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*Original Article*

# The Relationship between the Use of Cold and Isothermic Blood Cardioplegia Solution for Myocardial Protection during Cardiopulmonary Bypass and the Ischemia–Reperfusion Injury

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**Purpose: In this study, we aimed to assess myocardial protection and ischemia–reperfusion injury in patients undergoing open heart surgery with isothermic blood cardioplegia (IBC) or hypothermic blood cardioplegia (HBC).**

**Materials and Methods: A total of 48 patients who underwent isolated coronary artery bypass grafting or isolated mitral valve surgery between March 2017 and October 2017 were evaluated as randomized prospective study. Study groups (HBC: Group 1, IBC: Group 2) were compared in terms of interleukin 6 (IL-6), IL-8, IL-10, and complement factor 3a (C3a) levels, metabolic parameters, creatine kinase-muscle/brain (CK-MB) and high-sensitivity Troponin I (hsTn-I), and clinical outcomes.**

**Results: Comparison of the markers of ischemia–reperfusion injury showed significantly higher levels of the proinflammatory cytokine IL-6 in the early postoperative period as well as IL-8, in Group 2 ($p < 0.001$), whereas the anti-inflammatory cytokine IL-10 was significantly higher during the X1 time period ($p = 0.11$) in Group 2, and subsequently it was higher in Group 1. Using myocardial temperature probes, the target myocardial temperatures were measured in the patients undergoing open heart surgery with different routes of cardioplegia, and significant differences were noted ($p = 0.000$).**

**Conclusion: HBC for open heart surgery is associated with less myocardial injury and intraoperative and postoperative morbidity, indicating superior myocardial protection versus IBC.**

**Keywords:** cold blood cardioplegia, warm blood cardioplegia, myocardial protection, ischemia–reperfusion injury, inflammatory response

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## Introduction

Cardioplegia is of utmost importance, not only for achieving cardiac arrest but also for maintaining myocardial protection.[1,2] However, the best method of protection remains a matter of controversy, as variable results have been reported with different temperatures of cardioplegia.[3] Most of the previous studies examined and compared the effects of warm blood and cold blood cardioplegia, and to some extent those of isothermic cardioplegia.[4–7] Although warm blood cardioplegia has been reported to be associated with lower postoperative cardiac enzyme levels and improved cardiac indices,

these benefits were not fully translated into clinical outcomes.[3] In one meta-analysis, no significant differences were found in clinical outcomes, while warm blood cardioplegia provided an increase in the cardiac index postoperatively.[8] In another study, hypothermic blood cardioplegia (HBC) was found to be more effective than warm blood cardioplegia in patients who had prolonged cross-clamp time and in high-risk patient groups.[9]

In some previous studies of hypothermic cardioplegia, cold blood cardioplegia was applied together with systemic hypothermia, and in some patients topical hypothermia was also used.[9,10] Subsequently, generalized body hyperthermia caused a higher occurrence of untoward effects in the long term. Conversely, in isothermic groups, body temperature was maintained over 35°C, and cardioplegia temperature was the same as the body temperature.

In this study, our objective was to determine the comparative myocardial protection and systemic inflammatory response elicited by two cardioplegia approaches involving similar body temperatures but different cardioplegia temperatures, in patients undergoing open heart surgery. Also, in contrast with many previous studies, myocardial temperatures were measured and assessed using myocardial temperature probes.

## Materials and Methods

In this prospective randomized study, a total of 48 patients undergoing isolated coronary artery bypass grafting (CABG) or valve surgery between March 2017 and October 2017 were included. Exclusion criteria were ejection fraction <35%, presence of comorbid cardiac conditions in addition to coronary artery disease, cardiac valvular disorders other than mitral valve disease, and the need for emergency surgery. Randomization into study groups was performed through allocation of consecutive patients who admitted to cardiovascular surgery clinic for elective surgery. Patients were allocated into groups by a single surgeon based on their order of admission without use of any specific selection criteria. This study was approved by the Ethics Review Board of Sakarya University Faculty of Medicine (22/01/2015-809). Informed and informed consent was obtained from all patients included in the study.

The study population had two main groups. Group 1 consisted of HBC patients, and Group 2 consisted of isothermic blood cardioplegia (IBC) patients. In both groups, body temperatures were maintained at a similar level.

There was no valve operated patients in Group 2 (IBC group), but there was five valve operated patients in Group 1. These were as follows: one aortic stenosis and due to stenosis interventricular septum was 14 mm. The other valve operated patients diagnosis was mitral valve insufficiency (n:3) combined with tricuspid valve insufficiency, mitral valve stenosis (n:1) patient combined with tricuspid insufficiency. Only one mitral valve insufficiency diagnosed patient has moderate left ventricular function.

Composition of cardioplegia is same in both groups. 30 mEq potassium, 10 mL 8.4% sodium bicarbonate, 10 mL 15% magnesium sulfate added to the blood given from cardiopulmonary bypass (CPB) machine as the first cardioplegia. Volume is determined to the patients' weight and 10 mL/kg total amount of cardioplegia is given to the patients. Half doses of the electrolytes are given to the repetitive cardioplegias but the volume was the same. We did not use retrograde cardioplegia due to not affect the measurement values because we collected blood samples via coronary sinus.

Except for the cardioplegia temperature, the same routine surgical procedures were followed in both the groups. Antegrade cardioplegia was carried out and repeated with 15-minute intervals during surgery. Samples for cytokine measurements were obtained from venous cardiac blood at different time-points using a retrograde cardioplegia cannula placed in the coronary sinus. Myocardial temperature probes were used to measure the myocardial temperature and its alterations in all patients.

In Group 1, a cardioplegia conduit with aluminum spiral and a line harboring the control units for pressure and temperature levels for cardioplegia were used. As for the markers of myocardial protection and injury, peripheral blood samples were obtained preoperatively and at postoperative 6 and 24 hours for creatine kinase-muscle/brain (CK-MB) and high-sensitivity Troponin I (hsTn-I) measurements. For the assessment of the inflammatory response according to intraoperative cardioplegia temperature, coronary sinus blood samples were obtained at the following time-points for interleukin 6 (IL-6), IL-8, IL-10 and complement factor 3a (C3a) measurements: before cross-clamp (X0), 15 minutes after cross-clamp (X1), 30 minutes after cross-clamp (X2), and after removal of the cross-clamp (X3). Patient temperature, myocardial temperature, alterations in myocardial, and cardioplegia pressure were recorded. In addition, duration of hospital and intensive care unit stay, inotrope use and duration, postoperative complications, and metabolic changes in the arterial blood gas were assessed.

**Table 1 Demographic data and preoperative characteristics between groups**

| | Group 1 (n = 28) | Group 2 (n = 20) | P value |
|---|---|---|---|
| Age, year | 61.5 ± 7.7 | 62.3 ± 7.6 | 0.72 |
| Sex, male, n (%) | 20 (71.4) | 13 (65) | 0.75 |
| HT, n (%) | 20 (71.4) | 20 (100) | 0.008 |
| DM, n (%) | 13 (46.4) | 9 (45) | 0.924 |
| Hyperlipidemia, n (%) | 11 (39.3) | 11 (55) | 0.291 |
| COPD, n (%) | 5 (17.9) | 5 (25) | 0.558 |
| Obesity, n (%) | 3 (10.7) | 3 (15) | 0.68 |
| PAD, n (%) | 4 (14.3) | 2 (10) | 1.00 |
| CAD, n (%) | 4 (14.3) | 2 (10) | 1.00 |
| LV-EF, % | 55.3 ± 7.6 | 59.7 ± 5.9 | 0.034 |
| Urea, mg/dL | 43.8 ± 17.4 | 37.5 ± 15.9 | 0.207 |
| Creatinine, mg/dL | 1.2 ± 0.7 | 0.96 ± 0.4 | 0.205 |
| New myocardial infarct, n (%) | 6 (21.4) | 4 (20) | 0.907 |
| FEV1, % | 83.1 ± 23.8 | 93.7 ± 22.3 | 0.151 |
| FVC, % | 79.4 ± 22.4 | 86.8 ± 21.1 | 0.289 |
| FEF 25–75, % | 85.8 ± 34.4 | 105.2 ± 37.6 | 0.095 |

Values are mean ± SD. CAD: carotid artery disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; FEF 25–75: forced expiratory flow; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; HT: hypertension; LV-EF: left ventricular ejection fraction; PAD: peripheral artery disease

### Statistical analyses

IBM SPSS V23 software pack was used for data analysis. The normal distribution of the data was tested with Shapiro–Wilk test. Independent sample t-test was used for the comparison of data with normal distribution, while Mann–Whitney U test was used for the comparison of data without normal distribution. Data with normal distribution were expressed as arithmetic mean ± standard deviation, while data without normal distribution were expressed as median value (minimum–maximum).

Initially, normality of the data was tested to determine the descriptive statistics for the data. Since the data did not conform to normal distribution, median values (minimum–maximum) were used for data presentation instead of arithmetic means and standard deviation. Otherwise, skewed data would either increase or decrease the arithmetic means. This should be a consideration in the assessment of the data. A p value between 0.1 and 0.05 was considered marginally significant, a p value between 0.01 and 0.05 was considered significant, 0.001 and 0.01 highly significant, and <0.001 very highly significant.

## Results

Preoperative data, patient characteristics, and demographics in study groups are shown in **Table 1**. Intraoperative and postoperative data are shown in **Table 2**. The two groups were comparable in terms of the number of grafts. Postoperative complication rates, and as can be seen from **Table 2**, were also similar for the two groups in this regard, as was also the case for early mortality and duration of intensive care and hospital stay.

Body temperature, cardioplegia temperature, and most importantly the myocardial temperature were recorded in each of the intraoperative stages. A comparison of the planned temperatures and the recorded data showed that the desired and statistically significant temperature differences could be achieved (**Table 3**).

In general, all patients undergoing CPB surgery are expected to develop an inflammatory response. While proinflammatory cytokines (C3a, IL-6, IL-8) are responsible for the initiation and elevation of the inflammatory response, the anti-inflammatory cytokine IL-10 is responsible for protection against this response.[11–13] Accordingly, proinflammatory and anti-inflammatory cytokine levels were examined in our study to assess the inflammatory status. In both groups, C3a increased during CPB, with the increase being more marked in Group 2 (**Fig. 1A**). Although IL-6 increased comparably in both groups during CPB, the increase during the hypothermia phase occurred with a delay (**Fig. 1B**). IL-8 increased in both groups during CPB, although statistically more significant increases at X0 (p = 0.08) and X1 (p = 0.001) time periods were noted in Group 2 (**Fig. 1C**). Again, IL-10 increased in both groups during CPB while

**Table 2 Intraoperative and postoperative surgical data**

| | Group 1 (n = 28) | Group 2 (n = 20) | P value |
|---|---|---|---|
| Number of grafts | 2.7 ± 0.6 | 2.2 ± 0.8 | 0.033* |
| ACCT, min | 71.6 ± 30.6 | 63.3 ± 31.1 | 0.361 |
| TPT, min | 110.6 ± 34.8 | 109.5 ± 50.6 | 0.932 |
| Inotrope usage, n (%) | 20 (71.4) | 17 (85) | 0.280 |
| Prolonged CPB, n (%) | 3 (10.7) | 6 (30) | 0.095** |
| IABP, n (%) | 1 (3.6) | 2 (10) | 0.375 |
| ECMO, n (%) | 1 (3.6) | 0 (0) | 0.404 |
| Intubation time, h | 11.7 ± 9.1 | 9.6 ± 7* | 0.405 |
| Inotrope time, h | 11.8 ± 23.4 | 11.5 ± 19.2 | 0.965 |
| Drainage, mL | 601.7 ± 311.3 | 604.2 ± 212.7 | 0.42 |
| Whole blood, unit | 0.3 ± 0.5 | 0.3 ± 0.4 | 0.808 |
| Erythrocyte suspension, unit | 0.9 ± 0.7 | 0.8 ± 0.7 | 0.461 |
| Fresh frozen plasma, unit | 2.7 ± 1 | 2.6 ± 0.9 | 0.715 |
| Urea, mg/dL | 54.7 ± 21.1 | 48.9 ± 15.5 | 0.305 |
| Creatinine, mg/dL | 1.4 ± 0.8 | 1.2 ± 0.4 | 0.205 |
| *Postoperatively complication incidence* | | | |
| Complication, n (%) | 11 (42.8) | 11 (55) | 0.417 |
| Bleeding, n (%) | 3 (10.7) | 1 (5) | 0.491 |
| Tamponade, n (%) | 0 | 0 | 1.00 |
| Effusion, n (%) | 1 (3.6) | 0 | 0.404 |
| Respiratory, n (%) | 10 (35.7) | 6 (30) | 0.687 |
| Neurological, n (%) | 0 | 1 (5) | 0.241 |
| Renal, n (%) | 4 (14.3) | 2 (10) | 0.666 |
| Hemodialysis, n (%) | 1 (3.6) | 0 | 0.404 |
| LCOS, n (%) | 3 (10.7) | 2 (10) | 0.938 |
| Atrial fibrillation, n (%) | 4 (14.3) | 4 (20) | 0.610 |
| Major infection, n (%) | 0 | 0 | 1.00 |
| ICU stay, day | 2.2 ± 0.9 | 3.1 ± 3.1 | 0.178 |
| Hospital stay, day | 7.4 ± 2.7 | 8.1 ± 2.5 | 0.330 |
| Mortality, n (%) | 1 (3.6) | 1 (5) | 0.812 |

Values are mean ± SD. *significant, **marginally significant.

The patient, whose intubation time is 340 hours, is excluded from statistical evaluation.

ACCT: aortic cross-clamp time; CPB: cardiopulmonary bypass; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; ECMO: extra corporeal membrane oxygenation; FEF 25-75: forced expiratory flow; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; HT: hypertension; IABP: intra-aortic balloon pump; ICU: intensive care unit; LCOS: low cardiac output syndrome; LV-EF: left ventricular ejection fraction; TPT: total perfusion time

the increase was more marked at X2 and X3 in Group 1 (**Fig. 1D**).

These results showed an earlier and a more prominent inflammatory response in Group 2. The differences were marginally significant, except for IL-8, which showed a significant difference. In general, a decrease/slowing down of the proinflammatory response and an augmentation in the anti-inflammatory response were previously shown for hypothermia.[14,15]

Finally, as the most sensitive markers of myocardial protection or an indicator of the level of injury, cardiac enzyme (CK-MB) and troponin (hsTn-I) blood levels were measured and compared at postoperative 6 and 24 hours, with no statistically significant differences. A comparison of the means showed higher values in Group 1 than in Group 2, although the data were not normally distributed in the test for normal distribution of the data. Therefore, median values were deemed more appropriate for comparisons. An assessment of the median values showed lower CK-MB in Group 1 at 6 hours while this pattern was reversed at 24 hours (**Fig. 2A**). On the other hand, hsTn-I levels were lower in Group 1 at 6 and 24 postoperative hours (**Fig. 2B**). These results suggest that although the differences were not statistically significant, avoidance from systemic hypothermia through the sole use of myocardial hypothermia may provide protection against both systemic and myocardial adverse effects.

**Table 3 Intraoperative temperature comparison, temperatures are in Celsius**

| | Group 1 (n = 28) | Group 2 (n = 20) | P value |
|---|---|---|---|
| Cardioplegia temperature, °C | 13.7 ± 2.7 (8-20.7) | 28.4 ± 1.9 (24.6-32) | <0.001†† |
| Cardioplegia pressure, mmHg | 169.7 ± 18.8 | 191 ± 27.2 | 0.003† |
| Body temperature 0, °C | 33.6 ± 0.4 | 33.5 ± 0.7 | 0.357 |
| Body temperature 1, °C | 30.6 ± 1.1 | 30.9 ± 1.3 | 0.311 |
| $M_0$ myocardial temperature, °C | 32.5 ± 0.8 | 32.8 ± 0.7 | 0.174 |
| $M_{0-1}$ myocardial temperature, °C | 21 ± 3.9 | 29.1 ± 2.4 | <0.001†† |
| $M_1$ myocardial temperature, °C | 22.8 ± 3 | 29.4 ± 1.5 | <0.001†† |
| $M_{1-1}$ myocardial temperature, °C | 16.6 ± 3.6 | 27.3 ± 1.6 | <0.001†† |

Values are mean ± SD. †highly significant, ††very highly significant. Body temperature 0: body temperature before cardioplegia. Body temperature 1: body temperature after cardioplegia. $M_0$: myocardial temperature before cardioplegia. $M_{0-1}$: myocardial temperature after the first cardioplegia. $M_1$: myocardial temperature before second cardioplegia. $M_{1-1}$: myocardial temperature after second cardioplegia.

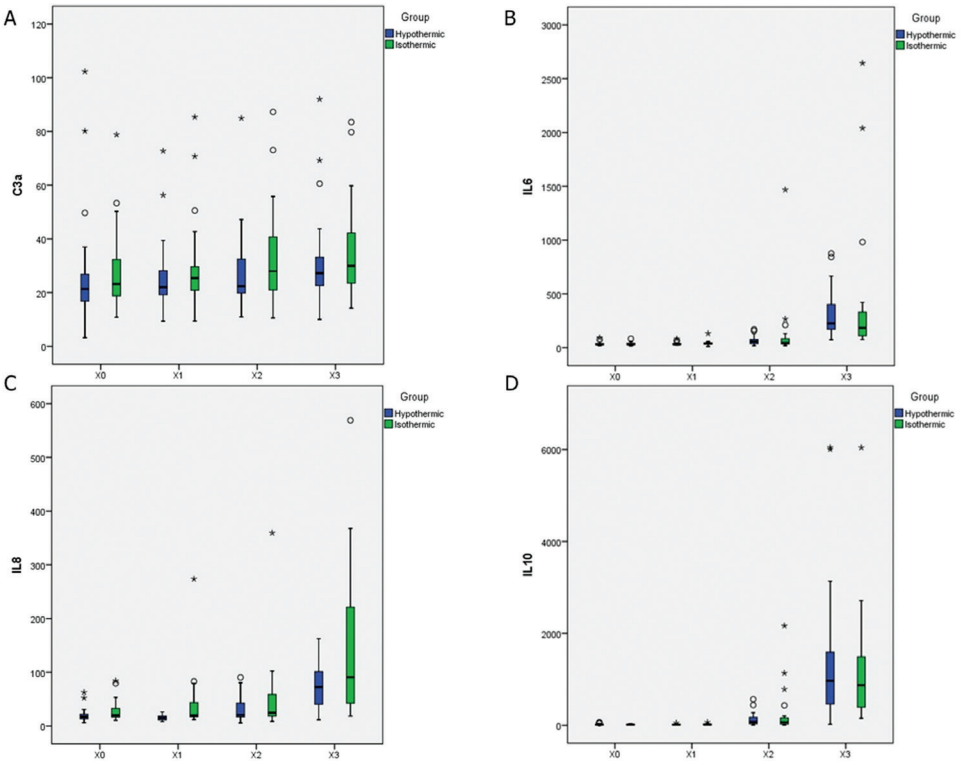


**Fig . 1** Proinflammatory (C3a, IL-6, and IL 8) and anti-inflammatory (IL-10) response to time.

## Discussion

Cardioplegia is of utmost importance not only for achieving cardiac arrest but also for the maintenance of myocardial protection. Together with technological advances, optimum cardioplegia methods have been sought by testing different routes of administration, temperatures, and content, in order to achieve best level of protection and postoperative outcomes. In most studies, cold and warm cardioplegia have been compared. In meta-analyses published by Abah et al. in 2012 and by Fan et al. in 2018, cold and warm blood cardioplegia were not significantly different with respect to overall mortality, myocardial infarction (MI), low cardiac output syndrome, intra-aortic balloon pump (IABP) use, or development of atrial fibrillation (AF) rhythm, although

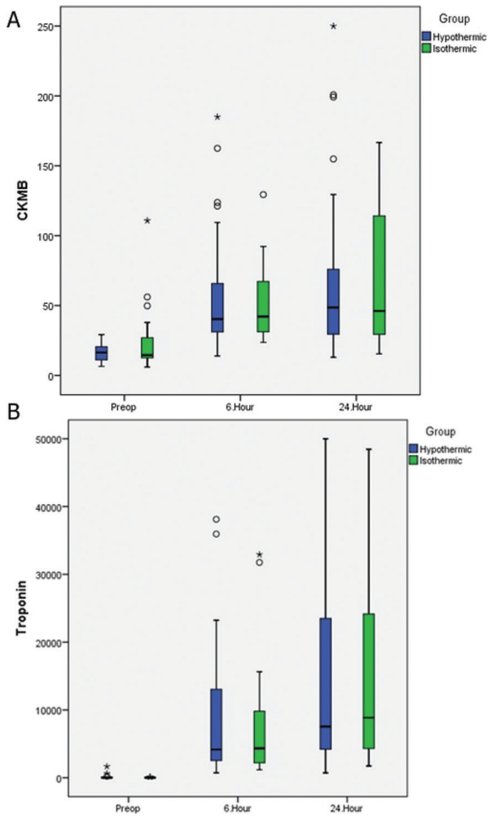


**Fig. 2** CK-MB and hsTn-I results comparison.

warm cardioplegia groups had better hemodynamic performance and lower cardiocyte injury.[3,16] In this regard, the main contribution of our study to the existing literature lies with the fact that it involved a comparison of isothermic and cold blood cardioplegia, which was performed in very few studies until now.

In parallel with the published data, the two groups were comparable in terms of overall mortality, length of intensive care stay, and IABP use. Also, in both groups, body temperatures were maintained at the same level, and in the hypothermia group, hypothermia was applied in a controlled manner to the myocardium only. This allowed protection against systemic side effects of prolonged systemic hypothermia. This was at least partially responsible for the absence of significant differences between the two groups in the rate of postoperative complications.

In contrast with the retrospective study published by Liakopoulos et al.[9] in 2010 where a lower rate of overall mortality, cardiac mortality, and cardiac death were reported in high-risk patients with a cross-clamp time ≥75 minutes, the risk profile, and cross-clamp time were similar in our study groups.

In a randomized study by Ascione et al. published in 2002, HBC was associated with lower ischemic stress and myocardial injury as compared to IBC in patients undergoing surgery due to aortic stenosis.[17] Hypertrophic left ventricle and ischemic cardiac disease lead to differential physiological responses against surgery. Therefore, it should be born in mind that in patients undergoing open heart surgery, different cardioplegia strategies may be chosen on the basis of the existing pathology.

In most studies, apart from clinical variables, CK-MB and troponin levels were measured as markers of the efficacy of myocardial protection or injury.[18] In the current study, comparison of CK-MB and hsTn-I levels at postoperative 6 and 24 hours failed to reveal any differences. The mean values were higher in Group 1 than in Group 2. However, the data did not conform to normal distribution, necessitating a comparison between median values. Thus, while Group 1 patients had lower CK-MB at 6 hours, this pattern was reversed at 24 hours. On the other hand, hsTn-I levels were lower both 6 and 24 hours postoperatively in Group 1 (**Figs. 2A** and **2B**). Despite the absence of statistically significant differences, these results suggest that avoidance from systemic hypothermia and use of myocardial cooling alone in the hypothermia group may allow protection against both systemic and myocardial adverse effects.

Anti-inflammatory mediators that are important for the inflammatory response (including C3a, IL-6, and IL-8) showed a more marked increase in IBC group, and in particular, significantly lower IL-8 levels were found in Group 1 (p value X1 < 0.001, X3 0.2). Similarly, in hypothermia group where a less marked inflammatory response was observed, higher IL-10 levels (secreted as a part of the anti-inflammatory response) were found compared to isothermic group both after placement and removal of the cross-clamp. This may explain why higher doses of inotropic agents were required after cross-clamp and why weaning from CPB was more complicated in the isothermic patient group due to less marked anti-inflammatory and higher inflammatory responses. Therefore, isolated cardiac hypothermia may provide protection against the adverse consequences of systemic hypothermia. This may be explained on the basis of the suppression of the inflammatory responses, by paying particular attention to provide localized, controlled, and moderate hypothermia. Previously, involving post-traumatic patients study, and another in vitro study showed that moderate hypothermia could delay the production of proinflammatory cytokines and suppress

the inflammatory response.[19,20] Although the length of intensive care unit stay was longer in the IBC group, analyses showed that the difference largely accounted for by a single patient experiencing a prolonged ICU stay, which increased the standard deviation in that small sample. When this case was excluded, the two groups were not significantly different.

The two groups in our study were not only compared using blood gas parameters in intraoperative blood samples but also using other parameters such as pH, lactate, and the base-deficit. Similar to the results reported by Bical et al.[21] in 2001, no significant differences were found.

In this regard, two questions should be addressed. First, can we really achieve the desired level of cooling in our target tissue, that is, the myocardium, using hypothermic or IBC? And second, are studies that incorporate two study groups by design really examining two different groups? Considering these two important questions, we decided to use myocardial temperature probes in our study to record pre- and post-cardioplegia myocardial temperatures before CPB and after cross-clamp. Accordingly, the desired level of hypothermia could be achieved in the HBC group, and the desired temperatures could be maintained in the IBC group. Comparisons showed a highly significant temperature difference between the two groups, confirming the actual difference between the targeted and comparative patient groups.

One limitation that precluded detection of significant differences in certain parameters was the small sample size. Undoubtedly, adequate sample size is a major determinant of the statistical power of a study.

### Conclusion

Although no differential effects on early mortality could be observed, hypothermic cardioplegia was able to offer better myocardial protection than isothermic cardioplegia, as suggested by a significant reduction in inflammatory responses, which are closely associated with mortality and morbidity. However, the generalizability of these initial observations to all patient groups remains unclear, warranting further prospective randomized studies with larger sample size.

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## Disclosure Statement

All authors do not have any possible conflicts of interest.

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