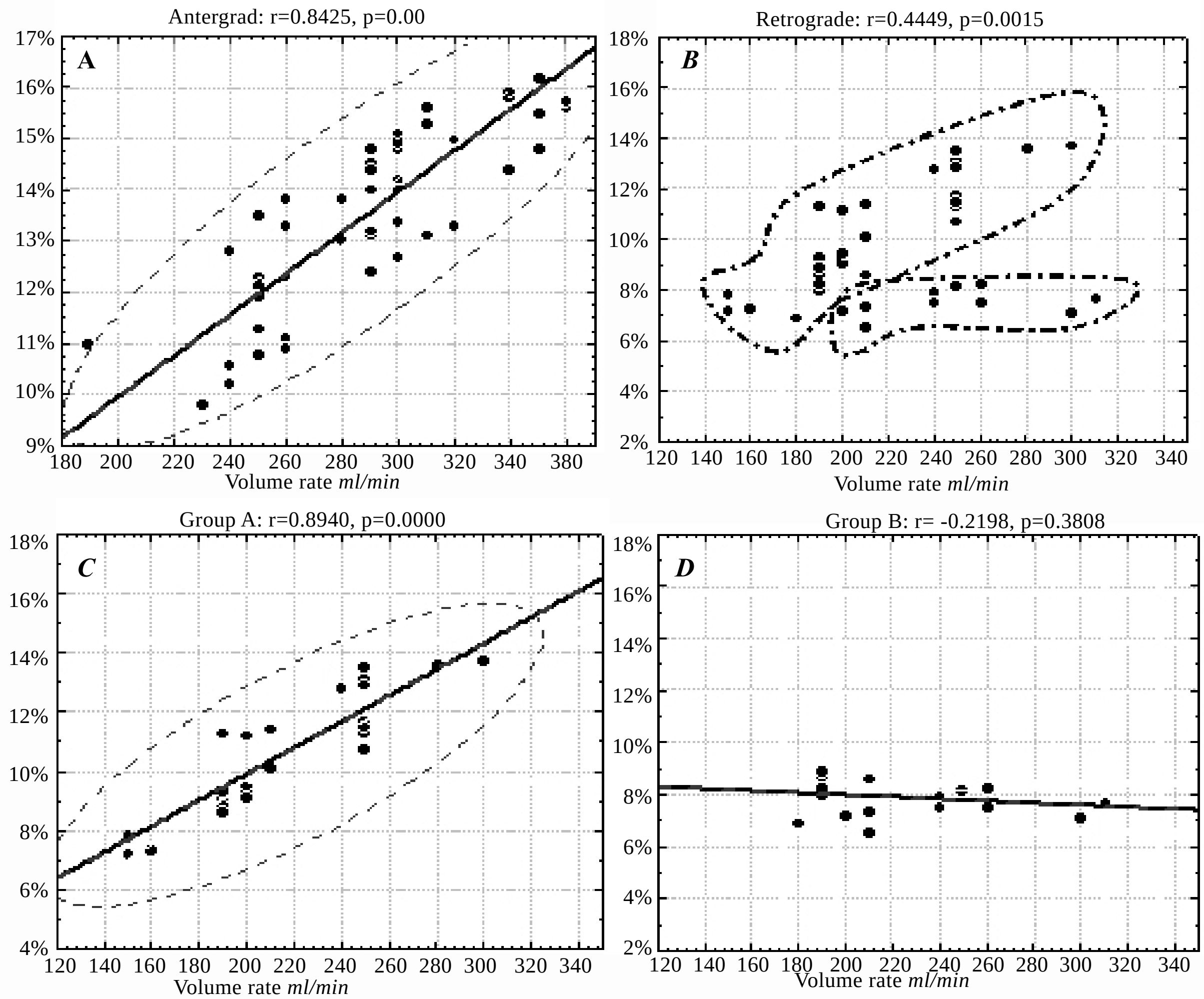

FIGURE 2. Correlation between the volume rate of myocardial perfusion and the deacrease level of Zlf when antegrade (A) and retrograde (B) and infusion of cardioplegic solution and during retrograde (C, D) cardioplegic solution infusion

entail change of low-frequency impedance.

The median cardiac vein, which drains blood from some areas of IVS (interventricular septum), opens into the coronary sinus very close to its orifice. The median distance between the coronary sine and the median cardial vein is 1.7 0.6 *mm* in adults. Accordingly, it cannot be guaranteed the position of the cylinder under the retrograde cardioplegia (RC) in the sinus without the occlusion of the veins opening there.

According to the method of coronary sinus cannulation the patients were divided into two subgroups: the inner coronary sine occlusion by an inflated cylinder and the external occlusion by a cystic suture. Results of bioimpedance spectroscopy in subgroups with different methods of coronary sine occlusion did not reveal any reliable differences.

All of the above-mentioned impedance changes occurred mainly due to Zlf, which characterizes the volumetric changes of extracellular space.

In 15-20 minutes of intraoperative ischemia under anaerobic glycolysis, lactate and protons accumulate in the cytoplasm and intracellular acidosis developed. Hyperhydration of the endoplasmic reticulum channels and the vacuolization of the insertion disks occurred. In increasing ischemia condition an excessive accumulation of hydrogen

TABLE 3

Mean values of the onset of descent and Z-PM decrease at the height of ischemia

	Averagetime	ΔZ-hf
Group 1	177.6 ±2.1	0.9% ±0.3%
Group 2	148 ±3.9	1.4% ±1.5%
Group 3	69.5 ±1.5	1.6% ±1.2%

ions, which leads to widespread edema, primarily of the perinucleus region, expansion and swelling of the channels of the sarcoplasmic reticulum and the T system were observed. With the progressive disruption of the cell's electrolyte exchange and ionic equilibrium, osmotic pressure increased in myocytes. It resulted in the partial transfer of extracellular water to myocytes and the formation of cell swelling. At this stage of myocardial damage, hydration of capillary endothelium was also observed due to the partial movement of tissue water into the endothelial cells.

These changes lead to an increase in the total intracellular space and consequently to an increase in the electrical conductivity of the myocardium what results in impedance decrease.

Cardioplegia prolongs cell swelling to varying degrees.

In some patients in certain period of time after the aortic compression, impedance decreased mainly due to high frequency (Fig. 1, gap 8-4). The Zhf decrease level at the height of myocardial ischemia and the average time Zlf started to decline for each group of patients are shown in table 3.

Strong correlation that cannot be well described by a linear function was revealed when analyzing the correlation between aortic compression time and Zhf changes. We tried to find a function describes this correlation in the best way. Then we check her "acceptance" of the data (Fig. 3).

In groups with pharmacocholoidcardioplegics, a high degree of dependence was observed ($r=0.93$ $p<0.001$ group 3 and $r=0.88$ $p<0.001$ group 2) between the aortic compression time and the Zhf decrease. In the group 1 the correlation was minimal $r=0.49$ ($p<0.05$), which provides relative stability of the intracellular space sum during aortic compression.

After removal of the aortic clamp and reconstruction of coronary blood flow velocity, the electrical resistance of the myocardium decreased to the original values, mainly due to low-frequency. Further some of patients continued to reduce the high frequency impedance below the baseline impedance (Fig. 1, interval -5-6).Reconstruction of coronary blood flow velocity after prolonged aortic pinch, can lead to massive calcium entry into myocytes, leading to sharp osmotic swelling of the sarcoplasmic reticuluum and T-system. The disposal of ATP by Ca2 -ATFase is accelerated, mitochondrial production of ATP is suppressed, which

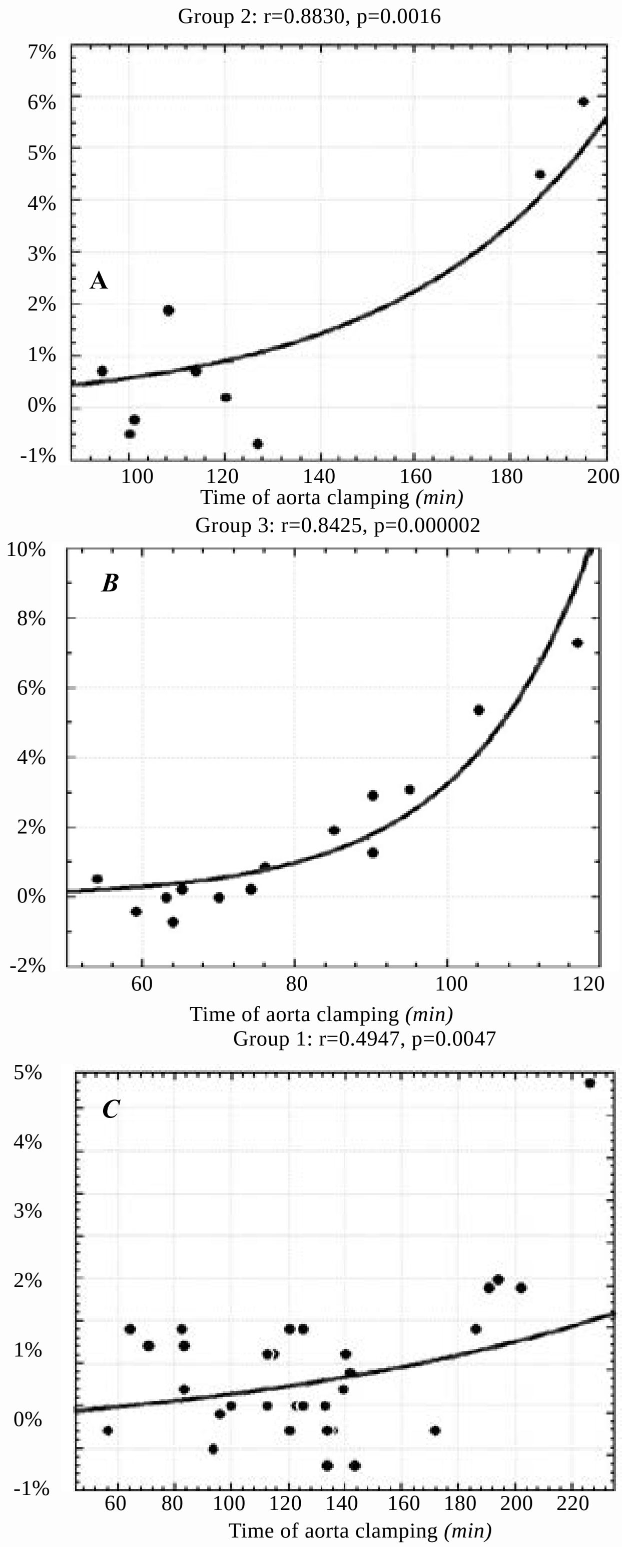

FIGURE 3.** Correlation between aortic clamping time and Zhf decrease level in each patient groups: (**A**)* Custodiol; (B***) - Solution No3 and (***C***) -Backberg treatment

leads to depletion of macroergic phosphates.A complex disorder of phospholipid metabolism occurs, consisting of activation of phospholipases, suppression of reacylation and catabolism of lysophosphoglycerides, and inhibition of de novo phospholipid synthesis. Amphiphilic compounds that affect the physical properties of phospholipid bilayer accumulate in cell membranes. Membrane integrity, electrolyte exchange and cell ion equilibrium are disturbed. It leads to “explosive” swelling of cells and electric impedance myocardium decrease.Significant endotheliocyte edema up to capillary opturation, in turn also leads to an increase in total intracellular space.

The time and level of maximum decrease of Zhf after reconstruction of coronary blood flow velocity are shown in table 4.

After the reconstruction of coronary blood flow velocity the least decrease in myocardial resistance was observed in group 1, averagely 2.8%.Whereas in the group 2 and group 3 the decrease level was averagly 6.6% and 10.3% respectively, which is significantly higher ($p < 0.05$) than in the group 1. When analyzing the relationship between the aortic pinch time and the maximum decrease level of Zhf after coronary blood flow reconstruction a high correlation was found in groups with pharmacocholid cardioplegia ($r = 0.93$ $p<0.0001$ group 2 and $r = 0.87$ $p<0.005$ group 3). For multilateral assessment of the adequacy of myocardial protection and comparison with the results of electrical impedance, we also used some conventional methods of research.

A direct correlation between the decrease level of electric bioimpedance and myocardial oxygen consumption, after recovery of coronary blood flow has been revealed.

TABLE 4

Time of maximum decrease of Zhf, after recovery of coronary blood flow

	Averagetime	ΔZ-hf	Maximum decrease ΔZ-hf
Group 1	14.9 ±0.7	2.8% ±0.6%	7.5%
Group 2	20.6 ±1.1	6.6% ±1.8%	12.7%
Group 3	18.4 ±0.8	10.3% ±3.2%	24.5%

In 16 patients, the response to non-controlled blood supply through coronary vessels after the cessation of global myocardial ischemia was its “deafening” - myocardial stunning, as confirmed by ECHO, ECG and general clinical methods of study. Decrease in the electric impedance of the myocardium was observed in all patients, in remained 38 patients, a decrease in impedance was observed in only 20%, and the level of decrease was significantly lower than in the first case.

We determined the maximum aortic pinch time at which the decrease in impedance did not precede myocardial “deafening” in each cardioplegic group. As bioimpedance spectroscopy this period of time we named is the time of safe aortic pinch (Fig. 4).

As can be seen from the diagram, blood cardioplegia provides safety for longer aortic pinch than crystalloid cardioplegia variants.

Thus, the results of our study make it possible to draw the following conclusions:

The myocardium electrical impedance makes it possible to estimate the level of filling of the intersti-

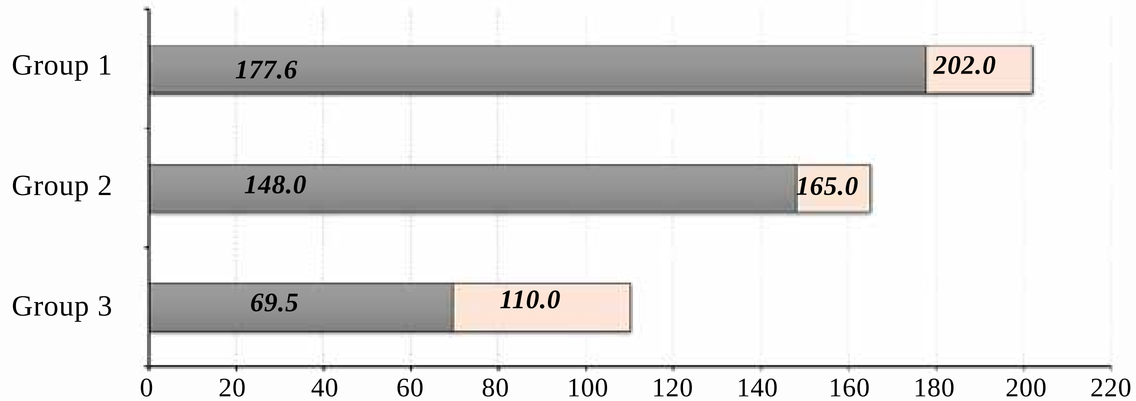

FIGURE 4. Time of safe aortic clamping in each cardioplegic group

tial space during infusion of the cardioplegic solution.

During the retrograde cardioplegia, bioimpedance spectroscopy makes it possible to assess the adequacy of perfusion of the right ventricle anterior wall and to change the route of introduction of the cardioplegic solution if necessary in time.

The decrease in myocardial electrical resistance is one of the early signs of ischemic cardiomyocyte damage, which in real time can predict the level of prior reperfusion damage to varying degrees.

Examination of he electric impedance of the myocardium after the restoration of coronary blood flow allows to assess the level of reperfusion damage to cells and the stage of myocardial edema.

Myocardial electrical impedance study may be a significant addition to already existed methods for heart protection adequacy assesing.

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