Original Article

Cold crystalloid versus warm blood cardioplegia in patients undergoing aortic valve replacement

Paolo Nardi[1], Sara R. Vacirca[1], Marco Russo[1], Dionisio F. Colella[2], Carlo Bassano[1], Antonio Scafuri[1], Antonio Pellegrino[1], Gerry Melino[3], Giovanni Ruvolo[1]

[1]Division of Cardiac Surgery, [2]Division of Anesthesiology, [3]Department of Experimental Medicine and Surgery, Faculty of Medicine and Surgery, Tor Vergata University, Rome, Italy

Contributions: (I) Conception and design: P Nardi, SR Vacirca, A Pellegrino, G Ruvolo; (II) Administrative support: SR Vacirca, C Bassano, G Melino, G Ruvolo; (III) Provision of study materials or patients: M Russo, A Scafuri; (IV) Collection and assembly of data: DF Colella, C Bassano; (V) Data analysis and interpretation: P Nardi, M Russo, G Ruvolo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Marco Russo, MD. Tor Vergata University Hospital, Viale Oxford 81, 00133 Rome, Italy. Email: mar.russo1987@gmail.com.

Background: Myocardial protection techniques during cardiac arrest have been extensively investigated in the clinical setting of coronary revascularization. Fewer studies have been carried out of patients affected by left ventricular hypertrophy, where the choice of type and temperature of cardioplegia remain controversial. We have retrospectively investigated myocardial injury and short-term outcome in patients undergoing aortic valve replacement plus or minus coronary artery bypass grafting with using cold crystalloid cardioplegia (CCC) or warm blood cardioplegia (WBC).

Methods: From January 2015 to October 2016, 191 consecutive patients underwent aortic valve replacement plus or minus coronary artery bypass grafting in normothermic cardiopulmonary bypass. Cardiac arrest was obtained with use of intermittent antegrade CCC group (n=32) or WBC group (n=159), according with the choice of the surgeon.

Results: As compared with WBC group, in CCC group creatine-kinase-MB (CK-MB), cardiac troponin I (cTnI), aspartate aminotransferase (AST) release, and their peak levels, were lower during each time points of evaluation, with the greater statistically significant difference at time 0 ($P<0.05$, for all comparisons). A time 0, CK-MB/CK ratio >10% was 5.9% in CCC group versus 7.8% in WBC group ($P<0.0001$). At time 0 CK-MB/CK ratio >10% in patients undergoing isolated aortic valve replacement was 6.0% in CCC group versus 8.0% in WBC group ($P<0.01$). No any difference was found in perioperative myocardial infarction (0% versus 3.8%), postoperative (PO) major complications (15.6% versus 16.4%), in-hospital mortality (3.1% versus 1.3%).

Conclusions: In aortic valve surgery a significant decrease of myocardial enzymes release is observed in favor of CCC, but this difference does not translate into different clinical outcome. However, this study suggests that in presence of cardiac surgical conditions associated with significant left ventricular hypertrophy, i.e., the aortic valve disease, a better myocardial protection can be achieved with the use of a cold rather than a warm cardioplegia. Therefore, CCC can be still safely used.

Keywords: Cold crystalloid cardioplegia (CCC); warm blood cardioplegia (WBC); myocardial protection; aortic valve replacement

Submitted Aug 30, 2017. Accepted for publication Feb 09, 2018.
doi: 10.21037/jtd.2018.03.67
View this article at: http://dx.doi.org/10.21037/jtd.2018.03.67

Introduction

The use of cardioplegia solution is aimed to avoid myocardial muscle damage leading poor contraction and abnormal increased release of cardiac biomarkers enzymes during cardiac arrest (1).

Cold crystalloid cardioplegia (CCC) associated with mild-to-moderate hypothermia has the advantage to decrease the oxygen consumption, offers some degree of myocardial protection during period of low flow or low perfusion pressure, and it is inexpensive and simple to use.

Alternatively, warm blood cardioplegia (WBC) is been proposed as a safe technique for myocardial protection based on the rationale that blood, as opposed to crystalloid solution, could potentially improve postoperative (PO) cardiac outcomes, because it more closely approximates the normal physiology, i.e., carrying oxygen to the myocardium or ensuring a less hemodilution.

In order to protect the hypertrophic myocardium, i.e., during cardiac surgery for the replacement of a diseased aortic valve, several studies published in 80s and 90s have not showed substantial differences between type (crystalloid versus blood), temperature of solution (cold, tepid, or warm), or via administration (antegrade versus retrograde) of the cardioplegia (2-6).

The aim of this study was to evaluate retrospectively whether in patients undergoing aortic valve replacement, isolated or in association with coronary artery bypass grafting, myocardial protection and in-hospital outcome were differently affected by two types of cardioplegic solution currently used in cardiac surgery: cold crystalloid St. Thomas cardioplegia and WBC.

Methods

From January 2015 to October 2016 at the Cardiac Surgery Unit of the Tor Vergata University Hospital of Rome 191 consecutive patients (mean age of 72±9 years) underwent aortic valve replacement, isolated or in association with coronary artery bypass grafting. Cardiac arrest during normothermic cardiopulmonary bypass was obtained using CCC group (n=32) or WBC group (n=159) according to the choice of the surgeon, both administered intermittently and via antegrade. The two groups of patients represented the object of the present study.

All patients performed preoperatively trans-thoracic echocardiography and cardiac catheterization with selective coronary angiography, and postoperatively a trans-thoracic echocardiography on the 3rd to 4th PO day.

Patients affected by other significant concomitant heart valve diseases, operated in emergency, or needing a redo operation were excluded from the study. The study was approved by the Institutional Review Board of the Tor Vergata University Hospital, which waived the need for patient consent. The study was designed to be as retrospective one. All patients gave informed surgical consent.

Data collection

In all patients were evaluated serum levels myocardial enzymes, i.e., total creatine-kinase (CK), creatine-kinase-MB (CK-MB), aspartate aminotransferase (AST), cardiac troponin I (cTnI), and their peak levels, at the end of operation [time 0, i.e., at the admission in intensive care unit (ICU)], 24 and 48 PO hours after surgery. The value of CK-MB/CK ratio greater than (>) 10% was measured at the same times. Perioperative myocardial infarction was defined as an increase of cTnI above 10 ng/mL in association with an increase of CK-MB more than 10% of the total CK and the onset of electrocardiogram (ECG) anomalies.

Complete revascularization was defined when each of three major vascular territories subtended by a significant coronary artery stenosis was grafted. PO low output cardiac syndrome was defined by a cardiac index value less than 2.0 L/min/m^2, requiring the inotropic support (i.e., epinephrine, enoximone or levosimendan with or without norepinephrine intravenous infusion), for a period greater than 24 hours, and or the use of intra-aortic balloon pump. Preoperative and at weaning form cardiopulmonary bypass hematocrit level and haemoglobin value were evaluated.

Major non-cardiac complications were also analysed. Pulmonary complication was defined as an episode of primary respiratory failure requiring mechanical ventilation for more than 48 hours, re-intubation, or intermittent application of non-invasive positive-pressure ventilation. Permanent neurological complication due to focal or general cerebral lesion was defined as a stroke; transient ischemic attack was defined when neurological symptoms lasted less than 24 hours before disappearing. Acute kidney injury was defined as a two-fold increase of preoperative creatinine serum level or oliguria requiring need of continuous veno-venous hemofiltration.

Operative mortality included death for any causes in-hospital after operation, at anytime or within 30 days after discharge.

Surgical procedure

Surgery was carried out in all patients by means of a complete longitudinal sternotomy, cardiopulmonary bypass with right atrial or bi-caval cannulation and arterial cannulation in the ascending aorta, and aortic cross-clamping. The composition of the crystalloid cardioplegia was referring to the St. Thomas Hospital solution II, with the adding of HCO_3 8.4 mmol.

Type of cardioplegia was given in accordance with the surgeons' choice: one surgeon (GR) used in 45 patients WBC from January 2015 to April 2016, and subsequently, in the other 32 patients cold crystalloid St. Thomas cardioplegia. All the other surgeons have adopted WBC throughout the entire period of the study.

In the CCC group intermittent antegrade cold (4 ℃) crystalloid cardioplegia (10 mL/Kg the first dose, followed by doses of 5 mL/Kg) was administered every 25–30 minutes. In the WBC group intermittent antegrade warm (35–36 ℃) blood cardioplegia (600 mL the first dose, followed by doses of 400 mL, each in 2 minutes) was administered every 20–25 minutes.

Cardiopulmonary bypass temperature in all patients was maintained at 35–36 ℃. In presence of isolated aortic valve stenosis cardioplegia was administered into the aortic root, in presence of mixed pathology or pure insufficiency of the aortic valve it was done through the selective infusion into the coronary ostia.

When required, coronary artery bypass was performed using in most cases the left internal mammary artery graft to the left anterior descending artery, in association with saphenous vein grafts, single or in Y-graft composition, to the right coronary artery and/or to the left circumflex artery branches. The aortic valve was replaced according with the standard surgical technique, with the implant of a biological pericardial or a mechanical aortic valve prosthesis, based on patient's age and choice.

Statistical analysis

Statistical Analysis was performed with Stat View 4.5 (SAS Institute Inc., Abacus Concepts, Berkeley, CA, USA). The continuous variables were calculated as mean values plus minus standard deviation, the categorical variables as number and percentage. The ANOVA test was used to calculate the repeated measures of myocardial enzymes levels at the time 0, and at 24 and 48 hours after surgery. The differences between the two groups of patients were detected by means of the Student's *t*-test for continuous data, and the χ^2 or Fisher's exact test for categorical data. All P values less than 0.05 were considered statistically significant.

Results

Preoperative characteristics of the two groups of patients are reported in *Table 1*. Both groups were similar for preoperative characteristics, except for a greater incidence in CCC group of hypertension (P=0.034) and concomitant aortic valve insufficiency (P=0.001). Intraoperative data are summarized in *Table 2*. In comparison with WBC group, cardiopulmonary bypass time was longer in WBC group (P=0.017). As expected, the mean number of cardioplegia's doses per patient was higher in WBC group (2.5±1.0 versus 1.8±0.7; P<0.0001), despite the mean number of distal coronary artery anastomoses per patient was similar in the two groups (0.5±0.8 versus 0.4±0.7). Complete revascularization was achieved in all patients of both groups.

Before cardiopulmonary bypass, mean hematocrit level and hemoglobin value were not statistically different in both groups, whereas after the weaning from cardiopulmonary bypass their values remained favorably higher in WBC group, with a slight levels of statistical significance (P=0.082, and P=0.047, respectively) (*Table 2*).

Serum levels of total CK, CK-MB, AST and cTnI were lower in CCC group in each time of evaluation. In particular, the greater statistically significant differences were found at time 0, either for the serum level of the enzymes (mean values and their peaks) (P<0.05, for all comparisons) than for the value of the CK-MB/CK ratio >10% (5.9% versus 7.8% of the patients; P<0.0001) (*Figures 1-5*) (*Table 3*). In the subgroup of patients undergoing isolated AVR, the CK-MB/CK ratio >10% at time 0 was 6.0% in CCC group versus 8.0% in WBC group (P<0.01). Similar statistically significant differences of the values of CK-MB/CK ratio >10% at time 0 was observed for aortic cross-clamp times greater than 60 minutes (5.0% versus 7.0%, P<0.01) or less (6.0% versus 8.0%, P=0.001).

In the CCC group was found a significantly higher incidence of the use of norepinephrine intravenous infusion for a time greater than 24 hours after operation (9.4% versus 0.6%; P=0.002) (*Table 4*).

The incidence of PO low output cardiac syndrome, perioperative myocardial infarction, overall PO incidence of major complications (i.e., neurological damage, acute

Table 1 Preoperative characteristics

Variable	WBC group (n=159)	CCC group (n=32)	P value
Age (year)	72.6±9.8	70.7±7.9	0.249
EuroSCORE II (%)	2.3±1.7	2.3±1.7	0.904
Sex (female), n (%)	78 (49.1)	13 (40.6)	0.384
Body surface area (m^2)	1.8±0.2	1.8±0.2	0.933
Body mass index (kg/m^2)	27.5±4.6	26.7±4.4	0.362
Hypertension, n (%)	139 (87.4)	32 (100.0)	0.034
Diabetes on insulin therapy, n (%)	14 (8.8)	2 (6.3)	0.634
Chronic lung disease, n (%)	21 (13.2)	2 (6.3)	0.270
Extracardiac arteriopathy, n (%)	13 (8.2)	2 (6.3)	0.712
Creatinine (mg/dL)	1.2±1.3	1.5±2.5	0.296
Creatinine clearance (mL/min)	68.5±30.4	68.5±34.9	0.995
Renal impairment on dialysis, n (%)	2 (1.3)	1 (3.1)	0.438
NYHA III–IV class, n (%)	86 (54.1)	17 (53.1)	0.921
Unstable angina, n (%)	18 (11.3)	4 (12.5)	0.849
Recent myocardial infarction, n (%)	13 (8.2)	1 (3.1)	0.317
Cardiac troponin I (cTnI) (ng/mL)	0.09±0.68	0.03±0.29	0.718
CK-MB (ng/mL)	1.45±1.31	1.26±0.99	0.776
CK (U/L)	73.7±65.8	114±95.7	0.238
LVEF (%)	56.0±6.7	60.3±8.9	0.079
LVEDD (mm)	56.4±10	53.6±9.6	0.098
LVESD (mm)	38.6±9.2	36.4±7.9	0.224
PW thickness (mm)	14.1±9.5	14.4±9.2	0.895
LVS thickness (mm)	13.9±2.5	14.1±2.2	0.974
No. of diseased coronary vessels, n (%)			
One	30 (18.9)	6 (18.8)	0.988
Two	16 (10.1)	4 (12.4)	0.681
Three	9 (5.7%)	0	0.168
Left main stem disease	5(3.1)	0	0.309
Aortic valve disease, n (%)			0.001
Stenosis	105 (66.0)	11 (34.4)	
Mixed pathology or isolated insufficiency	54 (34.0)	21 (65.6)	

EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVS, left ventricle septum; NYHA, New York Heart Association; PW, posterior wall; WBC, warm blood cardioplegia; CCC, cold crystalloid cardioplegia; CK, creatine-kinase; CK-MB, creatine-kinase-MB.

Table 2 Intraoperative variables

Variable	WBC group (n=159)	CCC group (n=32)	P value
CPB time (min)	95.5±33.3	80.3±28.3	0.017
Cross-clamp time (min)	73.2±27.0	65.4±20.2	0.123
Isolated AVR CPB time (min)	74.2±13.5	64.6±20.2	0.066
Isolated AVR cross-clamp time (min)	61.2±12.1	56.6±14.4	0.313
No. of cardioplegia's doses	2.5±1.0	1.8±0.7	<0.0001
Isolated AVR, n (%)	108 (67.3)	22 (68.8)	0.873
AVR plus CABG, n (%)	51 (32.7)	10 (31.2)	0.927
No. of coronary grafts per patient	0.5±0.8	0.4±0.7	0.450
Hematocrit pre-CPB (%)	36.2±5.7	35.3±4.6	0.440
Hematocrit post-CPB (%)	27.2±3.2	25.6±3.2	0.082
Hemoglobin pre-CPB (g/dL)	12.1±1.9	11.6±1.5	0.245
Hemoglobin post-CPB (g/dL)	9.0±1.1	8.5±1.1	0.047

AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; WBC, warm blood cardioplegia; CCC, cold crystalloid cardioplegia.

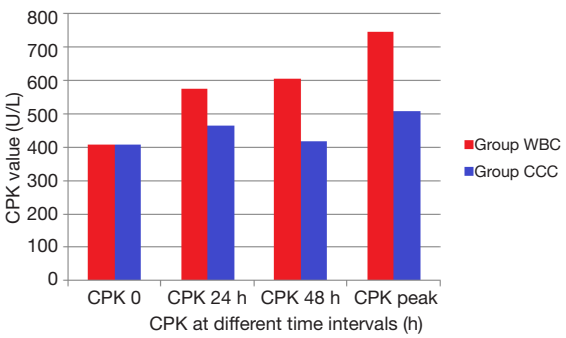

Figure 1 Postoperatively (at time 0, 24, 48 hours) release of creatine-phospho-kinase (CPK) expressed as U/L, and peak value. WBC, warm blood cardioplegia; CCC, cold crystalloid cardioplegia.

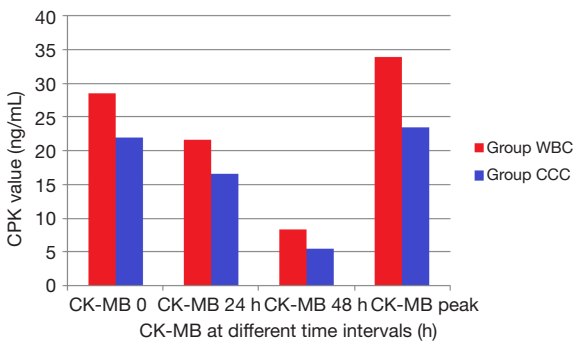

Figure 2 Postoperatively (at time 0, 24, 48 hours) release of creatine-kinase-MB (CK-MB) expressed as ng/mL, and peak value. WBC, warm blood cardioplegia; CCC, cold crystalloid cardioplegia; CPK, creatine-phospho-kinase.

kidney injury, pulmonary complications), re-exploration for bleeding, atrio-ventricular blocks requiring need for pacemaker implantation, mean number of units of blood transfused per patient, in-ICU and PO length of stay were similar in both groups (*Table 4*).

In the CCC group was observed a major incidence of primary respiratory pulmonary failure (9.4% versus 1.3%) with a slight statistical relevance (P<0.05).

Operative mortality was 1.3% (n=2) in WBC group, 3.1% in CCC group (P=0.438). Two deaths occurred for cardiac causes, one was due to neurological damage, respectively.

As compared with CCC group, the incidence of PO paroxysmal atrial fibrillation was higher in WBC group (53.5% versus 34.4%), although this difference did reach a slightly level of statistical significance (P=0.053) (*Table 4*).

Discussion

Over the past decades, the question of which solution, temperature or mode of administration of different types of cardioplegia provides a better myocardial protection during cardiac surgery has been widely discussed. Experimental

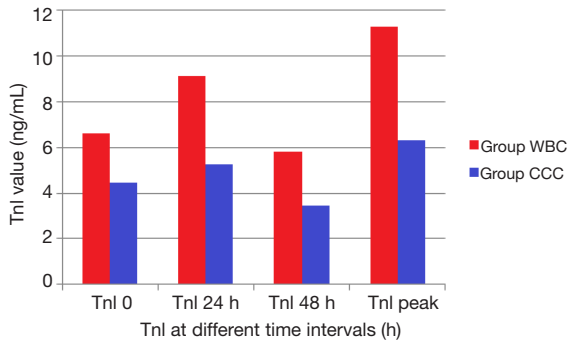

Figure 3 Postoperatively (at time 0, 24, 48 hours) release of cardiac troponin I (cTnI) expressed as ng/mL, and peak value. WBC, warm blood cardioplegia; CCC, cold crystalloid cardioplegia.

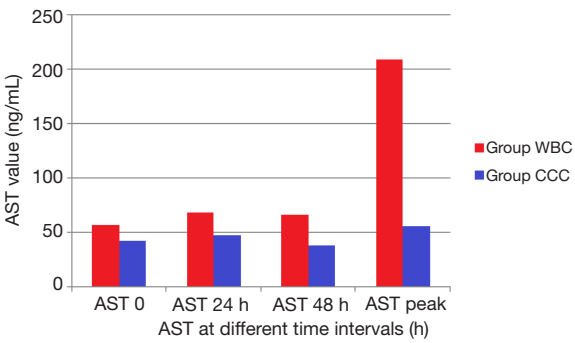

Figure 4 Postoperatively (at time 0, 24, 48 hours) release of aspartate aminotransferase (AST) expressed as ng/mL, and peak value. WBC, warm blood cardioplegia; CCC, cold crystalloid cardioplegia.

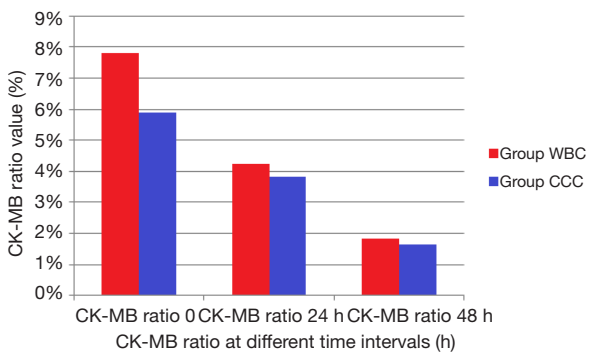

Figure 5 Mean value (%) of the ratio greater than 10% between creatine kinase MB (CK-MB) and total creatine-phospho-kinase (CPK) postoperatively measured (at time 0, 24 and 48 hours). WBC, warm blood cardioplegia; CCC, cold crystalloid cardioplegia.

Table 3 Serum levels of cardiac enzymes

Mean value	WBC group (n=159)	CCC group (n=33)	P value
CK-MB (ng/mL)			
Time 0	28.47	21.88	0.041
24 h	21.67	16.51	0.071
48 h	8.38	5.48	0.094
Peak	33.91	23.43	0.009
CK (U/L)			
Time 0	407.4	408.6	0.992
24 h	575.4	464.2	0.133
48 h	606.0	418.0	0.170
Peak	743.9	506.3	0.042
cTnI (ng/mL)			
Time 0	6.61	4.46	0.047
24 h	9.12	5.23	0.063
48 h	5.81	3.44	0.159
Peak	11.29	6.33	0.024
CK-MB/CK ratio >10% (%)			
Time 0	7.8	5.9	<0.0001
24 h	4.2	3.8	0.327
48 h	1.8	1.6	0.541
AST (U/L)			
Time 0	56.4	41.8	0.021
24 h	67.9	46.7	0.114
48 h	66.0	37.3	0.043
Peak	208.7	55.3	0.025

WBC, warm blood cardioplegia; CCC, cold crystalloid cardioplegia; CK, creatine-kinase; CK-MB, creatine-kinase-MB; AST, aspartate aminotransferase; cTnI, cardiac troponin I.

studies have suggested a more favorable outcome with the use of blood cardioplegia in comparison with CCC. Several clinical studies with or without randomization have been performed to assess which cardioplegic solution guarantees a better myocardial protection, but some studies have reported a favorable outcome of the blood (cold or warm) cardioplegia (2-5,7,8), others have not been able to demonstrate any difference (9-11). In another study a worse

Table 4 Postoperative results

Variable	WBC group (n=159)	CCC group (n=32)	P value
Low output cardiac syndrome, n (%)	7 (4.4)	2 (6.3)	0.327
Norepinephrine use >24 hours, n (%)	1 (0.6)	3 (9.4)	0.002
Intra-aortic balloon pump	0	0	–
Perioperative myocardial infarction, n (%)	6 (3.8)	0	0.331
Pulmonary complications, n (%)	2 (1.3)	3 (9.4)	0.027
Neurological damage, n (%)	2 (1.3)	0	0.524
Acute kidney injury, n (%)	22 (13.8)	1 (3.1)	0.089
Re-exploration for bleeding, n (%)	13 (8.2)	1 (3.1)	0.317
LVEF (%)	56.0±6.7	59.1±6.3	0.019
Creatinine peak level (mg/dL)	1.37	1.50	0.684
Creatinine clearance (mL/min)	59.6	60.9	0.829
Paroxysmal atrial fibrillation, n (%)	85 (53.5)	11 (34.4)	0.053
Need for pacemaker implantation, n (%)	7 (4.4)	0	0.225
No. of units of blood transfused per patient	0.6±1.4	0.6±1.5	0.906
ICU stay (days)	3.7±5.1	4.0±2.6	0.628
Postoperative in-hospital stay (days)	9.9±8.7	9.1±3.1	0.397
Deaths, n (%)	2 (1.3)	1 (3.1)	0.438

LVEF, left ventricular ejection fraction; ICU, intensive care unit; WBC, warm blood cardioplegia; CCC, cold crystalloid cardioplegia.

outcome for patients receiving cold blood cardioplegia has been reported (12).

Also with respect to the surgical treatment of congenital heart diseases, no clear demonstrably clinical advantage has been shown with the use of antegrade cold blood cardioplegia over CCC (13). However, data from a more recently published clinical meta-analyses show a more favorable outcome with the use of cold blood cardioplegia in comparison with cold crystalloid solutions, although also these studies have not been conclusive regarding which type of cardioplegia provides the best protection method. Several possible reasons for these findings can be depend on the heterogeneous groups of patients included in these studies, i.e., affected by coronary artery disease, different valve pathologies, other diseases, to the different surgical procedures, and to the duration of the aortic cross clamp time. Guru, Jacob and their coworkers (14,15) in two meta-analyses showed that cold blood cardioplegia provides a favorable outcome in terms of lower incidence of low cardiac output syndrome, CK-MB release in comparison with CCC, but the incidence of myocardial infarction and death were similar. In another two meta-analyses Fan, Abah, and their colleagues (16,17) showed no difference between warm and cold cardioplegia on the short-term mortality. Jacquet and Coworkers (18), on 200 patients undergoing coronary artery bypass grafting showed as a better method of myocardial protection the antegrade warm cardioplegia in comparison with combined antegrade and retrograde CCC on the PO cardiac enzymes release, although ischemic arrest duration was significantly shorter in the warm group. In a large prospective randomized study Ovrum and coworkers (19) on 1,440 patients undergoing coronary artery bypass did not detect any difference in clinical outcome. However, the mean cross clamp time was only 34 minutes, and this could be too short to show a potential difference. For these reasons, we select a relatively homogeneous group of patients, less frequently investigated in the literature, who underwent cardiac surgery with a relatively long cross clamp time and affected by myocardial hypertrophy, that are two relevant variables to test the efficacy of myocardial protection achieved by two types of cardioplegia routinely used. The degree of the myocardium

hypertrophy measured on the left ventricular septum and the posterior wall, the mean duration of the aortic cross-clamping time, and the incidence of associated coronary artery bypass grafting, i.e., about one third of patients in each group, were similar in both groups (*Table 2*). We observed that the mean duration of the aortic cross-clamping time was slightly longer in the WBC group, but, as expected, it was likely due to the greater required mean number of cardioplegia's doses administered. A similar difference was recorded for the duration of the aortic cross-clamping time in the subgroups of patients undergoing isolated aortic valve replacement only (*Table 2*).

The main aspect highlighted in our study is that a better myocardial protection in the presence of myocardial hypertrophy can be achieved by using a type of cold rather than hot cardioplegia, either in all patients of the two groups of patients, than in patients undergoing isolated aortic valve replacement. Improved protection of the hypertrophic myocardium by cold rather than warm cardioplegia has also been demonstrated in the prospective randomized study of Boening *et al.* (5) in terms of oxygen consumption during aortic valve replacement surgery. Except that, unlike our study, the comparison was performed using cold and WBC.

During the first 24 PO hours after operation we observed that CK-MB, cTnI release, their serum peak levels, and the ratio of the CK-MB were lower in the CCC group, whereas the release of the AST remained lower also up to 48 PO hours (*Figures 1-4*) (*Table 3*). Also the difference in the CK-MB/CK ratio >10% between the two groups was about 2% at the time 0 of investigation, in favor of CCC group (*Figure 5*). PO left ventricular ejection fraction was also better in CCC group in comparison with WBC group, but this difference was likely due to its preoperative mean value, that was higher in CCC group. In literature there are little data comparing warm blood and CCC in the aortic valve replacement surgery. Braathen and Tønnessen in 80 patients undergoing isolated aortic valve replacement showed a better myocardial protection with the use of cold blood cardioplegia in comparison with CCC (20). In contrast to the observed value of CK-MB in our study that was less than 20 ng/mL at 24 PO hours in the CCC group, they found a CK-MB value greater than 45 micrograms (mcg)/L at 20 PO hours with the use of the CCC. Whereas, CK-MB value in the cold blood group was similar to that observed in our study in the cold crystalloid group. On the contrary, Bouchart and colleagues on 60 patients undergone isolated aortic valve replacement reported a statistically significant high level of CK-MB at 6 hours (70 mcg/L) with the use of intermittent cold blood cardioplegia in comparison with continuous WBC (33 mcg/L) and CCC (45 mcg/L) (12). Kaul *et al.* (21) on 123 patients undergoing combined valve (aortic or mitral) and coronary artery bypass surgery found a significant reduced release in AST enzyme in favor of cold blood cardioplegia in comparison with cold crystalloid or with the use of ischemic cardiac arrest. Ascione and coworkers (22) found a significant reduced release of cTnI at 1, 24, 48 hours postoperatively in favor of cold blood cardioplegia in comparison with WBC. Interestingly, the mean value of cTnI at 24 and 48 hours reported using cold and WBC was similar to that observed in our study in the CCC group and in the WBC group, respectively. However, although the reported study and other studies have underlined some different degree of myocardial protection in favor of one or of the another type of cardioplegia, no differences have been observed in terms of perioperative myocardial infarction, low output cardiac syndrome, PO non-cardiac major complications, and death (12,20-23). These findings are in accordance with those observed in our study: in fact, although the release of cardiac enzymes was in favor of CCC, the perioperative outcome was similar in both groups of patients. Ovrum and Colleagues (24), in a prospective randomized study on 345 aortic valve patients, found no difference between retrograde cold blood cardioplegia and retrograde CCC in terms of bleeding, need for blood transfusions, perioperative myocardial infarction, stroke, renal function, infections or mortality. On the contrary, Calafiore and colleagues on 271 patients undergoing aortic valve replacement showed a lower cardiac-related mortality in favor of WBC in comparison with cold blood cardioplegia (25).

As expected, and also as reported in previous studies (2,26), in the CCC group was observed lower hematocrit level and hemoglobin value at the end of cardiopulmonary bypass (*Table 2*). The mean number of units of blood transfused per patient was similar (*Table 4*). Consequently, the lower level of hematocrit could justify the greater use of norepinephrine infusion in the PO period, as also reported in other studies (8,14,16,17), although this need did not cause any difference in the in-ICU and in-hospital stay in comparison with the WBC group of patients.

Finally, in a propensity-matched analysis of more than 7,000 patented patients undergoing aortic valve replacement recently published by Hoyer and colleagues, no significant differences were demonstrated for operative mortality, PO complications and long-term survival with the use of cold blood cardioplegia and CCC Custodiol (27).

The greater incidence of primary respiratory pulmonary complications observed in the CCC group appears more difficult to be explain in our experience, nor even in literature we did found consistent data that demonstrate a correlation with the use of one type of cardioplegia compared to another.

The study has several limitations. First, it is a retrospective and observational analysis. Second, the analyzed sample that constituted the CCC group was quite small. However, this study took into account a short surgical period in order to avoid bias. Moreover, the population in question regarded a quite homogeneous group of patients undergoing aortic valve replacement in association or not with coronary artery surgery. Third, we have compared only two types of cardioplegia, intermittently and antegrade administered.

Conclusions

From the data obtained in this study, we cannot try any definitive conclusion about what is the best method of myocardial protection during aortic valve surgery. The clinical bottom line of our findings is that in patients undergoing aortic valve replacement CCC or WBC during normothermic cardiopulmonary bypass have resulted in similar rate of perioperative myocardial infarction, PO complications, and death. Therefore, the statistically significant difference observed in the myocardial enzymes release in favor of crystalloid cardioplegia did not translate into different clinical outcome.

However, this study suggests that in presence of cardiac surgical conditions associated with a significant myocardium hypertrophy, i.e., in presence of aortic valve disease, a better protection can be achieved with the use of a cold rather than a warm cardioplegia. Therefore, CCC can be still safely used.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Institutional Review Board of the Tor Vergata University Hospital, which waived the need for patient consent. The study was designed to be as retrospective one. All patients gave informed surgical consent.

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Cite this article as: Nardi P, Vacirca SR, Russo M, Colella DF, Bassano C, Scafuri A, Pellegrino A, Melino G, Ruvolo G. Cold crystalloid versus warm blood cardioplegia in patients undergoing aortic valve replacement. J Thorac Dis 2018;10(3):1490-1499. doi: 10.21037/jtd.2018.03.67

