

Published in final edited form as:

J Cardiovasc Surg (Torino). 2018 February 01; 59(1): 115–120. doi:10.23736/S0021-9509.17.09979-7.

Is cold blood cardioplegia absolutely superior to cold crystalloid cardioplegia in aortic valve surgery?

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Abstract

Background—Experimental evidence suggests that blood cardioplegia (BCP) may be superior to cold crystalloid cardioplegia (CCP) for myocardial protection. However, robust clinical data are lacking. We compared post-operative outcome of patients undergoing aortic valve replacement (AVR) using cold anterograde-retrograde intermittent BCP versus anterograde (CCP).

Methods—Adult consecutive isolated AVR performed between April 2006 and February 2011 at the Royal Infirmary Hospital of Edinburgh were retrospectively analyzed. The use of anterograde CCP was compared with that of intermittent anterograde-retrograde cold BCP. End points were intra-operative mortality, 30-day hospital re-admission, need for RBC or platelet transfusion, mechanical ventilation time and renal failure.

Results—Of total 774 cases analyzed, 592 cases of BCP and 182 cases of CCP were identified. Demographics did not differ between groups (mean patient age in years): 67±12 CCP and 69±12

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Conflicts of interest. None declared.

BCP. Groups (BCP vs CCP) were indistinguishable ($p > 0.05$, NS) based on: average aortic cross clamp time (min) 77.01 ± 14.47 vs 75.78 ± 18.78 , cardiopulmonary bypass time (min) 104.07 ± 43.70 vs 100.34 ± 25.90 , surgery time (min) 190.53 ± 61.80 vs 204.04 ± 51.09 and post-operative total blood consumption (units) 1.38 ± 2.11 vs 1.61 ± 2.4 . The percentage of patients who required platelets' transfusion was similar: 12.8% BCP and 18.7% CCP (Fisher exact test, $p=0.053$). Prevalence of respiratory failure was lower in BCP than in CCP: 2.6% vs 6.3% ($p=0.028$). Admission time (days) at ICU was 3.63 ± 21.90 in BCP and 3.07 ± 8.04 in CCP (NS). Intra-hospital mortality, 30-day hospital re-admission, renal failure, sepsis, wound healing and stroke did not differ between groups.

Conclusions—BCP was strictly not superior to CCP in every aspect. In particular it was definitely not superior in terms of post-operative ventricular function. Our results question the absolute superiority of BCP over CCP in terms of hard outcomes. Likelihood of serious complications should be considered to improve risk profile of patients before choosing a cardioplegic solution.

Keywords

Cardioplegia; Aortic Valve; Retrospective study

Introduction

Myocardial ischemia reperfusion (IR) injury occurs during cardiac surgery using aortic cross clamping. It is crucial to provide adequate myocardial protection to achieve successful clinical outcome. Myocardial protection refers to the strategies and techniques used at the perioperative period to prevent IR injury by decreasing myocardial metabolic demands, myocardial stunning and necrosis. Administration of cardioplegic solutions can achieve this by preserving metabolic substrates, electrolyte homeostasis and pH. Intracellular solutions with negligible sodium or calcium concentrations and extracellular preparations containing high sodium, magnesium and calcium may be used. Potassium (1-20 mmol/L) is present in both types of solutions, which may be added with osmotically active substances like mannitol, lignocaine, amino acids, and bicarbonate buffers.¹ Two main techniques have gained widespread acceptance: cardiac arrest induced and maintained with either a blood-based, or a crystalloid-based solution. Both crystalloid and blood cardioplegic solutions allow safe and satisfactory myocardial protection, and show comparable long-term clinical outcomes. Several prospective studies comparing the two approaches have been reported.²⁻⁵ Yet, the reasons why BCP has become the default method are not evident.⁶ Blood cardioplegia (BCP) as opposed to crystalloid cardioplegia (CCP) has been claimed to improve post-operative outcomes, as it is believed that it more closely approximates normal physiology with regard to oxygen carrying capacity.⁷ This concept has been reinforced by observations, that BCP reduces the post-operative increase in cardiac biomarker levels.^{8,9} However, definite clinical benefits of BCP versus CCP have not been confirmed. Disadvantages of using BCP include impaired visualization during coronary artery bypass and minimally invasive procedures,¹⁰ and increased cost of BCP delivery systems.¹¹ Additionally, inadequate delivery of warm BCP is associated with myocardial injury and low-cardiac output syndromes.¹² On the other hand, CCP is known for its safety, cost-

effectiveness, and ease of administration, but it has concerning reports of increased post-operative ventricular fibrillation rates,¹³ hemodilution with increased transfusion requirements,¹⁴ and electrolyte abnormalities.¹⁵ Regardless of the abovementioned aspects, there have been no significant differences found between BCP and CCP in mortality or early post-operative hard outcomes, such as ventilator support or the duration of hospitalization.^{2,16} The aim of our study is to compare the post-operative outcome of patients undergoing aortic valve replacement (AVR) with CCP versus BCP, to provide additional information intended to aid physicians in clinical decision making along with the corpus of knowledge up to date.

Materials and methods

Patients

A total of 774 cases of consecutive adult patients (403 men, 371 women, mean age 68.6 ± 12.3 years) undergoing isolated AVR between April 2006 and February 2011 at the Royal Infirmary Hospital of Edinburgh entered this retrospective study. Cases undergoing other surgical procedures on the aortic wall, aortic arch, other valves or the myocardium, were excluded. The majority of the patients underwent their first cardiac surgery on an elective basis. Informed consent from the patients was not required since both methods for myocardial protection are universally accepted. Surgeons were randomly assigned to either BCP or CCP according with the technique indicated by the consultant. The hospital database provided demographic information, pre-operative risk factors, operative techniques, and clinical outcomes. Post-operative outcome was measured in intensive therapy unit (ITU), high dependency unit (HDU) and at the ward until discharge.

Surgical technique and cardiopulmonary bypass details

The patient was placed on cardio-pulmonary bypass after systemic heparinization, achieving an ACT (activated clotting time) > 400 s, with a right atrial two-staged venous cannula, and an arterial cannula into the distal ascending aorta. Systemic cooling to 32°C was used. Pericardial CO_2 was delivered at 2 L/min during surgery. The aorta was cross-clamped. An initial induction dose antegrade cardioplegia of 1 L was delivered into the aortic root. When required, additional retrograde cardioplegia solution was administered into the coronary sinus, with a delivery pressure not exceeding 40 mmHg, to achieve optimal electromechanical cardioplegic heart arrest. Optimal diastolic electromechanical arrest was defined as the complete absence of ECG-monitored electrical activity in a non-contracting and non-distended heart. Left ventricular venting was used to avoid ventricular distension during surgery and cardioplegia delivery. The aortic valve was exposed with proximal aortotomy. Electromechanical cardioplegic arrest was maintained with 20-min interval delivery, antegrade cardioplegia directly into the coronary ostia, and retrograde cardioplegia into the coronary sinus. Table 1 shows the composition of the two cardioplegia solutions. Blood cardioplegia (BCP) solution was cooled to 4°C and mixed with oxygenated blood (1:4). Progressive systemic rewarming to 37°C was performed after the prosthetic aortic valve was seated. Following closure of the aortotomy and de-airing routine, the aortic cross-clamp was released, and de-airing continued via an aortic root vent. After a period of 37°C warm supported reperfusion, cardiopulmonary bypass was weaned, and heparin reversal was

achieved with Protamine administration. During surgery, a blood conserving technique was used in all cases using Cell Saver® 5+ (Haemonetics, USA).

Study Endpoints

Post-operative outcome was measured in ITU, HDU and at the ward until discharge. Primary intra-operative endpoints were: aortic cross clamp time, perfusion time and total operation time. Main primary post-operative end points were: intra hospital mortality, hospital discharge, prolonged mechanical ventilation time (>24 h post-op), renal failure (requiring dialysis), stroke with residual deficit and full clinical recovery, other central nervous system complications, cardiac rhythm alterations, wound healing compromised, and sepsis. Blood products consumption was defined as the number of units transfused according with haemostatic needs.

In our hospital, biochemical markers of myocardial damage are routinely determined in coronary artery bypass graft surgery (CABG) but not in AVR and were not measured in this study.

Statistical Analysis

Results were submitted to ANOVA using a general linear model analysis of variance. Data were expressed as mean \pm SD for parametric (ordinal) variables. Student's t test (parametric) or Chi-Square, Fisher-Exact test and binomial tests (non-parametric) allowed inter-group comparison. A p value < 0.05 was considered statistically significant (IBM SPSS 15.0).

Results

Over 774 total AVR cases analyzed, 182 cases (23.5%) were carried by 5 surgeons (1 consultant) using CCP and 592 cases (76.5%) were carried by 10 surgeons (5 consultants) using BCP for myocardial protection. Demographics were similar in both groups with a mean patient age of 67 ± 12 years in CCP and 69 ± 12 years in BCP. More than 50% of patients were ex-smokers and men. Hypertension and overweight were prevalent. Surgery had been indicated due to aortic valve stenosis diagnosed in more than 89% of cases regardless the group. Pre-operative EF and creatinine ($\mu\text{mol/L}$) values were respectively: $57.28 \pm 10.67\%$ and 0.989 ± 0.317 in CCP, and $55.13 \pm 11.23\%$ and 1.246 ± 0.912 in BCP, showing no differences between groups (Table 1).

Cardiopulmonary bypass time (min) was 100.34 ± 25.90 in CCP and 104.07 ± 43.70 in BCP (N.S.). Cross-clamp time (min) did not differ between groups: 75.78 ± 18.78 in CCP and 77.01 ± 14.47 in BCP. Operation time (min) did not differ between groups 204.04 ± 51.09 in CCP vs 190.53 ± 61.8 in BCP (N.S.). Post-surgery blood usage did not depend on cardioplegia group. The percentage of patients requiring platelets' administration in theatre was 18.7% in CCP vs 12.8% in BCP ($p = 0.053$, N.S.) (Table 2).

Admission time (days) at ICU was not different between groups (3.07 ± 8.04 in CCP vs 3.63 ± 21.90 in BCP, NS). Days in HDU for CCP and BCP were comparable to each other (1.4 ± 2.3 vs 1.8 ± 4.5 , NS). Re-ventilation therapy due to respiratory failure was required in 6.3% of cases in CCP group compared with 2.6% of cases in BCP ($p = 0.028$) (Table 3).

Discussion

This study was conducted to compare the clinical outcomes of using two different myocardial protection strategies: crystalloid versus blood cardioplegia. In parallel to previous papers, our study found no major differences between the two methods. However, the need for perioperative RBC and/or platelet transfusions was significantly higher in the CCP group, as well as the prevalence of postoperative respiratory failure requiring ventilation. Additionally, blood cardioplegia was associated with a slightly reduced operation time, but this was not statistically significant. Despite the relative benefits of using BCP in this study, 3 patients died in theatre in the BCP group and none in the CCP group. The three intraoperative deaths in the BCP group were operated on by two surgeons. All of the three cases were redo operations. Two of them were redo AVR and one case redo after CABG. In the CCP group there were redo operations too.

Unlike blood cardioplegia, myocardial protection provided with crystalloid requires a large volume of crystalloid solution, often resulting in hemodilution and disruption in osmolality.¹⁷ After cardiopulmonary bypass, platelets are often required to reduce persistent bleeding,¹⁸ which usually results from hemodilution,¹⁹ hypothermia,²⁰ acidosis^{21,22} and/or electrolyte imbalance.²² In our study, hemodilution due to fluid infused with CCP solution might explain coagulation abnormalities accounting for the requirement of platelets during CCP¹⁹.

Although we did not observe statistically significant adverse outcomes for our sample population receiving CCP, the increased use of platelets may be associated with prolonged ITU times^{23,24}, increased risk for multiple organ failure²⁵ and increased hospital costs²⁶. Over twenty years, specifically between the 70's and 90's, CCP was established as the method of choice for cardiac protection. In 1990, the use of BCP started to replace CCP. BCP uses blood as a carrier for oxygen and it was considered to be more effective than CCP in order to protect the aerobic metabolism in the myocardium during aortic cross clamp. By now, the current idea is that in low risk cases, CCP and BCP whether given antegrade and/or retrograde, produce relatively comparable clinical results.²⁷ Present findings agree with this idea: all patients had preserved left ventricular function and cardiac protection showed no differences between CCP and BCP. However, it has been suggested elsewhere that patients with considerable left ventricular dysfunction may fare better with BCP, even though there is no difference in early or late survival compared to CCP.²⁸ In our study, no differences were found in post-op biventricular failure with regard to the cardioplegic solution. On this basis, low cost CCP might be considered alternatively to BCP even in patients with more advanced left ventricular dysfunction.

As mentioned in Introduction, both BCP and CCP have relative advantages and disadvantages. CCP is easier to prepare and is less expensive than BCP, however it requires a higher amount of fluids infused to the patients during surgery,²⁹ which might pose an increased risk for hemodilution. BCP is more similar to human blood in terms of physiological composition and osmotic pressure favoring oxygen delivery and buffering activity³⁰, and the scavenging properties of RBCs may reduce reperfusion damage.³¹

In our study, the rate of cardiac arrest in BCP group was 3 times (10/592 vs 1/182, 0.017 vs 0.01) that in CCP group. Though it did not achieve statistical significance, clearly there was an overall clear trend to better post-op outcome in the CCP group. The absolute assertion that BCP is superior to CCP in every aspect is questionable upon present evidence. There are several examples where CCP was superior to BCP in this study. The length of stay was 2 days longer in BCP group vs CCP. Though the small difference was not significant (please see Supplementary Data, Table A), it undeniably benefited the patients. To dissipate doubts and confirm or rule out any small difference, a larger number of cases should be analysed.

It is also known that cardiopulmonary bypass (CBP) can affect the pulmonary function triggering the activation of the inflammatory cascade. In this process, inflammatory mediators, proteases, free radicals, arachidonic acid, leukotrienes and other markers are involved.³² Additionally, other more specific factors linked to CCP like hypervolemia and hemodilution are associated to pulmonary dysfunction^{33,34} and could justify the slight increase observed in postoperative respiratory failure requiring ventilation in this group.

There is a need for more prospective studies and analysis of long term complications to correlate data. Nevertheless, the findings in our study clearly represent the huge amount of patients with a clear protection pattern linked to our hospital in this 'single centre experience'. Most important, the need for prospective studies is supported by our findings, questioning the by-default assertion that BCP is definitely superior to CCP.

Limitations

This is a retrospective study and the size of the sample analyzed in BCP and CCP groups is largely different. Different surgeons performed the procedures and standardization is lacking in this regard. However, surgeons were randomly assigned to either BCP or CCP, according to the technique indicated by the consultant. As a result, most of the surgeons performed both techniques

Primary end points were achieved during hospitalization time and may not necessarily reflect long-term changes, e.g.: necrosis may appear months to years after surgery.

Conclusions

Within the wide spectra of variables evaluated, only small differences were observed favoring each method. Even though BCP reduced post-operative demand for platelets and the prevalence of respiratory failure requiring re-ventilation, 3 patients died in theatre in BCP while none did in CCP. Hence, we conclude that BCP may not be actually superior to CCP in every aspect.

Our study provides concrete evidence that may be help to reduce costs and optimise economical resources. Our National Health Service (NHS) system is under economical pressure and would benefit from reduction in costs of materials and equipment, as far as clinical outcome is privileged and patients' welfare is granted. We have highlighted that CCP could be as safe as BCP for myocardial protection during AVR. Due to the huge

amounts of patients in our centre, using CCP when indicated instead of the default BCP technique, could translate into a significant reduction in the operative cost for AVR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Composition of cardioplegia solutions

Components (mM)	BCP	CCP
Sodium (Na ⁺)	36.75	-
Potassium (K ⁺)	16	15.83
Magnesium (Mg ⁺)	20	15.70
Calcium (Ca ⁺⁺)	2	-
Chloride (Cl ⁻)	400	-
Procaine	1.25	1.00

BCP: 1L bag diluted 1:4 on the pump, CCP: 20mL vial diluted in 1L ringer solution

Crystalloid cardioplegia (CCP) comes in 20mL vials from Martindale Pharmaceuticals that are diluted in 1L of ringer solution containing: disodium edetate (Na₂-EDTA) and sodium hydroxide. This solution is readily delivered 1:1 via a plegia set on the pump. Blood cardioplegia (BCP) from Terumo Lab, comes prepared in high strength potassium 80mmol/L bags ready for use and it is diluted 1:4 by the cardioplegia set on the pump. Dilution ratio may be adjusted by the perfusionist as required. Average delivery temperature is between 4°C-8°C.

Table 2
Demographic and pre-operative data

	BCP	CCP	P value
N_{total} = 774	N=592	N=182	
Age (years)	69±12	67±12	NS
Men (%)	51.7	53.3	NS
Ex smokers (%)	58.3	60.4	NS
Creatinine (µmol/L)	1.25 ± 0.91	0.99 ± 0.32	NS
Hypertension (%)	66.0	66.3	NS
Body Mass Index	28.26±5.23	29.09±5.16	NS
Aortic valve stenosis (%)	89.5	89.6	NS
Dyspnoea Grade			
NYHA I (%)	17.2	14.8	NS
NYHA II(%)	23.6	20.9	NS
NYHA III (%)	45.6	53.3	NS
NYHA IV (%)	13.5	11.0	NS
EF			
Fair (%)	18.9	13.8	NS
Good (%)	73.1	81.7	NS
Poor (%)	8.0	4.6	NS

EF: Fair (EF=30-49%), Good (EF= > 50%), Poor (EF=Poor < 30%)

Table 3
Comparative findings in this study

	BCP (n=592)	CCP (n=182)	P value
Cardiopulmonary bypass time (min)	104.07±43.70	100.34±25.90	NS
Cross-clamp time (min)	77.01±14.47	75.78±18.78	NS
Operation time (min)	190.53±61.81	204.04±51.09	NS
Post-surgery blood usage (units)	1.38±2.11	1.61±2.4	NS
Platelets requirement in theatre (%)	12.8	18.7	NS
Admission time at ICU (days)	3.63± 21.90	3.07 ± 8.04	NS
Days in HDU	1.8±4.5	1.4 ± 2.3	NS
Respiratory failure (%)	2.6	6.3	0.028
Deaths in theatre (%)	0.5	0.0	NS

P < 0.028 between BCP and CCP groups