

COLD MODIFIED DEL NIDO CARDIOPLEGIA IN ADULTS UNDERGOING AORTIC VALVE REPLACEMENT (AVR)

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Abstract

Investigations were carried out on the modified del Nido (MDN) cardioplegia with a longer period of cardiac arrest. The study population included 152 patients treated with aortic valve replacement (AVR). A significant difference was observed in the need for inotropic support, with Kirklin cardioplegia having a significantly higher need of moderate doses, while MDN more frequently allowed for the absence of inotropic support ($p < 0.001$). Mean ICU stay and in hospital stay were statistically significantly higher in patients treated with Kirklin cardioplegia compared to those with MDN cardioplegia ($p < 0.001$ and $p = 0.02$, respectively).

Key words: cardiac surgery, cardioprotection, del Nido cardioplegia, modified del Nido cardioplegia

Introduction. Myocardial protection during surgical interventions takes a vital role in cardiac surgery practice. In 1995, Professor Pedro del Nido patented his cardioplegic solution [1]. The solution, which we have named del Nido cardioplegia (DN) induces depolarizing arrest during cardiac surgery and is more diluted solution (1:4, blood:crystalloid) compared to traditional blood cardioplegia 4:1. The basis of del Nido solution is reduced content of Ca^{2+} [2]. On the other hand, Kirklin's solution is a well-studied crystalloid cardioplegia, administered repeatedly at short intervals during surgery. An elevation in myocardial acidosis between doses has been noted, adversely affecting postoperative outcome.

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It would be useful if the interval between doses can be increased, thereby reducing their total number during surgery. The potential practical advantage of DN is the fact that it provides for a longer period of arrest before a subsequent dose is required [3].

The need for additional inventory when using a blood vehiculum for classical del Nido cardioplegia, forced us to simplify surgical interventions. Our institution developed a modified solution based on the electrolyte composition of del Nido's cardioplegic solution, while removing the blood component and replacing it with the additional NaHCO_3 . Routine use of our modified del Nido cardioplegia has proven dependable and effective. The concept was based on previous modifications of the solution in which Ringer solution was used as the main solvent instead of the classically used Plasma Lyte [4, 5]. We are of the opinion that the blood component is not the basis of the proven good results in DN plegia, namely the reduced concentration of Ca^{2+} in Plasma Lyte.

The aim of this study is to demonstrate whether the modified del Nido (DN) cardioplegia with a longer period of cardiac arrest provides sufficiently effective and reliable myocardial protection in patients undergoing on aortic valve replacement compared with the Kirklin cardioplegia standard used in our institution.

Material and methods. Patient population. This ambispective clinical-epidemiological study was conducted in "St. Anna" University Hospital in Sofia in the period between January 2017 and September 2021. It covered 152 patients in total, divided into the following two groups: 1) intermittent cardioplegia Kirklin (Kn, $n = 67$) used in patients between January 2017 and June 2019; and 2) modified del Nido cardioplegia (MDN, $n = 85$) used from June 2019 to September 2021.

Inclusion and exclusion criteria. *Inclusion criteria.* The study included all patients undergoing aortic valve replacement.

Exclusion criteria.

1. All patients undergoing combined surgical intervention were excluded from the study:
 - Bypass surgery;
 - Double valve replacement/valvuloplasty;
 - Surgeries using vascular prosthesis (Bentall de Bono, a modo David, a modo Yacub, a modo Wheat).
2. All patients undergoing aortic valve repair were excluded from the study.
3. All patients undergoing surgical intervention for ascending aortic dissection were excluded from the study.

Application in cardioplegia. All interventions were performed using a standard protocol of general anesthesia in valvular patients, conventional or upper partial sternotomy and cardiopulmonary bypass in systemic normothermia. Myocardial protection was achieved by Kn or MDN cardioplegia as follows: In both groups, the heart is arrested by an induction dose (1 L) cold (2–4 °C) cardioplegia using antegrade delivery. A supplemental dose of cardioplegia was delivered through the coronary ostia, delivered once every 45 minutes with Kn. A second dose (500 mL) of MDN was provided only when the clamping time exceeded 60 minutes. An initial double dose is given at the discretion of the operator in cases with massive myocardial hypertrophy.

Statistical methods. The data was entered and processed with IBM SPSS Statistics 25.0 and MedCalc Version 19.6.3 statistical packages, as well as in MS Office 2021 Excel. A significance level rejecting the null hypothesis was adopted as $p < 0.05$.

The following methods were applied:

1. Descriptive analysis – the frequency distribution of the reviewed attributes is presented in a tabular form.
2. Graphical analysis – to visualize the results obtained.
3. Comparing relative shares.
4. Fisher's exact test, Fisher–Freeman–Halton exact test and χ^2 test – to check hypotheses for the existence of a relationship between category variables.
5. Nonparametric Kolmogorov–Smirnov and Shapiro–Wilk test – to test the distribution for normality.
6. Student t -test – to test hypotheses about differences between the means of two independent samples.
7. Non-parametric Mann–Whitney U test – to test hypotheses for difference between two independent samples.
8. Student t -test – to test hypotheses of difference between means of two dependent samples.
9. Wilcoxon signed-rank test – to test hypotheses for difference between two dependent excerpts.
10. Regression analysis – to test hypotheses about the existence of a relationship between quantitative traits and the choice of a mathematical model.
11. Friedman test – to test hypotheses of difference between several dependent samples.

12. Multiple linear regression analysis – to test hypotheses about the presence of dependence of one quantitative trait on several other traits.

Results. Baseline demography. The study clinical population had a mean age of 65.22 ± 10.36 years in the range 31–90 years. Of the sampled study participants, 87 (57.2%) were male and 65 (42.8%) were female. The mean age of the group with classic cardioplegia was 65.87 ± 9.49 , and of those with modified cardioplegia – 64.71 ± 11.03 . The difference between them is statistically insignificant ($p = 0.396$). The average value of the studied cohort according to BMI was 28.22 ± 4.87 kg/m² with no significant difference between the two treatment groups ($p = 0.126$).

The two study groups were statistically equal on the known confounding factors of gender and age which suggests a correct basis for subsequent comparisons.

Descriptive statistics. For the purpose of the present study, patients were divided into two treatment groups: Classical Cardioplegia (CN) – $n = 67$ (44.1%) and Modified Cardioplegia (MDN) – $n = 85$ (55.9%).

General characteristics of the groups. Regarding the quantitative preoperative characteristics examined (Table 1):

- A statistically significant difference between the two treatment groups was found in the parameters creatinine clearance (CrCl), creatinine phosphokinase MB fraction (MB), peak and mean gradient. Higher mean values were observed in the modified cardioplegia group;
- The difference between the two groups was statistically insignificant for the rest of the indicators.

The comparative analysis of the treatment groups by the studied categorical preoperative characteristics revealed the following:

- Significant difference was observed only for the indicator of preoperative atrial fibrillation (AF) – the higher relative proportion belongs to the classical cardioplegia group ($p = 0.004$);
- The difference between the two groups was statistically insignificant for the rest of the indicators.

Intra- and postoperative variables and outcomes. The comparative analysis of the treatment groups by the studied categorical intra- and postoperative characteristics (Table 2) revealed the following:

- A significant difference was only observed in the need for inotropic support – classic cardioplegia having a significantly higher need of moderate doses, while modified cardioplegia more frequently allowed for the absence of inotropic support ($p < 0.001$);

T a b l e 1

Comparative analysis of treatment groups by exploratory quantitative and categorical preoperative characteristics

Quantitative index	Classical cardioplegia			Modified cardioplegia			<i>p</i>
	<i>n</i>	$\bar{X}$	SD	<i>n</i>	$\bar{X}$	SD	
Euroscore (%)	64	4.96	4.10	77	4.58	4.00	0.439
Hemoglobin	67	133.64	18.71	85	134.66	21.09	0.757
Erythrocytes	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	67	68.91	24.81	84	75.52	30.41	0.038
Creatinine phosphokinase	66	100.23	57.32	83	122.24	60.14	0.152
MB fraction	62	15.71	9.26	77	18.70	10.48	0.011
Ejection fraction	67	54.07	9.81	85	55.66	9.30	0.406
Peak gradient	56	66.50	22.63	66	79.86	28.25	0.003
Average gradient	56	36.48	14.14	66	44.09	16.98	0.006
LV hypertrophy (mm)	67	14.28	2.16	85	14.69	2.32	0.324
Categorical index	Classical cardioplegia		Modified cardioplegia		<i>p</i>		
	<i>n</i>	%	<i>n</i>	%			
Diabetes mellitus	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 atrial fibrillation	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 regurgitation					0.660		
None	18	26.9	26	30.6			
1 st degree	11	16.4	17	20.0			
2 nd degree	14	20.9	10	11.8			
3 rd degree	21	31.3	28	32.9			
4 th degree	3	4.5	4	4.7			
Mitral regurgitation	30	44.8	44	51.8	0.418		
Pulmonary hypertension	13	19.4	10	11.8	0.255		

- For the other indicators included in Table 1: fibrillation rate, IABP use rate, new-onset atrial fibrillation, new-onset myocardial infarction, new-onset stroke, and mortality, the difference between the two groups was statistically insignificant.

Regarding the quantitative intra- and postoperative characteristics examined (Table 2):

- A statistically significant difference between the two treatment groups was found in the creatinine phosphokinase parameters when entering ICU (CPK0), creatinine phosphokinase MB fraction upon admission to an ICU (MB0), with higher median values of these indicators observed in the modified cardioplegia group ($p = 0.001$ and $p < 0.001$, respectively).

T a b l e 2

Comparative analysis of the therapeutic groups according to the investigated categorical and quantitative intra- and postoperative characteristics

Quantitative index	Classical cardioplegia			Modified cardioplegia			<i>p</i>
	<i>n</i>	$\bar{X}$	SD	<i>n</i>	$\bar{X}$	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
CCT (min)	64	59.25	13.97	84	64.33	15.43	0.029
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
Categorical index	Classical cardioplegia		Modified cardioplegia		<i>p</i>		
	<i>n</i>	%	<i>n</i>	%			
Frequency of fibrillations	5	7.5	4	4.7	0.508		
Need of additional plegia	17	25.4	22	25.9	1		
Need of inotropic support					<0.001		
Absence during cessation	44	65.7	77	90.6			
Moderate doses	22	32.8	7	8.2			
High doses	1	1.5	1	1.2			
Frequency of use of IABP	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		

- The mean extracorporeal circulation time (CPB) in patients with modified cardioplegia was about 101 ± 24.1 min and was statistically significantly higher than that in classical cardioplegia 93 ± 24.8 min ($p = 0.023$).
- The mean aortic cross-clamp time (CCT) in patients with modified cardioplegia was about 64 ± 15 min and was statistically significantly higher than the classic cardioplegia 59 ± 14 min ($p = 0.029$). The need to use an additional dose of cardioplegia occurred in about 1/4 of the cases, and the difference in the relative proportions of the two types of cardioplegia was statistically insignificant.
- Mean ICU stay and hospital stay were statistically significantly higher in patients treated with Kirklin cardioplegia compared to those with MDN cardioplegia ($p < 0.001$ and $p = 0.02$, respectively).

- For the other parameters included in Table 2 – creatinine phosphokinase at 24 h after ICU admission (CPK24), creatinine phosphokinase MB fraction at 24 h after ICU admission (MB24), postoperative creatinine clearance (CrCl post) and postoperative creatinine (Cr post) – the difference between the two groups was statistically insignificant.

Comparison of the type of prosthesis used, average size of prosthesis used and surgical access between the two groups shows the following:

- The two treatment groups did not differ statistically in the type of prosthesis used – mechanical prosthesis was used in almost all cases, but their difference in terms of surgical access was significant ($p < 0.001$);
- Conventional access was used significantly more in classic cardioplegia ($n = 32$ about 48% vs. $n = 2$ about 2%), whereas minimally invasive access was used in modified cardioplegia ($n = 83$ about 98% vs. $n = 35$ or 52%).

The average prosthesis size used in both groups was about $21\text{--}22 \pm 2$ mm. The difference for this indicator is statistically insignificant.

Determination of the dependence of MB24 on MB preoperatively, MB after ICU admission, and aortic valve clamping time. Classical cardioplegia. After elimination of the extreme CPK24 values, multiple linear regression analysis (Backward procedure) was completed, which showed that there was a significant dependency ($R^2 = 0.470$, $p < 0.001$) of CPK24 on the predictive factors examined, which at step 1 was described by a regression equation with the following parameters:

$$\text{CPK24} = 249.901 - 0.143\text{CPK} + 0.992\text{CPK0} - 0.830 \text{ Aortic Cross-Clamp},$$

where CPK24 is creatine phosphokinase at the 24th hour after ICU admission, CPK is creatine phosphokinase preoperatively, CPK0 is creatine phosphokinase after ICU admission, and CCT is aortic cross-clamp time.

From the standardized coefficients β (Fig. 1), it can be seen that the largest influence on the CPK24 is the CPK0, followed by CCT and CPK.

The resulting values of the non-standardized coefficients provide information on the following fact:

- A 1 U/L elevation in CPK results in an average decline in CPK24 of approximately 0.143 U/L;
- A 1 U/L increase in CPK0 results in an average increase in CPK24 of approximately 0.992 U/L;
- A 1-minute increase in CCT results in an average decrease in CPC24 of approximately 0.830 U/L.

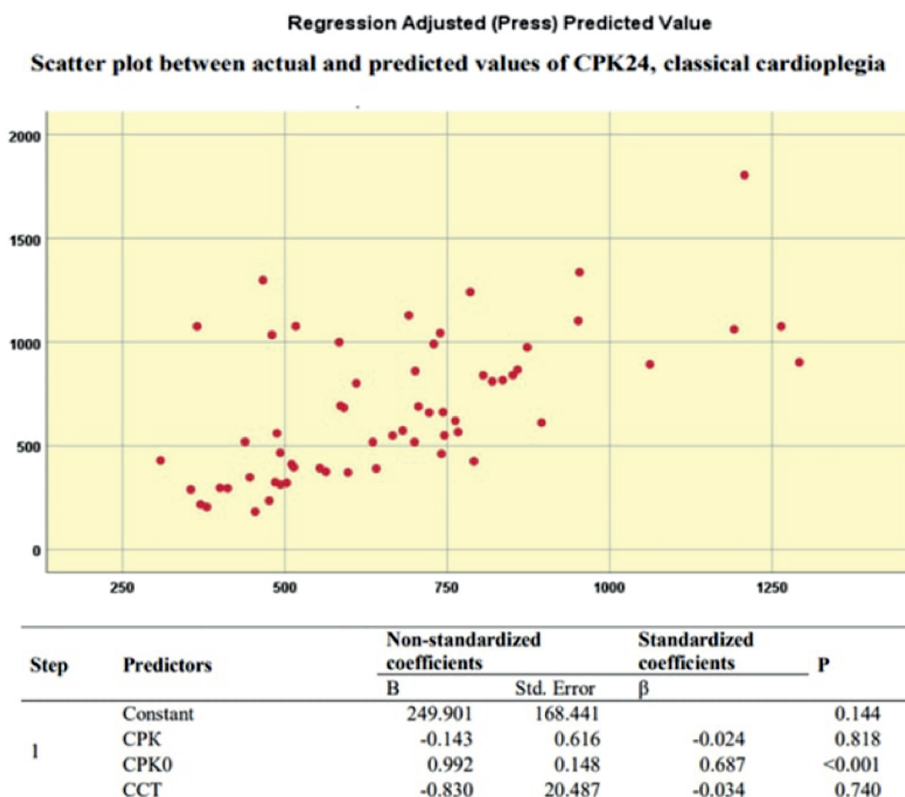


Fig. 1

The coefficient of determination (R^2) value of 0.470 implies that, according to the model studied, the three indicators account for about 47% of the variation in CPK24. The moderate strength of the model is also observed on the scatter plot between the actual and predicted values of CPK24 (Fig. 1).

Modified cardioplegia. After elimination of the extreme CPK24 values, multiple linear regression analysis (Backward procedure) was completed, which showed that there was a significant dependency ($R^2 = 0.329$, $p < 0.001$) of CPK24 with the predictive factors examined, which at step 1 was described by a regression equation with the following parameters:

$$\text{CPK24} = 169.618 + 0.573\text{CPK} + 0.719\text{CPK0} + 0.642\text{CCT},$$

where CPK24 is creatine phosphokinase at the 24th hour after ICU admission, CPK is preoperative creatine phosphokinase, CPK0 is creatine phosphokinase after ICU admission, and CCT is aortic cross-clamp time.

From the standardized coefficients β (Fig. 2), it can be seen that the largest influence on the CPK24 is the CPK0, followed by CPK, and the weakest is CCT.

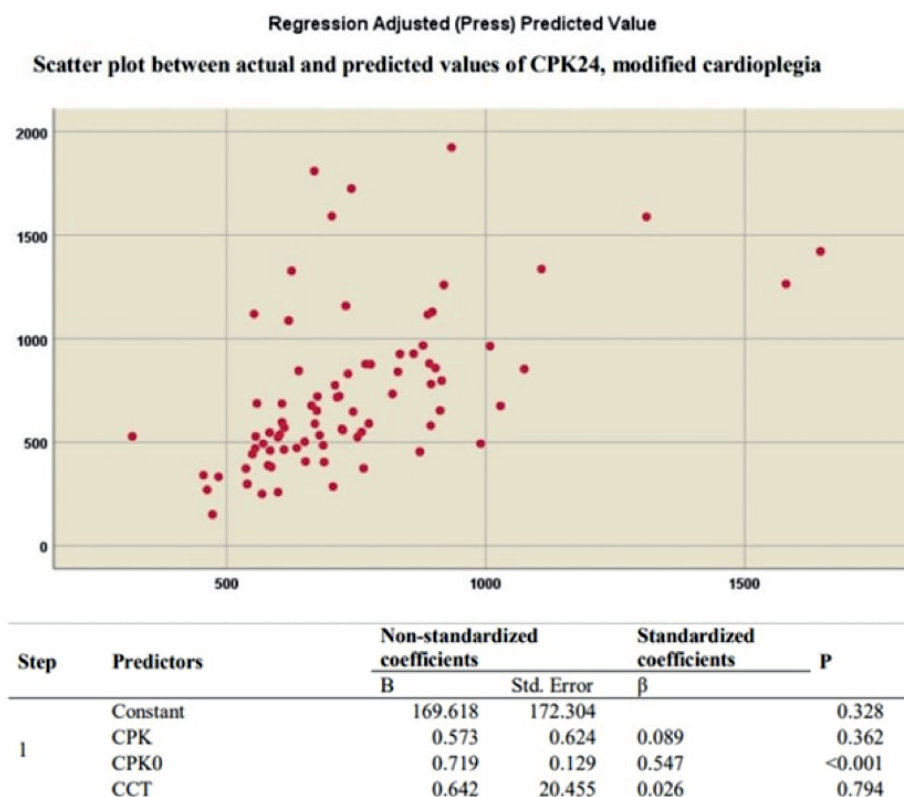


Fig. 2

The resulting values of the non-standardized coefficients provide information on the following facts:

- A 1 U/L increase in CPK results in an average increase in CPK24 of approximately 0.573 U/L;
- A 1 U/L increase in CPK0 results in an average increase in CPK24 of approximately 0.719 U/L;
- A 1-minute increase in CCT results in an average increase in CPC24 of approximately 0.642 U/L.

The coefficient of determination (R^2) value of 0.329 implies that, according to the model studied, the three indicators account for about 33% of the variation in CPK24. The moderate strength of the model is also observed on the scatter plot between the actual and predicted values of CPK24 (Fig. 2).

Discussion. Cardioplegic solutions play a key role in protecting the heart from myocardial damage during cardiac surgery. The DN solution has been used successfully in pediatric cardiac surgery [2, 5]; however, its use in adult cardiac

surgery has only recently been detailed [6–9]. In this study, we present our experience with MDN cardioplegia in patients undergoing isolated aortic valve replacement and compare it with a group of patients who received Kirklin cardioplegia.

The difference in the times of clamping and extracorporeal circulation is due to the individual skills and experience of the surgeons. Longer times in surgeries using MDN showed no increase in the need for an additional dose of cardioplegia, but also did not demonstrate a statistically significant difference. A significant difference was observed in the need for inotropic support, with Kirklin cardioplegia having a significantly higher need of moderate doses, while MDN more frequently allowed for the absence of inotropic support ($p < 0.001$). Mean ICU stay and hospital stay were statistically significantly higher in patients treated with Kirklin cardioplegia compared to those with MDN cardioplegia ($p < 0.001$ and $p = 0.02$, respectively). A statistically significant difference between the two treatment groups was found in the creatinine phosphokinase parameters when entering ICU (CPK0), creatinine phosphokinase MB fraction upon admission to an ICU (MB0), with higher median values of these indicators observed in the modified cardioplegia group ($p = 0.001$ and $p < 0.001$, respectively). These are the main findings evident from our study, which is consistent with earlier studies using DN in adult patients [6–9].

Conclusions. Evidence from this study suggests that the use of modified cardioplegic protection of del Nido in routine practice in adult patients undergoing aortic valve replacement may be safe, and it may result in comparable clinical outcomes and streamline the surgical workflow. The elevated cardiac enzyme values in modified del Nido cardioplegia did not affect the postoperative clinical outcome for the patients. Reducing the need for inotropic support in modified cardioplegia represents a significant advantage over the control group. The observed shortened ICU and hospital time provide a promising outlook. The trend for reduced incidence of new-onset postoperative rhythm disturbance, intraoperative DC shocks, and in-hospital mortality should be further investigated, as it may suggest superiority of myocardial protection with the modified solution. More prospective long-term studies should be designed to investigate the applications of MDN cardioplegia and confirm current findings.

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