Intermittent antegrade warm myocardial protection compared to intermittent cold blood cardioplegia in elective coronary surgery – do we have to change?\textsuperscript{\textregistered}

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Abstract

Objective: Intermittent antegrade warm blood cardioplegia (IAWBC) is a simple and cost-effective method of myocardial preservation. However, there are only few prospective trials comparing this type of cardioplegia to established cardioplegic strategies in elective on-pump coronary surgery with respect to myocardial protection and outcome. Methods: In a prospective, randomized trial IAWBC (33°C) (n = 100) was compared to intermittent antegrade cold (4°C) blood cardioplegia (n = 100), regarding clinical outcome and myocardial protection using cardiac troponin-I (cTNI) and creatine kinase MB isoenzyme (CK-MB) measurements to assess ischemia. Results: Preoperative parameters were comparable in both groups. Results demonstrated no differences in-between the groups regarding mortality (2.0% both), incidence of perioperative myocardial infarction (2 versus 3%), need for intra-aortic balloon pump (3 versus 4%), length of ICU stay (2.0 ± 2.5 versus 2.1 ± 3.0 days) and incidence of postoperative atrial fibrillation (41 versus 34%). However, the necessity of defibrillation after cardiac arrest (18 versus 43%, P < 0.001) was significantly less frequent and of lower intensity (3.4 ± 10.8 versus 10.8 ± 20.6 J, P < 0.001) in the IAWBC-group. Postoperatively the ischemia markers were significantly lower in the IAWBC-group, cTNI within the first 72 h (from P < 0.001 to P = 0.013) and even CK-MB within the first 24 h (from P = 0.004 to P < 0.011). Conclusion: IAWBC is a safe and simple method in elective on-pump coronary artery bypass surgery. Significantly lower ischemic markers suggest an improved myocardial protection compared to cold blood cardioplegia in these patients. © 2003 Elsevier Science B.V. All rights reserved.

Keywords: Myocardial protection; Coronary surgery; Warm blood cardioplegia; Cold blood cardioplegia; Cardiac troponin I

1. Introduction

The techniques of myocardial protection in cardiac surgery are innumerable. There is a big variety regarding the kind of solution and the way of application [1]. Despite of a minority working with intermittent clamping most cardiac surgeons prefer cardioplegia in on-pump cardiac surgery. However, a discussion persists concerning the optimal strategy. Despite of this great variety most studies could not demonstrate significant differences of clinical outcome, especially in respect to mortality and incidence of perioperative myocardial infarction, when different techniques have been compared [2–4]. Improvements of myocardial preservation have been concluded on basis of enzymatic, morphological or molecular evaluations. In this context cardiac troponin-I (cTNI) has been proven as a very sensitive marker for cardiac ischemia. It allows detection and quantification of cellular damage due to myocardial ischemia even in the absence of infarction [5–7].

After first reports by Salerno [8] and Lichtenstein [9] concerning clinical use of warm blood cardioplegia Calfi and colleagues [10] published superior clinical results by use of a simple method of application of intermittent warm blood cardioplegia (IAWBC). Normothermic oxygenated blood was infused into the aortic root using a roller pump. Only a distinct concentration of K\textsuperscript{+} was added to this blood line via a syringe pump. Although the IAWBC is used by an increasing number of heart centers world wide, there are only few publications comparing IAWBC systematically with other established methods of cardioplegia.

The aim of this study was the assessment of the quality of

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myocardial protection of IAWBC compared to intermittent cold blood cardioplegia according to Buckberg (IACBC), usually applied in our department.

2. Material and methods

2.1. Patients

From January 2001 to January 2002, 200 consecutive patients elected for elective coronary surgery only were prospectively randomized into the two study groups of IAWBC or IACBC, respectively. Patient characteristics are demonstrated in Table 1. Exclusion criteria were urgent or emergency procedures, combined procedures with valve or aortic surgery, age of or higher than 80 years and a reduced left ventricular ejection fraction of less than 40%. Randomization was performed at the time of anesthesiological introduction by drawing lots.

2.2. Surgical procedures

There was no difference regarding the surgical technique. All operations were performed on cardiopulmonary bypass (CPB) through a median sternotomy. During CPB at a mild systemic hypothermia of 33–34°C the flow was maintained at 2.5 l/min per m² and the arterial pressure between 50 and 60 mmHg. Using solitary as well as sequential grafts distal anastomoses were performed during a single aortic cross-clamp time. Proximal anastomoses were constructed within the reperfusion interval using tangential clamping of the ascending aorta. The left internal thoracic artery (ITA) was used in all patients. Independent from the cardioplegia strategy arterial grafts were preferred for patients younger than 65 years. Mostly one radial artery and seldom the right ITA were used as graft material in these patients.

2.3. Application of cardioplegia

In all patients cardioplegia was applied via the aortic root immediately after aortic cross-clamping.

In the IAWBC-group oxygenated blood was infused at 33–34°C into the aortic root by means of 1/4-inch tubing and a roller pump. A syringe pump containing KCl and MgSO₄ (40 ml of 2 mmol/ml KCl, 10 ml of 2 mmol/ml MgSO₄) was connected to the tubing to deliver the cardioplegic solution. The initiation of cardiac arrest was achieved by a roller pump flow rate of 300 ml/min and a bolus injection of 2 ml followed by a continuous infusion of 150 ml/h of the syringe pump. The initial application time of this cardioplegic mixture was 3 min. An additional shot of cardioplegia was given every 20–25 min maintaining the cardioplegic arrest. Flow rates of these redo infusions were reduced according to the protocol of Calafiore et al. [10].

Patients of the IACBC-group received Buckberg-solution cooled at 4°C by a separate heat exchanger for a time of 5 min [11]. As in the IAWBC-group an additional second or third shot of cardioplegia was administered each 20–25 min for a duration of 2 min.

2.4. Ischemia markers

Quality of myocardial protection was assessed by ischemia markers cTNI and creatine kinase MB isoenzyme (CK-MB). For evaluation of postoperative enzyme kinetics patients suffered from a myocardial infarction within the peri-operative course were excluded to avoid interferences with incidence and enzyme release.

The cTNI-concentrations were measured by the Access® Accu TnI Troponin I Assay (Beckman Coulter GmbH, Unterschleissheim, Germany). The CK-MB activities were analyzed by the SYNCHRON® Test (Beckman Coulter GmbH, Unterschleissheim, Germany).

2.5. Definitions and data collection

Operative mortality was considered as death within the hospital stay. A diagnosis of postoperative myocardial infarction was made according to the following criteria: new Q-waves in two or more contiguous electrocardiographic leads, poor R-wave progression, new left bundle-branch block, and unstable ventricular rhythm. Values of the myocardial-specific cTNI were considered significant reaching a level of more than 10 ng/ml at 24 h postoperatively, according to a previous publication [5]. Cardiac enzymes and electrocardiogram were evaluated immediately after admission to ICU and at the 1st, 2nd, 3rd and 7th postoperative day.

<table>
<thead>
<tr>
<th>Table 1 Preoperative and demographic parameters a</th>
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<tbody>
<tr>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Gender (male/female)</td>
</tr>
<tr>
<td>Body mass index</td>
</tr>
<tr>
<td>Preoperative LVEF (%)</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
</tr>
<tr>
<td>Preoperative creatine (mmol/l)</td>
</tr>
</tbody>
</table>

 a IAWBC, intermittent antegrade warm blood cardioplegia; IACBC, intermittent antegrade cold blood cardioplegia; and LVEF, left ventricular ejection fraction.
2.6. Statistical analysis

Statistical analyses were performed using the SPSS for Windows 10.0 software system (SPSS Inc., Chicago, IL). Variables were expressed as mean ± one standard deviation. Univariate analyzes in-between groups were compared by Mann–Whitney test, χ²-test and Fisher’s exact test, where appropriate. Univariate analysis of variance (ANOVA) as well as ANOVA with repeated measurements were used for the comparison of the groups regarding the values of cTNI and CK-MB. Significance was assumed, if the P-value was less than 0.05. Correlation of ischemia markers cTNI and CK-MB with the cumulative amount of defibrillation energy and preoperative creatine was estimated by the method of Pearson.

3. Results

Preoperative and demographic data were comparable in both groups (Table 1). In contrast to a higher age patients of the IAWBC-group had a better preoperative kidney function.

Intraoperative analysis revealed significant differences in-between the groups regarding cumulative amount of cardioplegia solution as well as time until isoelectrical arrest of the heart. Hearts of the IACBC-group needed more cardioplegia solution and more time until isoelectrical cardiac arrest compared to the hearts of the IAWBC-group. Time at cardiopulmonary bypass and cross-clamp time were insignificantly shorter in the IAWBC-group caused by the procedure depending shorter application time of cardioplegia compared to the IACBC-group.

The necessity of defibrillation after cardiac arrest was significantly less frequent (18 versus 43%, P < 0.001) and of lower intensity (3.4 ± 10.8 versus 10.8 ± 20.6, J, P < 0.001) in the IAWBC group in spite of same potassium levels (4.5 ± 0.6 versus 4.6 ± 0.6 mmol/l, P = 0.451). However, groups showed no differences regarding hemodynamic stability and need for catecholamines at the end of the operation (Table 2).

Clinical outcome demonstrated no differences in-between the groups regarding mortality, incidence of peri-operative myocardial infarction, need for intraaortic balloon pump, length of stay on intermediate care unit and incidence of postoperative atrial fibrillation. However, patients of the IACBC group required significantly more frequent re-thoracotomy due to bleeding within the early postoperative course (Table 3).

Postoperatively both ischemia markers, cTNI and CK-MB, respectively, were significantly lower in the IAWBC group using univariate ANOVA. At day 0 (1.73 ± 5.94 versus 0.66 ± 1.74 ng/ml, P < 0.001) and day 1 (2.01 ± 4.39 versus 0.95 ± 2.08 ng/ml, P < 0.001) cTNI levels were more then double in the IACBC-group. Also at days 2 (0.98 ± 1.52

![Table 2](https://academic.oup.com/ejcts/article-abstract/23/3/341/520911)

<table>
<thead>
<tr>
<th>Intraoperative data</th>
<th>IAWBC (n = 100)</th>
<th>IACBC (n = 100)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time on cardio-pulmonary bypass (min)</td>
<td>92.6 ± 30.2</td>
<td>95.8 ± 29.2</td>
<td>0.365</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>47.0 ± 12.3</td>
<td>51.2 ± 16.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Reperfusion time (min)</td>
<td>35.0 ± 17.6</td>
<td>35.2 ± 17.8</td>
<td>0.784</td>
</tr>
<tr>
<td>Cumulative time of cardioplegia application (min)</td>
<td>6.0 ± 5.4</td>
<td>7.1 ± 2.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cumulative amount of cardioplegia (ml)</td>
<td>1340 ± 478</td>
<td>2120 ± 712</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time until cardiac arrest (s)</td>
<td>36.2 ± 36.3</td>
<td>103.1 ± 32.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Number of patients with electrical activity during aortic cross-clamp time (%)</td>
<td>24</td>
<td>30</td>
<td>0.34</td>
</tr>
<tr>
<td>Number of distal anastomoses</td>
<td>3.6 ± 0.9</td>
<td>3.6 ± 0.10</td>
<td>0.759</td>
</tr>
<tr>
<td>Necessity of defibrillation (%)</td>
<td>18</td>
<td>43</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cumulative energy of defibrillation (J)</td>
<td>3.4 ± 10.8</td>
<td>10.8 ± 20.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stable hemodynamics at the end of operation (%)</td>
<td>83</td>
<td>78</td>
<td>0.342</td>
</tr>
<tr>
<td>Dosage of norepinephrine at the end of operation (µg/kg per min)</td>
<td>0.032 ± 0.07</td>
<td>0.036 ± 0.070</td>
<td>0.323</td>
</tr>
</tbody>
</table>

* Corresponding to the assessment of the surgeon at the end of the operation using the three values ‘stable’, ‘stable using catecholamines’ and ‘unstable’ hemodynamics.

![Table 3](https://academic.oup.com/ejcts/article-abstract/23/3/341/520911)

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>IAWBC (n = 100)</th>
<th>IACBC (n = 100)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day-mortality (%)</td>
<td>2</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Perioperative acute myocardial infarction (%)</td>
<td>2</td>
<td>3</td>
<td>0.651</td>
</tr>
<tr>
<td>Need for IABP (%)</td>
<td>3</td>
<td>4</td>
<td>0.701</td>
</tr>
<tr>
<td>Re-thoracotomy due to bleeding (%)</td>
<td>0</td>
<td>6</td>
<td>0.013</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>5</td>
<td>4</td>
<td>0.734</td>
</tr>
<tr>
<td>Postoperative atrial fibrillation (%)</td>
<td>41</td>
<td>34</td>
<td>0.308</td>
</tr>
<tr>
<td>Postoperative ventilation time (h)</td>
<td>10.3 ± 17.4</td>
<td>15.3 ± 53.2</td>
<td>0.146</td>
</tr>
<tr>
<td>Time at intensive care unit (days)</td>
<td>2.0 ± 2.5</td>
<td>2.1 ± 3.0</td>
<td>0.575</td>
</tr>
</tbody>
</table>

* IABP, intra-aortic balloon pump.
ers who found that the arrested, normothermic heart requires 75–80% less oxygen than does the normal working heart. [12]. However, the continuous blood flow is a limitation of safety in coronary surgery. Calafiore and associates reported a very simple technique of intermittent antegrade warm blood cardioplegia in 1995 in a historical comparative study [10]. The beneficial outcome of this kind of cardioplegia was described by a lot of cardiac surgeons regarding cardiac metabolism [13,14–16]. Only few prospective randomized trials are available comparing the IAWBC with established cardioplegic strategies [14,17]. Aim of our study was the comparison of IAWBC to our standardized cardioplegia protocol with intermittent antegrade cold blood cardioplegia according to Buckberg [11]. To avoid interferences with systemic perfusion temperature or other perfusion conditions both study groups received the identical peri-operative protocol with the exception of cardioplegia solution and cardioplegia temperature. The IAWBC technique of Calafiore was modified by lowering the cardioplegia temperature to the systemic perfusion temperature of 33–34°C and by magnesium supplementation according to Caputo and colleagues [18]. The magnesium supplementation was necessary because of a high rate of failed electromechanical arrest after application of cardioplegia at the time of preparation of this study. Also Pelletier and colleagues described a failure rate of 13% to achieve sustained electromechanical arrest by use of warm blood cardioplegia [17]. Using the magnesium supplementation this phenomenon did not appear in our experience. In a recent study the beneficial effect of magnesium as a supplement to warm blood cardioplegia on incidence of peri-operative arrhythmias was described. However, the decrease of atrial fibrillation observed by Yeatman and colleagues could not confirmed in our analysis [15].

The results of our study demonstrate no differences of mortality and peri-operative infarction as well as need for intra-aortic balloon pump. However, patients of the IAWBC group needed less frequent defibrillation due to ventricular arrhythmias during reperfusion. The lower rate of ventricular arrhythmias was also observed by other investigators [10,17]. Additionally, Calafiore et al. [10] found a lower mortality, a less frequent use of intra-aortic balloon pump (IABP) and a lower incidence of inotropic support for weaning from cardiopulmonary bypass in his historical comparison. As the patients of Calafiore our patients of the IAWBC group could weaned from ventilation earlier then patients patients with IACBC.

The ischemia markers cTNI as well as CK-MB were significantly lower in the IAWBC group within the first postoperative days. These results confirm the observations of most other investigators [13,14,16]. They are corresponding to the data of Pelletier and colleagues who compared IAWBC and IACBC too. These authors also found a not different clinical outcome, however, a lower rate of ventricular arrhythmias and lower ischemic markers in patients with IAWBC.

4. Discussion

The warm blood cardioplegia was established into the clinical use by the warm heart surgery investigators group [8,9] basing on the observations of Buckberg and co-work-

![Figure 1](https://example.com/figure1.png)

Fig. 1. Comparison of cTNI (A); and CK-MB (B) in the postoperative course. Patients with acute myocardial infarction were excluded. Standard deviation see results. Statistical significance was estimated by ANOVA with repeated measurements. (pod – post operative day).
The cause of impaired myocardial protection using hypothermia is assumed in a prolonged disturbance of cardiac metabolism. Especially all adenosine triphosphate-dependent reactions are impaired, with a resulting negative influence on membrane stability, energy production, enzyme function, aerobic glucose utilization, adenosine triphosphate generation and utilization, cyclic adenosine monophosphate production, and osmotic homeostasis [10,19]. Biagioli et al. demonstrated a significant increase of oxidative stress measured by the glutathion redox status in cold blood cardioplegia [16]. Mehlhorn and colleagues found an activation of constitutive nitric oxide synthase (cNOS or NOS-III) and an increased cGMP content after hypothermic blood cardioplegia compared to warm blood cardioplegia [20]. They concluded that increased NO release secondary to NOS-III activation may have contributed to ischemia-reperfusion injury with decreased left ventricular function. Additionally, in our patients the time until isoelectrical cardiac arrest was significantly shorter in the IAWBC group compared to the IAABC group. The fast cardiac arrest might preserve the adenosine triphosphate content of the myocardium in the early ischemic period and influence the cell damage.

Intermittent antegrade warm blood cardioplegia according to Calafiore et al. is a technically very simple method. In contrast to cold blood cardioplegia no additional heat exchanger is necessary and the used drugs are available without preoperative mixture by a pharmacist resulting in lower costs for cardioplegia of less then the half.

5. Conclusion

IAWBC is a safe and cost-effective method in elective on-pump coronary artery bypass surgery. Mortality and incidence of perioperative myocardial infarction demonstrated no differences in-between IAWBC group and IAABC group. However, significant lower incidence of ventricular arrhythmias and significantly lower ischemic markers due to reduced myocardial cell damage suggest an improved myocardial protection compared to cold blood cardioplegia in these patients.

References

Appendix A. Conference discussion

Dr R. Przybylski (Zabrze, Poland): My question is why you chose a group of patients with hearts with an ejection fraction of 60%? According to the guidelines of the American Heart Association, hearts with such an ejection fraction are very resistant to ischemia. So probably your results are just by chance.

Dr Franke: The reason was to avoid any kind of interference with other parameters when cardioplegic solution was used. Another issue was the temperature. We used a systemic temperature of 33–34°C in both groups in contrast to the original protocol of intermittent warm blood cardioplegia, which used 36–37°C. And the advantage for warm blood cardioplegia is also the warm. Our aim was to avoid all interferences with other parameters, when we compared our original Buckberg-strategy with the intermittent warm blood cardioplegia.

Dr S. Chocron (Besancon, France): I would like to thank Dr Franke, who confirms with this study the results of a study we published 2 years ago in the Journal of Thoracic and Cardiovascular Surgery. It is somewhat comforting, that with the same initial question and the same study design, you obtained the same answers. My question is, what do you think about warm reperfusion before aortic unclamping as an adjunct to myocardial protection?

Dr Franke: I can’t answer your question because of our data. We have no experience with this kind of myocardial protection.

Dr A. Albert (Lahr, Germany): What do you think is the reason for the differences in the CK-MB and troponin I release? Is it the temperature of the solution or the Buckberg solution?

Dr Franke: The literature reflects a lot of data regarding the optimal strategy. Cardiac arrest is the most important factor. The influence of temperature on the quality of myocardial protection is more difficult to define. The low temperature leads to a disarrangement on a molecular basis. It is proposed, that the warm cardioplegia can better preserve the hemostasis of the cells.

Dr J. Vaage (Stockholm, Sweden): You have two variables here, that is, the administration or the volume of cardioplegia you give as well as the temperature. How much is related to the volume and the frequency that you give the cardioplegia and how much is related to temperature?

Dr Franke: I can’t answer that because we used the original techniques as described by the publishers. The Buckberg solution technique needs a longer application time than the Calafole technique until the isoelectrical cardiac arrest. This very short time was caused by the higher level of potassium, which was administered, very fast.

Dr S. Al-Ruzzeh (London, UK): I have two questions. The first question is, you have shown that there is a difference in the bypass time, which didn’t reach statistical significance, and the second one is the need for defibrillation, which reached statistical significance. My question is, don’t you think that the longer bypass time could be the explanation of your troponin T release, or troponin I release, I can’t remember, and not really of the myocardial damage? The longer you stay on bypass, the longer you release troponin. That is a fact.

And the other thing is the need for defibrillation. When were you defibrillating the patient? Was the patient back to eurythermia or still hypothermic?

Dr Franke: The difference for the cardiopulmonary bypass time was only caused by the difference of the longer application time for cardioplegia. When we eliminated this part of the bypass-time the cardiopulmonary bypass time, as well as the aortic cross-clamp time, were same in both groups. We performed defibrillation within the reperfusion time, about 5 min after declamping. The patients have 2–3–5 min reperfusion.

Dr Al-Ruzzeh: Was the patient eurythermic or hypothermic?

Dr Franke: 33–34°C in both groups.

Dr Al-Ruzzeh: This means he was hypothermic, or the patient was hypothermic?

Dr Franke: Mild hypothermic.

Dr Al-Ruzzeh: In my experience, defibrillation doesn’t work in hypothermia. You need to wait until the patient is eurythermic and then defibrillate, if you agree.

Dr Franke: No, I don’t agree, because in all patients the first shot of defibrillation was useful and we have had no differences in-between the groups.