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Microplegia versus Cardioplexol® in Coronary Artery Bypass Surgery with Minimal Extracorporeal Circulation: Comparison of Two Cardioplegia Concepts

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Abstract

Background The aim of this study is to compare the combined use of the Myocardial Protection System and our microplegia (Basel Microplegia Protocol) with Cardioplexol® in coronary artery bypass grafting using the minimal extracorporeal circulation.

Methods The analysis focused on propensity score matched pairs of patients in whom microplegia or Cardioplexol® was used. Primary efficacy endpoints were high-sensitivity cardiac troponin-T on postoperative day 1 and peak values during hospitalization. Furthermore, we assessed creatine kinase and creatinine kinase-myocardial type, as well as safety endpoints.

Results A total of 56 patients who received microplegia and 155 patients who received Cardioplexol® were included. The use of the microplegia was associated with significantly lower geometric mean (confidence interval) peak values of high-sensitivity cardiac troponin-T (233 ng/L [194–280 ng/L] vs. 362 ng/L [315–416 ng/L]; $p = 0.001$), creatinine kinase (539 U/L [458–633 U/L] vs. 719 U/L [645–801 U/L]; $p = 0.011$), and creatinine kinase-myocardial type (13.8 µg/L [9.6–19.9 µg/L] vs. 21.6 µg/L [18.9–24.6 µg/L]; $p = 0.026$), and a shorter length of stay on the intensive care unit (1.5 days [1.2–1.8 days] vs. 1.9 days [1.7–2.1 days]; $p = 0.011$). Major adverse cardiac and cerebrovascular events occurred with roughly equal frequency (1.8 vs. 5.2%; $p = 0.331$).

Conclusions The use of the Basel Microplegia Protocol was associated with lower peak values of high-sensitivity cardiac troponin-T, creatinine kinase, and creatinine kinase-myocardial type and with a shorter length of stay on the intensive care unit, as compared with the use of Cardioplexol® in isolated coronary artery bypass surgery using minimal extracorporeal circulation.

Keywords
- ► cardiopulmonary bypass (CPB)
- ► coronary artery bypass grafts surgery (CABG)
- ► myocardial protection/ cardioplegia
- ► perfusion

Introduction

Coronary artery bypass grafting (CABG) using extracorporeal circulation (ECC) is the gold standard in the treatment of complex coronary artery disease.[1–3] The minimal extracorporeal circulation (MiECC) system, a minimized and closed form of the ECC, maintains their advantages, but reduces the area of artificial surfaces and avoids blood–air contact.[4] The use of MiECC in CABG surgery has been reported to be associated with excellent mid- and long-term outcomes.[4–9] Moreover, regarding perioperative myocardial damage reflected by cardiac markers, the use of MiECC was comparable to off-pump coronary artery bypass grafting (OPCABG),[10] and has now been implemented into the European Association for Cardio-Thoracic Surgery/European Association of Cardiothoracic Anaesthesiology (EACTS/EACTA) guidelines.[11]

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In our hospital MiECC is the standard perfusion strategy in isolated CABG surgery if OPCABG is not performed. Until May 2017, Cardioplexol® (Bichsel, Interlaken, Switzerland) was used to induce cardiac arrest. Cardioplexol® is a single-shot cardioplegia (100 mL) which is directly applied via the aortic root.[5,9,11–13] However, there is literature showing significantly higher values of cardiac markers in the subgroup of patients with isolated left main trunk (LMT) stenosis (> 50%) compared with patients with severe three vessel disease (3-VD) or combined LMT and 3-VD when Cardioplexol® was used as cardioplegia.[14]

To further ameliorate cardiac protection during surgery, we have introduced the Myocardial Protection System (second-generation, MPS) as an additional tool to the MiECC to deliver a refined microplegia (Basel Microplegia Protocol).[15] The use of microplegia was previously found to be beneficial in regard to adverse events, length of stay on the intensive care unit (ICU), and in-hospital stay compared with traditional cardioplegia, as well as with lower incidence of postoperative low cardiac output syndrome in isolated CABG surgery.[16,17]

Our first experience showed that the use of the Basel Microplegia Protocol is safe and reliable, and associated with low postoperative cardiac markers, indicating an excellent myocardial protection during surgery.[15] This study aims to investigate whether the finding of low cardiac markers is indeed a consequence of the application of the microplegia, instead of being due to mere patient selection. This is why we conducted a propensity-matched cohort study with a 3:1 matching to compare the two cardioplegic solutions: Basel Microplegia Protocol versus Cardioplexol®.

Patients and Methods

Ethical Approval

The local ethical committee (EKNZ BASEC Req-2018–00926) approved the study protocol, which is in accordance with the principles of the declaration of Helsinki. The ethical committee has waived the need to obtain informed consent.

The trial was registered at ClinicalTrials.gov (ID NCT03612388). The authors designed the study, gathered and analyzed the data, vouched for the data and analysis, wrote the paper, and decided to publish.

Technical Aspects and Cardioplegia Protocol

Technical aspects and development of our microplegia solution were previously described in detail.[15] In brief, the surgical technique remains unchanged to the use of MiECC with Cardioplexol® except for repeated microplegia administration at 20-minute intervals, as well as the "hot-shot" application prior to declamping,. The microplegia (composed of patient's blood with K, Mg, and Lidocaine, thus normovolemic) is applied under pressure and flow control via the aortic root. The targeted flow is approximately 300 mL/min and for safety reasons, the pressure is limited to 250 mm Hg (measured directly in the MPS console). Microplegia protocol consists of 4 minutes induction time (with reduced dosage of K after 2 minutes) and repetitive administration of 2 minutes in every 20 minutes. Before declamping, a hot shot is given for 1 minute[15] (►**Table 1**).

The technique of the application of Cardioplexol® was also described in detail before.[6,10,12–15,18] The Cardioplexol® is a single-shot cardioplegia (100 mL) based on procaine, magnesium (Mg), and potassium (K). It is directly and manually applied via the aortic root. Cardioplexol® ensures a controlled cardiac arrest for approximately 45 minutes per 100 mL shot and repetitive administration up to four times with a maximum dosage of 500 mL is feasible (►**Table 2**).[6,10,12–15,18]

Patients and Study Design

MiECC-assisted surgery or OPCABG are the standard procedures for isolated CABG in our institution. Conventional ECC is predominantly applied in emergency operations or nonCABG surgeries.[15] Before the introduction of the second-generation MPS and the development of the Basel Microplegia Protocol, Cardioplexol® was used standardly to induce cardiac arrest when using the MiECC. In May 2017, we started to deliver our institutionally refined microplegia (Basel Microplegia Protocol) using the MPS, as an adjunct to the MiECC.[15] Since it performed excellent results, this combination became routine in isolated CABG with MiECC. To investigate the quality of the two cardioplegia strategies (Basel Microplegia Protocol vs.

Table 1 Composition of the microplegia applied via the MPS (Basel Microplegia Protocol)

	Time (min)	Potassium (mmol/L)	Magnesium (g/L)	Lidocaine (mg/L)	Flow (mL/min)
Induction	2	20	1.6	40	300
	2	13	1.6	40	300
Repetition dose	2	6	1.6	40	300
Hot shot	1	–	1.6	40	300

Table 2 Composition of Cardioplexol®

	Potassium (mmol/100 mL)	Magnesium (mmol/100 mL)	Procaine (mmol/100 mL)	Xylitol (mmol/100 mL)
Induction 100 mL	10	16.2	1.1	29.6
Repetition dose 100 mL	10	16.2	1.1	29.6

Source: Matt, Arbeleaz et al. Thorac Cardiovasc Surgeon 2012.

Cardioplexol®) on the basis of our own observational data, we chose a propensity score-matched cohort study design with a 3:1 matching to reduce a bias by indication (more details in section “Statistical Analysis”). Patients with OPCABG surgery, nonstandard cardioplegic strategy, concomitant ablation, or previous myocardial infarction within 7 days before the operation were excluded (►Fig. 1) from this analysis.

Using a prospectively maintained institutional registry (Intellect 1.7, Dendrite Clinical Systems, Henley-on-Thames, United Kingdom), we identified all patients who underwent isolated CABG in our institution after February 2010 when our laboratory introduced high-sensitivity cardiac troponin (hs-cTn). The clinical data were exported from this registry where data have been regularly controlled for completeness and accuracy. Intraoperative data were collected prospectively in a standardized fashion.[15] Serological parameters were assessed according to the standard algorithm in our hospital, starting on postoperative day (POD)-1 at 6:00 a.m. This was continued during the following days until a normalization of the values was noticed. As a correlate for perioperative myocardial damage, high-sensitivity cardiac troponin-T (hs-cTnT), creatine kinase (CK), and creatine kinase-myocardial type (CK-MB) were analyzed (first postoperative as well as peak values). Furthermore, we assessed major adverse cardiac and cerebrovascular events (MACCE) as a further safety endpoint. Moreover, we recorded intra- and perioperative data, such as length of stay on the intensive care unit (ICU), in-hospital mortality, postoperative atrial fibrillation (AFIB), aortic cross-clamping time, and number of distal anastomoses.

Statistical Analysis

We conducted a propensity-matched analysis, and included age, body mass index (BMI), ejection fraction, hypertension, and prior myocardial infarction (MI) into the propensity model. We trimmed the tails of the propensity score distribution at the more centered 2.5th and 97.5th percentile of

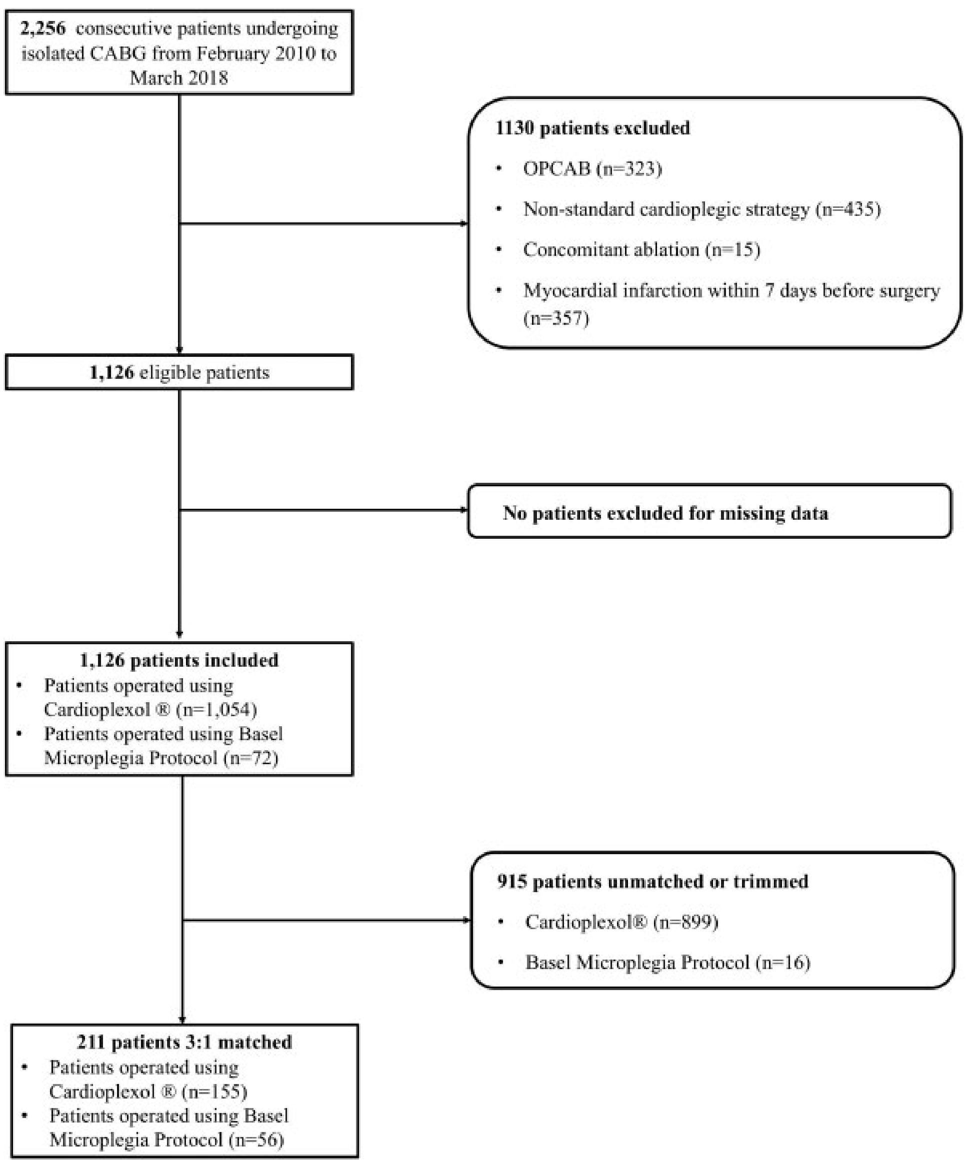

Fig. 1 Patient flow chart. CABG, coronary artery bypass grafting; OPCAB, off-pump coronary artery bypass. *Note*: the matching procedure did not find three matched pairs for each patient who underwent surgery with use of Basel Microplegia Protocol.

the two groups (►**Supplementary Fig. S1**; available online only). We used nearest neighbor matching with caliper width one-quarter of the standard deviation (SD) of propensity score. To account for matched pairs, mixed models were used for continuous variables and conditional logistic regression for binary variables, except if the model did not converge, in which case we used Fisher's exact test. Differences between the treatment groups (Basel Microplegia Protocol and Cardioplexol®) before and after matching were expressed as standardized differences, to assess the difference independently of the number of observations. As a sensitivity analysis of the main analysis, we used a generalized linear model of the Poisson family with logarithmic link function and robust standard errors. As a second sensitivity analysis, we used the Kruskal–Wallis rank test that ignores the matched-pairs structure. Continuous data are reported as mean ± SD if normally distributed or as geometric mean with confidence interval if skewed, and categorical data are reported as numbers with percentages. Confidence intervals and *p*-values are two-sided, a *p*-value below 0.05 was considered significant. All analyses were performed by a biostatistician (BG) using Stata 14 (Stata Corp, Texas).

Results

Preoperative Data

From February 2010 until March 2018, 2,256 consecutive patients underwent isolated CABG surgery, 1,126 of which met the inclusion criteria and thus represented the cohort of this study (►**Fig. 1**). Patients receiving Cardioplexol® were younger (mean [SD] 65.6 [9.5] vs. 69.5 [8.6] years, $p = 0.001$). Ejection fraction (EF) was lower in the Cardioplexol® group than in the microplegia group (53.6 [10.4]% vs. 56.1 [10.8]%, $p = 0.045$; ►**Table 3**). After trimming, 67 patients remained in the intervention group and 981 in the control group of whom 56 microplegia patients could be matched to 155 Cardioplexol® patients. More precisely, 44 microplegia patients could be matched with three Cardioplexol® patients ($n = 132$), 11 microplegia patients with two Cardioplexol® ($n = 22$), and one microplegia patient with only one Cardioplexol® patient.

Table 3 Patient characteristics

	Before matching				After matching			
	Microplegia $n = 72$	Cardioplexol® $n = 1054$	Diff.	*p*-Value	Microplegia $n = 56$	Cardioplexol® $n = 155$	Diff.	*p*-Value
Age, m (SD)	69.5 (8.6)	65.6 (9.5)	0.434	0.001	69.3 (8.4)	68.7 (8.2)	0.069	0.629
Female, *n* (%)	15 (20.8)	162 (15.4)	−0.021	0.220	11 (19.6)	31 (20)	0.001	0.974
BMI in kg/m^2, m (SD)	28.6 (5.1)	27.8 (4.3)	0.158	0.160	28.7 (5.2)	28.4 (4.5)	0.068	0.644
Diabetes mellitus, *n* (%)	30 (41.7)	403 (38.2)	−0.017	0.563	22 (39.3)	52 (33.5)	−0.028	0.386
Current smoker, *n* (%)	11 (15.3)	258 (24.5)	0.037	0.080	6 (10.7)	30 (19.4)	0.031	0.146
Peripheral artery disease, *n* (%)	10 (13.9)	141 (13.4)	−0.002	0.902	8 (14.3)	21 (13.5)	−0.003	0.887
Preoperative stroke, *n* (%)	2 (2.8)	68 (6.5)	0.008	0.226	2 (3.6)	7 (4.5)	0.002	0.754
Renal disease, *n* (%)	2 (2.8)	49 (4.6)	0.004	0.465	1 (1.8)	9 (5.8)	0.008	0.207
Dialysis[a], *n* (%)	0 (0.0)	9 (0.9)	0.001	1.000	0 (0)	0 (0)	0.000	1.000
COPD, *n* (%)	13 (18.1)	152 (14.4)	−0.013	0.400	9 (16.1)	18 (11.6)	−0.015	0.473
Hypertension, *n* (%)	60 (83.3)	964 (91.5)	0.027	0.023	50 (84.7)	137 (84.0)	0.003	0.872
Hypercholesteremia, *n* (%)	55 (76.4)	891 (84.5)	0.032	0.071	48 (85.7)	134 (87.1)	0.048	0.030
NYHA III or IV, *n* (%)	13 (18.1)	225 (21.3)	0.013	0.509	10 (17.9)	39 (25.2)	0.030	0.301
Atrial fibrillation, *n* (%)	4 (5.6)	24 (2.3)	−0.006	0.095	4 (7.1)	8 (5.2)	−0.005	0.483
Prior myocardial infarction, *n* (%)	22 (30.6)	514 (48.8)	0.091	0.003	15 (26.8)	39 (25.2)	−0.007	0.681
Emergency operation[a], *n* (%)	0 (0.0)	16 (1.5)	0.001	0.618	0 (0)	1 (0.6)	0.000	1.000
3-vessel coronary artery disease, *n* (%)	63 (87.5)	925 (87.8)	0.001	0.948	48 (85.7)	135 (87.1)	0.005	0.798
Left main trunk stenosis, *n* (%)	23 (31.9)	316 (30.0)	−0.009	0.725	18 (32.1)	53 (34.2)	0.010	0.646
Ejection fraction in %, m (SD)	56.1 (10.8)	53.6 (10.4)	0.240	0.045	55.7 (10.3)	57.3 (8.7)	−0.170	0.255
logistic EuroSCORE[b]	2.8 (2.4–3.3)	2.9 (2.7–3.0)	−0.019	0.880	2.8 (2.3–3.4)	2.9 (2.6–3.2)	−0.036	0.795
EuroSCORE II[b]	1.4 (1.3–1.7)	1.3 (1.3–1.4)	0.127	0.315	1.4 (1.2–1.7)	1.3 (1.2–1.5)	0.092	0.550

Abbreviations: COPD, chronic obstructive pulmonary disease; Diff., standardized differences to express the difference independent of the number of observations; NYHA, New York Heart Association; SD, standard deviation.
[a]For nonconvergence of the model no accounting for matched pairs.
[b]Geometric mean (confidence interval).
Note: Data are presented as mean and standard deviation or as numbers (%). Note that the matching procedure did not find three matched pairs for each patient who underwent surgery with use of microplegia.

After matching, there were no relevant differences between the study groups, as all absolute standardized difference values were below 0.2. However, hypercholesteremia did not occur equally frequently in either group (75.0 vs. 87.1%; $p = 0.030$).

Intraoperative Data

There was no difference regarding intraoperative data, such as number of distal anastomoses, or the usage of left internal mammary artery (LIMA), right internal mammary artery (RIMA), or both internal mammary arteries (BIMA), neither before nor after matching. Aortic clamping time and perfusion time were comparable in both groups. Need for defibrillation (related to the whole operation) was higher in the microplegia group, but did not reach statistical significance (21.8 versus 11.1%; $p = 0.066$). Intraoperative data are provided in ►**Table 4**.

Postoperative Data

In-hospital mortality was low in both groups (microplegia: 0% vs. Cardioplexol®: 1.3%; $p = 1.0$). Patients operated using microplegia stayed significantly shorter on the ICU (geometric mean [confidence interval]: 1.5 days [1.2–1.8 days] vs. 1.9 days [1.7–2.1 days]; $p = 0.011$), whereas length of hospital stay was comparable in both groups. MACCE were equally frequent in both groups (1.8 vs. 5.2%; $p = 0.331$). The proportion of postoperative renal failure (defined as a doubling of the preoperative creatinine value and a postoperative creatinine value > 172 micromol/L, or new onset of need for dialysis) was similar in both groups. The same was seen for postoperative AFIB.

Endpoint Analysis

With respect to the cardiac markers, group differences were larger after matching than before (►**Table 6**). Furthermore, group differences were more emphasized in the peak measurements than in first postoperative measurements. Geometric mean (confidence interval) hs-TnT on the first POD (223 ng/L [184–269 ng/L] vs. 296 ng/L [262–336 ng/L]; $p = 0.016$) as well as peak hs-cTnT (233 ng/L [194–280 ng/L] vs. 362 ng/L [315–416 ng/L]; $p = 0.001$) were significantly lower in the microplegia group than in the Cardioplexol® group (►**Fig. 2**). The same was observed for CK-MB on the first (13.2 µg/L [10.5–16.7 µg/L] vs. 17.9 µg/L [15.8–20.3] µg/L; $p = 0.025$) and the peak of CK-MB (13.8 µg/L [9.6–19.9 µg/L] vs. 21.6 µg/L [18.9–24.6 µg/L]; $p = 0.026$). CK on the first POD (462 U/L [372–572 U/L] vs. 542 U/L [486–605 U/L]; $p = 0.182$) showed a trend toward lower values in the microplegia group but did not reach statistical significance. Peak CK was significantly lower in the microplegia group compared with the Cardioplexol® group (539 U/L [458–633 U/L] vs. 719 U/L [645–801 U/L]; $p = 0.011$; ►**Fig. 3**).

Both sensitivity analyses indicated significantly reduced peak TnT values in the microplegia group, as compared with the Cardioplexol® group. The generalized linear model yielded $p = 0.001$, Kruskal–Wallis-test resulted in $p = 0.0003$.

Discussion

This propensity score-matched cohort study with a 3:1 matching aimed to compare two cardioplegia protocols, an institutionally refined microplegia applied with the MPS (Basel Microplegia Protocol) and Cardioplexol® in patients

Table 4 Intraoperative data

	Before matching				After matching			
	Microplegia $n = 72$	Cardioplexol® $n = 1,054$	Diff.	*p*-Value	Microplegia $n = 56$	Cardioplexol® $n = 155$	Diff.	*p*-Value
Total arterial revascularisation, *n* (%)	14 (19.4)	170 (16.1)	−0.013	0.463	11 (19.6)	27 (17.4)	−0.009	0.714
Use of LIMA, *n* (%)	68 (94.4)	1009 (95.7)	0.003	0.606	52 (92.9)	148 (95.5)	0.006	0.360
Use of RIMA, *n* (%)	9 (12.5)	156 (14.8)	0.008	0.594	7 (12.5)	19 (12.3)	−0.001	0.871
Use of BIMA, *n* (%)	9 (12.5)	145 (13.8)	0.004	0.764	7 (12.5)	18 (11.6)	−0.003	0.774
Use of radial artery, *n* (%)	16 (22.2)	269 (25.5)	0.014	0.534	13 (23.2)	38 (24.5)	0.006	0.878
IV inotropes at the end of operation, *n* (%)	10 (14.3)	241 (22.9)	0.034	0.099	6 (11.1)	31 (20.1)	0.033	0.197
Number of distal anastomoses, m (SD)	3.7 (1.1)	3.8 (0.9)	−0.092	0.403	3.7 (1.2)	3.7 (1.0)	−0.035	0.817
Aortic clamping time in min, m (SD)	60.9 (17.4)	58.8 (19.2)	0.115	0.364	60.9 (16.3)	58.6 (17.5)	0.138	0.381
Perfusion time in min[a]	88.3 (83.1–93.9)	88.4 (86.9–89.9)	−0.004	0.977	88.2 (82.5–94.3)	87.0 (83.2–91.0)	0.049	0.756
Need for defibrillation, *n* (%)	13 (18.1)	116 (11.0%)	−0.025	0.076	12 (21.8)	17 (11.1)	−0.040	0.066

Abbreviations: BIMA, both internal mammary arteries; BMP, Basel Microplegia Protocol; Diff., standardized differences to express the difference independent of the number of observations. IV, intravenous; LIMA, left internal mammery artery; RIMA, right internal mammary artery; SD, standard deviation.
[a]Geometric mean (confidence interval).
Note: Data are presented as mean and standard deviation or as numbers (%). Note that the matching procedure did not find three matched pairs for each patient who underwent surgery with use of microplegia.

Table 5 Postoperative data

	Before matching				After matching			
	Microplegia $n = 72$	Cardioplexol® $n = 1054$	Diff.	*p*-Value	Microplegia $n = 56$	Cardioplexol® $n = 155$	Diff.	*p*-Value
In-hospital mortality[a], *n* (%)	0 (0.0)	17 (1.6)	0.001	0.620	0 (0)	2 (1.3)	0.001	1.000
MACCE, *n* (%)	1 (1.4)	64 (6.1)	0.009	0.133	1 (1.8)	8 (5.2)	0.006	0.331
Reoperation for bleeding[a], *n* (%)	1 (1.4)	17 (1.6)	0.000	0.884	1 (1.8)	4 (2.6)	0.001	1.000
Atrial fibrillation at discharge, *n* (%)	22 (30.6)	236 (22.4)	−0.036	0.113	17 (30.4)	42 (27.1)	−0.015	0.721
Pulmonary infection, *n* (%)	2 (2.8)	63 (6.0)	0.007	0.272	2 (3.6)	5 (3.2)	−0.001	0.944
Postoperative MI[a], *n* (%)	0 (0.0)	33 (3.1)	0.004	0.264	0 (0)	5 (3.2)	0.004	0.328
Postoperativ stroke, *n* (%)	1 (1.4)	27 (2.6)	0.002	0.543	1 (1.8)	2 (1.3)	−0.001	0.741
Postoperative renal failure, *n* (%)[a]	1 (1.4)	65 (6.2)	0.009	0.129	1 (1.8)	9 (5.8)	0.008	0.296
Renal substitution therapy[a], *n* (%)	0 (0.0)	9 (0.9)	0.001	1.000	0 (0)	2 (1.3)	0.001	1.000
Intubation > 72 h[a], *n* (%)	0 (0.0)	25 (2.4)	0.003	0.399	0 (0)	4 (2.6)	0.003	0.575
Length of ICU stay in days[b]	1.4 (1.2–1.7)	1.9 (1.9–2.0)	−0.449	0.000	1.5 (1.2–1.8)	1.9 (1.7–2.1)	−0.386	0.011
Length of hospital stay in days, m (SD)	9.1 (3.5)	10.0 (8.5)	−0.142	0.359	9.2 (3.8)	9.5 (4.1)	−0.082	0.597

Abbreviations: Diff., standardized differences to express the difference independent of the number of observations; ICU, intensive care unit; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; SD, standard deviation.
[a]For nonconvergence of the model no accounting for matched pairs.
[b]Geometric mean (confidence interval).
Note: data are presented as mean and standard deviation or as numbers (%). Note that the matching procedure did not find three matched pairs for each patient who underwent surgery with use of microplegia.

Table 6 Cardiac markers

	Before matching				After matching			
	Microplegia $n = 72$	Cardioplexol® $n = 1054$	Diff.	*p*-Value	Microplegia $n = 56$	Cardioplexol® $n = 155$	Diff.	*p*-Value
hs-cTnT, 1. POD, ng/L	220 (184–263)	278 (264–293)	−0.293	0.033	223 (184–269)	296 (262–336)	−0.380	0.016
Peak hs-cTnT, ng/L	230 (194–272)	328 (310–346)	−0.435	0.002	233 (194–280)	362 (315–416)	−0.557	0.001
CK-MB 1. POD, µg/L	13.2 (10.5–16.5)	16.7 (15.9–17.5)	−0.264	0.059	13.2 (10.5–16.7)	17.9 (15.8–20.3)	−0.363	0.025
Peak CK-MB, µg/L	13.7 (9.9–19.1)	19.2 (18.2–20.2)	−0.281	0.077	13.8 (9.6–19.9)	21.6 (18.9–24.6)	−0.389	0.026
CK 1. POD, U/L	457 (371–563)	534 (509–560)	−0.182	0.214	462 (372–572)	542 (486–605)	−0.213	0.182
Peak CK, U/L	539 (461–631)	737 (707–768)	−0.454	0.004	539 (458–633)	719 (645–801)	−0.445	0.011

Abbreviations: CK, creatine kinase; CK-MB, creatine kinase-myocardial type; Diff., standardized differences to express the difference independent of the number of observations; hs-cTnT, high-sensitivity cardiac troponin T; POD, postoperative day.
Note: Data are presented as geometric mean (confidence interval). Note that the matching procedure did not find three matched pairs for each patient who underwent surgery with use of microplegia.

undergoing isolated CABG surgery using the MiECC. We report *five* major findings.

First, the use of the Basel Microplegia Protocol is safe and feasible in isolated CABG surgery. *Second*, MACCE was comparably low in both groups, which indicates the safety of the MiECC system in CABG surgery. *Third*, there were no differences regarding postoperative AFIB between both groups. *Fourth*, patients operated by using microplegia were significantly shorter on the ICU compared with patients operated using the Cardioplexol®. *Fifth*, and probably of most clinical significance, the use of microplegia was associated with significantly lower postoperative values of hs-cTn, CK-MB, and CK, which is indicative for less myocardial injury and optimal cardiac protection during surgery. This was seen for peak values of hs-cTnT, CK, and CK-MB, as well as for the values on POD-1 for hs-cTnT and CK-MB (►**Fig. 4**). CK values on POD-1 showed a trend toward lower values in the microplegia group, but did not reach statistical significance.

These data corroborate our promising first experience of introducing our institutionally refined dose/volume dependent

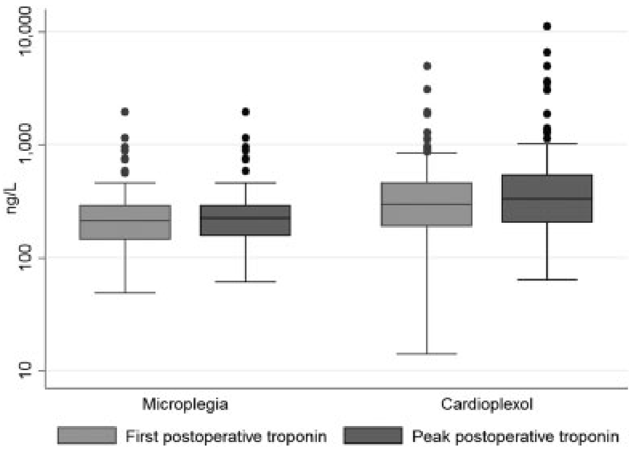

Fig. 2 Boxplots hs-cTnT.

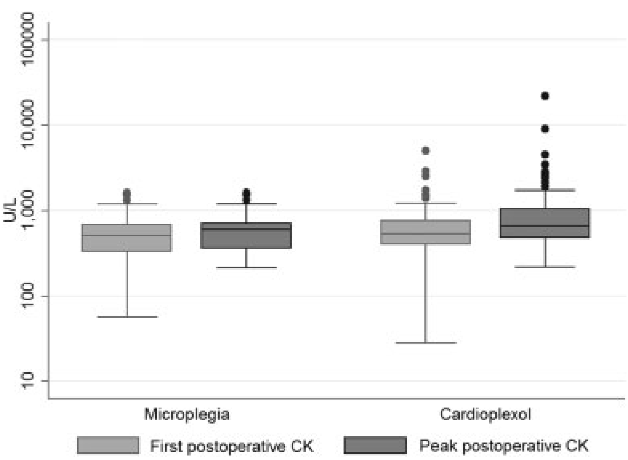

Fig. 3 Boxplots CK. CK, creatine kinase.

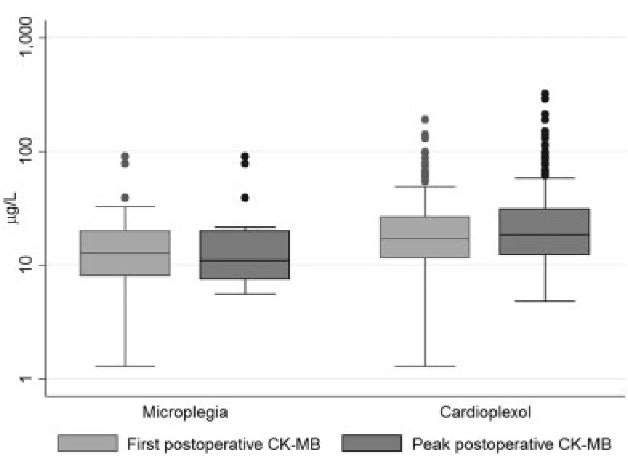

Fig. 4 Boxplots CK-MB. CK-MB, creatine kinase-myocardial type.

microplegia applied with the MPS in isolated CABG surgery using the MiECC.[15] There were no differences in intraoperative data, such as number of distal anastomoses, aortic clamping time, or perfusion time, between the two cardioplegia concepts indicating satisfactory conditions for the surgeons.

Because of the closed system of the MiECC and the possible risk of volume overload, only few cardioplegic solutions qualify for the combined use with MiECC and high-volume crystalloid cardioplegic solutions are not feasible.[4] This led to the development of Cardioplexol®. However, we believe that this technique has two major disadvantages compared with the use of microplegia applied with the MPS: *First*, Cardioplexol® is a low volume cardioplegia which is given at a volume of 100 mL.[6,10,12–15,17] Though this avoids hemodilution, it may lead to running-off of the cardioplegic solution to less stenotic vessels and could additionally pose the risk of a higher loss of cardioplegic solution in the aortic root and tubes. In contrast, when using microplegia applied with the MPS, the heart is supplied with high-volume blood cardioplegia without any hemodilution due to the use of autologous blood.[15] *Second*, the application of microplegia with the MPS is provided in a flow- and pressure-controlled fashion, with a constant dosage per volume and a controlled pressure.[15] In contrast, the application of Cardioplexol® is performed manually, without any control of pressure and flow. Therefore, we believe, that the delivery of microplegia using the MPS in MiECC assisted surgery is beneficial, especially in high grade stenoses.[15] Regarding differences between isolated LMT stenosis and 3-VD, subgroup analyses were not possible due to the small number of patients with isolated LMT that were operated using microplegia ($n = 4$).

Need for defibrillation (related to the entire procedure) was higher in the microplegia group compared with the Cardioplexol® group, but did not reach statistical significance (21.8 vs. 11.1%; $p = 0.066$). However, the rate of defibrillation in the microplegia group was lower compared with Buckberg cardioplegic solution in CABG surgery but was higher compared with the results from our feasibility study and compared with Calafiore cardioplegia in CABG surgery (Buckberg cardioplegic solution: 39.6%; MPS feasibility study: 11%; Calafiore cardioplegic solution: 9.3%).[15,19] This needs further investigations.

There was only a trend toward lower rates of MACCE, in-hospital mortality, and postoperative MI in the microplegia group in our study. However, there is literature showing an association between high postoperative values of cTn and adverse outcomes after on-pump cardiac surgery including CABG.[20–22] Moreover, the association between elevated values of cTn and adverse outcome in high-risk patients with coronary artery disease or after noncardiac surgery has been shown in various studies.[23–26] Therefore, we strongly believe that optimizing cardioplegic solutions, reflected by low postoperative cardiac markers, is a crucial cornerstone in CABG surgery to provide best possible outcomes. Additionally, these low values corroborate our primary results when introducing this technique in our daily routine. It endows the surgeon with the reliance for a good cardiac protection also during longer operations. Nonetheless, the clinical significance of reduced postoperative cardiac markers especially for long-term outcomes has to be further evaluated.

Patients operated using microplegia were significantly shorter on the ICU compared with patients receiving Cardioplexol®. This is in line with a previous study using microplegia.[16] The use of microplegia was shown to be beneficial regarding postoperative low cardiac output syndrome.[17]

Therefore, a beneficial hemodynamic situation after the use of microplegia can be assumed.

Though it is well known that the use of MiECC significantly reduces the incidence of postoperative AFIB when compared with conventional ECC (class of recommendation I, level of evidence A),[4] the incidence of postoperative AFIB was relatively high in both groups of our patient cohort (microplegia: 30.4% vs. Cardioplexol®: 27.1%; $p = 0.721$). We believe that this is more because of a stringent definition of AFIB in our clinic rather than the cardioplegia regime. Every postoperative AFIB > 48 hours or > two episodes during the hospital stay is defined as postoperative AFIB, independently of the existing rhythm at the moment of discharge.[15]

Some limitations warrant consideration when interpreting the findings of this study. First, it was an observational single-center study, which may compromise the external validity of our findings. Second, due to the matching method, the final study populations are relatively small, and therefore, the generalizability of our results may be questioned. Further studies with larger sample sizes will be more beneficial to enlighten the topic. On the other hand, the standardized differences after propensity matching indicate that the treatment groups are very similar with respect to patient characteristics, so differences observed during postoperative course are likely to be related to the treatment.

Third, due to the retrospective analysis of patients operated using the Cardioplexol®, we only can provide defibrillation rates related to the entire operation and not specific after removal of the aortic clamp.

Forth, the as arrest agents used ingredients (K, Mg, and Lidocain) have the drug approval and are licensed to use in humans. However, a possible off-label use is to consider.[15]

Conclusions

In conclusion, the use of the Basel Microplegia Protocol is beneficial regarding postoperative biomarker values, and it is associated with a significantly shorter stay on the ICU compared with the use of Cardioplexol® in isolated coronary artery bypass grafting using the MiECC.

Authors' Contributions

Author L.K.: study design, collection of data, data analysis/interpretation, and writing the manuscript; author B.R.: data collection and critical revision of the manuscript; author B.G.: study design, data collection, data analysis/interpretation, writing the manuscript, and critical revision of the manuscript; author DB: critical revision of the manuscript and operating surgeon; author MG: critical revision of the manuscript and operating surgeon; author FE: critical revision of manuscript and operating surgeon; author OR: study design, data analysis/interpretation, writing manuscript, critical revision of the manuscript, and operating surgeon.

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Conflict of Interest

None declared.

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