MEDICAL UNIVERSITY – PLEVEN

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DEPARTMENT OF SURGICAL DISEASES

Georgi Jordanov Stoitsev, MD

Comparative analysis between classic and modified crystalloid cardioplegic solutions

ABSTRACT

of a dissertation for awarding an educational and scientific degree "Doctor"
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Scientific supervisor:

Assoc. professor Vassil Gegouskov, MD, phd

Official Reviewers:

Assoc. professor Vladimir Kornovski, MD, PhD

Assoc. professor Vassil Velchev, MD, PhD

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The author graduated from the National High School of Natural Sciences and Mathematics in 2002. He holds a Master's degree in Medicine from the Medical University in Sofia in 2008. He completed his specialization in Cardiac Surgery at Medical University Sofia, Department of Cardiac Surgery in 2018.

After graduating from the Medical University of Sofia, Faculty of Public Health, in 2020 he obtained a Master's degree in Health Management. Since 2009 he has been working continuously as a physician in the clinic of Cardiac Surgery at the University Hospital "St. Anna" - Sofia.

By order № 2951/27.11.2018 he was enrolled as a part-time Ph.D. student (government order) in the scientific specialty "General Surgery" at the Department of Surgical Diseases at the Medical University - Pleven.

The dissertation work contains 146 pages, 32 tables, 41 figures. The literature review includes 170 references, of which 1 is in Cyrillic and 169 are in Latin.
The dissertation work has been approved and directed for defense by the extended departmental council of the Department of Surgical Diseases, Faculty of Medicine, Medical University - Pleven. The public defense of the dissertation work will take place on 26.10.2023 at ………. in the ………………. hall at Medical University - Pleven, in accordance with the regulations for the conditions and procedures for acquiring scientific degrees and based on Order No. 2109/25.07.2023г. by Medical University - Pleven, before a scientific jury consisting of:

Scientific jury members: Internal:

Prof. Snejanka Tomova Tisheva-Gospodinova, M.D., D.Sc., University Hospital "Dr. Georgi Stranski" JSC - Pleven, Medical University - Pleven

Assoc. Prof. Pencho Tonchev Tonchev, M.D., University Hospital "Dr. Georgi Stranski" JSC - Pleven, Medical University - Pleven

Reserve member: Prof. D.Sc. Sergey Dimitrov Iliev, M.D., University Hospital "Dr. Georgi Stranski" JSC - Pleven; Medical University - Pleven

External:

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Assoc. Prof. Vasil Dimitrov Velchev, M.D., University Hospital "Sveta Anna" - Sofia, Medical University - Sofia

Assoc. Prof. Vladimir Borisov Kornovski, M.D., "Heart and Brain" Hospital - Burgas; University "Prof. Dr. Asen Zlatarov" - Burgas

Reserve member: Prof. D.Sc. Georgi Todorov Baychev, M.D., Military Medical Academy - Sofia.

Contents

I. Introduction

Demographic changes leading to an increasingly aging and comorbid patient population, as well as the rising complexity of cases with structurally impaired hearts, are increasing the demands on contemporary cardioplegia. The need for combined cardiac interventions is becoming more common. This, in turn, extends the aortic cross-clamp time, subsequently increasing the necessity for adequate and safe myocardial protection. Despite accumulating vast experience, myocardial protection under conditions of total cardiac ischemia during aortic cross-clamping in cardiopulmonary bypass (CPB) surgeries remains one of the most pressing issues. The undeniable successes of modern cardiac surgery and the expansion of indications for operative treatment are associated with the development and improvement of myocardial protection methods. However, not all cardioplegic solutions fully meet the needs of cardiac surgery. This is particularly relevant in cases requiring prolonged aortic cross-clamping in patients with initially impaired myocardial function and in patients with coronary artery disease whose myocardial tolerance to ischemia is significantly reduced. The success of surgical treatment in ischemic disease is largely related to the effectiveness of intraoperative myocardial protection.

Inadequate protection leads to significant cardiac tissue edema, development of ischemic disorders, electrical instability, and stunning, which are the main causes of acute cardiac failure in the early perioperative period. The deficiencies of a given protective method become particularly evident after a prolonged period of aortic cross-clamping. Despite the achievements in the field of cardiac protection, acute cardiac failure accounts for a large share of the overall mortality in patients with intraoperative myocardial ischemia exceeding 80 minutes.

Continual improvement of myocardial protection methods and the diversity of approaches in choosing a cardioplegia type, especially in patients with ischemic heart disease, indicate the lack of an optimal method and affirm the necessity for further research on the issue. This, in turn, justifies the scientific and practical relevance of the study, its aim, and objectives.

II. The aim and objectives of the study

1. Aim

The aim of this dissertation work is to analyze the effectiveness and reliability of modified del Nido cardioplegia (MDN) in adult patients with a moderately long period of cardiac arrest. The study aims to compare MDN with one of the most commonly used classic crystalloid cardioplegic solutions, Kirklin (Laboratorium

Dr G. Bichsel AG) (KN). It combines data from two types of cardiac surgical interventions: aortic valve replacement (AVR) and elective coronary artery bypass grafting (CABG). The primary goal of the research is to examine the qualities of myocardial protection in these two patient groups, analyzing the effectiveness, reliability, and potential drawbacks of the two cardioplegic solutions.

2. Objectives

- Determine the relationship between the used cardioplegia and the occurrence of postoperative myocardial infarction (MI), the need for inotropic support, intra-aortic balloon pump (IABP) assistance, time spent in the intensive care unit, hospital stay, and mortality.
- Investigate the correlation between the cross-clamping time and the need for an additional dose of cardioplegic solution.
- Monitor the dynamics of creatine phosphokinase (CPK) and creatine phosphokinase-MB (CPK-MB) levels pre- and post-operatively.

III. Materials and Methods

1. Study Design

This ambispective clinical-epidemiological study was conducted at the Department of Cardiac Surgery, St. Anna University Hospital, Sofia, Bulgaria. A total of 267 patients who underwent only one of the two types of surgical interventions were examined. Each of the surgical techniques was considered separately, and the reliability of the used protective solutions was investigated for both procedures. Out of the total number of patients, 115 underwent coronary revascularization, while the remaining 152 patients underwent aortic valve surgery due to aortic valve defects. The study included all cases of aortic valve replacement performed between January 2016 and September 2021. To balance the larger number of patients requiring coronary revascularization, the remaining 115 patients who underwent this specific surgical intervention between January 2017 and September 2021 were randomly selected using a random number generator. The patients were divided into two cohorts based on the type of cardioplegia applied during each type of surgical intervention separately.

A. For patients undergoing aortic valve replacement:

Group 1: Patients treated with intermittent cold crystalloid cardioplegia Kirklin (KN, n = 67).

Group 2: Patients treated with modified del Nido cardioplegia (MDN, n = 85).

B. For patients undergoing coronary revascularization:

Following the inclusion and exclusion criteria, 120 patients were initially selected. After further data processing from the group of patients treated with Kirklin cardioplegia, an additional 5 patients were excluded due to the use of on-pump beating heart technique, resulting in a total of 115 patients.

Group 1: Patients treated with intermittent cold crystalloid cardioplegia Kirklin (KN, n = 55).

Group 2: Patients treated with modified del Nido cardioplegia (MDN, n = 60).

2. Inclusion and Exclusion Criteria

A. For patients undergoing aortic valve replacement:

- **Inclusion criteria:**

All patients undergoing aortic valve replacement due to valve defects were included in the study.

- **Exclusion criteria:**
  - Patients undergoing combined surgical interventions:
    - Coronary artery bypass grafting (CABG)
    - Double valve replacement/repair
  - Patients requiring surgical techniques involving vascular prostheses:
    - Bentall de Bono procedure
    - David procedure
    - Yacub procedure
    - Wheat procedure
  - Patients undergoing aortic valve repair.
  - Patients undergoing surgical intervention for ascending aortic dissection.

B. For patients undergoing coronary revascularization:

- **Inclusion criteria:**

All patients undergoing coronary revascularization for ischemic heart disease were included in the study.

- **Exclusion criteria:**

- Patients undergoing combined surgical interventions, as well as patients with post-infarction complications:
    - Valve replacement
    - Ventricular septal defect repair
    - Left ventricular aneurysm repair
- Patients undergoing off-pump beating heart coronary artery bypass grafting without the use of extracorporeal circulation (OPCAB).
- Patients undergoing on-pump beating heart surgical interventions performed under extracorporeal circulation (ECC).

3. Development and Composition of Modified del Nido Cardioplegia

In the early 1990s, Professor Pedro del Nido and his team at the University of Pittsburgh developed a cardioplegic solution to meet the specific needs of neonatal and pediatric cardiac surgery. The solution, now called del Nido cardioplegia (DN), induces depolarization and stops heart function during cardiac surgery. It is a more diluted solution (1:4 blood: crystalloid solution) compared to the traditional blood cardioplegia, where the most commonly used ratio is 4:1 in favor of blood. The distinguishing features of del Nido solution are the reduced content of Ca^{2+} and the addition of the depolarizing agent Lidocaine. The potential practical advantage of DN is that it provides a longer arrest period before a subsequent dose is required. Several reports have been published reporting the clinical experience with the use of DN cardioplegia in adults, showing good results with a single dose or longer intervals between doses.

The concept of creating a simplified del Nido solution is based on previous modifications where the primary solvent is replaced with Ringer's solution instead of the traditionally used Plasma-Lyte (Baxter Healthcare Corporation, Deerfield, IL). It is noteworthy that the previously developed modified cardioplegia solutions always included a blood component in their composition.However, the authors argue that it is not the blood component that is the basis of the proven good results of DN cardioplegia, but rather the reduced concentration of Ca^{2+} in Plasma-Lyte (Baxter Healthcare Corporation, Deerfield, IL). Having a blood component in the classic del Nido cardioplegia leads to the need for additional equipment, which complicates the surgical intervention. To simplify the surgical procedures, a modified solution was developed, based entirely on the electrolyte and drug composition of the del Nido cardioplegic solution, while eliminating the blood component and replacing it with additional $NaHCO_3$. This maneuver aims to preserve the essential buffering function provided by the use of blood.

Composition of MDN

The individual dose of modified del Nido cardioplegia is prepared with the assistance of the hospital pharmacist, and the pharmaceutical composition of the solution includes:

- Plasma-Lyte (Baxter Healthcare Corporation, Deerfield, IL) - 1000 ml
- Mannitol 20% (B.Braun Melsungen AG) - 16 ml (3.2 g)
- $MgSO_4$ 50% (Wörwag Pharma) - 4 g (16 mmol Mg^{2+})
- $NaHCO_3$ 8.4% (B.Braun Melsungen AG) - 20 ml (20 mmol HCO_3^-)
- KCl 14.9% (B.Braun Melsungen AG) - 13 ml (26 mmol K^+)
- Lidocaine 1% (Sopharma pharmaceuticals) - 13 ml (130 mg).

4. Application of Cardioplegia

Each patient from the two surgical groups is visited and consulted by an anesthesiologist at least one day before the surgery for planned interventions. Allergies, medication intolerances, and any difficulties during previous anesthesia are clarified. All patients are prepared for general anesthesia. According to the protocol, all antiplatelet and anticoagulant medications are stopped 4-7 days before hospitalization. In patients with urgent emergency cases or Non-ST segment elevation myocardial infarction (NSTEMI), intravenous infusion of unfractionated heparin is continued until the start of anesthesia. Preoperative medication therapy is reviewed individually and continued until the day of the surgical intervention. If necessary, patient monitoring begins the day before, with a focus on monitoring arterial blood pressure (ABP), heart rate and rhythm, urine output, and oxygen saturation.

Once in the operating room, monitoring is initiated. Initially, ECG, non-invasive ABP, and oxygen saturation are monitored. At least two peripheral venous catheters are placed. Anesthesia induction starts with 2-20 μg/kg fentanyl for analgesia, 0.15-0.3 mg/kg midazolam for sedation, and pipecuronium 80-100 μg/kg for muscle relaxation. The patient is then intubated, and arterial catheter for invasive ABP monitoring, central venous catheter, urethral catheter, nasopharyngeal and rectal thermometers are placed. To continue and maintain anesthesia, intermittent fentanyl (2-5 μg/kg) is applied. After the surgery starts, unfractionated heparin (300-400 IU/kg) is injected intravenously, as per the surgeon's instructions, so that the measured activated clotting time (ACT) is > 400 seconds.

A. For patients undergoing aortic valve replacement:

On the operating table, the patient is placed in a supine position. All surgeries are performed by one lead surgeon and two assisting surgeons. The operative access is through a median or upper partial sternotomy. Usually, venous injection of heparin is administered immediately after sternotomy. After checking the activated clotting time, the cardiopulmonary bypass machine is initiated under systemic normothermia. Once the initially calculated flow rate is reached, the aorta is clamped, and cardiac ischemia begins. Myocardial protection is achieved using either KN or MDN cardioplegia, as follows: In both groups, the heart is arrested using an initial dose (1000 ml) of cold (2-4°C) cardioplegia, delivered antegrade. An additional dose of cardioplegia is administered through the coronary ostia, with KN group receiving it every 45 minutes. A second dose (500 ml) of MDN is provided only when the aortic cross-clamp time exceeds 60 minutes. An initial double dose is given at the operator's discretion in cases with massive myocardial hypertrophy.

B. For patients undergoing coronary revascularization:

Again, the patient is in a supine position. The operative access is through a median sternotomy. After reaching the target values of the activated clotting time, the cardiopulmonary bypass is initiated. The aorta is clamped once the initially calculated flow rate is achieved. In both groups, the heart is arrested using an initial dose (1000 ml) of cold (2-4°C) cardioplegia, delivered antegrade. An additional dose of cardioplegia is administered in the aortic root and/or through the grafts, with KN group receiving it every 30 minutes. A second dose (500 ml) of MDN is provided only when the aortic cross-clamp time exceeds 50 minutes. An initial double dose is given at the operator's discretion in cases with acute coronary syndrome.

5. **Demographic Characteristics**

A. For patients undergoing aortic valve replacement:

The studied clinical cohort has an average age of 65.22 ±10.36 years within the range of 31 to 90 years. Out of the participants included in the study, 87 (57.2%) are male, and 65 (42.8%) are female (Figure 1).

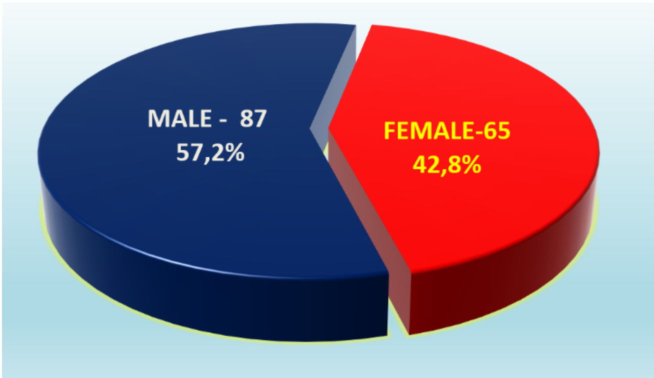

Figure 1: Frequency distribution of the studied cohort by gender

The age group with the highest number (39) of male participants is 60-69 years, followed by 70-79 years with 19, and the lowest number (1) is in the 30-39 years age group. Among females, the age group with the highest number (32) is 70-79 years, followed by 60-69 years with 23, and the lowest numbers (1 each) are in the 30-39 and 40-49 years age groups (Figure 2).

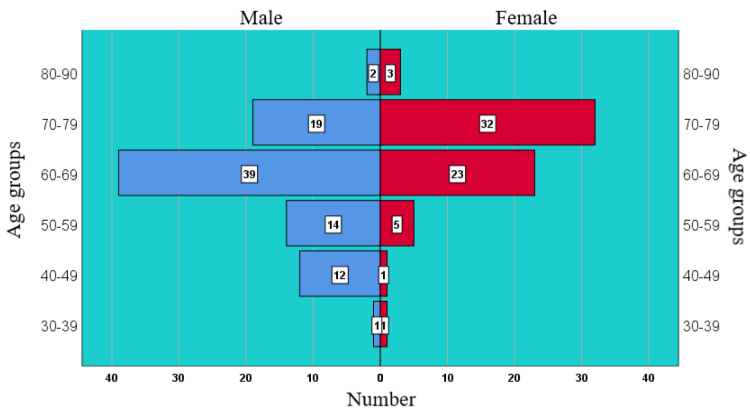

Figure 2: Distribution of study participants by gender and age groups

B. For patients undergoing coronary revascularization:

The studied clinical cohort has an average age of 64.16± 9.15 years within the range of 40 to 81 years. Out of the participants included in the study, 79 (68.7%) are male, and 36 (31.3%) are female (Figure 3).

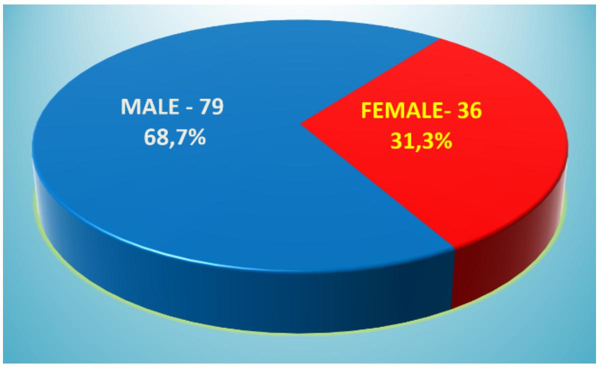

Figure 3: Frequency distribution of the studied cohort by gender

The age group with the highest number (31) of male participants is 60-69 years, followed by 50-59 and 70-79 years with 20 each, and the lowest number (1) is in the 80-81 years age group. Among females, the age group with the highest number (17) is 60-69 years, followed by 70-79 years with 17, and the lowest number (1) is in the 40-49 years age group (Figure 4).

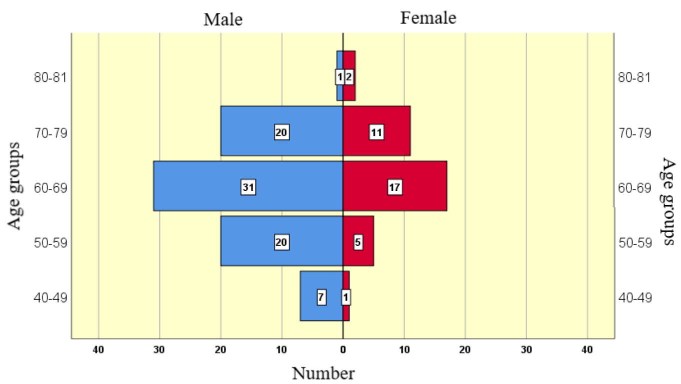

Figure 4: Distribution of study participants by gender and age groups

6. Statistical methods

The data were entered and processed using the statistical packages IBM SPSS Statistics 25.0 and MedCalc Version 19.6.3, as well as Excel from Office 2021. A significance level of p<0.05 was adopted, where the null hypothesis is rejected.

The following methods were applied:

1. Descriptive analysis - The frequency distribution of the variables under study is presented in tabular form.
2. Graphical analysis - Visualization of the obtained results.
3. Comparison of relative proportions.
4. Fisher's exact test, Fisher-Freeman-Halton exact test, and Chi-square test - Used to test hypotheses for the presence of dependencies between categorical variables.
5. Kolmogorov-Smirnov and Shapiro-Wilk tests - Used to test the normality of distributions.
6. Paired samples t-test (Student's t-test for paired samples) - Used to test hypotheses for differences between the means of two dependent samples.
7. Mann-Whitney U test - Used to test hypotheses for differences between two independent samples.
8. Wilcoxon signed-rank test - Used to test hypotheses for differences between two dependent samples.
9. Regression analysis - Used to test hypotheses for the presence of dependencies between quantitative variables and to select appropriate mathematical models.
10. Friedman test - Used to test hypotheses for differences between multiple dependent samples.
11. Multiple linear regression analysis - Used to test hypotheses for dependencies of one quantitative variable on several other variables.

IV. Results

1. Descriptive statistics

A. For patients undergoing aortic valve replacement

For the purposes of this study, the patients were divided into two therapeutic groups (Figure 5):

Classical cardioplegia KN – n=67 (44.1%)

Modified cardioplegia MDN – n=85 (55.9%).

[Note: The description states that the patients undergoing aortic valve replacement are divided into two therapeutic groups: the classical cardioplegia (KN) group with 67 patients (44.1%) and the modified cardioplegia (MDN) group with 85 patients (55.9%).].

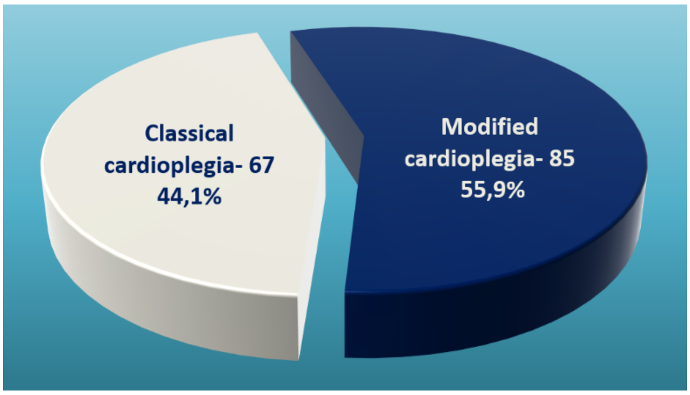

Figure 5: Frequency distribution of the study cohort by therapeutic groups for patients undergoing aortic valve replacement.

B. For patients undergoing coronary revascularization

For the purposes of this study, the patients were divided into two therapeutic groups (Figure 6):

Classical cardioplegia KN – n=55 (47.8%)

Modified cardioplegia MDN – n=60 (52.2%).

[Note: The description states that the patients undergoing coronary revascularization are divided into two therapeutic groups: the classical cardioplegia (KN) group with 55 patients (47.8%) and the modified cardioplegia (MDN) group with 60 patients (52.2%).].

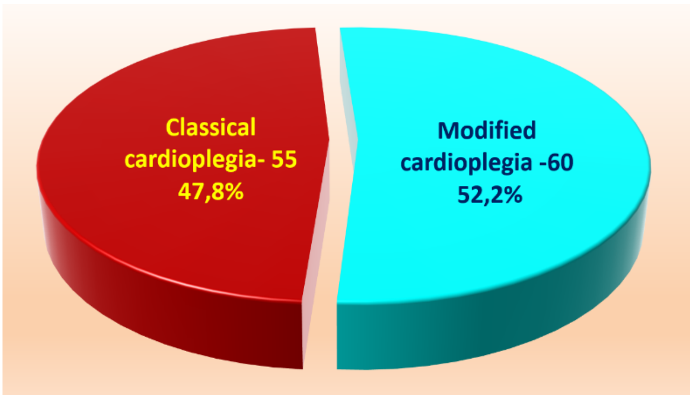

Figure 6: Frequency distribution of the study cohort by therapeutic groups.

2. **General characteristics of the groups**

A. For patients undergoing aortic valve replacement:

1. Table 1 shows that:

- The mean age of the group with classical cardioplegia is 65.87±9.49, and for those with modified cardioplegia, it is 64.71±11.03. The difference between them is statistically insignificant.
- The mean value of the study cohort for BMI is 28.22±4.87 kg/m2, and the difference between the two therapeutic groups is not statistically significant.
- The two study groups are statistically balanced regarding known confounding factors such as gender and age, which provides a proper basis for subsequent comparisons

Index	**Total**		**Classical cardioplegia**		**Modified cardioplegia**		**P**
	$\overline{X}$	SD	$\overline{X}$	SD	$\overline{X}$	SD	
Age (years)	65,22	10,36	65,87	9,49	64,71	11,03	0,396
BMI (kg/m^2)	28,22	4,87	27,56	3,89	28,73	5,49	0,126
	n	**%**	**n**	**%**	**n**	**%**	
Gender							1,000
Men	87	57,2	38	56,7	49	57,6	
Women	65	42,8	29	43,3	36	42,4	

Table 1: Comparative analysis of the study groups based on age, BMI, and gender

2. Regarding the investigated preoperative quantitative characteristics (Table 2):

- A statistically significant difference between the two therapeutic groups is observed in the indicators of creatinine clearance, creatine phosphokinase-MB fraction, peak and mean gradient.

  Higher mean values are observed in the group with modified cardioplegia.
- For the remaining indicators included in the table - Euroscore, hemoglobin, erythrocytes, creatinine, creatine phosphokinase (CPK), left

ventricular ejection fraction (LVEF), and left ventricular hypertrophy (HLV), the difference between the two groups is statistically insignificant.

Index	Classical cardioplegia			Modified cardioplegia			P
	n	$\overline{X}$	SD	n	$\overline{X}$	SD	
Euroscore (%)	64	4,96	4,10	77	4,58	4,00	0,439
Hemoglobin (g/l)	67	133,64	18,71	85	134,66	21,09	0,757
Erythrocytes (g/l)	67	4,53	0,63	85	4,57	0,58	0,771
Creatinine (µmol/l)	64	99,38	19,73	83	99,14	26,64	0,537
Creatinine clearance (ml/min)	67	68,91	24,81	84	75,52	30,41	**0,038**
CPK (U/l)	66	100,23	57,32	83	122,24	60,14	0,152
CPK-MB (U/l)	62	15,71	9,26	77	18,70	10,48	**0,011**
LVEF (%)	67	54,07	9,81	85	55,66	9,30	0,406
Peak gradient (mmHg)	56	66,50	22,63	66	79,86	28,25	**0,003**
Mean gradient (mmHg)	56	36,48	14,14	66	44,09	16,98	**0,006**
left ventricular hypertrophy (mm)	67	14,28	2,16	85	14,69	2,32	0,324

Table 2: Comparative analysis of the therapeutic groups based on the investigated preoperative quantitative characteristics

3. The conducted comparative analysis of the therapeutic groups based on the investigated preoperative categorical characteristics reveals (Table 3) that:

- A significant difference is observed only in the indicator of preoperative atrial fibrillation (AF), with a higher relative proportion in the group with classical cardioplegia.
- For the remaining indicators included in the table - diabetes mellitus (DM), myocardial infarction, stroke, balloon dilatation/stent, pacemaker, aortic regurgitation, mitral regurgitation, and pulmonary hypertension, the difference between the two groups is statistically insignificant.

Index	Classical cardioplegia		Modified cardioplegia		P
	n	%	n	%	
DM	16	23,9	18	21,2	0,700
Myocardial infarction	5	7,5	5	5,9	0,750
Stroke	3	4,5	4	4,7	1,000
Preoperative AF	23	34,3	12	14,1	**0,004**
Balloon dilatation/stent	6	9,0	7	8,2	1,000
Pacemaker	4	6,0	1	1,2	0,170
Aortic insufficiency					0,660
Absence	18	26,9	26	30,6	
1 grade	11	16,4	17	20,0	
2 grade	14	20,9	10	11,8	
3 grade	21	31,3	28	32,9	
4 grade	3	4,5	4	4,7	
Mitral insufficiency	30	44,8	44	51,8	0,418
Pulmonary hypertension	13	19,4	10	11,8	0,255

Table 3: Comparative analysis of the therapeutic groups based on the investigated preoperative categorical characteristics

B. For patients undergoing coronary revascularization

1.Table 4 shows that:

- The mean age of the group with classical cardioplegia is 65.47±9.15, and for those with modified cardioplegia, it is 62.95±9.25. The difference between them is statistically insignificant.
- The mean value of the study population by BMI is 28.95±5.18 kg/m2, and the difference between the two therapeutic groups is not statistically significant.
- The two study groups are statistically balanced regarding known confounding factors such as gender and age, which provides a proper basis for subsequent comparisons.

Index	Total		Classical cardioplegia		Modified cardioplegia		P
	$\overline{X}$	SD	$\overline{X}$	SD	$\overline{X}$	SD	
Age (years)	64,16	9,15	65,47	8,93	62,95	9,25	0,140
BMI (kg/m2)	28,95	5,18	28,17	4,98	29,67	5,29	0,121
	n	**%**	**n**	**%**	**n**	**%**	
Gender							0,548
Men	79	68,7	36	65,5	43	71,7	
Women	36	31,3	19	34,5	17	28,3	

Table 4: Comparative analysis of the study groups based on age, BMI, and gender

2.Regarding the investigated preoperative quantitative characteristics (Table 5):

- A statistically significant difference between the two therapeutic groups is observed in the indicators of creatinine and creatinine clearance.
- The higher mean value of creatinine is observed in the group with classical cardioplegia, while the higher mean value of creatinine clearance is observed in the group with modified cardioplegia.
- For the remaining indicators included in the table - Euroscore, hemoglobin, erythrocytes, creatine phosphokinase, creatine phosphokinase-MB fraction, ejection fraction, and left ventricular hypertrophy, the difference between the two groups is statistically insignificant.

Index	Classical cardioplegia			Modified cardioplegia			P
	n	$\overline{X}$	SD	n	$\overline{X}$	SD	
Euroscore (%)	51	4,57	3,85	60	5,16	4,68	0,929
Hemoglobin (g/l)	55	137,93	16,18	60	137,73	18,47	0,953
Erythrocytes (g/l)	55	4,63	0,61	60	4,69	0,56	0,569
Creatinine (µmol/l)	51	108,78	32,21	57	94,81	22,57	**0,011**
Creatinine clearance (ml/min)	54	67,26	28,41	60	83,67	35,02	**0,007**
CPK (U/l)	51	135,22	104,78	58	131,87	79,84	0,540
CPK-MB (U/l)	51	20,02	13,21	57	19,77	12,27	0,626
LVEF (%)	55	50,33	8,68	60	53,33	9,31	0,050
left ventricular hypertrophy (mm)	55	9,62	6,04	60	9,32	6,19	0,735

Table 5: Comparative analysis of the therapeutic groups based on the investigated preoperative quantitative characteristics

3.The conducted comparative analysis of the therapeutic groups based on the investigated preoperative categorical characteristics reveals (Table 6) that:

- A significant difference is observed only in the indicator of preoperative atrial fibrillation (AF).

  The group with classical cardioplegia has a significantly higher percentage of patients with preoperative atrial fibrillation.

- For the remaining indicators included in the table - diabetes mellitus (DM), myocardial infarction, stroke, balloon dilatation/stent, chronic kidney failure (CKD), mitral regurgitation, pulmonary hypertension, and presence of stenosis of the common trunk of the left coronary artery (SCTLCA), the difference between the two groups is statistically insignificant.

Index	Classical cardioplegia		Modified cardioplegia		P
	n	%	n	%	
DM					0,458
Absence	28	50,9	26	43,3	
Presence	27	49,1	34	56,7	
Myocardial infarction					
Absence	27	49,1	39	65,0	
Acute	9	16,4	6	10,0	
Experience	19	34,5	15	25,0	
Stroke	7	12,7	3	5,0	0,190
Preoperative AF	9	16,4	2	3,3	**0,025**
Balloon dilatation/stent	12	21,8	11	18,3	0,650
CKD	8	14,5	5	8,3	0,381
Mitral insufficiency	26	47,3	24	40,0	0,457
Pulmonary hypertension	7	12,7	4	6,7	0,348
SCTLCA	23	41,8	19	31,7	0,333

Table 6: Comparative analysis of the therapeutic groups based on the investigated preoperative categorical characteristics

3. **Study of the relationship between aortic cross-clamp time and the need for an additional dose of cardioplegia**

A. For patients undergoing aortic valve replacement

The average aortic cross-clamp time for patients with modified cardioplegia is approximately 64±15 minutes, which is statistically significantly higher than that for classical cardioplegia (59±14 minutes) (Table 7). The need for an additional dose of cardioplegia has arisen in about 1/4 of the cases, with the difference in the relative proportions of the two types of cardioplegia being statistically insignificant (Table 8).

Index	Classical cardioplegia			Modified cardioplegia			P
	n	$\overline{X}$	SD	n	$\overline{X}$	SD	
Cross-clamp time (min.)	64	59,25	13,97	84	64,33	15,43	**0,029**

Table 7: Comparative analysis of the therapeutic groups based on aortic cross-clamp time.

Need for an additional dose cardioplegia	Classical cardioplegia		Modified cardioplegia		P
	n	%	n	%	
No	50	74,6	63	74,1	1,000
Yes	17	25,4	22	25,9	

Table 8: Comparative analysis of the therapeutic groups based on the need for an additional dose of cardioplegia

B. For patients undergoing coronary revascularization

The average aortic cross-clamp time for patients with modified cardioplegia is approximately 60±13 minutes, which is statistically significantly higher than that for classical cardioplegia (48±12 minutes) (Table 9). The need for an additional dose of cardioplegia has arisen in 60% of patients with classical cardioplegia and in 48.3% of patients with modified cardioplegia, but the difference in the relative proportions is statistically insignificant (Table 10).

Index	Classical cardioplegia			Modified cardioplegia			P
	n	$\overline{X}$	SD	n	$\overline{X}$	SD	
Cross-clamp time (min.)	55	47,76	11,60	60	59,75	13,13	**<0,001**

Table 9: Comparative analysis of the therapeutic groups based on aortic cross-clamp time.

Need for an additional dose cardioplegia	Classical cardioplegia		Modified cardioplegia		P
	n	%	n	%	
No	22	40,0	31	51,7	0,262
Yes	33	60,0	29	48,3	

Table 10: Comparative analysis of the therapeutic groups based on the need for an additional dose of cardioplegia

4. Comparative analysis of the therapeutic groups based on the investigated quantitative and categorical intra- and postoperative characteristics

A. For patients undergoing aortic valve replacement

1.The conducted comparative analysis of the therapeutic groups based on the investigated categorical intra- and postoperative characteristics reveals (Table 11) that:

- A significant difference is observed only in the need for inotropic support – moderate doses are significantly more required in classical cardioplegia, while in modified cardioplegia, there is no need for inotropic support at discharge.
- For the remaining indicators included in the table: the need for DC shocks, frequency of IABP usage, new-onset atrial fibrillation, new-onset myocardial infarction, new-onset stroke, and mortality, the difference between the two groups is statistically insignificant.

Categorical Index	Classical cardioplegia		Modified cardioplegia		P
	n	%	n	%	
DC shocks need	5	7,5	4	4,7	0,508
Need for inotropic support					**<0,001**
Absence during discharge	44	65,7	77	90,6	
Moderate doses	22	32,8	7	8,2	
High doses	1	1,5	1	1,2	
Frequency of IABP usage	2	3,0	1	1,2	0,583
New-onset atrial fibrillation	4	6,0	2	2,4	0,406
New-onset myocardial infarction	0	0,0	0	0,0	-
New-onset stroke	0	0,0	0	0,0	-
Mortality	4	6,0	2	2,4	0,460

Table 11: Comparative analysis of the therapeutic groups based on the investigated categorical intra- and postoperative characteristics

2.Regarding the investigated quantitative intra- and postoperative characteristics (Table 12):

- A statistically significant difference between the two therapeutic groups is observed in the indicators of creatine phosphokinase upon admission to an intensive care unit (CPK0), creatine phosphokinase-MB fraction upon admission to an intensive care unit (MB0), extracorporeal circulation (CPB), intensive care unit stay, and hospital stay.
- Higher mean values for the first three indicators are observed in the group with modified cardioplegia, while for the last two indicators, they are observed in the group with classical cardioplegia.
- For the remaining indicators included in the table - creatine phosphokinase 24 hours after admission to an intensive care unit (CPK24), creatine phosphokinase-MB fraction 24 hours after admission to an intensive care unit (MB24), creatinine clearance after admission to an intensive care unit (CrCl post), and creatinine after admission to an

intensive care unit (Creat. Post), the difference between the two groups is statistically insignificant.

Quantitative Index	**Classical cardioplegia**			**Modified cardioplegia**			**P**
	n	$\overline{X}$	SD	n	$\overline{X}$	SD	
CPK0	66	509,11	262,14	84	649,38	292,66	**0,001**
MB0	64	50,55	18,93	85	68,32	22,21	**<0,001**
CPK24	65	801,31	528,87	83	766,43	442,54	1,000
MB24	66	43,61	26,63	82	39,38	14,82	0,588
CrCl post	67	66,73	29,01	85	68,33	30,96	0,687
Creat. Post (µmol/l)	64	107,73	25,99	82	111,93	29,72	0,383
CPB (min)	64	93,47	24,80	84	101,35	24,10	**0,023**
Stay in the ICU (days)	67	5,22	2,69	85	3,86	2,89	**<0,001**
Hospital stay (days)	67	11,99	3,03	85	11,11	3,48	**0,020**

Table 12: Comparative analysis of the therapeutic groups based on the investigated quantitative intra- and postoperative characteristics

B. For patients undergoing coronary revascularization

1.The conducted comparative analysis of the therapeutic groups based on the investigated categorical intra- and postoperative characteristics reveals (Table 13) that:

- A significant difference is observed in the need for inotropic support and the use of IABP - significantly more in moderate and high doses, as well as the use of IABP, in classical cardioplegia, while in modified cardioplegia, there is no need for inotropic support at discharge.
- For the remaining indicators included in the table: the need for DC shocks, new-onset atrial fibrillation, new-onset myocardial infarction, and mortality, the difference between the two groups is statistically insignificant.

Categorical Index	Classical cardioplegia		Modified cardioplegia		P
	n	%	n	%	
DC shocks need	9	16,4	5	8,3	0,256
Need for inotropic support					**<0,001**
Absence during discharge	9	16,4	31	51,7	
Moderate doses	30	54,5	22	36,7	
High doses	16	29,1	7	11,7	
Frequency of IABP usage	12	21,8	4	6,7	**0,029**
New-onset atrial fibrillation	3	5,5	1	1,7	0,348
New-onset myocardial infarction	4	7,3	2	3,3	0,424
Mortality	5	9,1	2	3,3	0,257

Table 13: Comparative analysis of the therapeutic groups based on the investigated categorical intra- and postoperative characteristics

2.Regarding the investigated quantitative intra- and postoperative characteristics (Table 14):

- A statistically significant difference between the two therapeutic groups is observed only in MB0 - the higher mean value is in the group with modified cardioplegia.
- For the remaining indicators included in the table - creatine phosphokinase upon admission to an intensive care unit, CPK24, MB24, creatinine clearance after admission to an ICU (CrCl post), creatinine after admission to an ICU (Creat. post), extracorporeal circulation, intensive care unit stay, and hospital stay, the difference between the two groups is statistically insignificant.

Quantitative Index	Classical cardioplegia			Modified cardioplegia			P
	n	$\overline{X}$	SD	n	$\overline{X}$	SD	
CPK0	52	579,04	296,64	57	654,98	284,42	0,089
MB0	52	62,75	32,06	58	67,64	16,40	**0,045**
CPK24	52	1040,31	701,14	58	1033,40	727,08	0,808
MB24	51	59,39	53,51	58	63,45	45,41	0,251
CrCl post	55	63,10	24,03	60	72,45	30,86	0,074
Creat. post (µmol/l)	55	133,95	123,76	60	117,88	41,81	0,769
CPB (min)	55	101,56	45,49	58	101,95	25,29	0,073
Stay in the ICU (days)	52	3,75	1,79	59	3,64	1,88	0,726
Hospital stay (days)	52	11,46	3,64	59	11,61	4,25	0,169

Table 14: Comparative analysis of the therapeutic groups based on the investigated quantitative intra- and postoperative characteristics

5. Comparative analysis of the surgical approach, type of used prosthesis (biological/mechanical), and average prosthesis size in patients undergoing aortic valve replacement.

Table 15 shows that:

- The two therapeutic groups do not differ significantly in terms of the type of used prosthesis - almost all cases involve mechanical prostheses, but there is a significant difference in the surgical approach;
- For classical cardioplegia, the conventional approach is significantly more applied (in about 48% vs. 2%) compared to modified cardioplegia, where the minimally invasive approach is predominantly used (in about 98% vs. 52%).
- The average size of the used prostheses in both groups is approximately 21-22±2 mm. The difference in this indicator is statistically insignificant (Table 16).

Index	Classical cardioplegia		Modified cardioplegia		P
	n	%	n	%	
Type of used prosthesis					0,631
mechanical	66	98,5	82	96,5	
biological	1	1,5	3	3,5	
Surgical approach					**<0,001**
conventional	32	47,8	2	2,4	
minimally invasive	35	52,2	83	97,6	

Table 15: Comparative analysis of the therapeutic groups based on the type of used prostheses and surgical approach.

Index	Classical cardioplegia			Modified cardioplegia			P
	n	$\overline{X}$	SD	n	$\overline{X}$	SD	
Average prosthesis size (mm)	67	21,87	2,21	85	21,40	2,22	0,173

Table 16: Comparative analysis of the therapeutic groups based on the prosthesis size

6. Comparative analysis of the average number of distal anastomoses and the frequency of incomplete anastomoses in patients undergoing coronary surgery.

Table 17 and 18 show that the two therapeutic groups do not differ significantly in terms of the number of distal anastomoses and the proportion of incomplete anastomoses.

The percentage of incomplete anastomoses in the classical cardioplegia group is higher (18.2%) compared to 11.7% in the modified cardioplegia group, but this difference is only algebraically significant.

The average number of used distal anastomoses in the classical cardioplegia group is 2.82±0.70, and in the modified cardioplegia group, it is 2.73±0.61.

Index	Classical cardioplegia		Modified cardioplegia		P
	n	%	n	%	
Number of distal anastomoses					0,207
1	0	0,0	1	1,7	
2	19	34,5	18	30,0	
3	27	49,1	37	61,7	
4	9	16,4	4	6,7	
Incomplete anastomoses	10	18,2	7	11,7	0,432

Table 17: Comparative analysis of the therapeutic groups based on the number of distal anastomoses and incomplete anastomoses.

Index	Classical cardioplegia			Modified cardioplegia			P
	n	$\overline{X}$	SD	n	$\overline{X}$	SD	
Average number of distal	55	2,82	0,70	60	2,73	0,61	0,639

Table 18: Comparative analysis of the therapeutic groups based on the number of distal anastomoses

7. Study of the relationship between pre- and postoperative ejection fraction, creatinine, and creatinine clearance between the two cardioplegia groups.

A. For patients undergoing aortic valve replacement

Table 19 shows that:

- There is no significant difference between the pre- and postoperative ejection fraction values for both types of cardioplegia.
- The conducted statistical analysis found a statistically significant postoperative increase in creatinine values compared to the preoperative values. This is observed in both therapeutic groups.

- Regarding creatinine clearance, both types of cardioplegia show a reduction in values, but only in the modified cardioplegia group, this reduction is statistically significant.

Index	Cardioplegia Type	n	Preoperative		Postoperative		P
			$\overline{X}$	SD	$\overline{X}$	SD	
Ejection fraction (%)	Classical cardioplegia	67	54,07	9,81	52,94	8,80	0,134
	Modified cardioplegia	83	55,59	9,38	56,02	7,28	0,721
Creatinine (µmol/l)	Classical cardioplegia	63	100,05	19,13	106,51	24,26	**0,005**
	Modified cardioplegia	82	98,54	26,22	111,93	29,72	**<0,001**
Creatinine clearance (ml/min)	Classical cardioplegia	67	68,91	24,81	66,73	29,01	0,057
	Modified cardioplegia	84	75,52	30,41	67,19	29,31	**<0,001**

Table 19: Comparative analysis of pre- and postoperative values of ejection fraction, creatinine, and creatinine clearance for both types of cardioplegia.

For solving this task, a regression analysis was additionally applied.

1.Ejection Fraction

Classical Cardioplegia:

The conducted regression analysis revealed that out of the eleven models embedded in the statistical software IBM SPSS Statistics 25.0, the dependence between pre- and postoperative ejection fraction is best described by the following equation (R^2=0.584, p<0.001):

LVEF post = 3,743LVEF^{0,663}

Where LVEF post represents the postoperative ejection fraction, and LVEF represents the preoperative ejection fraction. The curve of the equation increases at a constant angle of approximately 40 degrees. The value of the coefficient of determination (R^2) shows that about 58% of the variations in the studied indicator after the surgery depend on its values before the operation, and the remaining 42% is influenced by other factors (Figure 7).

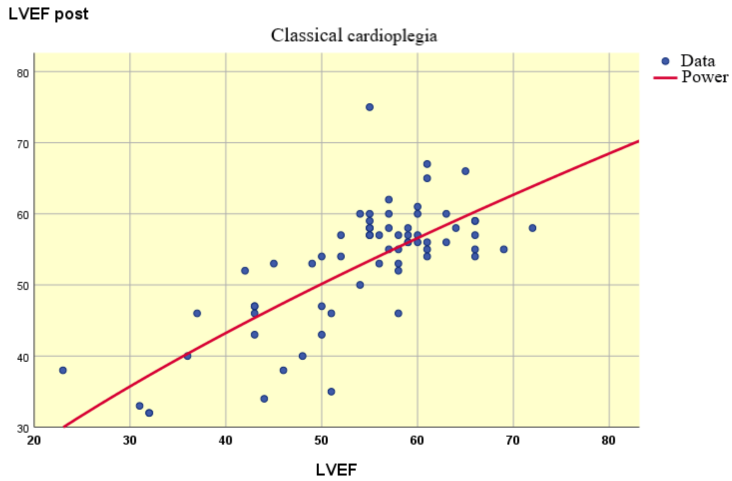

Figure 7: Regression model of the dependence between pre- and postoperative ejection fraction for classical cardioplegia.

Modified Cardioplegia:

The conducted regression analysis revealed that out of the eleven models embedded in the statistical software IBM SPSS Statistics 25.0, the dependence between pre- and postoperative ejection fraction is best described by the following equation (R^2=0.444, p<0.001):

LVEF post = 7,193LVEF^{0,511}

Where LVEF post represents the postoperative ejection fraction, and LVEF represents the preoperative ejection fraction. The curve of the equation increases at a constant angle of approximately 40 degrees. The value of the coefficient of determination (R^2) shows that about 44% of the variations in the studied indicator after the surgery depend on its values before the operation, and the remaining 56% is influenced by other factors (Figure 8).

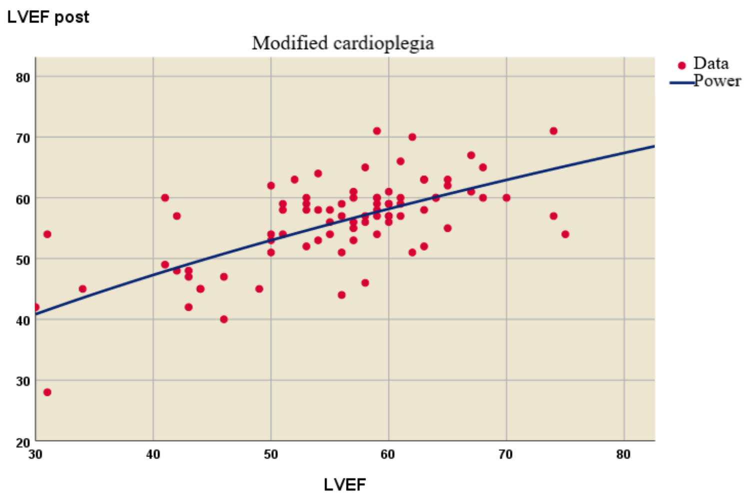

Figure 8: Regression model of the dependence between pre- and postoperative ejection fraction for modified cardioplegia.

2.Creatinine

For classical cardioplegia:

The conducted regression analysis revealed that out of the eleven models embedded in the statistical software IBM SPSS Statistics 25.0, the dependence between pre- and postoperative creatinine is best described by the following linear equation ($R^2=0.473$, $p<0.001$):

Creatinine post = 19.280 + 0.872Creatinine.

Where Creatinine post represents the postoperative creatinine, and Creatinine represents the preoperative creatinine. The curve of the equation increases at a constant angle of approximately 40 degrees. In the regression equation, the coefficient before the argument indicates that with an increase of one µmol/L in Creatinine, Creatinine post statistically increases by an average of 0.872 µmol/L. The value of the coefficient of determination (R^2) shows that about 47% of the variations in the studied indicator after the surgery depend on its values before the operation, and the remaining 53% is influenced by other factors (Figure 9).

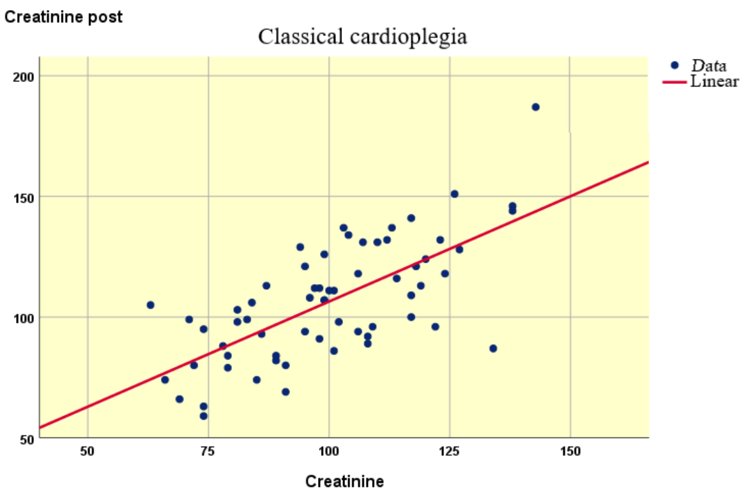

Figure 9: Regression model of the dependence between pre- and postoperative creatinine for classical cardioplegia.

For modified cardioplegia:

The conducted regression analysis revealed that out of the eleven models embedded in the statistical software IBM SPSS Statistics 25.0, the dependence between pre- and postoperative creatinine is best described by the following linear equation (R^2=0.525, p<0.001):

Creatinine post = 30.961 + 0.822Creatinine.

Where Creatinine post represents the postoperative creatinine, and Creatinine represents the preoperative creatinine. The curve of the equation increases at a constant angle of approximately 40 degrees. In the regression equation, the coefficient before the argument indicates that with an increase of one µmol/L in Creatinine, Creatinine post statistically increases by an average of 0.822 µmol/L. The value of the coefficient of determination (R^2) shows that about 52% of the variations in the studied indicator after the surgery depend on its values before the operation, and the remaining 48% is influenced by other factors (Figure 10).

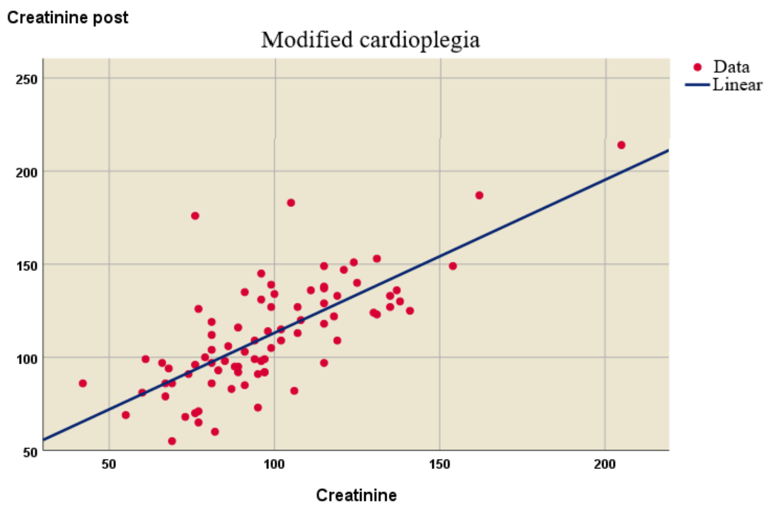

Figure 10: Regression model of the dependence between pre- and postoperative creatinine for modified cardioplegia.

3.Creatinine clearance

For classical cardioplegia:

The conducted regression analysis revealed that out of the eleven models embedded in the statistical software IBM SPSS Statistics 25.0, the dependence between pre- and postoperative creatinine clearance is best described by the following power equation (R^2=0.842, p<0.001):

CrCl post = 1,167CrCl^{0,951}

Where CrCl post represents the postoperative creatinine clearance, and CrCl represents the preoperative creatinine clearance. The curve of the equation increases at a constant angle of approximately 35 degrees. The value of the coefficient of determination (R^2) shows that about 84% of the variations in the studied indicator after the surgery depend on its values before the operation, and the remaining 16% is influenced by other factors (Figure 11).

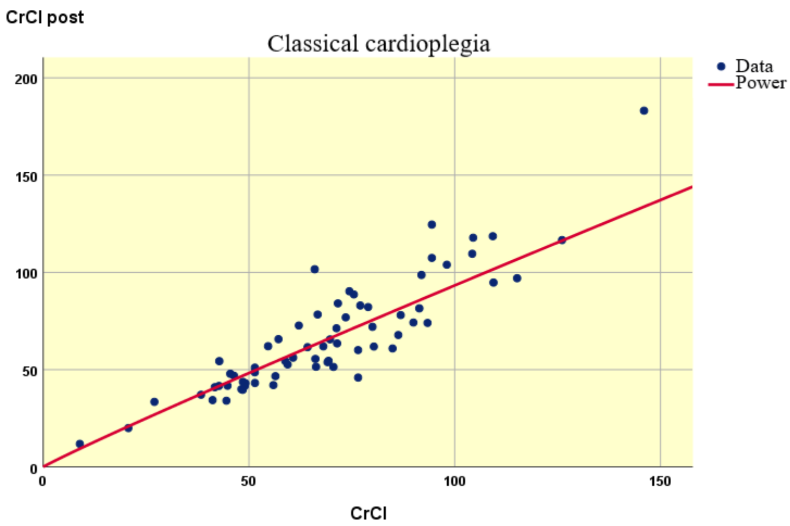

Figure 11: Regression model of the relationship between pre- and postoperative creatinine clearance in classical cardioplegia

For modified cardioplegia:

The conducted regression analysis established that out of the eleven models fitted in the statistical package IBM SPSS Statistics 25.0, the dependency between pre- and postoperative creatinine clearance is best described by the following equation (R^2=0.824, p<0.001):

$CrCl\ post = 1{,}158CrCl^{0{,}936}$

where CrCl post represents the postoperative creatinine clearance, and CrCl is the preoperative creatinine clearance. The curve of the equation increases steadily at an angle of approximately 35 degrees. The coefficient of determination (R^2) value indicates that around 82% of the variations in the investigated parameter after the operation depend on its preoperative values, while the remaining 18% is influenced by other factors (Figure 12).

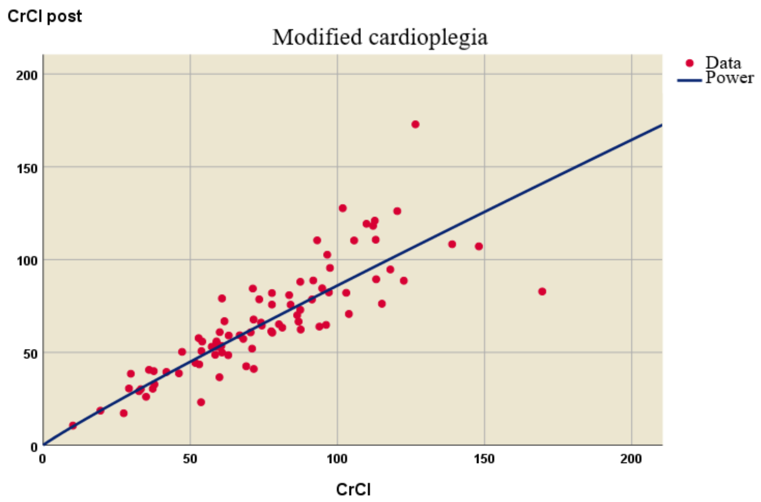

Figure 12: Regression model of the relationship between pre- and postoperative creatinine clearance in modified cardioplegia

B. For patients undergoing coronary revascularization

Table 20 reveals the following findings:

- There is no significant difference between pre- and postoperative **ejection fraction** values in both types of cardioplegia.
- An increase in **creatinine** values is observed in both types of cardioplegia, but it is statistically significant only in the group subjected to modified cardioplegia.
- The conducted statistical analysis identified a statistically significant postoperative decrease in **creatinine clearance** values compared to preoperative values. This observation is consistent in both therapeutic groups.

Index	Cardioplegia Type	n	Preoperative		Postoperative		P
			$\overline{X}$	SD	$\overline{X}$	SD	
Ejection fraction (%)	Classical cardioplegia	52	50,69	8,66	49,54	7,84	0,398
	Modified cardioplegia	59	53,27	9,37	52,39	8,46	0,358
Creatinine (µmol/l)	Classical cardioplegia	51	108,78	32,21	113,38	29,68	0,150
	Modified cardioplegia	57	94,81	22,57	111,04	25,74	**<0,001**
Creatinine clearance (ml/min)	Classical cardioplegia	54	67,26	28,41	62,79	24,14	**0,048**
	Modified cardioplegia	60	83,67	35,02	72,45	30,86	**<0,001**

Table 20: Comparative analysis of pre- and postoperative values of ejection fraction, creatinine, and creatinine clearance for both types of cardioplegia.

To solve this task, an additional regression analysis was applied.

1. **Ejection Fraction:**

Classical Cardioplegia

The conducted regression analysis, using the built-in statistical package IBM SPSS Statistics 25.0, determined that out of the eleven models, the relationship between pre- and postoperative ejection fraction is best described by the linear equation (R^2=0.586, p<0.001):

LVEF post = 14.419 + 0.693LVEF

where LVEF post represents the postoperative ejection fraction, and LVEF is the preoperative ejection fraction. The curve of the equation increases steadily at an angle of approximately 40 degrees. The coefficient before LVEF indicates that, on average, LVEF post increases by about 0.7% for every 1% increase in LVEF. According to the value of the coefficient of determination (R^2), approximately 59% of the variations in the investigated parameter after the operation depend on its preoperative values, while the remaining 41% are influenced by other factors (Figure 13).

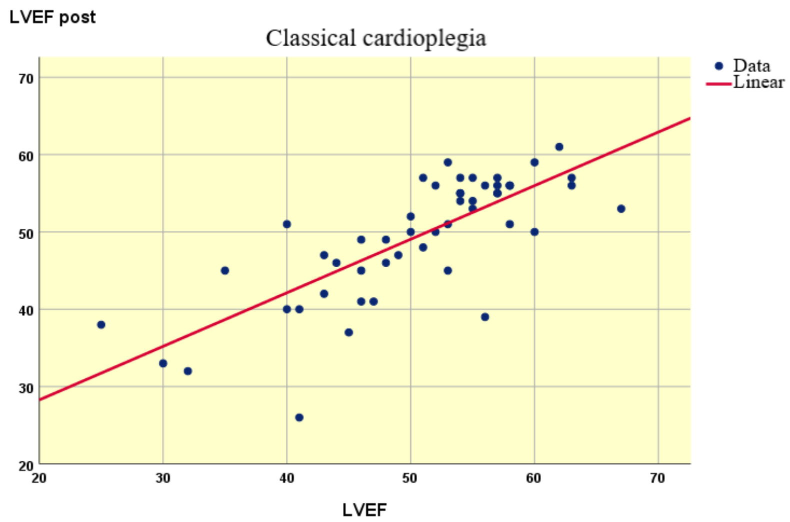

Figure 13: Regression model of the relationship between pre- and postoperative ejection fraction in classical cardioplegia

Modified cardioplegia

The conducted regression analysis, using the built-in statistical package IBM SPSS Statistics 25.0, determined that out of the eleven models, the relationship between pre- and postoperative ejection fraction is best described by the S-curve equation (R^2=0.503, p<0.001):

LVEF post = $e^{(4,521 - 29,609/LVEF)}$

where LVEF post represents the postoperative ejection fraction, and LVEF is the preoperative ejection fraction. The curve of the equation increases more steeply up to approximately LVEF=55 and then more gradually thereafter. The coefficient of determination (R^2) value indicates that approximately 50% of the variations in the investigated parameter after the operation depend on its preoperative values, while the remaining 50% are influenced by other factors (Figure 14).

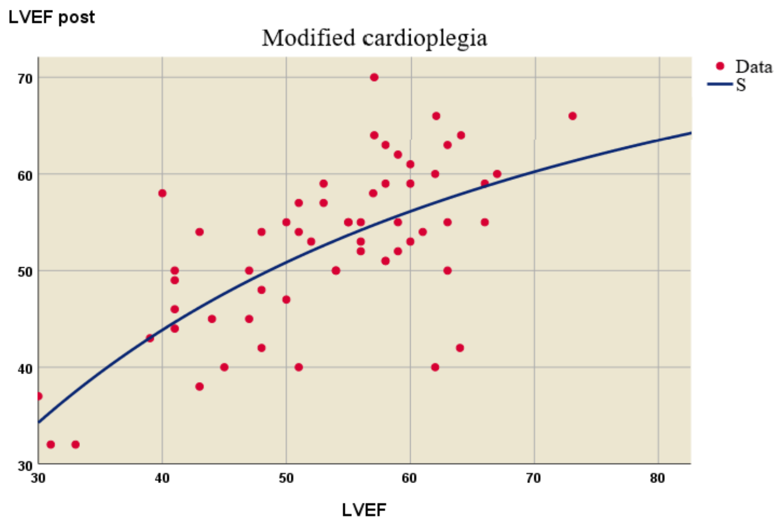

Figure 14: Regression model of the relationship between pre- and postoperative ejection fraction in modified cardioplegia

2. Creatinine

Classical Cardioplegia

The conducted regression analysis, using the built-in statistical package IBM SPSS Statistics 25.0, determined that out of the eleven models, the relationship between pre- and postoperative creatinine levels is best described by the linear equation (R^2=0.546, p<0.001):

Creatinine post= 39,313 + 0,681Creatinine

where Creatinine post represents the postoperative creatinine level, and Creatinine is the preoperative creatinine level. The curve of the equation increases steadily at an angle of approximately 45 degrees. In the regression equation, the coefficient before the argument indicates that, on average, for every 1 µmol/l increase in Creatinine, Creatinine post increases by about 0.681 µmol/l. The coefficient of determination (R^2) value indicates that approximately 55% of the variations in the investigated parameter after the operation depend on its preoperative values, while the remaining 45% are influenced by other factors (Figure 15).

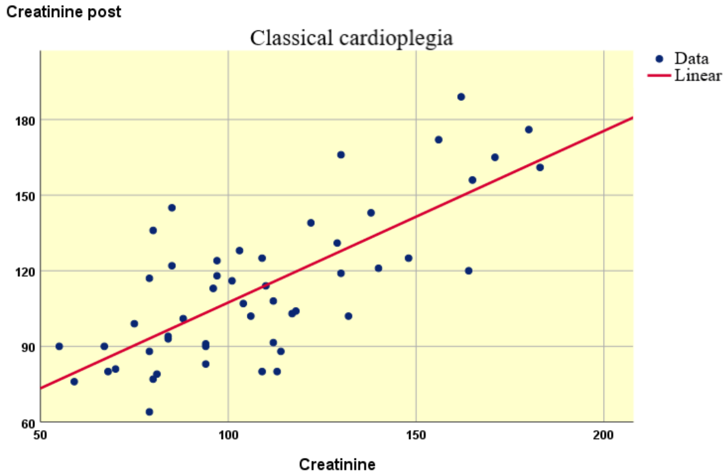

Figure 15: Regression model of the relationship between pre- and postoperative creatinine in classical cardioplegia

Modified cardioplegia

The conducted regression analysis, using the built-in statistical package IBM SPSS Statistics 25.0, determined that out of the eleven models, the relationship between pre- and postoperative creatinine levels is best described by the exponential equation ($R^2=0.508$, $p<0.001$):

Creatinine post= 52,249e$^{(0,007\text{Creatinine})}$

where Creatinine post represents the postoperative creatinine level, and Creatinine is the preoperative creatinine level. The curve of the equation increases steadily, slightly more gradually up to around 110 µmol/l, and then more steeply thereafter. The coefficient of determination (R^2) value indicates that approximately 51% of the variations in the investigated parameter after the operation depend on its preoperative values, while the remaining 49% are influenced by other factors (Figure 16).

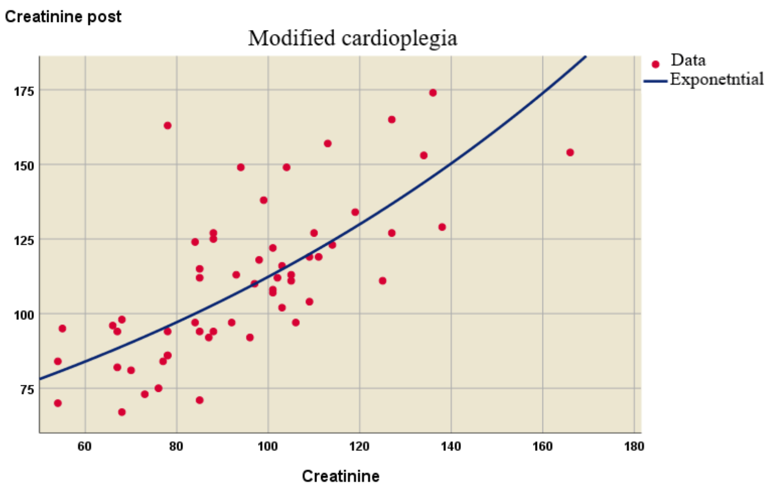

Figure 16: Regression model of the relationship between pre- and postoperative creatinine in modified cardioplegia

3. Creatinine Clearance

Classical Cardioplegia

The conducted regression analysis, using the built-in statistical package IBM SPSS Statistics 25.0, determined that out of the eleven models, the relationship between pre- and postoperative creatinine clearance is best described by the power equation (R^2=0.834, p<0,001):

CrCl post = 1,759CrCl^{0,850}

where CrCl post represents the postoperative creatinine clearance, and CrCl is the preoperative creatinine clearance. The curve of the equation increases steadily at an angle of approximately 45 degrees. The coefficient of determination (R^2) value indicates that approximately 83% of the variations in the investigated parameter after the operation depend on its preoperative values, while the remaining 17% are influenced by other factors (Figure 17).

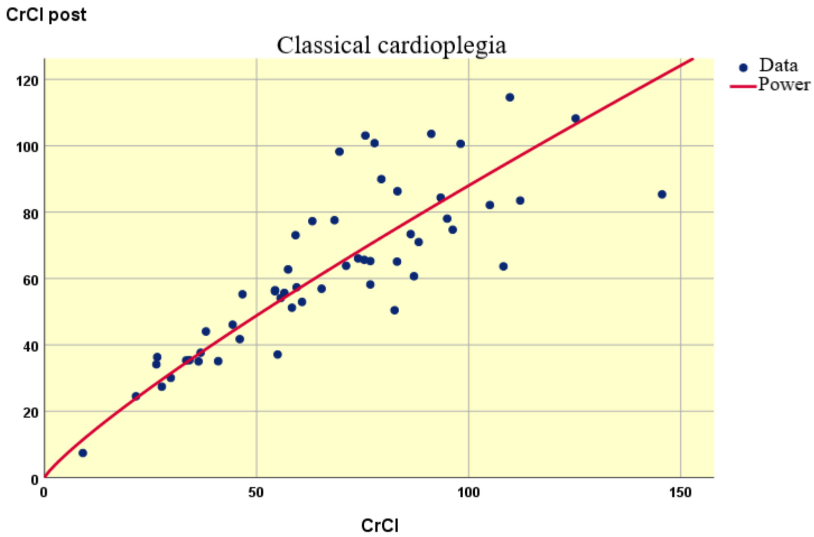

Figure 17: Regression model of the relationship between pre- and postoperative creatinine clearance in classical cardioplegia

The conducted regression analysis, using the built-in statistical package IBM SPSS Statistics 25.0, determined that out of the eleven models, the relationship between pre- and postoperative creatinine clearance is best described by the power equation (R^2=0.856, p<0,001):

CrCl post = 1,518CrCl^{0,872}

where CrCl post represents the postoperative creatinine clearance, and CrCl is the preoperative creatinine clearance. The curve of the equation increases steadily at an angle of approximately 45 degrees. The coefficient of determination (R^2) value indicates that approximately 86% of the variations in the investigated parameter after the operation depend on its preoperative values, while the remaining 14% are influenced by other factors (Figure 18).

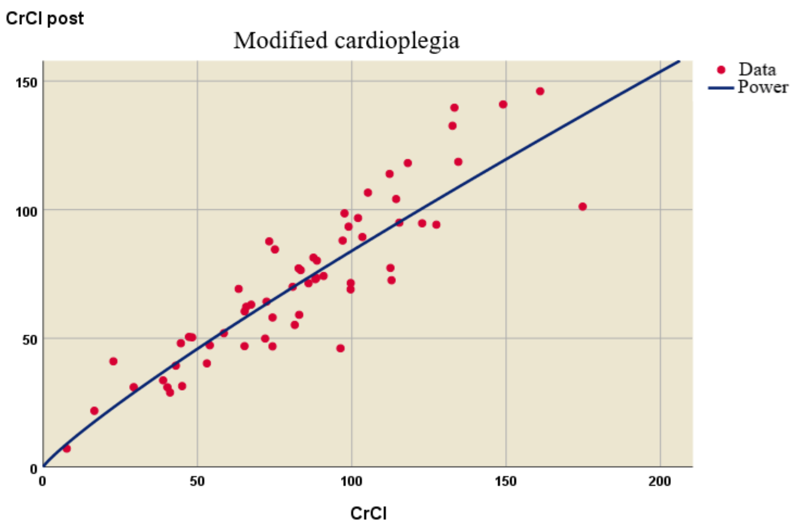

Figure 18: Regression model of the relationship between pre- and postoperative creatinine clearance in modified cardioplegia

8. Study of creatine phosphokinase and creatine phosphokinase MB fraction dynamics pre- and postoperatively in both cardioplegia groups

A. For patients undergoing aortic valve replacement

In Table 21 and Figures 19-20, it can be observed that:

- In both types of cardioplegia, the CPK and MB levels show a significant change at each measurement time.
- Creatine phosphokinase (CPK) exhibits a steady and statistically significant increase, with mean values differing significantly between the two types of cardioplegia only when leaving the operating room.
- The MB fraction shows a significant increase upon leaving the operating room compared to preoperative values, but after that, a statistically significant decrease is observed. A statistically significant difference between the two cardioplegia groups is observed both at the preoperative time point and at the second measurement moment.

Index	Cardioplegia Type		Measurement time						P		
			1. Preoperative		2. Postoperative		3. On 24th hour				
		n*	$\overline{X}$	SD	$\overline{X}$	SD	$\overline{X}$	SD	1-2	1-3	2-3
CPK	Classical cardioplegia	63	100,71	58,47	495,62	245,71	771,43	502,86	**<0,001**	**<0,001**	**<0,001**
	Modified cardioplegia	80	125,20	59,21	649,29	292,33	780,15	444,24	**<0,001**	**<0,001**	**0,009**
MB	Classical cardioplegia	58	15,35	9,13	50,36	19,28	42,03	26,34	**<0,001**	**<0,001**	**0,001**
	Modified cardioplegia	74	18,95	10,61	69,50	22,95	39,59	15,25	**<0,001**	**<0,001**	**<0,001**

Table 21: Dynamics of CPK and MB indicators pre- and postoperatively in both types of cardioplegia

*The analysis includes only patients who have data available for all three measurements.

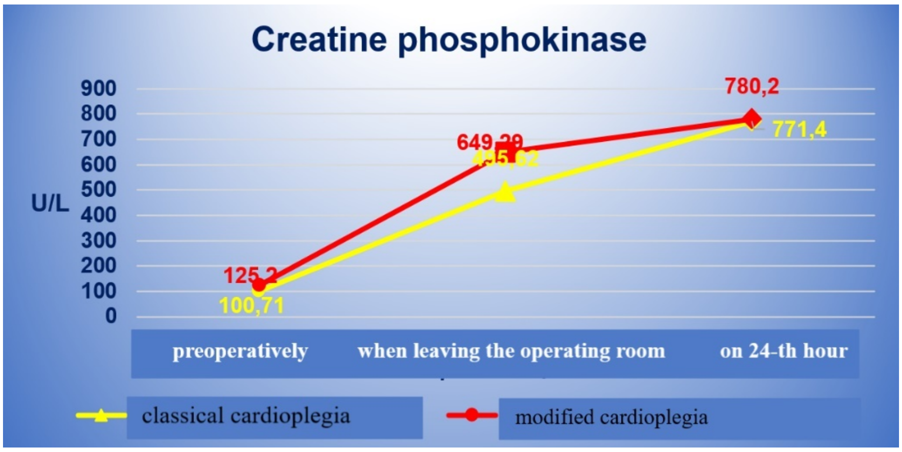

Figure 19: Dynamics of the average values of CPK pre- and postoperatively in both types of cardioplegia.

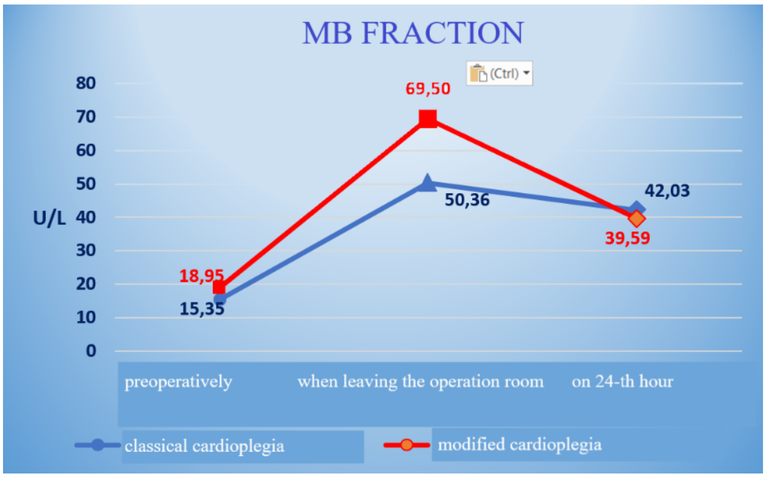

Figure 20: Dynamics of the average values of the MB indicator pre- and postoperatively in both types of cardioplegia

B. For patients undergoing coronary revascularization

In Table 22 and Figures 21-22, it can be observed that:

- In both types of cardioplegia, the CPK and MB levels show a significant change at each measurement time, except for MB0 and MB24 in the modified cardioplegia.
- **Creatine phosphokinase (CPK)** exhibits a steady and statistically significant increase, with mean values not differing significantly between the two types of cardioplegia throughout the monitoring period.
- **The MB fraction** shows a significant increase upon leaving the operating room compared to preoperative values. However, after that, a statistically significant decrease is observed in the classical cardioplegia group, and a decrease, but only in an algebraic sense, is observed in the modified cardioplegia group. Statistically significant differences between the two cardioplegia groups are observed only upon leaving the operating room.

Index	Cardioplegia Type		Measurement time						P		
			1. Preoperative		2. Postoperative		3. On 24th hour				
		n*	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	1-2	1-3	2-3
CPK	Classical cardioplegia	47	132,91	108,06	583,70	290,34	991,06	689,78	**<0,001**	**<0,001**	**<0,001**
	Modified cardioplegia	54	131,86	82,59	647,85	236,99	1026,13	740,22	**<0,001**	**<0,001**	**<0,001**
MB	Classical cardioplegia	46	19,54	13,15	60,67	23,93	53,07	45,76	**<0,001**	**<0,001**	**0,017**
	Modified cardioplegia	55	20,05	12,38	67,80	16,74	60,64	43,58	**<0,001**	**<0,001**	0,115

Table 22: Dynamics of CPK and MB indicators pre- and postoperatively in both types of cardioplegia

*The analysis includes only patients who have data available for all three measurements.

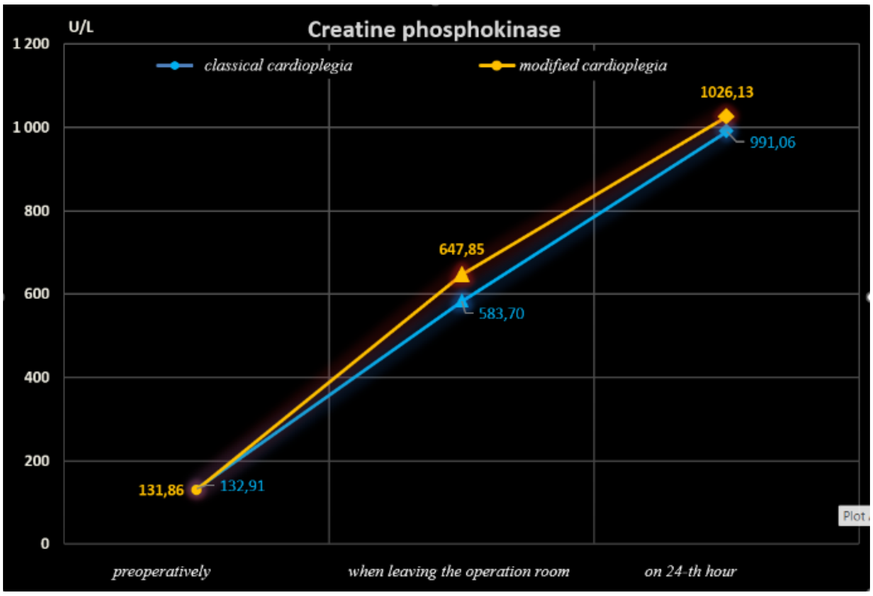

Figure 21: Dynamics of average CPK values pre- and postoperatively in both types of cardioplegia.

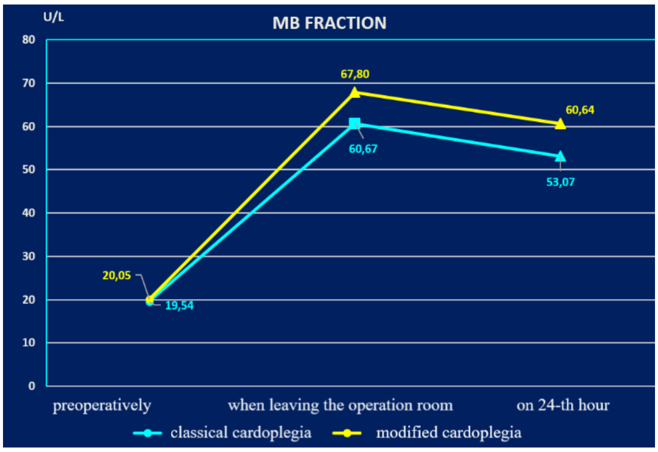

Figure 22: Dynamics of average MB values pre- and postoperatively in both types of cardioplegia.

9. **Determining the dependence of creatine phosphokinase at 24 hours after admission to an intensive care unit on preoperative creatine phosphokinase, creatine phosphokinase upon admission to an intensive care unit, and aortic cross-clamping time.**

A. For patients undergoing aortic valve replacement.

Classical cardioplegia.

After eliminating extreme CPK24 values, a multiple linear regression analysis (Backward procedure) was conducted, showing a significant dependence (R^2=0.470, p<0.001) of CPK24 on the examined predictive factors. At step 1, the regression equation is described by the following parameters:

CPK24 = 249.901 – 0.143CPK + 0.992CPK0 – 0.830CCT

where CPK24 is creatine phosphokinase at 24 hours after admission to an intensive care unit, CPK is preoperative creatine phosphokinase, CPK0 is creatine phosphokinase upon admission to an intensive care unit, and CCT is the aortic cross-clamping time.

From the standardized coefficients β (Table 23), it can be observed that CPK0 has the greatest influence on CPK24, followed by CCT and CPK.

The values obtained from the unstandardized coefficients provide the following information:

- An increase of CPK by 1 U/L leads to an average statistical decrease of CPK24 by approximately 0.143 U/L.
- An increase of CPK0 by 1 U/L leads to an average statistical increase of CPK24 by approximately 0.992 U/L.
- An increase of CCT by 1 minute leads to an average statistical decrease of CPK24 by approximately 0.830 U/L.

The coefficient of determination (R^2) of 0.470 indicates that the three indicators in the research model account for about 47% of the variations in CPK24. The moderate strength of the model can also be observed in the scatter plot between the actual and predicted values of CPK24 (Figure 23).

Stage	**Predictors**	**Unstandardized coefficients**		**Standardized coefficients**	**P**
		B	**Std. Error**	**β**	
1	Constant	249,901	168,441		0,144
	CPK	-0,143	0,616	-0,024	0,818
	CPK0	0,992	0,148	0,687	<0,001
	CCT	-0,830	20,487	-0,034	0,740

Table 23: Regression coefficients of the multiple regression model between CPK24 and the examined predictive factors for classical cardioplegia.

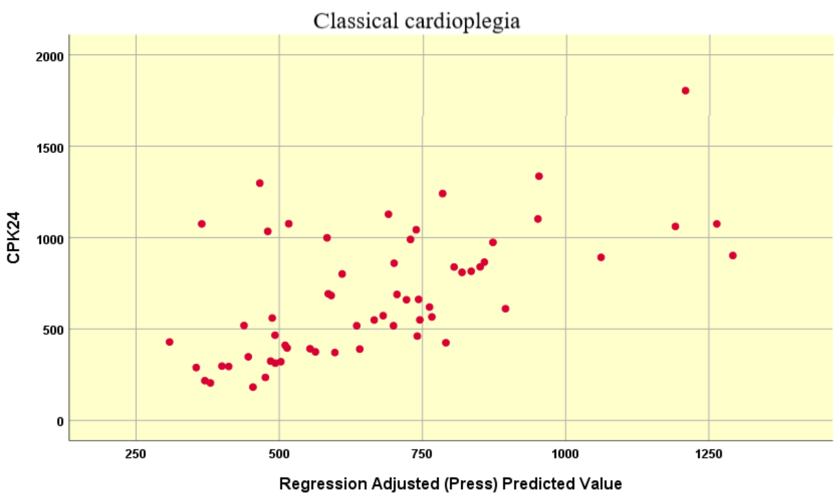

Figure 23: Scatter plot showing the relationship between actual and predicted values of CPK24 for classical cardioplegia.

For Modified cardioplegia:

After eliminating extreme values of CPK24, a multiple linear regression analysis (Backward procedure) was conducted, revealing a significant dependency (R^2=0.329, p<0.001) of CPK24 on the examined predictive factors. The regression equation at step 1 is as follows:

CPK24 = 169.618 + 0.573CPK + 0.719CPK0 + 0.642CCT.

Where CPK24 represents creatine phosphokinase at 24 hours after admission to an intensive care unit, CPK is the preoperative creatine phosphokinase, CPK0 is the creatine phosphokinase upon admission to a recovery, and CCT is the aortic cross-clamping time.

From the standardized coefficients β (Table 24), it can be observed that CPK0 has the greatest influence on CPK24, followed by CPK, and the least impact is from CCT.

The values of the unstandardized coefficients provide the following information:

- An increase of 1 U/L in CPK leads to a statistically significant increase in CPK24 by approximately 0.573 U/L.
- An increase of 1 U/L in CPK0 leads to a statistically significant increase in CPK24 by approximately 0.719 U/L.
- An increase of 1 minute in CCT leads to a statistically significant increase in CPK24 by approximately 0.642 U/L.

The coefficient of determination (R^2) of 0.329 indicates that the model, considering the three predictors, explains approximately 33% of the variations in CPK24. The moderate strength of the model is also evident in the scatter plot, comparing actual and predicted values of CPK24 (Figure 24).

Stage	Predictors	Unstandardized coefficients		Standardized coefficients	P
		B	Std. Error	β	
1	Constant	169,618	172,304		0,328
	CPK	0,573	0,624	0,089	0,362
	CPK0	0,719	0,129	0,547	<0,001
	CCT	0,642	20,455	0,026	0,794

Table 24: Regression coefficients of the multiple regression model between CPK24 and the examined predictive factors for modified cardioplegia.

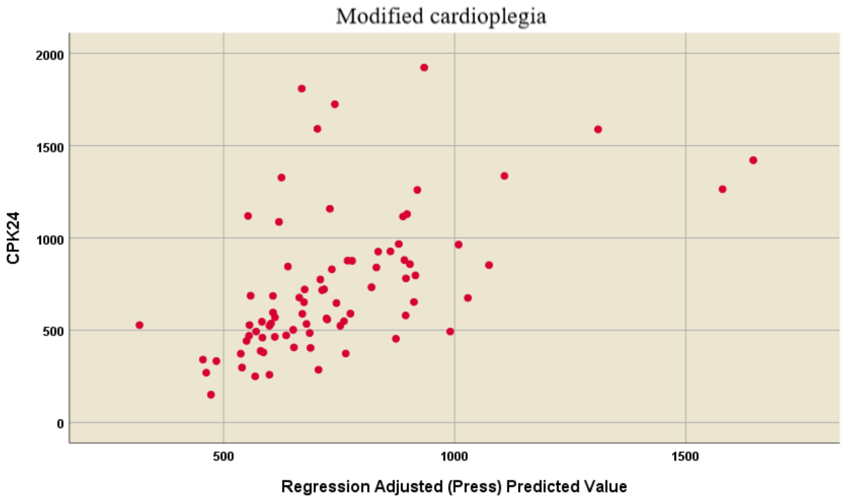

Figure 24: Scatter plot showing the relationship between actual and predicted values of CPK24 for modified cardioplegia.

B. For patients undergoing coronary revascularization with *classical cardioplegia:*

After eliminating extreme values of CPK24, a multiple linear regression analysis (Backward procedure) was performed, revealing a significant dependency (R^2=0.294, p=0.002) of CPK24 on the examined predictive factors. The regression equation at step 1 is as follows:

CPK24 = -37.031 + 0.029CPK + 1.154CPK0 + 7.342CCT

Where CPK24 represents creatine phosphokinase at 24 hours after admission to an intensive care unit, CPK is the preoperative creatine phosphokinase, CPK0 is the creatine phosphokinase upon admission to a recovery, and CCT is the aortic cross-clamp time.

From the standardized coefficients β (Table 25), it can be observed that CPK0 has the greatest influence on CPK24, followed by CCT, and the least impact is from CPK.

The values of the unstandardized coefficients provide the following information:

- An increase of 1 U/L in CPK leads to a statistically significant increase in CPK24 by approximately 0.029 U/L.
- An increase of 1 U/L in CPK0 leads to a statistically significant increase in CPK24 by approximately 1.154 U/L.
- An increase of 1 minute in CCT leads to a statistically significant increase in CPK24 by approximately 7.342 U/L.

The coefficient of determination (R^2) of 0.294 indicates that the model, considering the three predictors, explains approximately 29% of the variations in CPK24. The weak strength of the model is also evident in the scatter plot, comparing actual and predicted values of CPK24 (Figure 25).

Stage	Predictors	Unstandardized coefficients		Standardized coefficients	P
		B	Std. Error	β	
1	Constant	-37,031	375,640		0,922
	CPK	0,029	0,860	0,004	0,974
	CPK0	1,154	0,337	0,486	0,001
	CCT	7,342	7,774	0,128	0,350

Table 25: Regression coefficients of the multiple regression model between CPK24 and the examined predictive factors for modified cardioplegia.

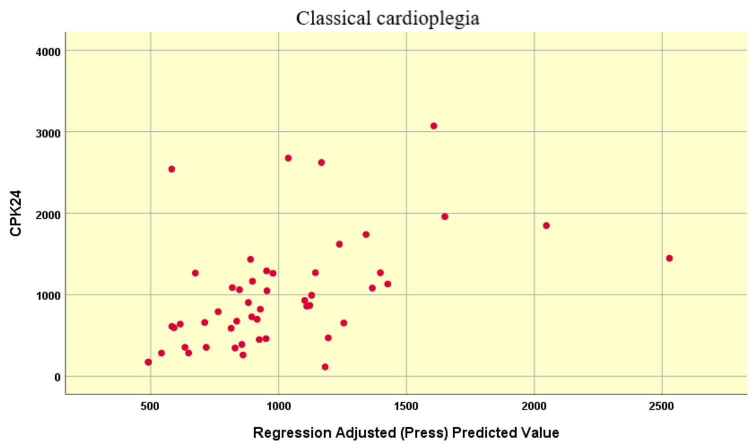

Figure 25: Scatter plot showing the relationship between actual and predicted values of CPK24 for classical cardioplegia.

modified cardioplegia:

After eliminating extreme values of CPK24, a multiple linear regression analysis (Backward procedure) was performed, revealing a significant dependency (R^2=0.256, $p<0.001$) of CPK24 on the examined predictive factors. The regression equation at step 1 is as follows:

CPK24 = -425.192 + 1.937CPK + 1.055CPK0 + 8.672CCT.

Where CPK24 represents creatine phosphokinase at 24 hours after admission to an intensive care unit, CPK is the preoperative creatine phosphokinase, CPK0 is the creatine phosphokinase upon admission to a recovery, and CCT is the aortic cross-clamp time.

From the standardized coefficients β (Table 26), it can be observed that CPK0 has the greatest influence on CPK24, followed by CPK, and the least impact is from CCT. The values of the unstandardized coefficients provide the following information:

- An increase of 1 U/L in CPK leads to a statistically significant increase in CPK24 by approximately 1.937 U/L.
- An increase of 1 U/L in CPK0 leads to a statistically significant increase in CPK24 by approximately 1.055 U/L.
- An increase of 1 minute in CCT leads to a statistically significant increase in CPK24 by approximately 8.672 U/L.

The coefficient of determination (R^2) of 0.256 indicates that the model, considering the three predictors, explains approximately 26% of the variations in

CPK24. The weak strength of the model is also evident in the scatter plot, comparing actual and predicted values of CPK24 (Figure 26).

Stage	Predictors	Unstandardized coefficients		Standardized coefficients	P
		B	Std. Error	β	
1	Constant	-425,192	430,441		0,328
	CPK	1,937	1,135	0,216	0,094
	CPK0	1,055	0,446	0,338	0,022
	CCT	8,672	8,499	0,150	0,312

Table 26: Regression coefficients of the multiple regression model between CPK24 and the examined predictive factors for modified cardioplegia.

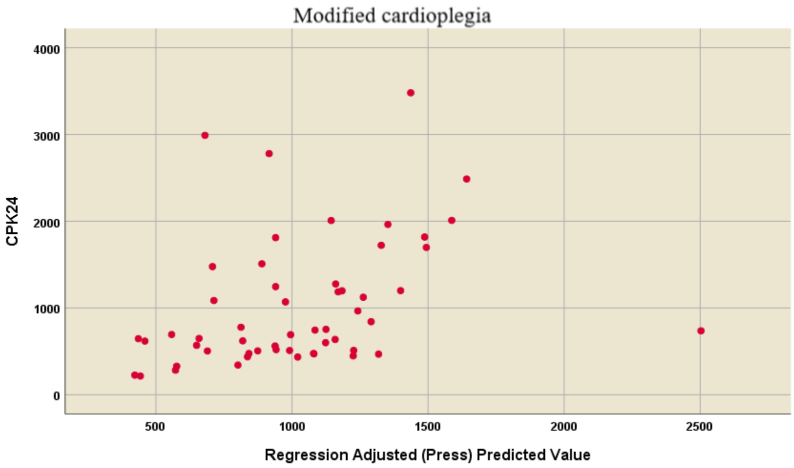

Figure 26: Scatter plot showing the relationship between actual and predicted values of MB24 for modified cardioplegia.

10. Determining the dependence of creatine phosphokinase MB24 on preoperative creatine phosphokinase MB, creatine phosphokinase MB upon admission to an intensive care unit, and aortic cross-clamp time.

A. For patients undergoing aortic valve replacement

classical cardioplegia:

After eliminating extreme values of MB24, a multiple linear regression analysis (Backward procedure) was performed, revealing a significant dependency (R^2=0.107, p=0.048) of MB24 on the examined predictive factors. The regression equation at step 1 is as follows (CCT has been omitted):

MB24 = 16.664 + 0.521MB + 0.352MB0

Where MB24 represents the MB fraction at 24 hours after admission to an intensive care unit, MB is the preoperative MB fraction, and MB0 is the MB fraction upon admission to a recovery.

From the standardized coefficients β (Table 27), it can be observed that MB0 has the greatest influence on MB24, followed by MB. The values of the unstandardized coefficients provide the following information:

An increase of 1 U/L in MB leads to a statistically significant increase in MB24 by approximately 0.521 U/L.

An increase of 1 U/L in MB0 leads to a statistically significant increase in MB24 by approximately 0.352 U/L.

The coefficient of determination (R^2) of 0.107 indicates that the model, considering the two predictors, explains approximately 11% of the variations in MB24. The weak strength of the model is also evident in the scatter plot, comparing actual and predicted values of MB24 (Figure 27).

Stage	Predictors	Unstandardized coefficients		Standardized coefficients	P
		B	Std. Error	β	
1	Constant	16,664	10,758		0,127
	MB	0,521	0,369	0,182	0,163
	MB0	0,352	0,176	0,257	0,051

Table 27: Regression coefficients of the multiple regression model between MB24 and the examined predictive factors for classical cardioplegia.

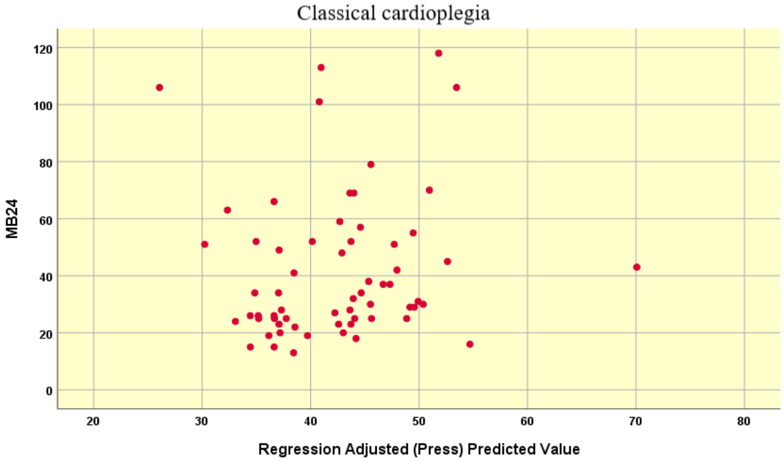

Figure 27: Scatter plot showing the relationship between actual and predicted values of MB24 for classical cardioplegia.

modified cardioplegia

After eliminating extreme values of MB24, a multiple linear regression analysis (Backward procedure) was performed, revealing a significant dependency (R^2=0.269, p<0.001) of MB24 on the examined predictive factors. The regression equation at step 2 is as follows:

MB24 = 23.497 - 0.153MB + 0.301MB0 - 0.054CCT.

Where MB24 represents the MB fraction at 24 hours after admission to an intensive care unit, MB is the preoperative MB fraction, MB0 is the MB fraction upon admission to a recovery, and CCT is the aortic cross-clamp time.

From the standardized coefficients β (Table 28), it can be observed that MB0 has the greatest influence on MB24, followed by MB, and CCT has the weakest influence.

The values of the unstandardized coefficients provide the following information:

- An increase of 1 U/L in MB leads to a statistically significant decrease in MB24 by approximately 0.153 U/L.
- An increase of 1 U/L in MB0 leads to a statistically significant increase in MB24 by approximately 0.301 U/L.
- An increase of 1 minute in CCT leads to a statistically significant decrease in MB24 by approximately 0.054 U/L.

The coefficient of determination (R^2) of 0.269 indicates that the model, considering the three predictors, explains approximately 27% of the variations in MB24. The relatively weak strength of the model is also evident in the scatter plot, comparing actual and predicted values of MB24 (Figure 28).

Stage	Predictors	Unstandardized coefficients		Standardized coefficients	P
		B	Std. Error	β	
2	Constant	23,497	7,487		0,003
	MB	-0,153	0,124	-0,129	0,221
	MB0	0,301	0,062	0,512	<0,001
	CCT	-0,054	0,098	-0,058	0,585

Table 28: Regression coefficients of the multiple regression model between MB24 and the examined predictive factors for modified cardioplegia.

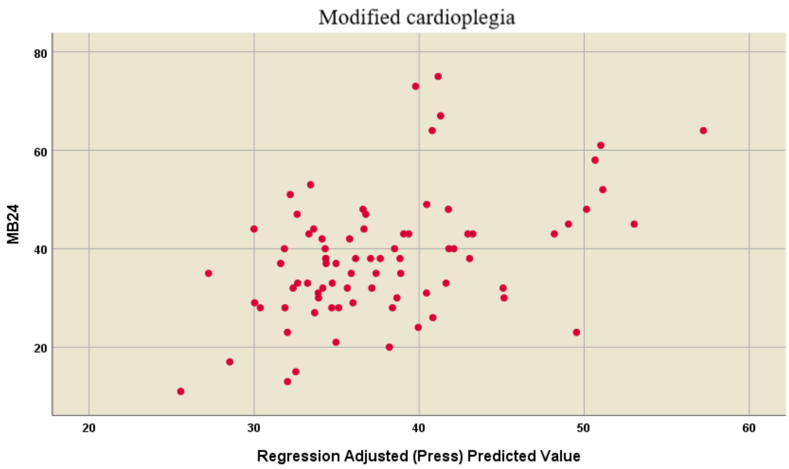

Figure 28: Scatter plot showing the relationship between actual and predicted values of MB24 for modified cardioplegia.

B. For patients undergoing coronary revascularization

classic cardioplegia

After eliminating extreme values, a multiple linear regression analysis (Backward procedure) was conducted, revealing a significant dependency (R^2=0.303, p=0.002) of MB24 on the examined predictive factors. The regression equation at step 1 is as follows:

MB24 = -15.782 - 0.183MB + 0.862MB0 + 0.353CCT.

Where MB24 represents the MB fraction at 24 hours after admission to an intensive care unit, MB is the preoperative MB fraction, MB0 is the MB fraction upon admission to a recovery, and CCT is the aortic cross-clamp time.

From the standardized coefficients β (Table 29), it can be observed that MB0 has the greatest influence on MB24, followed by CCT, and MB has the weakest influence.

The values of the unstandardized coefficients provide the following information:

- An increase of 1 U/L in MB leads to a statistically significant decrease in MB24 by approximately 0.183 U/L.
- An increase of 1 U/L in MB0 leads to a statistically significant increase in MB24 by approximately 0.862 U/L.
- An increase of 1 minute in CCT leads to a statistically significant increase in MB24 by approximately 0.353 U/L.

The coefficient of determination (R^2) of 0.303 indicates that the model, considering the three predictors, explains approximately 30% of the variations in MB24. The moderate strength of the model is also evident in the scatter plot, comparing actual and predicted values of MB24 (Figure 29).

Stage	Predictors	Unstandardized coefficients		Standardized coefficients	P
		B	Std. Error	β	
1	Constant	-15,782	23,231		0,501
	MB	-0,183	0,402	-0,061	0,651
	MB0	0,862	0,224	0,527	<0,001
	CCT	0,353	0,423	0,111	0,409

Table 29: Regression coefficients of the multiple regression model between MB24 and the examined predictive factors for classic cardioplegia.

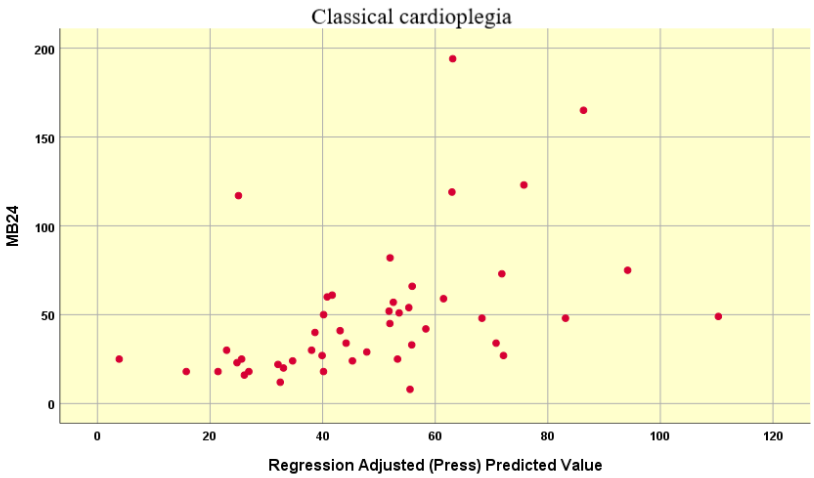

Figure 29: Scatter plot showing the relationship between actual and predicted values of MB24 for classic cardioplegia.

modified cardioplegia

After eliminating extreme values, a multiple linear regression analysis (Backward procedure) was conducted, revealing a significant dependency (R^2=0.144, p=0.021) of MB24 on the examined predictive factors. The regression equation at step 2 is as follows (MB was eliminated):

MB24 = 1.781 - 0.088MB0 + 1.002CCT

Where MB24 represents the MB fraction at 24 hours after admission to an intensive care unit, MB0 is the MB fraction upon admission to a recovery, and CCT is the aortic cross-clamp time.

From the standardized coefficients β (Table 30), it can be observed that CCT has the greatest influence on MB24, followed by MB0.

The values of the unstandardized coefficients provide the following information:

An increase of 1 U/L in MB0 leads to a statistically significant decrease in MB24 by approximately 0.088 U/L.

An increase of 1 minute in CCT leads to a statistically significant increase in MB24 by approximately 1.002 U/L.

The coefficient of determination (R^2) of 0.144 indicates that the model, considering the two predictors, explains approximately 14% of the variations in MB24. The small strength of the model is also evident in the scatter plot, comparing actual and predicted values of MB24 (Figure 30).

Stage	Predictors	Unstandardized coefficients		Standardized coefficients	P
		B	Std. Error	β	
2	Constant	1,781	24,385		0,942
	MB0	-0,088	0,281	-0,043	0,754
	CCT	1,002	0,351	0,390	0,006

Table 30: Regression coefficients of the multiple regression model between MB24 and the examined predictive factors for modified cardioplegia.

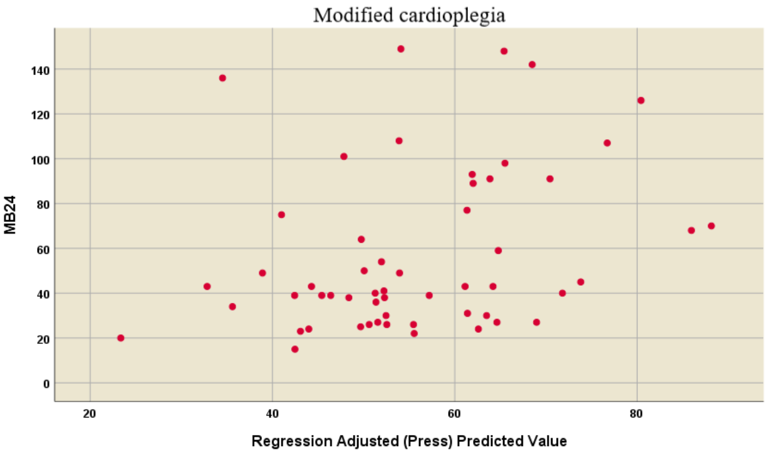

Figure 30: Scatter plot showing the relationship between actual and predicted values of MB24 for modified cardioplegia.

V. Conclusions:

General

- The modified cardioprotective solution based on Prof. Del Nido's formula proved to be sufficiently effective and safe in both types of surgical interventions studied.
- Clinical trial results showed that the modified Del Nido solution significantly reduces the need for inotropic support in the early postoperative period for both types of interventions.
- In both types of surgical interventions, a statistically significant increase in the initial postoperative MB fraction of creatine phosphokinase was observed in cases treated with MDN, which rapidly reversed within 24 postoperative hours.
- The use of modified Del Nido cardioplegia demonstrated a reduction in the dosage required for both types of surgical interventions, although statistical significance was not achieved in this study.

Coronary Revascularization

- In patients undergoing coronary revascularization, the frequency of intra-aortic balloon pump (I.A.B.P) use (mechanical cardiac support) is significantly reduced.

Aortic Valve Replacement

- In patients undergoing aortic valve replacement, the use of modified Del Nido cardioplegia significantly shortens the average stay in the intensive care unit and the overall hospital stay.
- In patients undergoing aortic valve replacement, a statistically significant increase in the initial postoperative creatine phosphokinase values was observed in cases treated with MDN, which rapidly reversed within 24 postoperative hours.

VI. Contributions of the Dissertation

1. The main techniques for myocardial protection have been reviewed and illustrated, citing numerous results from related studies.
2. An innovative modification of Del Nido cardioplegic solution, not previously presented in the literature, has been introduced.
3. The advantages and disadvantages of the modification have been investigated and compared with one of the established classical cardioplegias.
4. Publication results have been confirmed when using both classical Del Nido solutions and their modifications.

VII. Publications

Publications indexed in Scopus and Web of Science:

1. ***Stoitsev GJ**, Gavrilov V, Manchev G, Markov B, Goranovska V, Tsankov B, Gegouskov V. Therapy with L-thyroxine and Omnadren after Cardiac Surgery. A Case Report. Folia Medica, 2019, 61(4): 650-654; ISSN: 0204-8043; Web of Science, Scopus*
2. ***G. Stoitsev**, V. Gavrilov, V. Gegouskov. Aortic dissection type A in combination with acute anterior myocardial infarction. Myocardial protection. Journal of Biomedical and Clinical Research, 2023, in press; ISSN: 1313-6917; Web of Science*

Publications in Bulgarian medical journal

1. ***Стоицев Г.**, Гаврилов Г., Манче Г, Горановска В., Марков Б., Гегусков В. Интракавитарана мултифокална локализация на левокамерна политромбоза при пациент с постинфарктна аневризма на лява камера. Списание на българската лига по хипертония, 2021, бр.10, стр.44-48; ISSN: 2367-5225*

Participation in Scientific Forums:

1. V. Goranovska, V. Gegouskov, G. Manchev, G. Stoitsev. Bilateral internal mammary artery - a contemporary approach in myocardial revascularization. Ninth National Congress on Thoracic, Cardiac, and Vascular Surgery and Fifth National Congress of the Bulgarian Society of Cardiothoracic Surgery. May 26, 2022 - May 15, 2022, Golden Sands Resort, Bulgaria.
2. V. Goranovska, V. Gegouskov, G. Manchev, B. Markov, G. Stoitsev, V. Velchev, N. Stoyanov. Device-related endocarditis following ICD implantation in a patient with corrected congenital heart malformation. Ninth National Congress on Thoracic, Cardiac, and Vascular Surgery and Fifth National Congress of the Bulgarian Society of Cardiothoracic Surgery. May 26, 2022 - May 15, 2022, Golden Sands Resort, Bulgaria.