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Article

Impact of Minimally Invasive Cardiac Surgery Versus Conventional OPEN Valve Surgery on Myocardial Protection

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Abstract

Background: Minimally invasive cardiac surgery (MICS) offers several advantages that can be particularly beneficial for older patients. However, nothing is currently known about the impact of MICS on myocardial protection. Thus, this study aimed to compare myocardial protection in valve surgery between patients who received MICS and those who underwent conventional open cardiac surgery (OPEN). **Methods**: We retrospectively included all adult patients (≥18 years) who received elective or urgent valve surgery in our department. We compared the peak value and area under the curve (AUC) of the high-sensitive troponin T (TnT) and creatine kinase muscle-brain type (CK-MB) concentrations during the first, second, and third 24 h period and the cumulative catecholamine dosages of adrenaline, noradrenaline, and enoximone at 72 h after removal of the aortic cross-clamp in patients who received valve replacement or reconstruction for MICS versus OPEN. **Results**: The peak TnT release in the first ($p = 0.025$) and second 24 h interval ($p = 0.046$), as well as the TnT AUC in the first 24 h ($p = 0.024$), were lower in the MICS group with reconstruction. The peak CK-MB release was relevantly lower in the first ($p = 0.093$) and third 24 h period ($p = 0.067$), as well as the CK-MB AUC between 48 and 72 h ($p = 0.055$). However, the peak release and AUC for TnT and CK-MB did not differ between MICS and OPEN in the replacement population. The noradrenaline dosage was lower ($p = 0.023$) for MICS in the replacement population. In the reconstruction population, the dosage of adrenaline ($p = 0.036$), noradrenaline ($p = 0.043$), and enoximone ($p = 0.012$) was lower in the MICS group than in the OPEN group. **Conclusion**: In addition to known factors of myocardial protection, such as ischemia time and cardioplegia, MICS seems to promote improved myocardial protection during valve reconstruction, while the postoperative catecholamine requirement is reduced after valve reconstruction and replacement. These additional benefits of MICS might be especially advantageous for old and frail patients undergoing cardiac surgery.

Keywords: minimally invasive surgery; minimally invasive cardiac surgery; open heart surgery; open cardiac surgery; aging; frailty; valve surgery; myocardial protection; cardioplegia; Buckberg; Calafiore; Custodiol; HTK; histidine-tryptophane-ketoglutarate; Bretschneider's

1. Introduction

Minimally invasive cardiac surgery (MICS) has evolved continuously and gained popularity within the last two to three decades [1]. MICS is associated with numerous advantages, such as less postoperative respiratory dysfunction, avoidance of chest instability, reduced incidence of deep sternal wound infection, and quicker mobilization of the patient compared to conventional open heart surgery (OPEN) [1]. MICS can be performed for valve surgery [2–4], coronary artery bypass grafting [5], and, to a certain extent, even when rarely performed, on the aorta [6].

The mean age of patients in cardiac surgery slowly increases [7]. Old age is often associated with a certain degree of frailty, meaning the patient is less resilient against stressors such as a major surgical intervention [8]. Considering this, MICS could become even more important in the future. Despite the mentioned benefits, myocardial protection during MICS is highly important to ensure that the heart can maintain circulation in the body after surgery. Based on the limited surgical access, MICS procedures commonly require longer aortic cross-clamping times and thus, longer periods of myocardial ischemia. Myocardial protection is therefore crucial in MICS. The literature shows that the existing studies compared different cardioplegic solutions for myocardial protection during MICS, including blood cardioplegia, Histidine-Tryptophane-Ketoglutarate (HTK), del Nido solution, and St. Thomas Hospital solution [9]. However, currently, nothing is known about the impact of the MICS procedure on myocardial protection independent of the cardioplegic solution. Thus, we compared myocardial protection in valve surgery in patients who received MICS compared to OPEN.

2. Patients and Methods

2.1 Patient Population

We retrospectively included all adult (≥18 years) patients who received elective or urgent (within 24 h of diagnosis) valve surgery for single or multiple heart valve disease in our department, which is a tertiary care center with a volume of ca. 100 valve cases per year. Patients oper-

ated between 2015 and 2022 were included. All patients were operated by an experienced surgeon. We excluded all patients who received coronary artery bypass grafting (CABG) or other heart or vascular surgery procedures in addition to valve surgery. Cases that included CABG were excluded because coronary heart disease limits cardioplegic perfusion of the myocardium and could, therefore, lead to a bias in results. We also excluded reoperations. Catheter-based valve replacement or clipping, procedures on the beating heart, emergency cases, and cases with the onset of the operation under resuscitation were excluded. We compared patients who received MICS to those who received OPEN. We analyzed valve replacement and reconstruction separately.

2.2 Cardioplegia

The type of cardioplegia was used based on the surgeon's preference. Crystalloid HTK (Dr. Franz Köhler Chemie, Bensheim, Germany), as well as Buckberg (Dr. Franz Köhler Chemie, Bensheim, Germany), or Calafiore blood cardioplegia, was used. All types of cardioplegia were administered in antegrade fashion using a roller pump (Liva Nova S5, Munich, Germany) with a pump flow of 200–300 mL/min. For the HTK solution, the myocardium was perfused with an initial volume of 2000 mL of cardioplegia. A second dosage was given after 2–3 h of cardioplegic arrest. In the case of Calafiore blood cardioplegia, cardioplegic arrest was induced with a perfusor rate of 250 mL/h to add the KCl and $MgCl_2$ mixture over 2 min. Additional dosages were given every 20 min with a perfusion rate of 150 mL/min over 2 min. In the case of Buckberg cardioplegia, a 4:1 mixture of oxygenated blood and crystalloid cardioplegic solution was given over 4 min. Additional dosages were given every 20 min over 2 min.

2.3 Postoperative Hemodynamic Stabilization

The postoperative hemodynamic stabilization was achieved using a catecholamine regimen according to the patient's needs. Adrenaline, noradrenaline, and enoximone were given depending on the patient's requirements.

2.4 Endpoints

The study endpoints were the peak value and area under the curve (AUC) of highly sensitive troponin T (TnT) and creatine kinase muscle brain-type (CK-MB) during 0–24 h, 24–48 h, and 48–72 h after removal of the aortic cross-clamp. The regimen of cardiac enzyme measurement changed over the observation period. Thus, TnT and CK-MB information were unfortunately not always available for every patient at every time point. We determined the cumulative dosage of the catecholamines adrenaline, noradrenaline, and enoximone.

2.5 Calculation of the Area Under the Curve

For the three catecholamines, the total dose applied in the first 72 h after the cross-clamp removal was calculated for each agent. Therefore, the individual dose of each application was calculated by multiplying the concentration, volume applied, and duration of the application. The doses of individual applications were then cumulated.

For the cardiac enzymes TnT and CK-MB, the AUC was calculated for three consecutive 24-hour intervals after the end of the cross-clamp time to approximate the total amount secreted in each interval. Therefore, the AUC was calculated for each pair of consecutive data points within each 24-hour interval, assuming a linear behavior. These small areas were then summed up to calculate the total area under the curve. Due to the study's retrospective nature, often no data points exist at exactly 0 h, 24 h, 48 h, or 72 h. Consequently, in these cases, the value of the closest existing data point within the respective interval next to the timepoint of 0 h, 24 h, 48 h, or 72 h was included in the analysis as the value for 0 h, 24 h, 48 h, or 72 h.

2.6 Statistics

The statistical analysis was performed using IBM SPSS Statistics (Version 28.0.0.0, IBM Corp., Armonk, NY, USA). We performed a linear regression analysis to compare the groups, including an adjustment of the group difference based on age, sex, time of aortic cross-clamping, reperfusion time between removal of the aortic cross-clamp and weaning from cardiopulmonary bypass (CPB), single or multiple valve surgery, preoperative ventricular function categorized in normal (ejection fraction $>$50%), reduced (ejection fraction 30–50%) or majorly reduced (ejection fraction $<$30%) or missing, New York Heart Association (NYHA) class categorized in NYHA I, II, III, IV or missing (e.g., in case of endocarditis when no NYHA category was determined) and type of cardioplegia. Besides the outcome measures, the patient populations were compared using a χ^2 test for categorical data or a two-tailed unpaired classical *t*-test for variance homogeneity and a Welch *t*-test for variance inhomogeneity. Based on the explorative, hypothesis-generating nature of this retrospective study, *p*-values were also interpreted exploratively, meaning that small *p*-values suggested an important group difference.

3. Results

3.1 Patients

In the replacement population, the NYHA status, left-ventricular ejection fraction (LVEF), cardioplegia, number of operated valves, urgency, and the prevalence of smoking and diabetes differed between the MICS and the OPEN group (Table 1). In the MICS group, HTK was more frequently used, and surgery on one isolated valve was more prevalent. Endocarditis was more prevalent in the OPEN group compared to the MICS group. Aortic cross-clamp,

Table 1. Basic characteristics of the replacement population.

Parameter	Category	Patients with analyzed TnT			Patients with analyzed CK-MB			Patients with analyzed Catecholamines		
		MICS	OPEN	*p*-value	MICS	OPEN	*p*-value	MICS	OPEN	*p*-value
Sex	Male	133 (62.7%)	252 (63.2%)	0.918	130 (63.4%)	243 (63.1%)	0.943	134 (62.6%)	254 (62.6%)	0.989
	Female	79 (37.3%)	147 (36.8%)		75 (36.6%)	142 (36.9%)		80 (37.4%)	152 (37.4%)	
Age		65.9 ± 0.7	66.6 ± 0.5	0.419	65.9 ± 0.7	67.0 ± 0.5	0.207	65.8 ± 0.7	66.7 ± 0.5	0.325
Height (cm)		171.3 ± 0.7	171.0 ± 0.5	0.738	171.3 ± 0.7	171.0 ± 0.5	0.714	171.3 ± 0.7	170.9 ± 0.5	0.676
Weight (kg)		86.5 ± 1.2	85.1 ± 1.0	0.368	86.5 ± 1.2	85.2 ± 1.0	0.414	86.5 ± 1.2	85.0 ± 1.0	0.356
BMI		29.5 ± 0.4	29.1 ± 0.3	0.389	29.5 ± 0.4	29.1 ± 0.3	0.441	29.5 ± 0.4	29.1 ± 0.3	0.402
NYHA	NYHA I	14 (6.6%)	19 (4.8%)	0.001	14 (6.8%)	19 (4.9%)	0.005	14 (6.5%)	19 (4.7%)	<0.001
	NYHA II	85 (40.1%)	138 (34.6%)		84 (41.0%)	136 (35.3%)		85 (39.7%)	140 (34.5%)	
	NYHA III	107 (50.5%)	192 (48.1%)		101 (49.3%)	186 (48.3%)		109 (50.9%)	194 (47.8%)	
	NYHA IV	6 (2.8%)	31 (7.8%)		6 (2.9%)	28 (7.3%)		6 (2.8%)	34 (8.4%)	
	Unknown	0 (0.0%)	19 (4.8%)		0 (0.0%)	16 (4.2%)		0 (0.1%)	19 (4.7%)	
LVEF	>50%	157 (74.1%)	239 (59.9%)	0.001	152 (74.1%)	234 (60.8%)	0.003	158 (73.8%)	245 (60.3%)	0.002
	30–50%	50 (23.6%)	127 (31.8%)		48 (23.4%)	119 (30.9%)		51 (23.8%)	127 (31.3%)	
	<30%	3 (1.4%)	24 (6.0%)		3 (1.5%)	23 (6.0%)		3 (1.4%)	25 (6.2%)	
	Unknown	2 (0.9%)	9 (2.3%)		2 (1.0%)	9 (2.3%)		2 (0.9%)	9 (2.2%)	
Hypertension	Yes	177 (83.5%)	314 (78.7%)	0.061	173 (84.4%)	310 (80.5%)	0.083	178 (83.2%)	319 (78.6%)	0.065
	No	31 (14.6%)	61 (15.3%)		28 (13.7%)	52 (13.5%)		32 (15.0%)	63 (15.5%)	
	Unknown	4 (1.9%)	24 (6.0%)		4 (2.0%)	23 (6.0%)		4 (1.9%)	24 (5.9%)	
Smoker	Never	93 (43.9%)	132 (33.1%)	<0.001	89 (43.4%)	124 (32.2%)	<0.001	95 (44.4%)	136 (33.5%)	<0.001
	>2 months ago	54 (25.5%)	86 (21.6%)		53 (25.9%)	85 (22.1%)		54 (25.2%)	86 (21.2%)	
	Within 2 months	26 (12.3%)	47 (11.8%)		25 (12.2%)	45 (11.7%)		26 (12.1%)	47 (11.6%)	
	Unknown	39 (18.4%)	134 (33.6%)		38 (18.5%)	131 (34.0%)		39 (18.2%)	137 (33.7%)	
COPD	Yes	17 (8.0%)	43 (10.8%)	0.060	15 (7.3%)	43 (11.2%)	0.046	17 (7.9%)	43 (10.6%)	0.064
	No	182 (85.8%)	321 (80.5%)		177 (86.3%)	308 (80.0%)		184 (86.0%)	328 (80.8%)	
	Other lung disease	13 (6.1%)	24 (6.0%)		13 (6.3%)	24 (6.2%)		13 (6.1%)	24 (5.9%)	
	Unknown	0 (0.0%)	11 (2.8%)		0 (0.0%)	10 (2.6%)		0 (0.0%)	11 (2.7%)	
Diabetes	Yes	68 (32.1%)	127 (31.8%)	0.007	64 (31.2%)	123 (31.9%)	0.006	68 (31.8%)	129 (31.8%)	0.007
	No	144 (67.9%)	254 (63.7%)		141 (68.8%)	244 (63.4%)		146 (68.2%)	259 (63.8%)	
	Unknown	0 (0.0%)	18 (4.5%)		0 (0.0%)	18 (4.7%)		0 (0.0%)	18 (4.4%)	
Endocarditis	Yes	15 (7.1%)	127 (31.8%)	<0.001	15 (7.3%)	123 (31.9%)	<0.001	15 (7.0%)	128 (31.5%)	<0.001
	No	197 (92.9%)	272 (68.2%)		190 (92.7%)	262 (68.1%)		199 (93.0%)	278 (68.5%)	
Cardioplegia	HTK	177 (83.5%)	252 (63.2%)	<0.001	176 (85.9%)	249 (64.7%)	<0.001	178 (83.2%)	254 (62.6%)	<0.001
	Calafiore	32 (15.1%)	82 (20.6%)		26 (12.7%)	72 (18.7%)		32 (15.0%)	87 (21.4%)	
	Buckberg	3 (1.4%)	65 (16.3%)		3 (1.5%)	64 (16.6%)		4 (1.9%)	65 (16.0%)	
Valve number	Single	212 (100.0%)	345 (86.5%)	<0.001	205 (100.0%)	331 (86.0%)	<0.001	214 (100.0%)	350 (86.2%)	<0.001
	Multiple	0 (0.0%)	54 (13.5%)		0 (0.0%)	54 (14.0%)		0 (0.0%)	56 (13.8%)	

Table 1. Continued.

Parameter	Category	Patients with analyzed TnT			Patients with analyzed CK-MB			Patients with analyzed Catecholamines		
		MICS	OPEN	*p*-value	MICS	OPEN	*p*-value	MICS	OPEN	*p*-value
Replacement type	Biological	206 (97.2%)	336 (97.4%)	0.875	199 (97.1%)	324 (97.9%)	0.553	208 (97.2%)	341 (97.4%)	0.868
	Mechanical	6 (2.8%)	9 (2.6%)		6 (2.9%)	7 (2.1%)		6 (2.8%)	9 (2.6%)	
Urgency	Urgent	33 (15.6%)	171 (42.9%)	<0.001	33 (16.1%)	169 (43.9%)	<0.001	33 (15.4%)	173 (42.6%)	<0.001
	Elective	179 (84.4%)	228 (57.1%)		172 (83.9%)	216 (56.1%)		181 (84.6%)	233 (57.4%)	
Clamp time (min)		79.9 ± 1.7	90.1 ± 2.3	<0.001	80.3 ± 1.8	90.7 ± 2.4	<0.001	79.8 ± 1.7	90.5 ± 2.3	<0.001
Reperfusion time (min)		23.4 ± 1.4	27.6 ± 1.2	0.023	23.6 ± 1.5	27.8 ± 1.2	0.270	23.3 ± 1.4	27.9 ± 1.2	0.012
Operating time (h)		197.0 ± 3.7	218.1 ± 5.0	<0.001	198.0 ± 3.8	219.1 ± 5.2	0.001	196.6 ± 3.7	218.8 ± 5.0	<0.001
Days in ICU		5.0 ± 0.5	9.9 ± 0.6	<0.001	5.0 ± 0.5	10.0 ± 0.6	<0.001	5.0 ± 0.5	9.8 ± 0.6	<0.001
Days in hospital		11.0 ± 0.4	13.3 ± 0.5	<0.001	10.9 ± 0.4	13.3 ± 0.5	<0.001	11.0 ± 0.4	13.3 ± 0.5	<0.001
Ventilation hours		34.6 ± 7.5	87.5 ± 8.1	<0.001	35.4 ± 7.7	86.2 ± 8.0	<0.001	34.5 ± 7.5	86.7 ± 8.0	<0.001
pRBC units		2.2 ± 0.3	6.1 ± 0.5	<0.001	2.2 ± 0.3	6.2 ± 0.5	<0.001	2.2 ± 0.3	6.0 ± 0.5	<0.001
Platelets Units		1.1 ± 0.3	4.0 ± 0.4	<0.001	1.2 ± 0.3	4.0 ± 0.5	<0.001	1.1 ± 0.3	3.9 ± 0.4	<0.001
FFP Units		0.2 ± 0.1	1.1 ± 0.1	<0.001	0.2 ± 0.1	1.1 ± 0.1	<0.001	0.2 ± 0.1	1.1 ± 0.1	<0.001

BMI, Body Mass Index; FFP, Fresh frozen plasma; HTK, Histidine-Tryptophan-Ketoglutarate; ICU, Intensive care unit; LVEF, Left-ventricular ejection fraction; NYHA, New York Heart Association; CK-MB, Creatinekinase muscle brain type; COPD, Chronic obstructive pulmonary disease; MICS, Minimally-invasive cardiac surgery; pRBC, Packed red blood cells; TnT, High-sensitive troponin T; OPEN, open heart surgery.

Table 2. Basic characteristics of the reconstruction population.

Parameter	Category	TnT			CK-MB			Catecholamines		
		MICS	OPEN	*p*-value	MICS	OPEN	*p*-value	MICS	OPEN	*p*-value
Sex	Male	49 (65.3%)	34 (66.7%)	0.877	49 (65.3%)	30 (63.8%)	0.866	49 (65.3%)	34 (66.7%)	0.877
	Female	26 (34.7%)	17 (33.3%)		26 (34.7%)	17 (36.2%)		26 (34.7%)	17 (33.3%)	
Age		59.8 ± 1.7	64.4 ± 1.6	0.050	59.8 ± 1.7	64.9 ± 1.7	0.034	59.8 ± 1.7	64.4 ± 1.6	0.050
Height (cm)		173.9 ± 1.1	171.8 ± 1.3	0.211	173.9 ± 1.1	171.4 ± 1.4	0.161	173.9 ± 1.1	171.8 ± 1.3	0.211
Weight (kg)		76.1 ± 1.6	85.7 ± 2.7	0.003	76.1 ± 1.6	85.7 ± 2.9	0.005	76.1 ± 1.6	85.7 ± 2.7	0.001
BMI		25.0 ± 0.4	29.0 ± 0.8	<0.001	25.0 ± 0.4	29.1 ± 0.9	<0.001	25.0 ± 0.4	29.0 ± 0.8	<0.001
NYHA	NYHA I	9 (12.0%)	2 (3.9%)	0.067	9 (12.0%)	2 (4.3%)	0.085	9 (12.0%)	2 (3.9%)	0.067
	NYHA II	33 (44.0%)	15 (29.4%)		33 (44.0%)	15 (31.9%)		33 (44.0%)	15 (29.4%)	
	NYHA III	26 (34.7%)	24 (47.1%)		26 (34.7%)	23 (48.9%)		26 (34.7%)	24 (47.1%)	
	NYHA IV	3 (4.0%)	7 (13.7%)		3 (4.0%)	6 (12.8%)		3 (4.0%)	7 (13.7%)	
	Unknown	4 (5.3%)	3 (5.9%)		4 (5.3%)	1 (2.1%)		4 (5.3%)	3 (5.9%)	
LVEF	>50%	55 (73.3%)	31 (60.8%)	0.122	55 (73.3%)	29 (61.7%)	0.124	55 (73.3%)	31 (60.8%)	0.122
	30–50%	18 (24.0%)	16 (31.4%)		18 (24.0%)	14 (29.8%)		18 (24.0%)	16 (31.4%)	
	<30%	0 (0.0%)	3 (5.9%)		0 (0.0%)	3 (6.4%)		0 (0.0%)	3 (5.9%)	
	Unknown	2 (2.7%)	1 (2.0%)		2 (2.7%)	1 (2.1%)		2 (2.7%)	1 (2.0%)	

Table 2. Continued.

Parameter	Category	TnT			CK-MB			Catecholamines		
		MICS	OPEN	*p*-value	MICS	OPEN	*p*-value	MICS	OPEN	*p*-value
Hypertension	Yes	60 (80.0%)	34 (66.7%)	0.074	60 (80.0%)	32 (68.1%)	0.055	60 (80.0%)	34 (66.7%)	0.074
	No	11 (14.7%)	8 (15.7%)		11 (14.7%)	6 (12.8%)		11 (14.7%)	8 (15.7%)	
	Unknown	4 (5.3%)	9 (17.6%)		4 (5.3%)	9 (19.1%)		4 (5.3%)	9 (17.6%)	
Smoker	Never	36 (48.0%)	17 (33.3%)	0.433	36 (48.0%)	14 (29.8%)	0.248	36 (48.0%)	17 (33.3%)	0.433
	>2 months ago	15 (20.0%)	14 (27.5%)		15 (20.0%)	14 (29.8%)		15 (20.0%)	14 (27.5%)	
	Within 2 months	7 (9.3%)	6 (11.7%)		7 (9.3%)	5 (10.6%)		7 (9.3%)	6 (11.8%)	
	Unknown	17 (22.7%)	14 (27.5%)		17 (22.7%)	14 (29.8%)		17 (22.7%)	14 (27.5%)	
COPD	Yes	4 (5.3%)	10 (19.6%)	0.098	4 (5.3%)	10 (21.3%)	0.064	4 (5.3%)	10 (19.6%)	0.098
	No	60 (80.0%)	35 (68.6%)		60 (80.0%)	31 (66.0%)		60 (80.0%)	35 (68.6%)	
	Other lung disease	7 (9.3%)	4 (7.8%)		7 (9.3%)	4 (8.5%)		7 (9.3%)	4 (7.8%)	
	Unknown	4 (5.4%)	2 (4.0%)		4 (5.3%)	2 (4.3%)		4 (5.3%)	2 (3.9%)	
Diabetes	Yes	4 (5.3%)	11 (21.6%)	0.012	4 (5.3%)	11 (23.4%)	0.006	4 (5.3%)	11 (21.6%)	0.012
	No	69 (92.0%)	37 (72.5%)		69 (92.0%)	33 (70.2%)		69 (92.0%)	37 (72.5%)	
	Unknown	2 (2.7%)	3 (5.9%)		2 (2.7%)	3 (6.4%)		2 (2.7%)	3 (5.9%)	
Endocarditis	Yes	2 (2.7%)	5 (9.8%)	0.086	2 (2.7%)	5 (10.6%)	0.065	2 (2.7%)	5 (9.8%)	0.086
	No	73 (97.3%)	46 (90.2%)		73 (97.3%)	42 (89.4%)		73 (97.3%)	46 (90.2%)	
Cardioplegia	HTK	72 (96.0%)	39 (76.5%)	0.002	72 (96.0%)	38 (80.9%)	0.011	72 (96.0%)	39 (76.5%)	0.002
	Calafiore	3 (4.0%)	7 (13.7%)		3 (4.0%)	5 (10.6%)		3 (4.0%)	7 (13.7%)	
	Buckberg	0 (0.0%)	5 (9.8%)		0 (0.0%)	4 (8.5%)		0 (0.0%)	5 (9.8%)	
Valve number	Single	66 (88.0%)	44 (86.3%)	0.775	66 (88.0%)	40 (85.1%)	0.645	66 (88.0%)	44 (86.3%)	0.775
	Multiple	9 (12.0%)	7 (13.7%)		9 (12.0%)	7 (14.9%)		9 (12.0%)	7 (13.7%)	
Urgency	Urgent	9 (12.0%)	13 (25.5%)	0.050	9 (12.0%)	13 (27.7%)	0.029	9 (12.0%)	13 (25.5%)	0.050
	Elective	66 (88.0%)	38 (74.5%)		66 (88.0%)	34 (72.3%)		66 (88.0%)	38 (74.5%)	
Clamp time (min)		118.4 ± 4.0	85.4 ± 4.7	<0.001	118.4 ± 4.0	87.0 ± 4.9	<0.001	118.4 ± 4.0	85.1 ± 4.7	<0.001
Reperfusion time (min)		40.2 ± 2.9	32.0 ± 3.6	0.074	40.2 ± 2.9	33.0 ± 3.8	0.128	40.2 ± 2.9	32.0 ± 3.6	0.074
Operating time (h)		267.6 ± 5.4	223.7 ± 10.5	<0.001	267.6 ± 5.4	229.5 ± 10.8	<0.001	267.6 ± 5.4	223.7 ± 10.5	<0.001
Days in ICU		5.5 ± 0.6	9.3 ± 1.6	0.030	5.5 ± 0.6	9.8 ± 1.7	0.021	5.5 ± 0.6	9.3 ± 1.6	0.030
Days in hospital		11.5 ± 0.6	11.6 ± 0.7	0.921	11.5 ± 0.6	11.4 ± 0.8	0.949	11.5 ± 0.6	11.6 ± 0.7	0.921
Ventilation hours		40.1 ± 11.5	112.3 ± 31.3	0.034	40.1 ± 11.5	120.5 ± 33.7	0.028	40.1 ± 11.5	112.3 ± 31.3	0.034
pRBC units		2.3 ± 0.5	7.2 ± 2.2	0.032	2.3 ± 0.5	7.7 ± 2.3	0.027	2.3 ± 0.5	7.2 ± 2.2	0.032
Platelets Units		1.6 ± 0.5	7.3 ± 2.5	0.031	1.6 ± 0.5	7.9 ± 2.7	0.026	1.6 ± 0.5	7.3 ± 2.5	0.031
FFP Units		0.5 ± 0.1	1.8 ± 0.6	0.043	0.5 ± 0.1	2.0 ± 0.7	0.036	0.5 ± 0.1	1.8 ± 0.6	0.043

BMI, Body Mass Index; FFP, Fresh frozen plasma; HTK, Histidine-Tryptophan-Ketoglutarate; ICU, Intensive care unit; LVEF, Left-ventricular ejection fraction; NYHA, New York Heart Association; CK-MB, Creatinekinase muscle brain type; COPD, Chronic obstructive pulmonary disease; MICS, Minimally-invasive cardiac surgery; pRBC, Packed red blood cells; TnT, High-sensitive troponin T.

Table 3. Outcomes in the replacement group.

Timepoint	Type of surgery		unadjusted				adjusted			
	MICS	OPEN	Difference	*p*-value	95% CI		Difference	*p*-value	95% CI	
					low	high			low	high
TnT										
Peak 1 (ng/L)	1274.9 ± 477.2 n = 211	1184.9 ± 84.4 n = 399	90.0	0.806	–628.2	808.1	143.3	0.719	–638.1	924.6
Peak 2 (ng/L)	927.1 ± 489.1 n = 205	898.8 ± 77.3 n = 390	28.3	0.939	–698.4	755.0	153.2	0.705	–641.8	948.3
Peak 3 (ng/L)	983.8 ± 584.6 n = 171	718.4 ± 61.5 n = 351	265.4	0.525	–554.0	1084.8	371.6	0.423	–539.7	1283.0
AUC 1 ((ng/L)*h)	23,919.2 ± 10,572.6 n = 211	21,267.6 ± 1442.2 n = 399	2651.6	0.738	–12,931.3	18,234.9	3814.5	0.661	–13,265.4	20,894.4
AUC 2 ((ng/L)*h)	21,857.5 ± 11,732.8 n = 205	20,180.3 ± 1595.7 n = 390	1677.1	0.849	–15,567.5	18,921.7	4704.7	0.626	–14,231.1	23,640.6
AUC 3 ((ng/L)*h)	15,170.4 ± 5900.1 n = 171	17,069.1 ± 1458.6 n = 351	–1898.7	0.681	–10,964.7	7167.3	1013.2	0.839	–8794.4	10,820.8
CK-MB										
Peak 1 (µkat/L)	1.9 ± 0.6 n = 202	1.4 ± 0.2 n = 381	0.5	0.411	–0.7	1.7	0.6	0.290	–0.5	1.7
Peak 2 (µkat/L)	0.6 ± 0.1 n = 132	0.9 ± 0.1 n = 259	–0.2	0.189	–0.5	0.1	–0.1	0.580	–0.4	0.2
Peak 3 (µkat/L)	0.4 ± 0.1 n = 115	0.4 ± 0.03 n = 232	0.002	0.976	–0.1	0.1	0.03	0.675	–0.1	0.1
AUC 1 ((µkat/L)*h)	28.0 ± 7.3 n = 202	22.2 ± 1.1 n = 381	5.9	0.428	–8.7	20.4	7.6	0.208	–4.2	19.4
AUC 2 ((µkat/L)*h)	13.5 ± 1.8 n = 132	18.6 ± 2.0 n = 259	–5.0	0.063	–10.6	0.3	–2.4	0.456	–8.7	3.9
AUC 3 ((µkat/L)*h)	9.4 ± 1.2 n = 115	9.4 ± 0.6 n = 232	–0.03	0.978	–2.5	2.4	0.5	0.683	–2.0	3.0
Catecholamines (mg)										
	Type of surgery		unadjusted				adjusted			
	MICS	OPEN	Difference	*p*-value	95% CI		Difference	*p*-value	95% CI	
	n = 214	n = 406			low	high			low	high
Adrenaline	1.1 ± 0.6	5.1 ± 0.9	–4.0	<0.001	–6.1	–1.9	–1.7	0.213	–4.5	1.0
Noradrenaline	7.2 ± 1.6	37.2 ± 6.5	–29.9	<0.001	–43.0	–16.8	–22.3	0.023	–41.5	–3.1
Enoximone	15.4 ± 9.6	19.1 ± 5.7	–3.8	0.361	–24.4	16.9	5.8	0.613	–16.8	28.5

Peak or AUC 1 to 3 represent the respective value in the first, second, and third 24 h period after removal of the aortic cross clamp. AUC, Area under curve; CK-MB, Creatinekinase muscle brain type; MICS, Minimally-invasive cardiac surgery; TnT, High-sensitive troponin T.

Table 4. Outcomes in the reconstruction group.

TnT										
Timepoint	Type of surgery		unadjusted				adjusted			
	MICS	OPEN	Difference	*p*-value	95% CI		Difference	*p*-value	95% CI	
					low	high			low	high
Peak 1 (ng/L)	1495.4 ± 222.8 n = 75	1499.7 ± 231.4 n = 51	–4.3	0.990	–659.3	650.6	–845.4	0.025	–1584.8	–106.0
Peak 2 (ng/L)	998.2 ± 193.1 n = 73	1031.3 ± 179.3 n = 50	–33.1	0.905	–580.7	514.5	–631.9	0.046	–1253.2	–10.6
Peak 3 (ng/L)	937.7 ± 232.2 n = 56	778.6 ± 133.6 n = 44	159.0	0.582	–411.8	729.9	–437.0	0.190	–1095.3	221.3
AUC 1 ((ng/L)*h)	26,837.5 ± 4016.2 n = 75	26,854.2 ± 4136.8 n = 51	–16.7	0.998	–11,788.9	11,755.4	–15,183.3	0.024	–28,330.2	2036.4
AUC 2 ((ng/L)*h)	22,962.2 ± 4356.3 n = 73	23,305.6 ± 3845.7 n = 50	–343.3	0.956	–12,526.5	11,839.8	–13,122.6	0.063	–26,946.4	701.2
AUC 3 ((ng/L)*h)	21,920.9 ± 5332.9 n = 56	18,567.4 ± 3188.7 n = 44	3353.4	0.615	–9846.1	16,553.0	–10,003.7	0.194	–25,198.9	5191.4
CK-MB										
Peak 1 (µkat/L)	1.9 ± 0.2 n = 73	1.6 ± 0.2 n = 46	0.3	0.307	–0.3	1.0	–0.6	0.093	–1.2	0.1
Peak 2 (µkat/L)	1.0 ± 0.2 n = 50	0.8 ± 0.1 n = 31	0.2	0.507	–0.4	0.8	–0.4	0.240	–1.1	0.3
Peak 3 (µkat/L)	0.4 ± 0.04 n = 42	0.5 ± 0.1 n = 28	–0.1	0.363	–0.3	0.1	–0.2	0.067	–0.5	0.02
AuC 1 ((µkat/L)*h)	35.0 ± 4.2 n = 73	28.2 ± 2.6 n = 46	6.8	0.236	–4.5	18.2	–9.7	0.109	–21.5	2.2
AuC 2 ((µkat/L)*h)	21.4 ± 4.2 n = 50	17.6 ± 3.1 n = 31	3.8	0.520	–8.0	15.6	–7.8	0.260	–21.6	6.0
AuC 3 ((µkat/L)*h)	9.8 ± 1.1 n = 42	12.3 ± 2.8 n = 28	–2.5	0.350	–7.8	2.8	–6.0	0.055	–12.2	0.1
Catecholamines (mg)										
	Type of surgery		unadjusted				adjusted			
	MICS	OPEN	Difference	*p*-value	95% CI		Difference	*p*-value	95% CI	
	n = 75	n = 51			low	high			low	high
Adrenaline	1.1 ± 0.3	15.6 ± 7.0	–14.6	0.043	–28.7	–0.4	–14.2	0.036	–27.4	–1.0
Noradrenaline	6.2 ± 1.7	62.7 ± 22.8	–56.5	0.017	–102.4	–10.7	–46.8	0.043	–92.0	–1.5
Enoximone	9.4 ± 8.3	108.1 ± 50.8	–98.7	0.061	–202.0	4.7	–130.5	0.012	–231.5	–29.5

Peak or AUC 1 to 3 represent the respective value in the first, second, and third 24 h period after removal of the aortic cross clamp. AUC, Area under curve; CK-MB, Creatinekinase muscle brain type; MICS, Minimally-invasive cardiac surgery; TnT, High-sensitive troponin T.

reperfusion, and total operating time were longer in the OPEN group than in MICS. Days spent in the intensive care unit (ICU) and ventilation hours were also more in the OPEN group. More blood products were also transfused in patients who received open cardiac surgery.

In the reconstruction population, body weight and Body Mass Index (BMI) were higher in OPEN (Table 2). Diabetes was also more prevalent in this group. HTK was also more often used than blood cardioplegia in the MICS group. Cross-clamp and operation times were longer in MICS. However, MICS patients spent less time in the ICU and were mechanically ventilated for a shorter time than the OPEN patients. Again, more blood products were used in OPEN. However, in both populations, reconstruction and replacement, the outcome parameters were adjusted to relevant confounders.

3.2 Outcomes

The adjusted noradrenaline dosage was relevantly lower (adj. difference: –22.3 mg; $p = 0.023$) in the MICS group in the replacement population (Table 3). However, the adjusted release of TnT and CK-MB was not relevantly different. In the reconstruction population, the adjusted adrenaline (adj. difference: –14.2 mg; $p = 0.036$), noradrenaline (adj. difference: –46.8 mg; $p = 0.043$), and enoximone (adj. difference: –130.5 mg; $p = 0.012$) dosages were lower in the MICS group than in the OPEN group (Table 4). Considering the adjusted differences in all catecholamines, this result is clinically meaningful. The adjusted peak TnT release in the first 24 h (adj. difference: –845.4 ng/L; $p = 0.025$) and between 24 and 48 h (adj. difference: –631.9 ng/L; $p = 0.046$) after the onset of myocardial reperfusion and the adjusted TnT AUC (adj. difference: –15,183.3 (ng/L)*h); $p = 0.024$) were lower, and according to the absolute difference of release of clinical importance in the MICS group (Table 4). The adjusted peak CK-MB release was relevantly lower (adj. difference: –0.6 µkat/L) in the first 24 h and between 48 and 72 h, as well as the adjusted CK-MB AUC between 48 and 72 h after removal of the cross-clamp. A summary of the results is shown in Fig. 1.

4. Discussion

In this retrospective single-center comparison, we could show a decreased release of cardiac enzymes after valve reconstruction and a decreased catecholamine requirement after both valve replacement and reconstruction by MICS compared to OPEN. From this, we conclude that myocardial protection is more effective in MICS during valve surgery and is associated with a more stable hemodynamic situation for the patient after valve surgery.

4.1 Methodology

The analysis was adjusted for multiple covariates because myocardial contractility and hemodynamics also depend on various patient-specific and treatment-associated factors. Based on the literature, cardiac enzyme release depends on ischemia time, which is reflected by the aortic cross-clamping time [10]. The effects of myocardial ischemia also depend on sex [11]. During aortic cross-clamping, the myocardium is protected by the cardioplegic solution, which is also likely to affect cardiac enzyme release. Thus, cross-clamping time, sex, and cardioplegia were included as covariates. The number of operated valves affects the aortic cross-clamping time and was therefore also considered for the adjustment. The reperfusion time between removal of the aortic cross-clamp and weaning from CPB might have an effect, especially on the catecholamine dosage, and was therefore also included as a covariate. The stage of heart insufficiency and ventricular function correlates with the general state and potential resilience of the patient against certain stress, such as cardiac surgery, and was consequently also included as a covariate [12]. Although propensity score matching is often applied to create comparable populations, it has been shown by Cepeda *et al.* [13] that in the case of a higher number of events per confounder, which is the given reality in the present populations, regression is the more robust approach.

4.2 Outcome Measures

In the replacement population, the aortic cross-clamping time, which determines the myocardial ischemia time, was not relevantly different between MICS and OPEN. This finding was unexpected but might be based on the fact that complicated cases, such as surgery on multiple valves, are preferably operated in OPEN fashion. Consequently, more patients with multiple operated valves were included in the OPEN group.

In contrast, in the reconstruction population, the percentage of patients with single or multiple operated valves was comparable between MICS and OPEN. Thus, based on the limited operating space in MICS, the operating and ischemia time was longer than that of OPEN, as known from the literature [14]. Considering the prolonged ischemia time in the MICS population, we expected a more pronounced myocardial injury and, thus, higher cardiac enzyme release. However, the outcome measures were adjusted for this factor, and even after adjustment, the TnT release was lower and of clinical relevance in the MICS group. From this, we conclude that myocardial protection is not only time-dependent but also depends on surgical access and trauma, which is smaller and reduced in MICS. The obviously improved myocardial protection can also be a reason for the reduced postoperative catecholamine dosage in MICS, which can also be based on other secondary effects that promote stable hemodynamics after cardiac surgery. Sufficient circulation in the body based on low catecholamine requirement and short ventilation times enables early mobilization of the patient, which is especially beneficial for old and often frail patients [15].

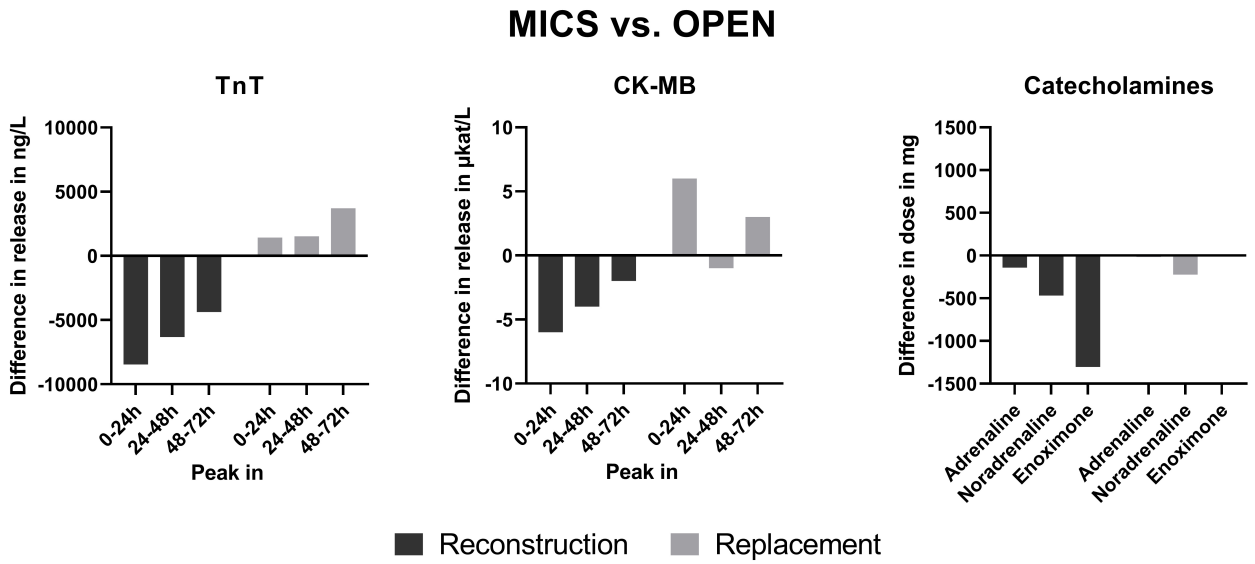

Fig. 1. Summary of results. Negative values indicate a lower release or dosage in MICS than in OPEN. MICS, Minimally-invasive cardiac surgery; TnT, High-sensitive troponin T; CK-MB, Creatinekinase muscle brain type.

The missing difference of cardiac enzyme release in the replacement group might be based on other factors of relevance for myocardial protection that might have overshadowed the potential protective effects of MICS. Accordingly, patients with valve replacement sometimes have a more complicated ventricular geometry that can make the surgical procedure more complicated and indirectly affect myocardial protection. In the literature, it has also been suggested that valve replacement can have a counterbeneficial effect on myocardial protection when ventricular geometry cannot be fully preserved or may have a more severe primary disease [16–18].

Other observed advantages of MICS are the shorter ICU and ventilation times and the decreased use of blood products compared to OPEN. This observation is congruent with other studies and might be based on decreased chest trauma because no median sternotomy is performed [19].

4.3 Limitations

Due to the retrospective nature of this study, not all outcome measures were available at every time point. However, we performed a commonly known mathematical approximation to minimize this limitation. We were unfortunately not able to compare the effect of different cardioplegic solutions within the subgroups due to the limited number of patients per cardioplegia.

4.4 Future Directions

Prospective studies, ideally using only one type of cardioplegia, are needed to prove the conclusions of the present retrospective study. TnT and CK-MB are clinically relevant biomarkers that correlate with clinically relevant outcomes such as arrhythmias or survival [20]. Other clinical outcomes, such as survival, ideally long-term, should also be assessed and correlated with myocardial injury markers. Additionally, further studies are needed to investigate if the improved myocardial protection also occurs in other cardiovascular surgery procedures that can also be performed minimally-invasive.

5. Conclusion

Our single-center retrospective study concludes that the surgical access seems to have an impact on myocardial protection. Therefore, MICS, compared to OPEN, shows improved myocardial protection, at least during valve reconstruction. Consequently, if possible, MICS should be preferred over OPEN in order to achieve improved myocardial protection. Additionally, MICS is associated with improved postoperative hemodynamics in valve reconstruction and replacement. Thus, this study provides novel insights into the additional benefits of MICS that might be especially in favor for old and frail patients in cardiac surgery. However, prospective studies are needed to confirm these results.

Availability of Data and Materials

Data and more information on materials are available upon reasonable request.

Author Contributions

LS and ALB performed the research. LS designed the research study, interpreted data, wrote the manuscript. ALB performed data extraction and analysis. MS assisted during data extraction. AS and GS performed critical review of the manuscript. GS and AS interpreted the results. All authors contributed to editorial changes in the manuscript. All authors read and approved the final

manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was carried out in accordance with the guidelines of the Declaration of Helsinki. The institutional ethical review committee of the University Hospital Halle reviewed and approved this investigation (reference: 2022-137; approval: 05 December 2022). Due to the retrospective nature of this study, no informed consent was necessary.

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Conflict of Interest

The authors declare no conflict of interest.

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