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The interval time for the St. Thomas cardioplegia solution in mitral valve surgeries

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Abstract

Background There is a lack of consensus on the appropriate St. Thomas cardioplegia solution interval for cardiac surgeries. The objective of this study was to determine a safe cardioplegia interval.

Method A total of 340 patients who underwent mitral valve surgery with St. Thomas solution were assessed and divided into 2 groups according to the average cardioplegia interval. In Group A, the average cardioplegia interval was <=30 min; in Group B, the average cardioplegia interval was greater than 30 min. Propensity score matching was used to adjust for confounders between the two groups. After propensity score matching, Groups A and B contained 125 patients each. The primary endpoints were creatine kinase MB, left ventricular ejection fraction, and troponin levels after surgery. Threshold effect analysis was used to assess the association of the cardioplegia interval with the postoperative CK-MB mass level.

Results After propensity score matching, postoperative CK-MB mass significantly differed between the two groups, and CK-MB levels were significantly greater in group B than in group A(Group A vs. Group B: 46.1 [46.1;48.3] ng/ml vs. 49.9 [46.1;62.7] ng/ml, $p < 0.001$). According to the threshold effect analysis, the interval needs to be above 27.6 min before it is associated with an increased risk of CK-MB mass level, and the interval needs to be above 31 min before it is associated with an increased risk of CK-MB mass level 7 h after surgery. There were no other significant differences between the two groups.

Conclusions The multidose cardioplegia interval above 30 min during mitral valve surgery is associated with a greater risk of myocardial damage. The relationships between the cardioplegia interval and other myocardial markers require further research.

Keywords Cardioplegia interval, Mitral valve surgery, Myocardial damage, St. Thomas solution, Creatine kinase MB (CK-MB)

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Introduction

Cardioplegia solution is an important component of cardiac surgery. Different cardioplegia solutions can be categorized by frequency (single dose or multidose delivery), or the composition of the solution (blood or crystalloids). The crystalloid myocardial protection solution has been widely used around the world since the 1950s [1]. Although the solution to cardioplegia has evolved for years, there is a lack of consensus on this technique [2].

St. Thomas solution is a widely used cardioplegia solution [3]. It is designed to induce rapid arrest and preserve the myocardial content of high-energy phosphate compounds [4]. Normally, the interval is approximately 20 min [5]. The multidose method in adults is believed to provide better myocardial protection than the single dose method [6]. Some studies have reported that ischemic time is an independent risk factor for operative mortality [7].

To provide a better prognosis for patients and increase surgical efficiency, we investigated the effect of a longer cardioplegia interval on myocardial protection in median sternotomy mitral valve surgeries.

Materials and methods

Study design and human ethics

This retrospective observational cohort study was approved by the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China (IRB approval issuing numbers: R077 in 2023). Ethical approval for this research was obtained from the Review of Ethics Committee in Clinical Research (ECCR) of the First Affiliated Hospital of Wenzhou Medical University (IRB approval number: R077 in 2023). The need for informed consent was waived by the Ethics Committee due to the retrospective nature of the study, which analyzed anonymized data from hospital records.

Study population

The study included 340 patients who underwent mitral valve surgery through median sternotomy at the First Affiliated Hospital of Wenzhou Medical University from January 2019 to May 2022. Patients were divided into the following 2 groups: group A ($n=164$), in which the average cardioplegia interval was <=30 min; group B ($n=176$), in which the average cardioplegia interval was greater than 30 min.

Data collection

We were not able to perform routine real-time myocardial protection evaluations for each patient, so we collected the following information: demographic characteristic data (age, sex, weight and height), comorbidity situation data (hypertension, hyperlipidemia, chronic obstructive pulmonary disease, diabetes), intraoperative data (cardiopulmonary bypass (CPB) time and aortic cross-clamp (ACC) time), echocardiography results (left ventricular ejection fraction) and laboratory test results before and after surgery, including BNP, troponin, serum creatinine level, hemoglobin level, creatine kinase MB. All data were collected from the hospital electronic medical records system or from operation records.

Cardioplegic solutions

After cardiopulmonary bypass is established, the aorta is cross-clamped. The standard St. Thomas solution was used as a cardioplegic solution. St. Thomas solution is a type of extracellular crystalloid-based multidose cardioplegia that requires a short interval of approximately 20 min.

Outcomes

The primary endpoints were creatine kinase MB, the left ventricular ejection fraction, troponin levels after surgery and the use of electric defibrillation. Creatine kinase MB and troponin T are well-established markers of myocardial damage in adults [8, 9]. After the changes in hospital laboratory testing methods in January 2021, the CK-MB level was replaced by the CK-MB mass level, and the cardiac troponin T (cTnT) level was replaced with the high-sensitivity cardiac troponin T (hs-cTnT) level.

The secondary endpoints included length of stay, creatinine levels, and BNP levels.

Statistical analysis

IBM SPSS Statistics 25 and R software (version: 4.3.1) were used to perform the statistical analyses. Continuous variables were compared using the t test, and categorical variables were compared using the chi-squared test or Fisher's exact test. All continuous variables are shown as the means (the standard deviation) followed by the median and the [interquartile range]. Propensity score matching (PSM) is an effective method for controlling bias in retrospective observational studies [10]. Propensity score matching was used to adjust for preoperative confounding factors, such as age, BMI, and LVEF between the two groups. A2-sided $P<0.05$ was considered to indicate statistical significance and is reported as a 2-sided 95% CI.

Results

Preoperative and intraoperative variables

Preoperative and intraoperative variables are shown in Table 1. BMI was significantly greater in Group A (Group A vs. Group B: 24.0 (3.33) vs. 23.2 (3.58), $p=0.031$). The LVEF was significantly greater in Group A (Group A vs. Group B: LVEF: 65.0 [59.0;68.0] vs. 63.0 [56.6;68.0], $p=0.045$). Among the preoperative factors, 2 groups showed no significant differences in demographic

Table 1 Preoperative and intraoperative variables

		Unmatched				Matched			
	All cases ***N*** **= 340**	**Group A** **<=30** ***n*** **= 164**	**Group B** **> 30** ***n*** **= 176**	**P**	**SMD**	**Group A** **<=30** ***n*** **= 125**	**Group B** **> 30** ***n*** **= 125**	**P**	**SMD**
Female (%)	165 (48.5)	84 (51.2)	81 (46.0)	0.396	0.104	61 (48.8)	57 (45.6)	0.704	0.064
Male (%)	175 (51.5)	80 (48.8)	95 (54.0)			64 (51.2)	68 (54.4)		
Age	58.3 (12.1)	59.0 (11.7)	57.7(12.5)	0.315	0.109	58.2 (11.9)	57.3(12.1)	0.571	0.062
Height (cm)	163 (8.45)	163 (8.86)	162 (8.07)	0.823	0.028	164 (8.57)	162 (7.90)	0.270	0.031
Weight (kg)	62.5 (11.2)	63.7 (10.6)	61.5 (11.6)	0.063	0.202	63.6 (10.5)	61.8(11.3)	0.178	0.045
BMI(kg/m^2)	23.6 (3.48)	24.0 (3.33)	23.2 (3.58)	0.031	0.231	23.7 (3.08)	23.4(3.46)	0.393	0.085
BSA (m^2)	1.64 (0.18)	1.65 (0.17)	1.63 (0.18)	0.128	0.163	1.66 (0.17)	1.63(0.18)	0.187	0.036
Diabetes (%)	42 (12.4)	17 (10.4)	25 (14.3)	0.352	0.117	10 (8.00)	17 (13.6)	0.221	0.125
Hypertension (%)	126 (37.2)	61 (37.2)	65 (37.1)	1.000	0.005	49 (39.2)	49 (39.2)	1.000	0.131
Hyperlipidemia (%)	117(34.5)	55 (33.5)	62 (35.4)	0.801	0.035	40 (32.0)	46 (36.8)	0.506	0.017
COPD (%)	4(1.18)	1 (0.61)	3(1.7)	0.624	0.102	1 (0.80)	2 (1.60)	1.000	0.121
LVEF (%)	64.0 [57.8;68.0]	65.0 [59.0;68.0]	63.0 [56.6;68.0]	0.045	0.222	64.7 [59.0;67.0]	64.4 [59.8;68.1]	0.544	0.088
CKMB(U/L)	11[8.0;14.0]	11.[8.0;14.0]	10.[8.0;14.]	0.579	0.096	11.[9.0;13]	11.[8.0;14]	0.745	0.130
CKMB mass (ng/ml)	1.53 [0.96;3.02]	1.58 [0.83;2.78]	1.38 [1.14;3.07]	0.924	0.020	1.48 [1.00;1.55]	1.27 [1.16;1.28]	0.445	0.012
hs-cTnI (ng/L)	0.01 [0.00;0.01]	0.00 [0.00;0.01]	0.01 [0.00;0.01]	0.063	0.107	0.00 [0.00;0.01]	0.01 [0.00;0.01]	0.060	0.096
hs-cTnt (ug/L)	14.8 [8.90;37.7]	14.8 [9.28;34.8]	14.9 [8.85;44.1]	0.885	0.089	11.7 [9.00;13.1]	12.5 [8.90;14.9]	0.087	0.109
Creatinine (umol/L)	73[61;89]	70[60;84.0]	76.[63;92]	0.058	0.127	70.[62;84]	76[64;92]	0.249	0.136
Bnp(pg/ml)	138 [55.0;272]	133 [55.0;240]	152 [55;305]	0.237	0.288	122 [49.0;208]	166 [56;281]	0.146	0.194
Intraoperative									
CPB time(min)	149 (41.2)	157 (41.1)	142 (40.0)	0.001		154 (35.3)	142 (40.8)	0.017	
ACC time(min)	112 (35.7)	117 (37.3)	107 (33.4)	0.011		113 (30.2)	107 (33.2)	0.125	
Electric defibrillation (%)	278 (81.8)	128 (78.0)	150 (85.2)	0.116		99 (79.2%)	105(84.0%)	0.414	

SMD(Standardized Mean Difference)

characteristics (age, gender, etc.), myocardial performance status (LV ejection fraction, troponin) or comorbidities (hypertension, hyperlipidemia, COPD, diabetes) after PSM.

The duration of the CPB (cardiopulmonary bypass) was significantly greater in Group A (Group A vs. Group B: 157 (41.1) vs. 142 (40.0), $p=0.001$). We found a statistically significant difference in ACC (aortic cross clamp) (Group A vs. Group B: 117 (37.3) vs. 107 (33.4), $p=0.011$), with Group A being significantly longer. There was no significant difference in ACC time after PSM (Group A vs. Group B: ACC time: 113 (30.2) vs. 107 (33.2), $p=0.125$). There were no significant differences in the use of electric defibrillation between the 2 groups.

Primary endpoints and secondary endpoints

Postoperative variables are shown in Table 2. Primary endpoints, including CK-MB, CK-MB mass-0 h (Group A vs. Group B: 46.1 [34.1;56.0] ng/ml vs. 47.0 [36.0;62.7] ng/ml, $p=0.391$), CK-MB mass-7 h (Group A vs. Group B: 33.5 [28.0;44.9] ng/ml vs. 34.3 [28.7;49.3] ng/ml, $p=0.439$), CK-MB mass-24 h (Group A vs. Group B: 25.0 [13.7;28.8] ng/ml vs. 20.6 [15.1;31.3] ng/ml, $p=0.670$), hs-cTnI (Group A vs. Group B: 5.97 [4.29;9.85] μg/L vs. 6.43 [4.08;9.83] μg/L, $p=0.614$) and hs-cTnT (Group A vs. Group B: 704 [537;1049] ng/L vs. 765 [464;1334] ng/L, $p=0.982$) levels did not show significant differences between two groups. The LV ejection fraction-24 h was significantly greater in Group A (Group A vs. Group B: 63.7 [59.9;69.0]% vs. 62.9 [54.8;67.4]%; $p=0.034$). After PSM, the following levels were significantly greater in Group B: CK-MB mass-0 h (Group A vs. Group: 46.1 [46.1;48.3] ng/ml vs. 49.9 [46.1;62.7] ng/ml, $p<0.001$) and CK-MB mass-7 h (Group A vs. Group B: 38.2 [32.3;42.2] ng/ml vs. 42.2 [32.6;49.3] ng/ml, $p=0.001$). The highest level of CK-MB mass was found shortly after surgery in both groups (Fig. 1). LV ejection fraction (Group A vs. Group B: 63.3 [59.4;68.0]% vs. 63.4 [55.5;67.9]%, $p=0.521$; Fig. 2), hs-cTnI (Group A vs. Group B: 6.04 [4.50;9.85] μg/L vs. 6.40 [4.08;9.26] μg/L, $p=0.711$) and hs-cTnT (Group A vs. Group B: 541 [482;629] ng/L vs. 569 [475;759] ng/L, $p=0.692$; Fig. 3) levels did not significantly differ between group A and group B.

The association of the cardioplegia interval with the postoperative CK-MB mass level

The relationship between the cardioplegia interval and postoperative CK-MB mass level 0 h and 7 h after surgery showed an approximate growth S-curve (Fig. 4). The model fits suggest that the relationship between the interval and the CK-MB mass level is nonlinear. For the level of CK-MB mass at 0 h, the threshold effect analysis suggested that the interval should be longer than 27.6 (95% CI 23.5, 45.5) minutes before it is associated with

Table 2 Postoperative variables

		Unmatched			Matched		
	All cases ***N*** **= 340**	**Group A** **<=30** ***n*** **= 164**	**Group B** **> 30** ***n*** **= 176**	**P**	**Group A** **<=30** ***n*** **= 125**	**Group B** **> 30** ***n*** **= 125**	**P**
Primary endpoints							
CKMB 0 (U/L)	65.0 [51.5;81.0]	66.0 [54.0;81.0]	62.0 [51.0;80.8]	0.378	67.0 [54.0;86.0]	69.0 [55.0;86.0]	0.809
CKMB > 7 h (U/L)	48.0 [37.0;59.0]	48.0 [37.0;56.0]	48.0 [37.5;60.5]	0.740	47.0 [40.0;59.0]	49.0 [40.0;60.0]	0.813
CKMB > 24 (U/L)	39.0 [29.0;50.0]	38.0 [29.0;50.0]	40.0 [30.0;50.0]	0.572	37.0 [29.0;51.0]	40.0 [30.0;47.0]	0.864
CKMB mass 0 h (ng/ml)	46.4 [35.2;60.6]	46.1 [34.1;56.8]	47.0 [36.0;62.7]	0.391	46.1 [46.1;48.3]	49.9 [46.1;62.7]	<0.001
CKMB mass 7 h (ng/ml)	34.2 [28.3;47.6]	33.5 [28.0;44.9]	34.3 [28.7;49.3]	0.439	38.2 [32.3;42.2]	42.2 [32.6;49.3]	0.001
CKMB mass 24 h (ng/ml)	21.1 [14.9;30.0]	25.0 [13.7;28.8]	20.6 [15.1;31.3]	0.670	25.2 [18.0;26.1]	20.6 [17.4;26.1]	0.101
LVEF24h (%)	63.3 [57.9;67.9]	63.7 [59.9;69.0]	62.9 [54.8;67.4]	0.034	63.3 [59.4;68.0]	63.4 [55.5;67.9]	0.521
hs-cTnT 24 h (ng/L)	718 [474;1245]	704 [537;1049]	765 [464;1334]	0.982	541 [482;629]	569 [475;759]	0.692
Hs-cTnI 24 h (ug/L)	6.12 [4.22;9.85]	5.97 [4.29;9.85]	6.43 [4.08;9.83]	0.614	6.04 [4.50;9.85]	6.40 [4.08;9.26]	0.711
Secondary endpoints							
Bnp 48 h (pg/ml)	298 [190;528]	278 [168;487]	319 [205;599]	0.073	274 [177;398]	311 [202;508]	0.118
Creatinine 24 h(umol/L)	80.0 [65.0;104]	80.0 [65.5;100]	80.0 [63.2;108]	0.887	82.0 [68.0;101]	81.0 [63.0;108]	0.553
ICU length (hour)	90.0 [66.0;122]	90.0 [66.0;128]	89.0 [64.0;121]	0.739	90.0 [66.0;135]	89.0 [64.0;116]	0.762
Time in Hospital (day)	20.0 [17.0;26.0]	20.0 [17.0;25.2]	21.0 [17.0;26.0]	0.434	20.0 [17.0;26.0]	20.0 [17.0;24.0]	0.600

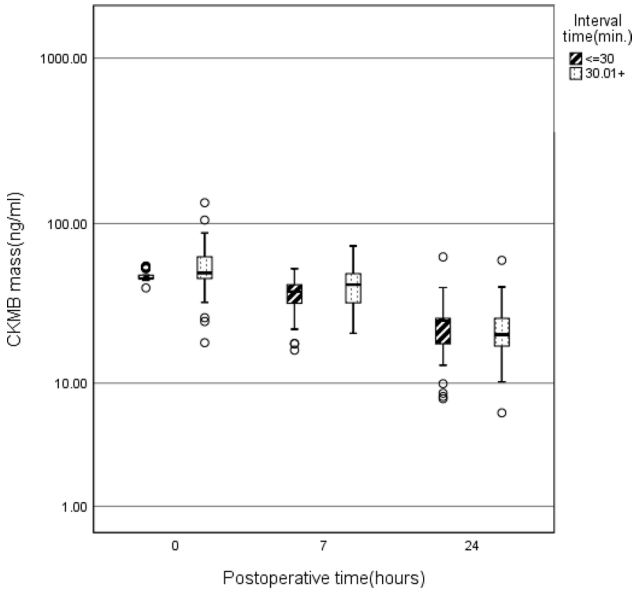

Fig. 1 The association between CKMB mass and postoperative time

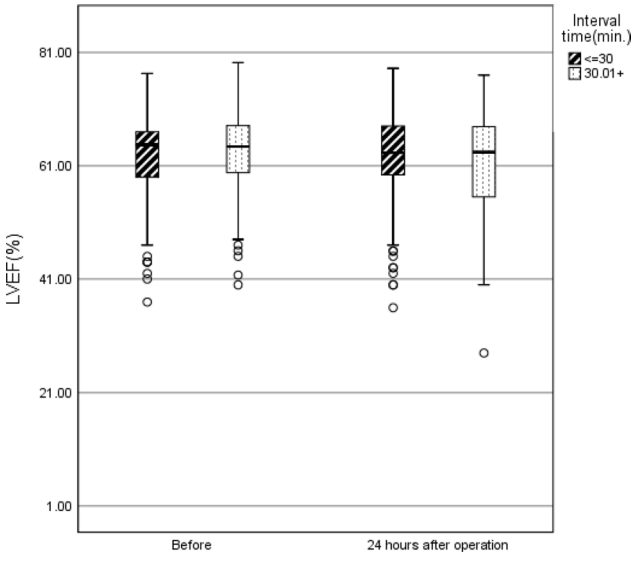

Fig. 2 The LVEF level before and after surgery

an increased risk of CK-MB mass level. For the level of CK-MB mass 7 h after the operation, the threshold effect analysis suggested that an interval greater than 31 (95% Cl 19.8, 43.5) minutes before the operation is associated with an increased risk of CK-MB mass level.

Secondary endpoints

There were no differences between the two groups in terms of ICU length of stay, creatinine levels, or BNP and NT-pro BNP levels.

Discussion

In this retrospective study, we evaluated the influence of multidose cardioplegia intervals from cases below 30 min to over 40 min in patients who underwent median sternotomy mitral valve surgery. Our primary endpoints were creatine kinase MB, the left ventricular ejection fraction, troponin levels and the use of electric defibrillation after surgery. The secondary endpoints were length of stay, creatinine levels, and BNP levels. After propensity score matching, postoperative CK-MB mass significantly differed between the two groups, and CK-MB levels were significantly greater in group B (interval > 30 min) than in group A (interval < 30 min). The slight, statistically significant reduction in LVEF observed in Group B compared to Group A postoperatively may be due to the lower

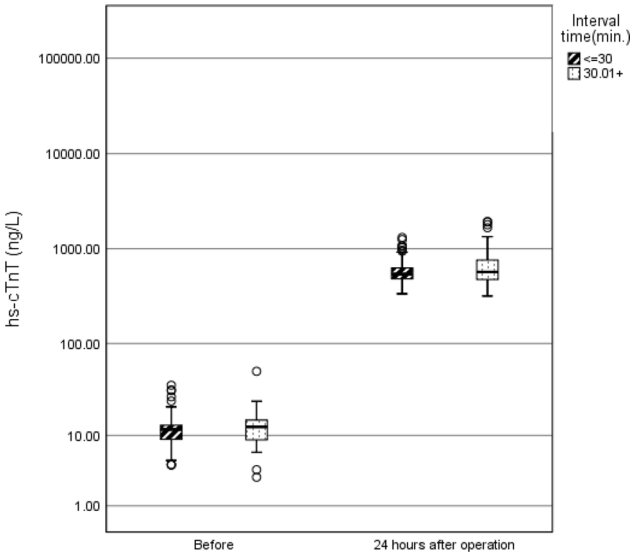

Fig. 3 The hs-cTnT level before and after surgery

baseline levels in Group B before surgery. This significant difference disappeared after data matching. There were no significant differences in the other biomarkers or postoperative factors between the two groups. Cardioplegia in antegrade infusion is normally reinfused approximately every 25 min [11]. However, some studies suggest that short-term multidose intervals are not applicable to every patient [12]. In addition, a longer interval has an advantage of shortening the total surgery time. Individual differences in patients or different operative procedures may result in such differences.

According to our analysis of the threshold effect, an interval needs to be above 27.6 min before it is associated with an increased risk of CK-MB mass level, and an interval needs to be above 31 min before it is associated with an increased risk of CK-MB mass level 7 h after surgery. The S-curve indicates a nonlinear relationship where the increase in CK-MB mass level accelerates after surpassing specific cardioplegia intervals. The threshold analysis identifies these intervals—27.6 min for immediate postoperative levels and 31 min for levels 7 h post-surgery—as critical points where the risk of myocardial damage, as indicated by CK-MB levels, begins to significantly rise. Understanding these thresholds is essential for surgical planning and patient management to improve outcomes. Any minimal perioperative myocardial ischemia can lead to a significant elevation of concentrations or activities of CK-MB mass level [13]. This study suggested an association between the severity of myocardial ischemia and the longer cardioplegia interval. Peak CK-MB levels correlate with left ventricular dysfunction, and clinical outcomes after myocardial infarction [14]. In other surgeries like CABG, CK-MB and troponin levels within 24 h are independently linked to higher intermediate and long-term mortality [15].

This study also comprises several limitations. Minimally invasive mitral valve surgery may be an alternative to conventional surgery, but has increased risks that require further study [16]. We hope that our research

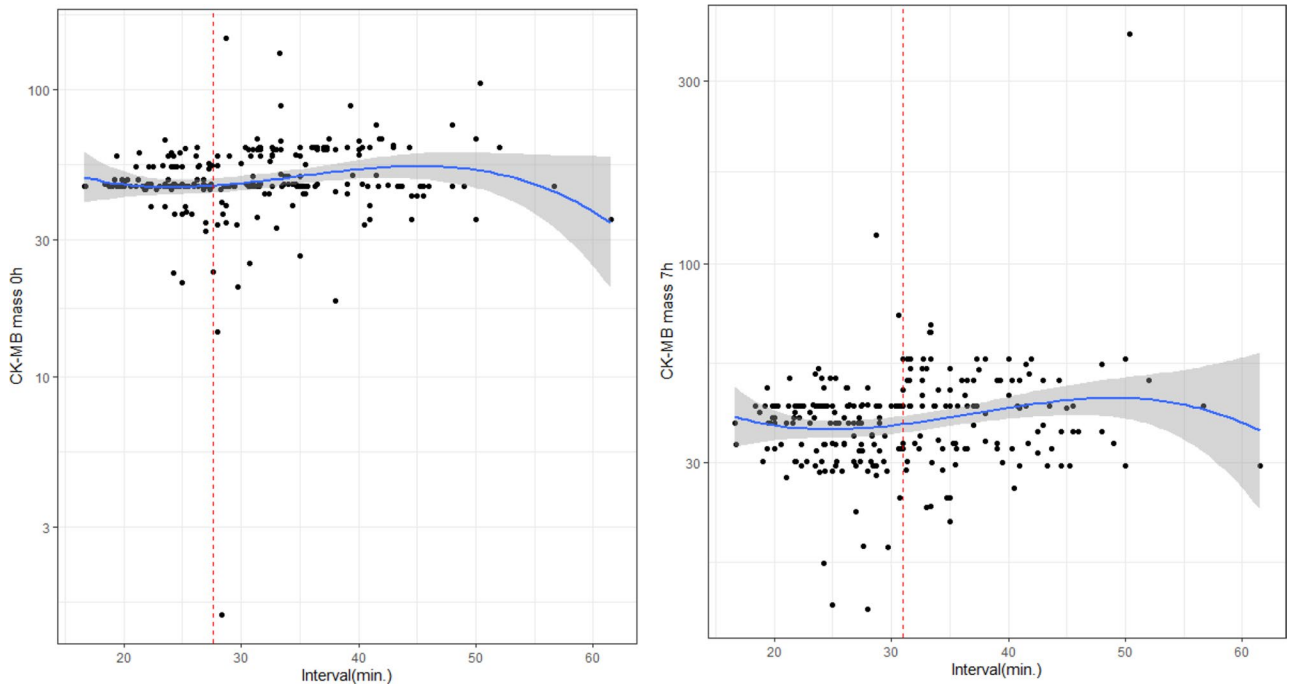

Fig. 4 The association of the cardioplegia interval with the postoperative CK-MB mass level

on cardioplegia time management in open mitral valve surgery can provide insights into different cardioplegia methods for minimally invasive mitral valve surgery. Based on our research findings, the St. Thomas solution may be feasible for shorter minimally invasive surgeries. Alternatively, the St. Thomas solution can be used as a supplement to the Del Nido solution. More research is needed to explore the applicability of the St. Thomas solution in minimally invasive surgeries. We attempted to better match the baseline characteristics before surgery, but intraoperative variables and patient-specific factors could not be accounted for in our PSM model. The troponin level is superior to the CK-MB level for detecting myocardial damage and for predicting 30-day mortality [17, 18]. However, an S-curve growth relationship was found only between the CKMB mass and cardioplegia interval. The curve may not represent the real status of myocardial damage. The longest single ischemic interval was not recorded in this study, which was demonstrated to be more important than the cumulative ischemic time [19]. We only evaluated mitral valve diseases from our hospital, and the statistical results cannot be generalized to all other cardiac operations. Our study is an attempt aimed at encouraging more prospective, multicenter collaborative research in the future. Future research should include a broader range of biomarkers and long-term clinical outcomes to provide a more comprehensive understanding of the impact of cardioplegia intervals. Despite the universal use of this cardioplegia method, this kind of 'depolarized arrest' has the disadvantage of producing hyperkalemia [20]. Crystalloid cardioplegia is only partially cardioprotective [21]. Therefore, more studies and clinical trials are needed in the future.

Conclusions

In conclusion, the multidose cardioplegia interval greater than 30 min in median sternotomy mitral valve surgeries is associated with a greater risk of myocardial damage.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-024-04328-6.

Supplementary Material 1

Supplementary Material 2

Author contributions

Sitong Tang, Na Chen wrote the main manuscript text. Jiajun Zhong, Hangfei Yan, Nan Jiang, Chiyin Wang, Mariam Omotolani Afolabi and Ailing Lin prepared the data analysis. All authors reviewed the manuscript.

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Data availability

Data is provided within the supplementary information files.

Declarations

Competing interests

The authors declare no competing interests.

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