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Del Nido cardioplegia in adult cardiac surgery: Clinical outcomes in a single center all-comer study

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Abstract

Introduction: The use of Del Nido Cardioplegia (DNC) has been extended in the latest years from pediatrics to adult cardiac surgery with encouraging results. We sought to investigate clinical and biochemical outcomes in adult patients who underwent cardiac surgery with different degrees of complexity who received DNC for myocardial protection.
Methods: Data on one-thousand patients were retrospectively collected from 2020 to 2022. The only exclusion criteria was off-pump adult cardiac surgery. Surgical procedures weight was categorized according EuroSCORE II in six groups: Single-CABG(G1), isolated non-CABG(mitral) (G2), isolated non-CABG(aortic) (G3), isolated non-CABG(any) (G4), 2-procedures(G5), 3/more-procedures(G6). Primary endpoint was to identify a binomial correlation between hs-TnT/CK-MB and the cross-clamp time (X-Clamp). A secondary endpoint was the comparison between the treatment groups of the vasoactive-inotropic score (VIS) and the need of mechanical circulatory support (MCS).
Results: A linear correlation was identified between hs-TnT and X-clamp in the overall population (rho:0.447, $p< .001$) and in the treatment groups (G1:rho=0.357, $p< .001$/G2:rho=0.455, $p< .001$/G3:rho=0.307, $p= .001$/G4:rho=0.165, $p= .257$/G5:rho=0.157, $p= .031$/G6:rho=0.226, $p= .015$). Similarly, a linear correlation between CK-MB and X-clamp in the overall population (rho=0.457, $p< .001$) and treatment group (G1:rho=0.282, $p< .001$/G2:rho=0.287, $p= .025$/G3:rho=0.211, $p= .009$/G4:rho=0.0878, $p= .548$/G5:rho=0.309, $p< .001$/G6: rho=0.212, $p= .024$) was identified. As regard for the secondary endpoint, no differences were reported between the treatment groups in terms of VIS and MCS (VIS G1:7; G2:4; G3:7; G4:7, G5:5.5, G6:6, p-value= .691) (MCS G1: 4.5%; G2:4.8%; G3:3.3%; G4:3.1%; G5:1.4%; G6:5.3%; p-value= .372).
Conclusions: Del Nido Cardioplegia is a safe and useful tool in adult cardiac surgery allowing operators to achieve a stable and durable cardioplegic arrest. Despite accounting with different types of surgery, the six subgroups of our study population showed similar perioperative results.

Keywords

del nido cardioplegia, vasoactive inotropic score, postoperative mechanical circulatory support, myocardial protection

Introduction

A stable and effective cardioplegic cardiac arrest is of paramount importance to achieve a reliable myocardial protection and to reduce ischemic-reperfusion damage during cardiac surgery.[1–4] Buckberg blood cardioplegia (BC, one part crystalloid: four parts whole blood) and St.Thomas crystalloid cardioplegia (STC) have for long represented the basis of myocardial protection strategies.[5–8] Despite being versatile, the short duration of action in terms of myocardial protection may require

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several repeated doses, especially in long and complex cardiac procedures, thus leading to a not negligible waste of cross-clamping time and infusion of high volume of fluids.[5–8]

In the effort to overcome the need of repeating doses, Histidine-Tryptophan-Ketoglutarate (HTK) solution emerged as an attractive alternative, providing a durable protection even in complex surgery with a single-dose infusion without interruption of the surgical flow.[9,10] However, the high volume of perfusate required, may induce volume and electrolytes imbalance, and histidine overload.[11] Furthermore, the effectiveness of this solution in patients with complex coronary disease is still a matter of debate.[12]

Del Nido cardioplegia (DNC) solution, firstly used in the 1990s for pediatric cardiac surgery, became an attractive alternative in adult cardiac surgery in the last decades. This blood and crystalloid solution (four parts crystalloid solution: 1-part whole blood) ensures a longer duration of a safe myocardial ischemic arrest of about 90 min after the first single infusion, thus reducing the need for repeated doses.[13,14] The peculiar composition of DNC is able to induce a rapid cardiac arrest with the main advantage of a safe and durable preservation of intracellular high-energy phosphates, maintenance of intracellular pH and reduction in calcium ion influx during either the ischemic arrest and the first phases of coronary reperfusion after aortic clamp removal.[3] Several studies addressed the safety and the efficacy of DNC in adult cardiac surgery comparing this latter with other cardioplegic solutions.[8,15–17] However, data about the effect of DNC in cardiac surgery procedures with different and incremental complexity is lacking.

We sought to investigate clinical and biochemical outcomes in adult patients who underwent cardiac surgery with different degrees of complexity who received DNC for myocardial protection.

Materials and methods

Between January 2020 and December 2022, records from 1000 all-comers patients who underwent adult cardiac surgery were retrospectively collected. Cardioplegic arrest and myocardial protection was achieved by means of DNC solution in all patients including urgency/emergency surgeries, infective endocarditis, redo surgeries and patients with reduced ejection fraction. Off-pump operations were excluded from this study. The Institutional Review Board approved this study (NP 1815). All patients included in the study signed an informed consent for anonymous data treatment.

Patients were stratified into six groups according to the EuroSCORE II surgery weight categories:

(1) Isolated Coronary Artery Bypass (G1)
(2) Isolated non-CABG (mitral valve repair/replacement) (G2)
(3) Isolated non-CABG (aortic valve replacement) (G3)
(4) Isolated non-CABG (other procedures) (G4)
(5) two procedures (G5)
(6) three or more procedures (G6)

Combined procedures are listed in detail in Table S1.

Surgical approaches included median sternotomy and minimally invasive cardiac surgeries, namely right J-shaped hemisternotomy for aortic surgery and anterior right minithoracotomy at the III intercostal space for mitral valve surgery.

Cardiopulmonary bypass (CBP) was performed with the LivaNova Stockert S5Heart-Lung Machine. Standard circuit consisted of a roller pump with a custom tubing pack with P.h.i.s.i.o coating (LivaNova), an oxygenator with a hard-shell reservoir. Two separated heater-cooler machines were used to manage systemic blood and cardioplegia temperature.

A 400 IU/kg heparin-dose was administered to obtain an Activated Clotting Time over 480 s. The pump flow during CPB was maintained at 2.4–3.0 mL/min/m2 to obtain a DO2 value of 280 mL/min/m2 visible with 550 CDI System and a mean arterial pressure in a range between 50 and 80 mmHg.

The composition of DNC is reported elsewhere.[13] Ready-for-use sacks of DNC solution were employed (Galenica Senese s.r.l.) with an addition of 12.3 mL of HCO_3^- before infusion. A custom-made cardioplegia circuit was used. The tubing system consisted of ¼ size tube for DN solution delivery and ¼ size tube for blood sample connected at the post-oxygenator bypass circuit with a twin roller pump. The DNC solution was mixed with whole blood in a 4:1 ratio and cooled to 4°C using a separated heater exchanger (Eurosets s.r.l., Medolla, Italy). An initial dose of 20 mL/kg was delivered with a maximum of 1000 mL for patients with body weight over 50 kg. An additional dose of 500 mL was administered before 90 min when the ischemic aortic cross-clamp time was expected to be over 120 min or if a spontaneous return of heart electrical activity was evident during surgery. Half dose of 10 mL/kg was administered for procedures requiring an aortic cross-clamping inferior to 45 min in patients without left ventricular hypertrophy.

DNC was delivered in both antegrade (Coronary Ostia/Aortic Root) and retrograde fashion:

- Antegrade: infusion in the aortic root was carried out with 250–300 mL/min flow pump and a pressure of 100–120 mmHg;
- Antegrade: through coronary ostia cardioplegia delivery in case of aortic regurgitation was carried out with 100–150 mL/min flow pump and a pressure of 100–120 mmHg.
- Retrograde: in Coronary Sinus with 200–250 mL/min flow pump and a pressure of 25–30 mmHg.

By reviewing anesthesiologic records, a Vasoactive-Inotropic Support score (VIS score) was retrospectively calculated as follows at the time of discharge from the operating room:

VIS = dopamine (mg/kg/min) + dobutamine (mg/kg/min) + 100x epinephrine (mg/kg/min) + 100x norepinephrine (mg/kg/min) + 10x milrinone (mg/kg/min) + 10,000x vasopressin (mU/kg/min).[18]

Daily monitoring of cardiac enzymes (CK-MB and high-sensitive Troponin T) was performed until the third postoperative day. Normal referral values were high-sensitive Troponin-T (hs-TnT) <14 ng/dl and CK-MB <6.2 mcg/L, respectively. At discharge, transthoracic echocardiography was performed to evaluate cardiac function.

Statistical analysis

Categorical variables (presented as frequencies and percentages) were compared by Chi-square test or Fisher exact test. Continuous variables were tested for normal distribution. Continuous variables with normal distribution were expressed as mean ± standard deviation, otherwise were expressed as median with interquartile range (IQR: 25th–75th). Continuous variables were compared using *t* test for independent samples if the variable had a normal distribution. Otherwise, the Mann–Whitney *U* test non-parametric test was used. Correlation between normal variables was tested using Spearman's test. Log-transformation was applied in certain cases for better data visual representation.

Endpoint of the study and definitions

Primary endpoint of this study was to analyze the correlation between the peak values of myocardial enzymes (CK-MB and Troponin T) and aortic cross-clamp duration in the six surgical groups divided for procedural complexity weight (single CABG, isolated mitral valve, isolated aortic valve, isolated procedures [other than G1, G2, G3], two procedures, three or more procedures).

Secondary outcome was to compare the vasoactive-inotropic score (VIS) and the need of mechanical circulatory support (MCS) after surgery (VA ECMO/IABP) among the different treatment groups.

Results

Baseline characteristics

Preoperative characteristics are summarized in Table 1. Median EuroSCORE II for the entire population was 1.9% (IQR: 1.1%–3.5%). Left ventricular hypertrophy (IVS thickness > 12 mm) was detected in 438 patients (43.8%). Surgery was performed in an urgent/emergency setting in 92 patients (9.2%). Patients underwent isolated CABG in 288 of cases (G1 = 28.8%), isolated mitral valve repair or replacement in 104 patients (G2 = 10.4%), isolated aortic valve replacement was performed in 153 patients (G3 = 15.3%), other isolated procedures were performed in 65 patients (6.5%); while 2-procedures (G4) and three- or more procedures (G5) were performed in 276 (27.6%) and 114 (11.4%) patients, respectively. Extensive description of associated procedures was reported on Table S1.

Intra and post-operative results

Intraoperative and postoperative results were reported in Tables 2 and 3, respectively. Median time to achieve a complete diastolic cardiac arrest was 30 s (IQR: 25–38 s) with no differences between the six groups (p= .088; Figure S1-(a)). A second dose of DNC was required in 176 patients (17.6%) and the median interval time between the first and the second dose was 75 min (IQR: 56–86 min). After removal of the aortic cross-clamp, the median time for a recovery to a spontaneous rhythm was 120 s (IQR: 60–180 s) with no differences reported between groups (p= .083; Figure S1-(b)). Patients requiring a second dose took a median time of 140 s (IQR: 70–240) to recover to a spontaneous rhythm. Spontaneous sinus rhythm was restored in 840 patients (84.0%), while epicardial pacing was necessary in 95 patients (9.5%). Ventricular fibrillation (VF) or tachycardia (VT) occurred in 65 patients (6.5%). Between the six treatment groups, no differences were reported in terms of SR, VF, and the need for epicardial pacing after cross clamp removal (p= .072), Figure 1. A DC shock was required in 70 patients (7.0%) for VF/VT onset after coronary reperfusion phase with prompt recovery to sinus rhythm. For patients requiring a second dose, spontaneous rhythm was restored in 147 patients (84.1%), while 10 patients (5.8%) a DC shock was first performed.

Table 1. Patient's preoperative characteristics.

Variables	Total	G1	G2	G3	G4	G5	G6
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
	1000	288 (28.8)	104 (10.4%)	153 (15.3%)	65 (6.5%)	276 (27.6%)	114 (11.4%)
Age (median, IQR) (years)	69 (60-75)	69 (62-74)	65 (55.5-73.5)	69 (61-75)	62.5 (53-73.25)	69 (61-75)	69 (62-75)
Ejection fraction (median, IQR)	55 (51-61)	55 (50-60)	64 (58-67)	55 (53-60)	55 (50-60)	55 (50-61)	56 (53-60)
IVS thickness (mm) (median, IQR)	13 (11-14)	12 (11-14)	11.5 (10-13.75)	14 (12-15)	12 (10-14)	13 (11-15)	12 (11-14)
Proximal IVS thickness >12 mm	435 (43.5)	105 (36.5)	32 (30.8)	99 (64.7)	20 (30.8)	134 (48.6)	45 (39.5)
PW thickness (mm) (median, IQR)	11 (10-12)	11 (10-12)	10 (9-11)	12 (11-13)	10 (9-12)	11 (9-12.5)	11 (10-12)
PAPS (mmHg) (median, IQR)	31 (25-40)	27 (20-30)	35 (30-45)	31 (25-40)	33 (28-40)	35 (28-41.75)	40 (33-50)
Pulmunary hypertension (PAPS>30 mmHg)	499 (49.9)	78 (27.1)	73 (70.2)	70 (45.8)	33 (50.8)	159 (57.6)	86 (75.4)
Fractional area change (%)	44 (40-48)	43 (40-48)	44 (42.5-47)	45 (40-50)	40 (37.75-42.75)	44 (40-48)	44 (40.75-47)
TAPSE (mm) (median, IQR)	22 (20-25)	22 (20-24)	23 (21-26)	22 (20-25)	20 (18-23.75)	21 (19-24.75)	21 (20-24.5)
BSA (median, IQR)	1.9 (1.7-2.0)	1.90 (1.78-2.00)	1.77 (1.64-1.94)	1.86 (1.71-2.00)	1.90 (1.71-2.00)	1.85 (1.70-1.98)	1.88 (1.77-2.02)
Serum creatinie (median, IQR)	1.0 (0.85-1.20)	1.00 (0.85-1.15)	0.95 (0.84-1.12)	0.98 (0.81-1.20)	1.00 (0.80-1.21)	1.02 (0.87-1.24)	1.06 (0.88-1.29)
Preoperative dialysis	15 (1.5)	5 (1.7)	0 (0.0)	2 (1.3)	0 (0.0)	4 (1.4)	4 (3.6)
EuroSCORE II (median, IQR)	1.9 (1.1-3.5)	1.32 (0.97-2.02)	1.14 (0.78-2.74)	1.50 (1.01-2.10)	2.60 (0.94-7.80)	2.76 (1.54-4.54)	3.51 (2.10-7.41)
Female sex	301 (30.1)	36 (12.5)	45 (43.3)	57 (37.3)	24 (36.9)	98 (35.5)	41 (36.0)
COPD FEV<60%	65 (6.5)	19 (6.6)	4 (3.9)	6 (3.9)	4 (6.2)	24 (8.7)	8 (7.1)
Hypertension	781 (78.1)	252 (88.1)	59 (57.8)	122 (79.7)	54 (84.4)	204 (74.2)	90 (79.6)
Diabetes mellitus	223 (22.3)	106 (36.9)	9 (8.8)	25 (16.4)	8 (12.5)	58 (21.1)	17 (15.0)
CAD	408 (40.8)	161 (56.5)	33 (32.7)	52 (34.4)	19 (31.1)	104 (38.2)	39 (34.8)
Dyslipidemia	613 (61.3)	234 (81.5)	46 (45.1)	91 (59.5)	22 (34.4)	158 (57.5)	62 (54.9)
Cerebrovascular disease	88 (8.8)	18 (6.3)	8 (7.8)	10 (6.5)	11 (17.2)	27 (9.8)	14 (12.4)
PAD	113 (11.3)	51 (17.8)	5 (4.9)	10 (6.5)	2 (3.1)	34 (12.4)	11 (9.7)
REDO	59 (5.9)	1 (0.3)	8 (7.7)	14 (9.2)	3 (4.7)	21 (7.6)	12 (10.5)
Urgent/emergency	169 (16.9)	60 (20.8)	12 (11.5)	8 (5.2)	29 (44.6)	40 (14.5)	20 (17.5)
Advanced NYHA class (III-IV)	279 (27.9)	36 (12.5)	34 (32.7)	47 (30.7)	21 (32.8)	94 (34.1)	47 (41.2)
Preoperative AF	166 (16.6)	13 (4.5)	14 (13.7)	21 (13.7)	9 (14.1)	67 (24.4)	42 (37.2)
Preoperative inotropic drugs	21 (2.1)	2 (0.7)	2 (1.9)	2 (1.3)	5 (7.7)	5 (1.8)	5 (4.4)
Preoperative IABP	13 (1.3)	5 (1.7)	1 (1.0)	0 (0.0)	0 (0.0)	6 (2.2)	1 (1.0)
ECMO	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infective Endocarditis	44 (4.4)	0 (0.0)	5 (4.9)	11 (7.2)	5 (7.7)	6 (2.2)	17 (15.0)

BSA: Body Surface Area, STS: Society of Thoracic Surgeon, COPD: Chronic Obstructive Pulmonary Disease, CAD: Coronary Artery Disease; PAD: Peripheral Artery Disease, NYHA: New York Heart Association, IVS: Interventricular septum; IABP: Intra-Aortic Balloon-Pump, ECMO: Extracoproreal Membrane Oxygenation.

Table 2. Intra-operative results.

Variables	Total	G1	G2	G3	G4	G5	G6
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
	1000	288 (28.8%)	104 (10.4%)	153 (15.3%)	65 (6.5%)	276 (27.6%)	114 (11.4%)
Operation time							
CPB time (min) (Median, IQR)	106 (83-135)	88 (69.75-108)	109 (90-131)	87 (79-102)	107 (80-132)	123 (103.75-150)	159 (132.25-182)
Aortic CXC time (min) (Median, IQR)	180 (61-100)	61 (49-75.25)	85 (69.5-96.5)	70 (61-82)	81 (55-94)	94 (76-116.5)	110 (88-133)
Cardioplegic solution delivery							
Antegrade	858 (85.8)	279 (96.9)	101 (97.1)	125 (81.7)	55 (84.6)	217 (78.6)	81 (71.1)
Retrograde	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	3 (2.6)
Both	138 (13.8)	9 (3.1)	3 (2.9)	28 (18.3)	10 (15.4)	58 (21.0)	30 (26.3)
First dose (ml) (median, IQR)	1000 (1000-1000)	1000 (1000-1000)	1000 (1000-1000)	1000 (1000-1000)	1000 (1000-1000)	1000 (1000-1000)	1000 (1000-1000)
Cardioplegic arrest induction time (sec) (median, IQR)	30 (26-37)	29 (25-34)	28.5 (25-33.25)	30 (26-38)	32 (27-46)	31 (26-39)	33.5 (27-39.5)
Repeated dose	176 (17.6)	35 (12.2)	12 (11.5)	27 (17.6)	13 (20.0)	60 (21.7)	29 (25.4)
Second dose (ml) (median, IQR)	500 (500-600)	500 (500-800)	500 (500-750)	500 (400-500)	550 (500-850)	500 (500-500)	500 (500-575)
CXC time for second dose(min) (median, IQR)	75 (56-86)	35.5 (15.5-60.5)	92 (57.75-102)	78 (38-83)	71 (57-83)	73 (57-86.75)	81 (72.50-94.25)
Spontaneous rhythm recovery time (sec) (median, IQR)	120 (60-180)	120 (60-180)	111 (55.5-180)	100 (50-150)	120 (60-180)	139 (73.75-240)	130 (60-347.5)
Spontaneous sinus rhythm	840 (84.0)	259 (89.9)	86 (82.7)	130 (85.0)	56 (86.2)	225 (81.5)	84 (73.7)
Type of rhythm							
PM induced	95 (9.5)	15 (5.2)	8 (7.7)	13 (8.5)	6 (9.2)	31 (11.2)	22 (19.3)
VF/VT	65 (6.5)	14 (4.9)	10 (9.6)	10 (6.5)	3 (4.6)	20 (7.2)	8 (7.0)
VF requiring DC shock	70 (7.0)	14 (4.9)	11 (10.6)	12 (7.8)	3 (4.6)	20 (7.2)	10 (8.8)
Second cross clamp	29 (2.9)	1 (0.3)	4 (3.8)	2 (1.3)	1 (1.5)	13 (4.7)	5 (4.4)
Second cross clamp time (median, IQR) (min)	36 (18-54)	37 (37-37)	29 (28-35)	83 (60.5-83.5)	7 (7-7)	36 (17-50)	41.5 (20.5-60.25)
Recovery time after 2nd CXC (sec) (median, IQR)	50 (30-76)	15 (15-15)	37 (30-40)	97.5 (66.25-128.75)	120 (120-120)	53 (37.5-62.5)	67 (40-150)
PBRC transfusion on CPB	174 (17.4)	50 (17.4)	22 (21.2)	21 (13.7)	9 (13.8)	52 (18.8)	20 (17.5)

CPB: cardiopulmunary bypass, CXC: cross clamp, IABP: intra-aortic balloon pump, IQR: interquartile range, OP: operating room, PM: pacemaker, VF: Ventricular fibrillation, PBRC: packed red blood cell, VIS: vasoactive-inotropic score.

Table 3. Postoperative results.

Variables	Total	G1	G2	G3	G4	G5	G6
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
	1000	288 (28.8%)	104 (10.4%)	153 (15.3%)	65 (6.5%)	276 (27.6%)	114 (11.4%)
ICU stay (hours) (median, IQR)	24 (21-69)	23 (20-48)	24 (21.5-48)	23 (19-43.25)	43.5 (22.75-129)	24 (21-70)	48 (24-120.75)
MAV time (hours) (median, IQR)	6 (5-11)	6 (4-10)	5 (4-8)	6 (4-9)	9 5-30.5)	7 (5-10)	10 (6-26)
MAV>48 h	68 (6.8)	8 (2.8)	5 (4.8)	5 (3.3)	11 (16.9)	18 (6.5)	21 (18.4)
Perioperative inotropic or vasoactive drug (any)	263 (26.3)	46 (16.0)	23 (22.1)	23 (15.0)	21 (32.3)	85 (30.8)	65 (57.0)
VIS SCORE at OR discharge (median, IQR)	6 (3-12)	7 (3-9)	4 2-12)	7 3.5-14.5)	7 (5-10)	5.5 (3-9)	6 (2.75-11)
Postoperative IABP	46 (4.6)	17 (5.9)	6 (5.8)	5 (3.3)	2 (3.1)	10 (3.6)	6 (5.3)
Postoperative ECMO	5 (0.5)	1 (0.3)	0 (0.0)	1 (0.7)	1 (1.5)	0 (0.0)	1 (0.9)
Postoperative mechanical support (new IABP/ECMO)	35 (3.5)	13 (4.5)	5 (4.8)	5 (3.3)	2 (3.1)	4 (1.4)	6 (5.3)
AKI	82 (8.2)	18 (6.2)	9 (8.7)	7 (4.6)	11 (16.9)	16 (5.8)	21 (18.4)
Postoperative dialysis	15 (1.5)	5 (1.7)	0 (0.0)	2 (1.3)	0 (0.0)	4 (1.4)	4 (3.5)
Postoperative AF	357 (35.7)	79 (27.4)	40 (38.5)	63 (41.2)	29 (44.6)	103 (37.3)	43 (37.7)
Postoperative PPI	33 (3.3)	3 (1.0)	1 (1.0)	3 (2.0)	3 (4.6)	15 (5.4)	8 (7.0)
Bleeding requiring surgical revision	45 (4.5)	14 (4.9)	4 (3.8)	5 (3.3)	3 (4.6)	9 (3.3)	10 (8.8)
Stroke/TIA	24 (2.4)	0 (0.0)	1 (1.0)	3 (2.0)	5 (7.7)	9 (3.3)	6 (5.3)
Postopeative AMI	9 (0.9)	3 (1.0)	0 (0.0)	1 (0.7)	0 (0.0)	2 (0.7)	3 (2.6)
Hospital length of stay (days) (median, IQR)	7 (6-9)	7 (6-8)	7 (6-9.75)	7 (6-8)	10 6-14)	7 (6-9.5)	8 (7-13)
Perioperative mortality	10 (1.0)	2 (0.7)	0 (0.0)	1 (0.7)	1 (1.5)	2 (0.7)	4 (3.5)
30 days mortality	19 (1.9)	6 (2.1)	3 (2.9)	5 (3.3)	3 (4.6)	2 (0.7)	5 (4.4)

AKI: Acute Kidney Injury, AMI: Acute Myocardial Infarction, ECMO: extracorporeal membrane oxygenator, IABP: intra-aortic balloon pump, ICU: Intensive Care Unit, IQR: interquartile range, MAV: Mechanical Assisted Ventilation, PPI: Permanent Pacemaker Implantation, TIA: transient ischemic attack.

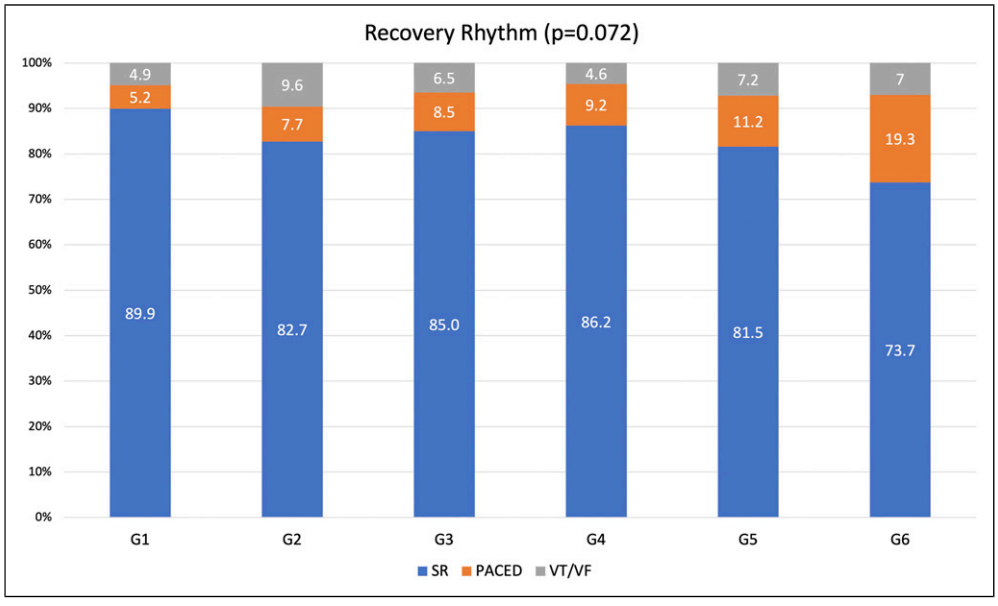

Figure 1. Rhythm recovery at cross clamp release.

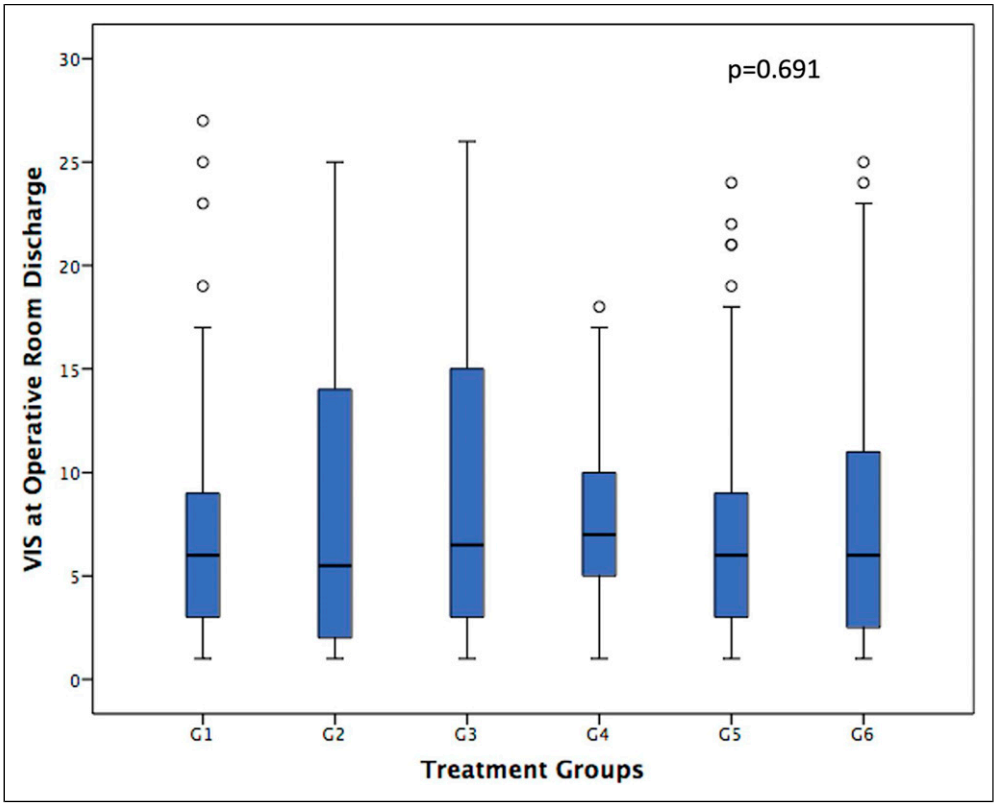

Figure 2. Median VIS (Vaso-Active Inotropic Score) at operative room discharge between groups.

At discharge from the operating room, 263 patients (26.3%) required inotropic or vasoactive drugs support with a calculated median VIS of six points (IQR: 3–12 point). Moreover, no differences were reported between the six treatment groups in terms of VIS (VIS G1: median seven; G2: median four; G3: median seven; G4: median 7, G5: median 5.5, G6: median 6, *p*-value= .691), Figure 2. In 59 patients (33.9%) requiring a second dose were discharged from the operating room with inotropic or vasoactive drugs support with a median VIS of eight points (IQR: 4–13). In the postoperative period 46 (4.6%) patients required mechanical circulatory support (MCS) with IABP and/or ECMO (IABP 46 patients; VA-ECMO five patients). Among these patients, 13 (1.3%) had a pre-operative mechanical support and underwent urgent/emergent surgery. Therefore, new postoperative mechanical support (IABP or VA-ECMO) occurred in 35 patients (3.5%). No significant differences were reported between groups in terms of need of postoperative MCS (G1: 4.5%; G2:4.8%; G3: 3.3%; G4: 3.1%; G5: 1.4%; G6: 5.3%; *p*-value= .372), Figure S2. Of note, among 13 patients with preoperative IABP and/or ECMO (one patient), mechanical circulatory supports were maintained after surgery and gradually weaned.

Median ventilation time and intensive care unit stay were respectively 6 h (IQR: 5–11 h) and 24 h (IQR: 21–69 h). Prolonged mechanical ventilation (>48 h) was required in 68 patients (6.8%). Perioperative mortality and 30-days mortality were respectively 1.0% and 1.9%.

Cardiac enzymes release

In the overall population peak of CK-MB and hs-TnT were respectively 31.1 mcg/L (IQR: 20.2–52.9) and 582 ng/dl (IQR: 352–1106), Figure S3, while for patients requiring a second dose the peak values were 33 mcg/L (IQR: 23–66) and 661 ng/dl (IQR: 384–1418), respectively. Excluding patients undergoing concomitant AF ablation, CK-MB and hs-TnT peaked at 30 mcq/L (IQR: 20–50) and 553 ng/dl (IQR: 344–962), respectively.

A positive correlation was identified through Spearman's test between aortic cross clamp time and CK-MB peak level in the overall population (rho=0.457, $p< .001$, Figure S4) and similarly, in the different treatment groups (G1: rho=0.282, $p < .001$; G2: rho=0.287, $p = .025$; G3: rho=0.211, $p = .009$; G4: rho=0.0878, $p = .548$; G5: rho=0.309, $p < .001$; G6:

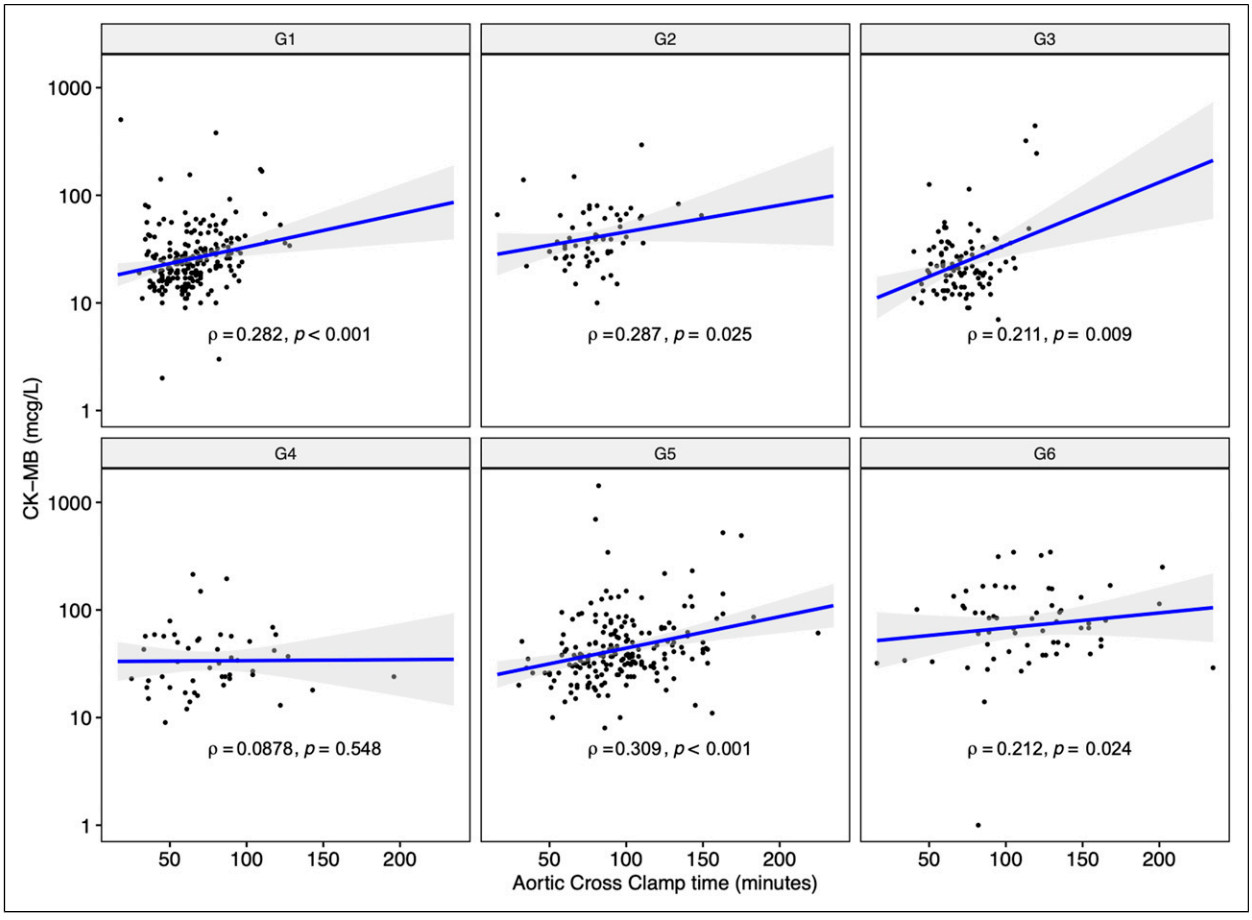

Figure 3. Spearman's correlation (rho) between CK-MB dismission peak and cross-clamp time in G1 (CABG), G2 (isolated mitral), G3 (isolated Aortic), G4 (isolated procedures), G5 (2 procedures), G6 (3 or more procedures). CK-MB is depicted after log transformation; blue line represents regression line with 95% confidence interval (grey shadow).

rho=0.212, p = .024), Figure 3. Likewise, a positive correlation was identified through Spearman's test between aortic cross clamp time and hs-TnT release peak level both in the overall population (rho: 0.447, p< .001, Figure S4) and in the different treatment groups (G1: rho=0.357, p< .001; G2: rho=0.455, p< .001; G3: rho=0.307, p= .001; G4: rho=0.165, p= .257; G5: rho=0.157, p= .031; G6: rho=0.226, p= .015), Figure 4). The correlations between postoperative peaks of myocardial enzymes release and cross-clamp time appear to be similar in the six treatment groups.

In the overall population, a complete CK-MB median values normalization was observed at the third postoperative day (D0: 27.3 mcg/L, D1: 23.9 mcg/L, D2: 9.5 mcg/L, D3: 4.0 mcg/L), Figure S5(a). At third postoperative day, the median value of CK-MB was below the referral cut-off for normality in all groups (G1: 3.2 mcg/L; G2: 4.3 mcg/L; G3: 3.2 mcg/L; G4: 3.6 mcg/L; G5: 4.8 mcg/L; G6: 6.3 mcg/L p< .001), Figure S5(b).

Discussion

The main findings of this study may be summarized as follows: (i) the use of DNC in different complexity degrees of surgery showed a positive correlation at Spearman's test between the peaks of hs-TnT and CK-MB and the duration of the cross-clamp times; (ii) in each treatment group the use of DNC showed normalization of median CK-MB values at third postoperative-day; (iii) the median VIS and the need of MCS stratified for the different procedures were comparable at the discharge from OR.

Nowadays the DNC solution has been reported as a safe and effective tool for myocardial protection. Previous studies compared clinical and biochemical outcomes of DNC with other cardioplegic solutions in adult cardiac surgery populations undergoing isolated procedures (i.e. isolated CABG, aortic valve replacement, mitral valve surgery or minimally invasive procedures).[8,15–17,19] Nonetheless, stratification for

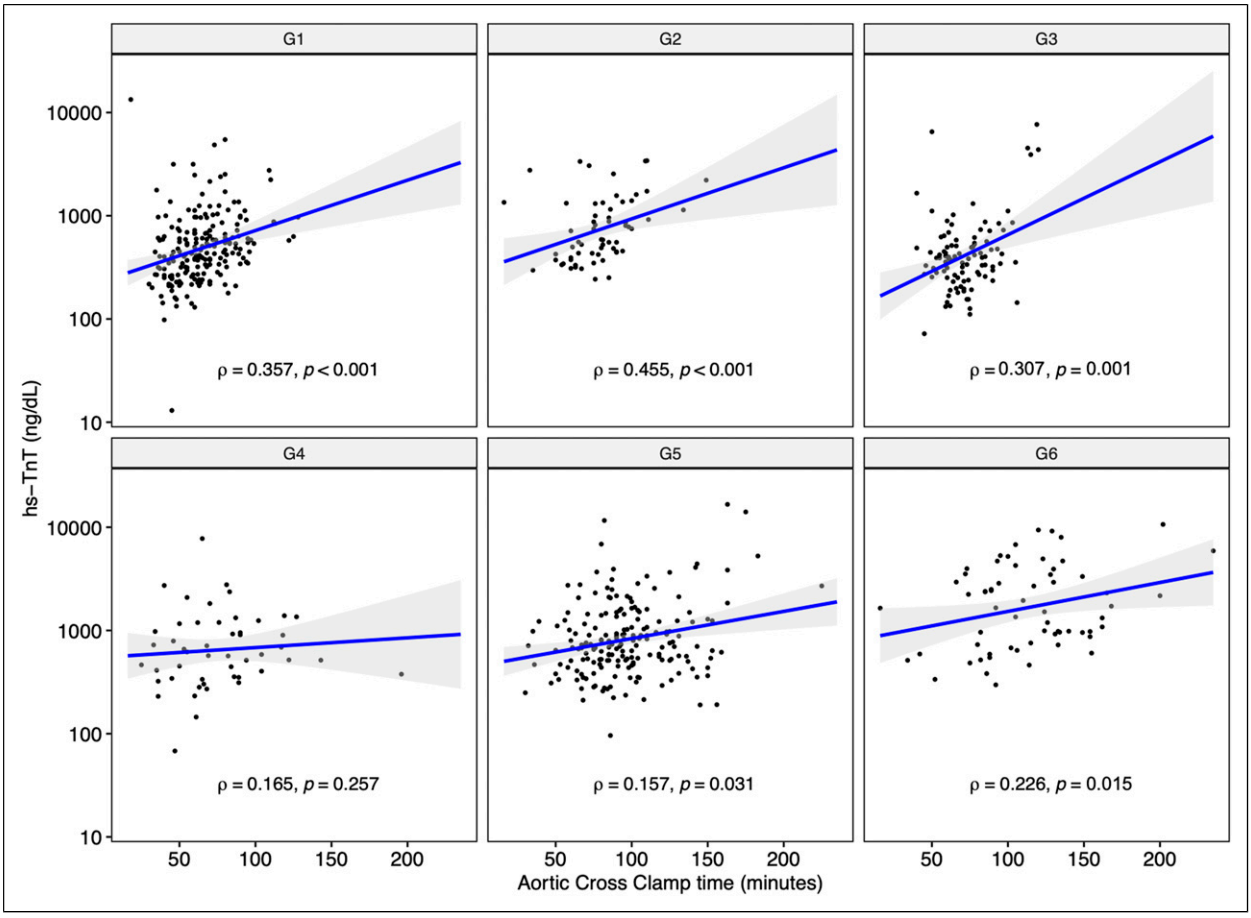

Figure 4. Spearman's correlation (rho) between hs-TnT dismission peak and cross-clamp time in G1 (CABG), G2 (isolated mitral), G3 (isolated Aortic), G4 (isolated procedures), G5 (2 procedures) G6 (3 or more procedures). Hs-TnT is depicted after log transformation; blue line represents regression line with 95% confidence interval (grey shadow).

procedural complexity is lacking. In this regard, the present study focused the analysis on safety and effectiveness of DNC in an all-comers study, thus results are reported in a stratified analysis based on the surgical procedural weight according to EuroSCORE II. Interestingly, we found a positive linear correlation between the peaks of CK-MB and hs-TnT and the duration of cross-clamp time both in the overall population and in five of six different groups (G1, G2, G3, G5, G6). These findings suggested the release of myocardial necrosis markers in patients receiving DNC for myocardial protection strategy is related to the duration of the cross-clamp time in patients who underwent cardiac surgery irrespective of the weight of the procedure. Moreover, the shape of the linear correlations appeared to be similar between either the whole population and the different types of surgeries, thus meaning that myocardial protection using DNC was comparable among the five treatment groups. A similar trend was observed from Lee et al. in a study comparing Del Nido and HTK cardioplegia in a mixed series of patients undergoing minimally invasive cardiac surgery.[2] Nonetheless, Spearman's test failed to identify a linear correlation in G4. Notably, this group showed a high heterogeneity in terms of endo/epimyocardial surgical injury (isolated MAZE IV procedure, cardiac tumors including sarcomas, post-infarction ventricular septal defects and Dor procedures), thus probably leading to a stochastic, not linear myocardial enzymes release. Drawing definitive conclusions regarding the impact of concomitant AF ablation is challenging due to the current lack of studies on the subject. A study focusing on cryoablation indicated elevated levels of cardiac enzymes compared to studies that excluded AF ablation.[20] Additionally, this study revealed that cryoablation procedures led to higher cardiac enzymes release levels compared to radiofrequency ablation.[21] This implies that not all alternative energy sources for AF ablation result in an increase in cardiac biomarkers beyond post-cardiac surgery levels. The discrepancy in biomarker levels

across energy sources may be attributed to the greater transmurality of cryoablation in contrast to radiofrequency ablation, although further research is needed to validate this hypothesis. In the current analysis, removal of patients undergoing concomitant AF ablation yielded slightly lower cardiac enzymes peaks.

Although the postoperative raise of CK-MB and hs-TnT serum levels showed multifactorial etiology (myocardial surgical manipulation, arrhythmia surgery and oxidative stress during ischemia phase), the determinant of these alterations has been proved to be mainly related to the degree of myocardial injury after cardiac arrest.[22] For this reason, these markers have been widely used as indirect indicators of myocardial protection quality in patients undergoing cardiac surgery with cardioplegic arrest. In the present study, the use of DNC was associated with a rapid decrease in CK-MB blood levels until normal values were reached at post-op day 3 both in the overall population as well as in all the six subgroups. A similar pattern was observed in hs-TnT levels, although normalization occurred less rapidly. These results are consistent with other studies[1,2] where CK-MB and hs-TnT showed a comparable trend. The rapid recovery towards normal blood levels of CK-MB and hs-TnT suggested a low toxicity and a high effectiveness in myocardial protection of DNC in all patients' subgroups. Several mechanisms have been hypothesized to explain these findings: in vitro, experimental studies showed aged myocardium as particularly susceptible to the reperfusion injury similarly to immature cells.[13] The low concentration of calcium and the addiction of lidocaine in the DNC solution is able to induce a more stable depolarizing potential during cardiac standstill phase. Opposite to other cardioplegic solutions, the cellular electrical stability observed in DNC results in a reduction of the cytoplasmic calcium overload. This latter mechanism represents the major cause of a Ca^{2+} mediated hypercontractility, thus associated with an increased myocardial stress and reperfusion injury.[13,23] These mechanisms of action and the cellular response to the reperfusion injury with the DNC are well described in immature myocardium cells. Aged myocardium cells showed similar pathophysiological mechanisms, thus explaining the rationale of the extension of the DNC from pediatric to adult cardiac surgery patients.[13]

Other complementary indirect parameters used to investigate myocardial protection in patients undergoing cardiac surgery were the VIS (vasoactive-inotropic score) and the incidence of postoperative need of MCS. In the present study, we found a median VIS at the time of discharge from OR of six points (range 3–12) without a significant difference between the six subgroups. Similarly, no differences were reported in the incidence of postoperative need of MCS between groups, thus suggesting a stable and effective myocardial protection was achieved with the use of the DNC solution regardless of the surgical complexity. Only Talwar et al.,[24] reported similar findings despite DNC being used in a pediatric study cohort. Furthermore, Lee and colleagues reported a mean VIS of 4.63 ± 6.29 in adult patients who underwent minimally invasive cardiac surgery.[2]

Lastly, the incidence of VF after cross-clamp removal is widely accepted as a surrogate of suboptimal myocardial protection. In this study, the incidence of VF was 6% in the overall population without significant differences between groups stratified for incremental surgical complexity. This incidence was lower if compared to other studies investigating different cardioplegic solutions.[1,10,17,19] Two main factors have been investigated influencing the rhythm and the electromechanical recovery of the myocardium after cross-clamp removal: (i) a rapid achievement of the cardiac arrest when cardioplegia infusion is given and, (ii) a stable and durable reduction of metabolic cellular activity during cardiac standstill without depletion of intracellular energetic substrate. Both these aspects help to reduce ATP consumption during the early phase of cardiac ischemia after aortic cross-clamp positioning and preserve myocardial energetic substrate storages during cardioplegic arrest.[25–27] The use of the DNC solution was able to provide a rapid onset of cardiac arrest after aortic cross-clamp. A stable and quick diastolic standstill was achieved with a median of 30 s (range 25–38). Furthermore, the use of lidocaine among the DNC constituents allowed to tackle the issue of a durable maintenance of membrane stability. As previously demonstrated, lidocaine inhibits the fast sodium channels in the myocardium, thus stabilizing the membrane against sodium currents, which might trigger spikes of depolarization and thus arrhythmias.[28]

Limitations

The retrospective nature of this study as well as the lack of a control group represent the main limitations. Moreover, data collected from a single-center and the high incidence of concomitant arrhythmia surgery may represent a confounding factor in the analysis of myocardial necrosis enzymes release. Release of CK-MB and hs-TnT failed to show a positive correlation with cross-clamp time in G4. Moreover, we may hypothesize that the high heterogeneity of the procedures included in G4 (including isolated MAZE IV procedure, cardiac tumors including sarcomas, post-infarction ventricular septal defects and Dor procedures) might have

jeopardized enzyme release and thus negatively impacted correlation in this single group.

Conclusions

Del Nido Cardioplegia is a safe and useful tool in adult cardiac surgery allowing operators to achieve a stable and durable cardioplegic arrest. The ease of the infusion protocols permits to perform most of the surgical procedures with a single infusion offering a reliable myocardial protection even in concomitant complex surgical procedures. Despite accounting with different types of surgery, the six subgroups of our study population showed similar perioperative results. Further studies are warranted in order to confirm our findings.

Declaration of conflicting interests

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Supplemental Material

Supplemental material for this article is available online

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Appendix

Abbreviations

BC	Buckberg Cardioplegia
DNC	Del Nido Cardioplegia
STC	Saint Thomas Cardioplegia
HTK	Histidine-Tryptophan-Ketoglutarate
CPB	Cardiopulmonary Bypass
VIS	Vasoactive-inotropic score
MCS	Mechanical circulatory support
ECMO	Extracorporeal Membrane Oxygenation
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
SR	Sinus Rhythm
AF	Atrial Fibrillation
IABP	Intra-aortic balloon pump