Original Article

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Myocardial Protection in Minimally Invasive Mitral Valve Surgery: Comparison of the Cold-Blood Cardioplegia of the Bretschneider Solution and the Warm-Blood Cardioplegia of the Calafiore Protocol

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Abstract

Objective: Minimal invasive mitral valve surgery using right thoracotomy is becoming a safe alternative and has an increasing impact in the clinical routine. The best strategy for myocardial protection for these patients is under discussion. Warm-blood cardioplegia, according to the protocol of Calafiore (group C), is well-established in coronary surgery throughout Europe, whereas the cold-crystalloid cardioplegia by Bretschneider (Custodiol®, group B) is in worldwide use in both heart surgery and organ transplantation.
Methods: All 107 patients with proposed mitral valve surgical repair through a right lateral mini-thoracotomy between July 2008 and September 2009 were evaluated and randomly selected for one of the two myocardial protection strategies described above. The quality of the myocardial protection was detected using the specific ischaemia markers cTNI and CK-MB on days zero, one and two following surgery. The study population represents 80% of all patients with isolated mitral surgery from the department. Demographic, as well as operative, data did not show any differences between the groups, and the hospitalization period was 13 days for both groups.
Results: The totally clinical mortality rate was 5% (2 patients in group B vs. 3 patients in group C, p=0.673). cTNI >10 µg/l levels 48 hours after the surgical procedure (p=0.055) were significantly higher in group C compared to group B, calculated by ANOVA for repeated measurement using SPSS® 17.0 software. However, the need for defibrillation was higher after Bretschneider`s cardioplegia (45% vs 10%, p<0,001), and heart arrest in the Calafiore group was attained at an average of nine seconds earlier. An IABP was implanted in one patient from the Calafiore group.
Conclusions: This prospective study suggests the superiority of myocardial protection using Bretschneider`s cold-crystalloid solution, compared to warm-blood cardioplegia using the Calafiore protocol in minimally invasive mitral valve surgery.

Keywords: *Myocardial protection, minimal invasive mitral valve*

Introduction

Minimal-invasive techniques for the surgical treatment of mitral valve disease have advanced over the last 15 years. The mid-term analysis did not demonstrate any compromise in the efficacy of mitral valve repair, when compared to the standard sternotomy approach, and is associated with decreased pain, reduced blood loss, faster recovery, superior cosmetic results and greater patient satisfaction [1,2]. New materials and techniques enable surgeons to overcome the initial difficulties related to surgical exposure, the approach, perfusion sys tems and instruments. An accurate learning curve is necessary and is inevitable, because technical differences with respect to conventional surgery still remain. Cardioplegia administration can still be a problem [3]. Numerous modifications to cardioplegic solutions, after the introduction of the cardioplegic principle by Melrose [4], have been applied. The multitude of different methods and techniques clearly demonstrate the persistent inadequacy of all of them, because none have shown a satisfactory solution for all ischaemia-related effects. The large variety of application techniques and cardioplegic solutions do not allow the homogeneous complaint of the effectiveness of myocardial protection, especially in long ischaemia cardiac procedures in patients without coronary disease nowadays [5]. Improvements in intra-operative myocardial protection amended post-ischaemic haemodynamic function, as well as attenuated the prevalence of perioperative infarction, and decreased mortality [6].

The clinical outcomes resulting from different techniques of surgical procedures with different myocardial protection have been compared in most studies by analyzing the mortality or the rate of myocardial infarctions [7,8]. A further disputable point in the discussion about cardioplegia was the neurological factor: a prospective randomization by Martin [9] (about cold blood and crystalloid solutions in 1001 CABG patients had to be stopped intercessionally for cold-crystalloid cardioplegia. The efficiency of myocardial support during a long ischaemia time (> 90 minutes) is, in view of molecular, enzymatic and morphologic elements, difficult to evaluate. The ischaemic cardiac marker of cellular alteration, cardiac Troponin-I (cTNI), has been used in a large number of studies [10-12] of coronary occlusion disease without the results of valve replacement surgery.

In our institute we apply two different cardioplegic principles in conventional cardiac surgery that require more than 90 minutes of aortic cross-clamp time with a single dose of cold-crystalloid histidine-triptophan-ketoglutarate solution (HTK) by Bretschneider; during relatively short procedures of cardiac surgery, cardioplegia was performed using a warm-blood potassium solution via repeated application of the Calafiore regime every 20 minutes. In most of the descriptions found in the literature, patients with a heterogeneous disease profile were included, such as patients with coronary artery disease with different degrees of myocardial ischaemia and stenosis graduation, or with a retrospective design of the study. All of these differences might also contribute to difficulties in interpreting the results. To circumvent these potentially confounding factors, we only included patients undergoing minimal invasive mitral valve surgery without any further sig tems and instruments. An accurate learning curve is necessary and is inevitable, because technical differences with respect to conventional surgery still remain. Cardioplegia administration can still be a problem [3]. Numerous modifications to cardioplegic solutions, after the introduction of the cardioplegic principle by Melrose [4], have been applied. The multitude of different methods and techniques clearly demonstrate the persistent inadequacy of all of them, because none have shown a satisfactory solution for all ischaemia-related effects. The large variety of application techniques and cardioplegic solutions do not allow the homogeneous complaint of the effectiveness of myocardial protection, especially in long ischaemia cardiac procedures in patients without coronary disease nowadays [5]. Improvements in intra-operative myocardial protection amended post-ischaemic haemodynamic function, as well as attenuated the prevalence of perioperative infarction, and decreased mortality [6].

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The aim of the study was to analyze, in the context of a prospective randomized trial, the efficacy of myocardial protection between an antegrade cold cardioplegia solution by Bretschneider and warm-blood cardioplegia using the Calafiore protocol for non-CHD patients, who underwent standard minimal invasive mitral valve repair / replacement via thoracoscopic approaches, combined with a right anterior mini-thoracotomy determined by the clinical course. Serial measurements of serum markers for myocardial damage and electrocardiographic changes were performed.

Materials and Methods

Study design

The prospective analysis evaluated 107 patients operated on between July 2008 and September 2009, who had been subjected to minimal invasive mitral valve surgery. Patients with comorbid cardiac disease, such as aortic valve disease or coronary artery disease, and emergency cases were excluded. All the patients consented to participate in the present study.

The MV surgery (repair or replacement) was done using a right lateral mini-thoracotomy and femoral cannulation for a cardio-pulmonary bypass (CPB).

Perioperative myocardial infarction (MI) and the following myocyte cell damage were defined by a significant increase in creatine kinase (> 10 times upper normal limit or >10% of the elevated creatine kinase level) or by an increased level of myocardial tissue specificity marker cTroponin (cTnI) (measurements exceeding the 99th percentile of a normal reference population = upper reference limit).

Demographic and operation data did not show significant differences between the groups (Table 1). The collected perioperative data allowed the evaluation of common parameters, like aortic clamping time, ECC duration, using IABP and times of defibrillation. All patients had a long ischaemia time (>90 min).

The local ethics committee approved the study and the subjects gave written informed consent.

Table 1. Demographic / OP Data

	Group B	Group C	p-value
Patients total, n	55	52	
Sex, male/female, %	56/44	69/31	0,230
Age, years	65 + 14	66 + 9	0,596
Height, centimetres	169 + 18	172 + 10	0,583
Weight, kilograms	77 + 19	74 + 13	0,374
No Diabetes, %	91	92	0,620
Ejection fraction (EF>70%) %	80	79	0,205
Operation MIC MKR	79%	73%	0,422
Cross clamping time (min)	161 + 47	156 + 43	0,978
Ischaemia time (min)	97 + 32	99 + 26	0,501
Flat line after (sec)	73 + 40	64 + 44	0,006
Defibrillation	45%	10%	<0,001
IABP	0%	2%	<0,001

Operative technique

The operation was done using the typical position for minimal invasive, thoracoscopic mitral surgery after a transoesophageal echocardiogram (TEE), performing analyzed segmental valve assessment using Carpentier techniques. Methods of valve reconstruction were leaflet resection (quadrangular for posterior mitral leaflet PML and triangular for anterior mitral leaflet AML), and chordal replacement with Gore-tex® loops. Prosthetic annuloplasty using rings was invariably availed to remodel the mitral annulus.

After, the introduction of ECC through the right femoral artery and vein mini-thoracotomy in the third intercostal space through a 5 cm skin incision was performed. Using a video thoracoscope (optic 2.7 mm 30° Endo TIPTM, Karl Storz Endoscope, Germany) and carbon dioxide insufflation (4 L/min), the pericardium was opened 2 cm anterior to the phrenic nerve. After aortic clamping, cardioplegia was administered through the aortic root (2000 ml Custodiol®, Koehler Chemie, Germany), or warm-blood cardioplegia modified the Calafiore protocol with readministration every 20 minutes. Incision of the left atrium was done through the interatrial groove. For retraction of the left atrium, the MitraXS (St. Jude Medical Inc., USA) method was used. Under a perfect view, the mitral valve was inspected for competence and replacement; the atriotomy was closed and the heart deaired via the aortic root.

Myocardial protection

One of the following cardioplegic solutions was applied for myocardial protection during the aortic clamping time.

Warm-blood cardioplegia, Calafiore: Patients of the Calafiore group (Group C) were treated according to the modified Calafiore protocol by Caputo, with a temperature of 35 °C immediately after aortic clamping for three minutes after the initiation of cardiac arrest. A single pump containing KCl and $MgSO_4$ (40 ml of 2 mmol/ml KCl, 10 ml of 2 mmol/ml

Table 2. Laboratory Data

		Group B (n=55)	Group C (n=52)	p-value
Creatinin	pre-op	0.97 + 0.31	1.06 + 0.38	0.125
(mg/dl)	1 pod	1.1 + 0.46	1.15 + 0.63	0.717
	2 pod	1.18 + 0.84	1.15 + 0.66	0.603
GFK	pre-op	75 + 17	72 + 17	0.252
(ml/min)	1 pod	68 + 21	70 + 20	0.687
	2 pod	71 + 27	70 + 23	0.383
CK	pre-op	99 + 133	78 + 38	0.925
(U/l)	6 h post-op	1046 + 754	1727 + 2274	0.157
	1 pod	1150 + 801	1430 + 1400	0.82
	2 pod	853 + 963	614 + 655	0.053
CK-MB	6 h post-op	58 + 34	134 + 278	0.037
(U/l)	1 pod	53 + 39	88 + 146	0.778
	2 pod	32 + 33	32 + 24	0.506
cTnI	6 h post-op	18.3 + 17.3	37.2 + 57.2	0.97
(µg/l)	1 pod	13 + 14.5	30.5 + 48.9	0.737
	2 pod	9 + 20.1	17.4 + 36.9	0.57
Lactat	1 pod	13.4 + 8.2	19 + 27.6	0.639
(mmol/l)				

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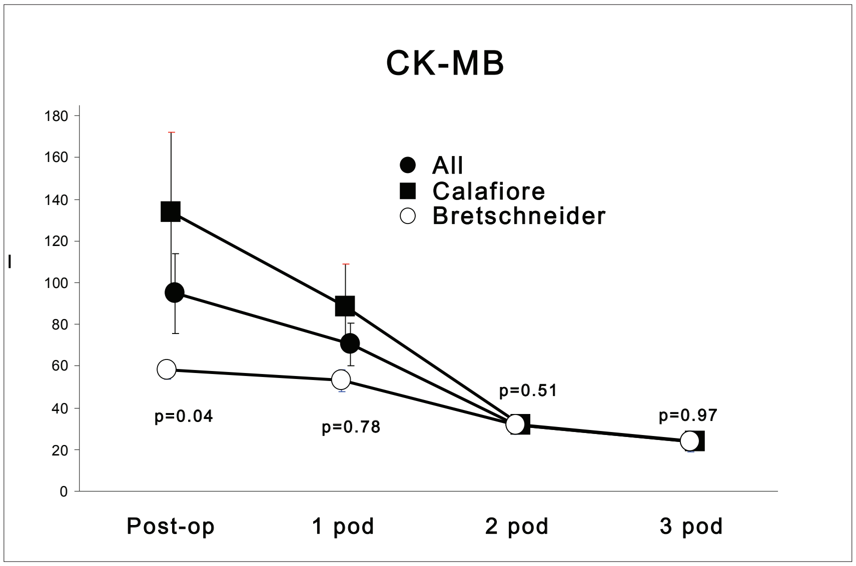

Figure 1. Panel shows middle levels of post-operative creatine kinase isoenzyme MB (CK-MB) concentrations with cold-crystalloid cardioplegia

Table 3. cTnI Laboratory Data

		Group B (n=55)	Group C (n=52)	p-value
6 h post-op	cTnI>10	69% (38)	62% (32)	0.425
1 pod	cTnI>10	44% (23)	45% (23)	1.00
2 pod	cTnI>10	8% (3)	26% (9)	0.055

$MgSO_4$) was connected to the tubing to deliver the cardioplegic solution. Re-administration was done every 20 minutes.

Antegrade cold-solution Custodiol®: Patients of the Bretschneider group (Group B) received one bolus of 2000 ml Custodiol® (Köhler Chemie, Bensheim, Germany) at 4 °C immediately after aortic cross clamping with a pressure of about 50 mm Hg. The solution takes in a special histidin buffer, which averted the intracellular acidosis process. After 90 minutes, another 1000 ml of the Bretschneider`s solution was administrated, if needed.

Application was done via the aortic root in both groups.

Ischaemia markers

The quality of myocardial protection was assessed by the cardiac ischaemia markers cTNI (μg/l) and creatine kinase MB isoenzyme (CK-MB, 37°C U/l). The level of cTNI and CK-MB also depends on the kidney function, so we evaluated the concentration of creatine kinase addicted from the glomerular filtration rate (GFR). The in-vitro test of the creatine level was measured using Roche Diagnostic GmbH, Mannheim, Germany. The upper normal reference limit (99th percentile) was less than 1.4 mg/dl. The equation for estimating GFR is MDRD formal: GFR (ml/min/1.73 m^2) = 186 x $(P_{CR})^{-1,154}$ x $(Age)^{-0,203}$ x (0.742 if female) (www.kidney.org/kls/patients) and usually higher than 90 ml/min. The kidney function based on GFR showed no difference at the beginning of the surgical treatment and during the 72 h post-operative phase between both groups. Creatine kinase MB (reference <25U/l) assays were detected using an immunologic UV-test by Roche Diagnostic GmbH, Mannheim, Germany. cTNI concentration (reference <0.16 mμg/l) was measured by AxSym Troponin-I ADV Assay, Abbott Diagnostic GmbH, Wiesbaden, Germany. The parameters were collected before

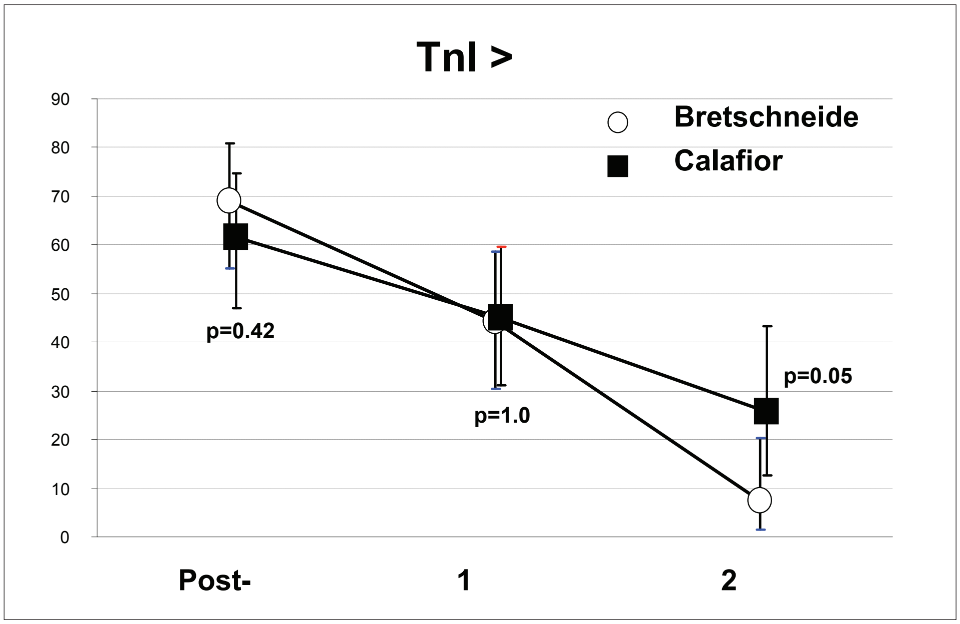

Figure 2. Panel shows middle levels of post-operative cardial troponin-I (cTnI) concentrations with cold-crystalloid cardioplegia

(pre-op), as well as 6 h (pod), 24 h (1 pod) and 48 h (2 pod) after the mitral valve replacement.

The implication of the anaerobic metabolism was estimated by choosing the Lactate (Lac) in the whole blood and plasma on the first post-operative day. Concentrations were detected by ABL 700 (Radiometer, Kopenhagen, Denmark) using ion-selective electrodes with lactate oxidase as the enzyme.

Statistical analysis

Statistical analysis was performed using the SPSS 17.0 software system (SPSS Inc. Chicago, IL) and SAS Version 9. For determination of the two data sets, which differ significantly, non-parametric analysis was used: that is the analysis of ranked variability and a two-stage Mann-Whitney-U-test. A comparison between quality parameters (like frequency dates) was done by the Chi^2-test and Fisher-test.

The P-value $\leq$ 0.05 was considered for explorative statistical significance. The method of Bonferroni was utilized for risk analysis for Type-I errors in cTnI and CK, CK-MB levels; the mean error of α=0.05 was divided through the rate of tests, and the compared related error α=0.01 was the result (adjustment).

Results

We did not find any significant differences regarding any of the variables presented in Table 1 of the patient characteristics, apart from the time until isoelectric arrest, which was nine seconds earlier in the Calafiore group (p=0.006), as well as the incidence of the need for defibrillation after cardiac arrest, which was 0.8x in Group B vs. 0.2x in Group C (p=0.001).

The 30-day mortality rate was 5%. Causes of death through a low cardiac output syndrome were observed in two patients using Bretschneider`s cardioplegia, and in three patients in the Calafiore group, patients underwent mitral valve replacement with a high preoperative risk profile. We could detect no causes of reoperation, sepsis or strokes. Some patients processed moderate acute respiratory insufficiency without clinical effects, so after 14 days, on average, they left hospital.

Laboratory data of ischaemia markers

The concentrations of myocardial damage markers CK-MB and cTnI showed no significant alterations in both groups, using non-parametric tests in post-operative follow-up analysis after 48 hours (Table 2). The first level of CK-MB (6 h post-op) was higher in Group C 134 $\pm$ 278(U/l), cTnI

37.2 ± 57.2(μg/l) compared to Group B 58 ± 34 (p=0.037), cTnI 18.3 ± 17.3(μg/l) (p=0.97). Haemofiltration was used in the surgical procedures using 2000 ml of Bretschneider`s solution. So, the effect was abolished after 24 h postoperatively (Figure 1, 2).

The analysis revealed significant higher cTnI levels on the two post-operative days in one of the two different cardioplegia forms: 26% of Group C patients compared to 8% of Group B patients showed a cTnI concentration of about 10μg/l, p=0.055 (Table 3). The classification of the ejection fraction differed to a moderate degree, independent of the used solution class: 79% of patients had EF>70% preoperatively, and after the surgical intervention, it showed only 52% of patients EF>70%; moderate left ventricular function (EF 40-70%) preoperatively had 13% vs. 42% after the operation.

There was no correlation between creatine kinase and lactate with a high scatter range in either group.

Discussion

The minimal-invasive treatment of mitral valve pathology is equivalent to that of conventional surgery [13]. The option for the best results and a safe surgical procedure should allow continued use of standards and familiar tools, so every single thing that simplifies a less-invasive procedure may help the surgeon to obtain the best results [3]. In our institution, HTK solution, which has low sodium and calcium, buffered with histidine and mannitol, is routinely applied in conventional heart surgery with a long ischaemia time, >90 min. The Calafiore procedure requires new administration of cardioplegia every 20-30 min, so it is limited for use in uncomplicated cases and short aortic clamping periods. The advantage of this cardioplegia is low costs and the avoidance of hemofiltration, which favors it for minimized extracorporeal circulation.

The present prospective randomized study demonstrates various beneficial outcomes in coronary healthy patients during long aortic clamping (>90min) using two different cardioplegia solutions: cold-crystalloid using the Bretschneider`s solution (Custodiol®) vs. warm-blood cardioplegia using the Calafiore protocol in the standardized surgical intervention of minimal invasive mitral valve surgical repair.

A description of the positive effects using warm-blood cardioplegia, demonstrated by many examinations, could be made on CABG patients. However, knowledge of occlusion graduation, myocardial thickness, with short ischaemia periods and other standardized facts are lacking, so a homogeneous prospective analysis in a wide range of patients seems to be impossible, even though the myocardial protection treatments are established [14,15]. (The first prospective examination of myocardial damage in isolated valve surgery (aortic) without coronary disease by using two different solutions is provided by the study of Braathen et al., and showed the benefit of cold-blood antegrade application through coronary ostia every 20 min during aortic cross-clamping time, regarding cardiac ischaemia markers [16] (The same authors examined the myocardial damage in elective mitral valve surgery and showed that one single dose of antegrade Bretschneider`s cardioplegia is as effective as repetitive antegrade cold-blood cardioplegia in protecting the myocardium, as measured by CK-MB and Troponin-T [17]. In this paper, the authors further stated that Bretschneider`s cardioplegia "is simpler to use than blood cardioplegia in mitral valve surgery because the operation can be performed continuously without interruptions, for up to 2 hours of ischaemia".

Video-assisted mitral valve surgery is safe with high rates of repair, low morbidity, and excellent outcomes, although associated with equal mortality and neurologic events despite a longer cardio-pulmonary bypass time [18]. We could repair more than 73% without bleeding or any neurologic complications. The reason for 5% hospital mortality by the mitral valve replacement group was low cardiac output syndrome, caused by an inexplicable reason of heart stunning after a long aortic clamping time during reperfusion time with treatment by IABP.

In conclusion, this study is the only published report comparing HTK and warm-blood cardioplegia in minimally invasive mitral valve surgery. The results of this analysis suggest that both methods are safe and effective, according to the observed in-hospital death, LOS and IABP.

The warm cardioplegia using the Calafiore regime resulted in less defibrillation times. On the other hand, the patients of the Bretschneider Group showed lower levels of cardiac Troponin I release and CK-MB (2 pod), and lower mortality rates compared to the blood cardioplegia group, thus suggesting efficient myocardial protection when using Bretschneider's cardioplegia. Either HTK or warm blood may be superior in certain clinical situations, such as prolonged cold or warm ischaemia time, but further study would be required to delineate the impact of the preservation solution on each of these factors individually.

Study limitations

The collection of data was prospectively, but the recruitment group, small (n=107). The laboratory equipment did not allow any markers for molecular and immunological damage.

Abbreviations: CHD = coronary heart disease, MV = mitral valve, CPB = cardio-pulmonary bypass, MI = myocardial infarction, ECC = extracorporeal circulation, TEE = transoesophageal echocardiogram, IABP = intraaortal balloon pump, PML = posterior mitral leaflet, AML = anterior mitral leaflet, cTNI = cardiac troponin I isoenzyme, CK= creatine kinase, CK-MB = creatine kinase MB isoenzyme, GFR = glomerular filtration rate, Lac = Lactate, ECMO = extracorporeal membrane oxygenation

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. We thank the staff of the Department of Cardio-thoracic Anaesthesiology and Cardiac Perfusions, Robert-Bosch Hospital, Stuttgart, Germany for helping to perform the prospective study. We also thank Ulrich Stefenelli from Services-In-Statistics, Würzburg, for valuable help regarding statistical analyses.

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