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The cardioprotective effects of HTK solution and conventional blood cardioplegia in patients with atrial fibrillation undergoing valvular replacement and Cox maze III procedure

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Abstract

Introduction The study was to assess the myocardial protection effects of the histidine-tryptophan-ketoglutarate (HTK) solution and the 4:1 blood cardioplegia (BC) in patients with atrial fibrillation (AF) who were subjected to valvular replacement concomitant with the Cox maze III surgery.

Methods A cohort of 148 individuals afflicted with AF, who received valve replacement surgery in conjunction with the Cox maze III procedure at our clinic within the period extending from 2015 to 2023, were enrolled. Subsequent to adjustment by propensity score matching (PSM), the patients were categorized into two distinct groups: the HTK group and the BC group. The primary end points assessed inotropic support requirements, complications, troponin trend, mechanical ventilation time and the intensive care unit stay. Arrhythmias, aortic cross-clamp and cardiopulmonary bypass times, and other clinical perioperative variables were considered as secondary end points.

Results No substantive disparities were observed concerning mortality rates, arrhythmias, neurological events, or renal complications. The duration of cardiopulmonary bypass and the aortic cross-clamp time did not demonstrate any marked variations between both groups, with p-values of 0.71 and 0.05, respectively. The time required for weaning from mechanical ventilation and the length of postoperative hospitalization were notably less in the group receiving HTK solution ($p < 0.001$ and $p = 0.03$, respectively). While inotropic support need was higher in the BC group ($p = 0.02$). Conversely, the dosage and frequency of perfusions were considerably increased in the BC group ($p < 0.001$

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for each parameter). Within subgroups stratified by longer than 150 min of aortic cross-clamping duration, those in the BC cohort had significantly elevated peaks of cardiac troponin I (cTnI) ($p=0.01$), whereas individuals in the HTK group experienced less mechanical ventilation time ($p=0.002$) and shorter durations of intensive care unit admission ($p<0.001$). The LVEF value in the HTK group was higher compared to that in the BC group in the 3-month follow-up data ($p=0.02$).

Conclusions Both the HTK and 4:1 blood cardioplegia could be used safely in patients with AF who were subject to valvular replacement and Cox maze III procedure. However, the utilization of HTK conferred a greater advantage in diminishing the duration of mechanical ventilation weaning and the duration of postoperative hospitalization. HTK may be a better myocardial protection in patients with long cross-clamp time. The follow-up data indicated that HTK might be superior to 4:1 blood cardioplegia in the short-medium term cardiac function.

Keywords Atrial fibrillation, Cardioplegia, Histidine-tryptophan-ketoglutarate, Myocardial protection, Valvular replacement, Cox Maze III

Introduction

Atrial fibrillation (AF), a prevalent cardiac dysrhythmia, manifests in approximately 1.5 to 2.0% of the general population. It is observed in a substantial proportion of patients—ranging from 40 to 60%—undergoing mitral valve surgical interventions, and it notably exacerbates the risk of mortality in the subsequent years post-operatively [1]. The Cox maze III surgery is considered the gold standard for managing atrial fibrillation [2]. This operation, colloquially termed the "cut-and-sew" maze technique, involves a meticulous and elaborate surgical approach, could restore the sinus rhythm (SR) above 90%. But due to surgical complexity and high technical requirements, this operation is not widely adopted among cardiac surgeons. But it continues to serve as the benchmark against which other surgical modalities for AF are compared, maintaining its position as a pivotal consideration, especially for those cases where the ablation of AF is deemed to be of paramount concern [3]. However, there are yet few relevant reports about the myocardial protection strategies in this type of complex Cox maze III surgery especially with longer myocardial ischemia time.

With the rising prevalence of aging populations and the accompanying multiple comorbidities, myocardial protection has become increasingly critical. Cardioplegia selection varied widely, with each type tailored according to established clinical protocols. Cardioplegic solutions needed to quickly cause diastolic arrest, reduce ischemic damage in the heart, protect against reperfusion injuries, help the heart recover after surgery, and have low extracardiac toxicity [4]. Among the various formulas, 4:1 blood cardioplegia (BC) mainly used in adult cardiac surgeries, advocating an extracellular strategy with a 4:1 blood-to-crystalloid ratio. Nevertheless, this approach required repeated doses every thirty minutes during the operative period. Blood naturally contained buffering capabilities which could potentially alleviate myocardial edema, in addition to its oxygen-carrying capacity, thus facilitating a quick induction of arrest while maintaining oxygenated conditions. On the other hand, the histidine-tryptophan-ketoglutarate (HTK) solution, distinguished by its low-sodium content and intracellular-type profile, demonstrated its effectiveness through the reduction of extracellular sodium concentrations, earning clinical acclaim for efficient organ preservation [5]. The widespread acceptance of the HTK protocol hinged on its single-use nature, offering prolonged myocardial protection beyond two hours of cardiac asystole. Although there was extensive research in the field, a conclusive consensus on the application of cardioplegia still had not been reached especially in cases of complex heart surgeries with prolonged cross-clamp times in ischemic conditions. Therefore, the aim of this study was to evaluate the perioperative myocardial protection effects of the HTK solution and BC in the Cox maze III procedure combined with valve surgery in patients with AF in a single center retrospective study.

Materials and methods

Patient selection

This retrospective single-center observational study was approved by the ethics review board of Jinling hospital (2018NZY-028-01). Waiver of individual consent for the study was granted. According to 2023 AHA/ACC/HRS guideline [6], persistent AF was defined as continuous AF for more than 7 days. Long-standing persistent AF was defined as continuous AF for more than 12 months. A total of 163 patients in our valve surgery database who had surgery with Cox maze III procedure for persistent or long-standing persistent AF between 2015 and 2023 at Department of Cardiovascular Surgery in Nanjing Jinling Hospital were examined consecutively. To be eligible, participants must be at least 18 years old and must have used either HTK or BC. Exclusion criteria: [1] serious systemic disease such as coagulation disorders, malignant tumor, cachexy and so on; [2] second surgery or multiple surgery; [3] complicated with severe coronary heart

Table 1 Composition and concentration of the two cardioplegias

	Ratio (Blood: Crystalloid)	Con (mM)	K^+	Ca^{2+}	Na^+	Mg^{2+}	Mannitol	Lidocaine	Histidine
		Type							
Crystalloid cardioplegia	-	HTK	9	0.015	15	4	18	-	180
Blood cardioplegia	4:1	BC	20	1.3	147.9	7	-	0.085	-

disease; [4] change the type of cardioplegic fluid during operation; [5] data loss and duplicate medical records. Information was obtained from the medical records of individual patients stored electronically.

Propensity score matching (PSM)

148 patients were included based on inclusion and exclusion criteria, among whom HTK group 81 cases and BC group 67 cases. To balance the baseline data between the two groups, we used propensity score matching (PSM). The propensity scores were developed from the non-parsimonious logistic regression model with baseline covariates consisting of age, gender, body mass index (BMI), high blood pressure, diabetes, smoking, history of stroke, and others, resulting in a total of 106 patients (53 in each group). The PSM used 1:1 matching based on the nearest neighbor method with a caliper width of 0.02.

Surgical management and myocardial protection

A single team of cardiac surgeons executed all operative procedures. All patients received surgery with general anesthesia, through a median sternotomy, using cardiopulmonary bypass and maintaining moderate hypothermia between 28–30℃. The maze procedure was carried out in concordance with the original methodology described by James Cox [7]. Monopolar radiofrequency (RF) ablation was used in addition to the standard cut-and-sew method for treating atrial fibrillation. Upon the establishment of complete cardiopulmonary bypass, the right atrial maze commenced. The procedure involved removing the right atrial appendage, making a side cut from the bottom of the removed appendage towards the inferior vena cava (IVC), and a back-to-front cut from deep within the superior vena cava (SVC) to deep into the IVC. Furthermore, a T-shaped cut began at the back longitudinal cut towards the tricuspid valve ring above the IVC tube, accompanied by a front right atrial opposing cut extending from the front-medial edge of the removed right atrial appendage to the front-medial tricuspid valve ring. Monopolar RF ablation was conducted at the tricuspid end of the T-shaped cut and the front-medial cut, using either the AtriCure tool from AtriCure, Inc. in Cincinnati, Ohio, or the Cardioblate tool from Medtronic, Inc. in Minneapolis, Minnesota. Subsequent to these steps, the aorta was occluded, and myocardial preservation was achieved through the infusion of cold HTK or BC solution administered antegrade. The left atrial appendage was surgically removed and securely closed at its base, with suture reinforcement bolstered by felt. An opening into the left atrium was made in the interatrial groove, dividing the atrial septum and terminating at the nadir of the fossa ovalis. The incision in the left atrium was continued downward along the back wall, positioned between the mitral valve and the openings of the pulmonary veins. Moreover, the top part of the incision in the left atrium surrounded the opening of the left superior pulmonary vein. The last cut, a vertical one at the back, followed a route from the opening of the lower right lung vein directly to the ring of the mitral valve, where RF ablation was used to focus on the coronary sinus and the end of the incision near the mitral valve ring. Valvular surgery was then undertaken. The right atrial incisions were closed after the aortic cross-clamp was removed. All atrial incisions were sutured with dual runs of full-layer mattress stitches for secure closure. The detailed composition, precise methods of infusion, and dosing instructions for HTK and BC are enumerated in Tables 1 and 2 respectively.

Table 2 The specific infusion methods and dosages of cardioplegias

	HTK	BC
Perfusion temperature (℃)	4 ~ 6	4 ~ 6
Perfusion pressure (mmHg)	200 (before EA); 100 (after EA)	200 ~ 250
Perfusion dose (ml/kg)	30	First dose: 20 Reperfusion dose: 10
Interval time (min)	120–180	20–30

EA, electrocardiogram alignment

Data collection

Patients' demographics, perioperative clinical data, blood transfusion volume and blood biochemical indexes were recorded. The concentration of cardiac troponin I (cTnI) were collected before surgery (T1), 10 min after ascending aorta opening (T2), 24 h after surgery (T3), and 48 h after surgery (T4). Follow-up information was obtained from subsequent clinic visits. The heart rhythm was evaluated mainly on the basis of 12-lead electrocardiogram (ECG) and partly by 24 h Holter ECG obtained at 1, 3, 6, 12 and 24 months after surgery. The postoperative cardiac function was evaluated mainly on cardiac color ultrasound obtained at 3, 6, 12, 18 and 24 months after surgery.

Table 3 Baseline characteristics

Characteristics		Entire population					Propensity-matched population				
		HTK (*n* = 81)		BC (*n* = 67)		*P*	HTK (*n* = 53)		BC (*n* = 53)		*P*
		n %		*n* %			*n* %		*n* %		
Age (years)	≤ 55	37	45.70	43	64.20	0.02	27	50.90	31	58.50	0.44
	> 55	44	54.30	24	35.80		26	49.10	22	41.50	
Gender	Male	36	44.40	29	43.30	0.89	29	54.70	24	45.30	0.33
	Female	45	55.60	38	56.70		24	45.30	29	54.70	
BMI	≤ 23.375	40	49.40	34	50.70	0.87	26	49.10	24	45.30	0.69
	> 23.375	41	50.60	33	49.30		27	50.90	29	54.70	
Smoke	no	57	70.40	47	70.10	0.98	33	62.30	36	67.90	0.54
	yes	24	29.60	20	29.90		20	37.70	17	32.10	
Hypertension	no	73	90.10	60	89.60	0.91	46	86.80	50	94.30	0.18
	yes	8	9.90	7	10.40		7	13.20	3	5.70	
Diabetes	no	75	92.60	62	92.50	0.99	48	90.60	49	92.50	0.73
	yes	6	7.40	5	7.50		5	9.40	4	7.50	
Cerebral Infarction	no	67	82.70	50	74.60	0.23	40	75.50	46	86.80	0.14
	yes	14	17.30	17	25.40		13	24.50	7	13.20	

BMI, Body Mass Index

Table 4 Characteristics of intraoperative cardiopulmonary bypass and operative characteristics of the patients

Cox-maze III combined valve surgery - no	HTK (*n* = 53)	BC (*n* = 53)	*P*
MVR	19(35.80)	24(45.30)	
MVR plus AVR	5(9.40)	14(26.40)	
MVR plus AVR plus TVr	4(7.50)	5(9.40)	
MVr	4(7.50)	1(1.90)	
TVr	0(0.00)	1(1.90)	
MVr plus TVr	10(18.90)	3(5.70)	
MVr plus TVr plus PDA	1(1.90)	0(00)	
MVR plus AVR plus TVr plus ASDr	1(1.90)	0(0.00)	
MVr plus TVr plus VSDr	1(1.90)	0(0.00)	
MVr plus AVr plus TVr	1(1.90)	0(0.00)	
MVr plus TVr plus ASDr	3(5.70)	0(0.00)	
AVR plus MVr plus TVr	1(1.90)	0(0.00)	
TVr plus ASDr	2(3.80)	0(0.00)	
MVR plus AVr plus TVr	1(1.90)	5(9.4.0)	
CPB time(min)	177.00 ± 26.69	174.66 ± 36.46	0.71
Aortic cross-clamp time(min)	124.68 ± 20.09	116.02 ± 24.54	0.05
Perfusion dose(ml)	2141.51 ± 247.60	3991.89 ± 983.80	<0.001
Number of doses of cardioplegia Perfusion times	1.21 ± 0.41	5.55 ± 1.14	<0.001

Data is displayed as numbers (%) or as the mean ± standard deviation. Valve replacement for MVR, Mitral valve repair for MVr, Aortic valve replacement for AVR, Tricuspid valve repair for TVr, Aortic valve repair for AVr, Atrial Septal Defect repair for ASDr, Ventricular Septal Defect repair for VSDr, and Patent Ductus Arteriosus repair for PDA.CPB Cardiopulmonary

Data analysis

Numeric data was shown as mean ± standard deviation, whereas categorical data was displayed as percentages. Intergroup comparisons of numeric data were executed via the paired t-test or paired Wilcoxon test according to the normality by Shapiro-Wilk test. Paired chi-square test was used for categorical data comparisons. Statistical evaluations were performed using GraphPad Prism 8 (GraphPad Software Inc). A p-value below 0.05 was considered to be statistically significant.

Results

Preoperative data

The foundational group attributes and historical medical data of patients within the HTK cohort and the BC cohort were subjected to assessment. A marked distinction between the two groups was discernible with regard to age ($p = 0.02$). Following PSM, there were no notable disparities in baseline group characteristics between the cohorts, as shown in Table 3.

Perioperative data

A comparison was made of the perioperative data for both groups of patients, specifically looking at the length of cardiopulmonary bypass (CPB), time of aortic cross-clamp, amount of perfusion used, number of perfusions, and surgical outcomes. The BC group manifested significantly greater perfusion doses and more numerous perfusion events in comparison to the HTK group ($p < 0.001$ for both parameters). In contrast, no statistically significant disparities were detected between the HTK and BC groups concerning CPB duration, aortic cross-clamp time, and surgical characteristics, as detailed in Tables 4 and 5; Fig. 1.

Postoperative data

The postoperative data for the respective groups were subjected to a comparative analysis. Evaluated variables

Table 5 Perioperative blood transfusion volume and blood biochemical indexes

	HTK($n=53$)		BC($n=53$)		*P*
	mean	sd	mean	sd	
Total perioperative blood transfusion(ml)	1963.68	577.04	1910.28	971.31	0.73
Plasma(ml)	400.58	180.07	420.78	230.23	0.59
Red Cell Suspension (RCS) (U)	5.40	2.28	5.75	3.81	0.52
Platelet(U)	1.30	0.61	1.09	0.66	0.09
Cryoprecipitate(U)	10.58	4.53	8.64	6.45	0.07
Pre-Hb(g/L)	138.43	15.47	139.23	16.09	0.79
Minimum postoperative Hb(g/L)	107.34	13.88	102.08	14.46	0.06
Hb deviation(g/L)	31.09	20.38	37.15	18.46	0.11
Postoperative maximum lactic acid(mmol/L)	9.59	4.01	10.41	3.72	0.25
Uric acid(umol/L)	410.89	103.01	381.81	100.28	0.14
Pre-Cr (umol/L)	71.51	15.77	66.19	16.78	0.09
Cr of the first day after surgery(umol/L)	103.81	40.59	91.87	32.25	0.09
Cr of the third day after surgery(umol/L)	114.21	90.96	90.72	53.45	0.11
Cr of the fifth day after surgery(umol/L)	107.92	117.65	76.96	54.24	0.09
Highest postoperative Cr(umol/L)	131.75	111.51	110.17	63.30	0.22
Cr elevation(umol/L)	60.25	108.09	43.98	59.87	0.34
Cr increase multiple	1.85	1.65	1.67	0.83	0.56

Hb hemoglobin, Cr creatinine

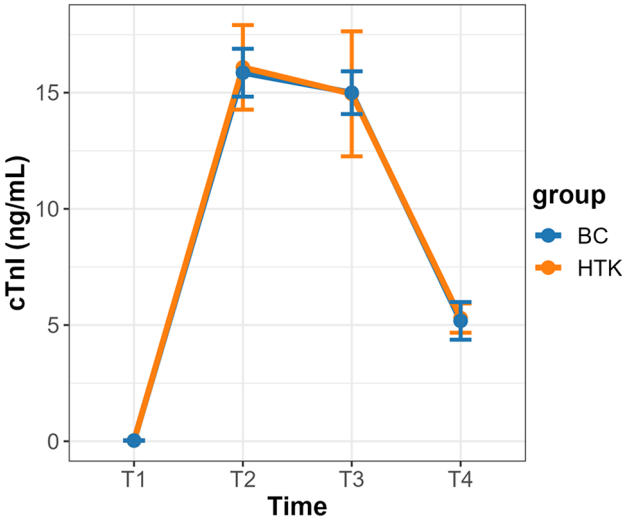

Fig. 1 Perioperative Cardiac troponin I (cTnI). cTnI, Cardiac troponin I

included the postoperative duration of mechanical ventilation, length of stay in the intensive care unit, hospitalization period following the surgery, left ventricular ejection fraction, left atrial and ventricular diameters, need for inotropic support, as well as incidences of renal and neurological complications, postoperative atrial arrhythmias, and mortality rates. It was observed that the weaning period from the mechanical ventilator was reduced in the HTK group ($p<0.001$), as was the postoperative hospitalization duration ($p=0.03$). Moreover, the need for inotropic medications was notably higher in the BC group compared to the HTK group ($p=0.02$). Other than these specified measures, no discernible differences emerged between the two groups concerning postoperative reoperations due to bleeding and tracheotomies. Moreover, comparative evaluations did not yield any significant disparities between the cohorts regarding mortality, or the rates of postoperative renal and neurological complications, as delineated in Tables 6 and 7.

Data is displayed as numbers (%) or as the mean±standard deviation. KDIGO stands for Kidney Disease Improving Global Outcomes, while AKI refers to Acute Kidney Injury. POAA is short for Postoperative Atrial Arrhythmia, and SWI indicates Superficial Wound Infection. Need for inotropic: An inotropic medication was required if the systolic blood pressure dropped below 90 mmHg or decreased by more than 40 mmHg from the initial pressure, even with appropriate fluid control, and if the cardiac index (CI) fell below 2 L/m^2/min. Dopamine was chosen as the primary medication for cases of low cardiac output (LCO). In the event that a secondary inotropic substance was required, epinephrine was incorporated into the treatment regimen. A need for a small dose of inotropes was determined when dopamine alone, at a maximum dose of 12 μg/kg/min, was enough to keep cardiac index above 2 L/m^2/min. A moderate amount was needed to ensure that the cardiac index stayed above 2 L/m^2/min when epinephrine, at doses up to 0.2 μg/kg/min, was added in conjunction with dopamine. A high dosage was defined as situations in which epinephrine doses surpassed 0.2 μg/kg/min were essential along with dopamine, or when mechanical assistance was needed.

A subgroup analysis on patients with a duration of myocardial blockade exceeding 150 min

To further investigate myocardial protection strategies in patients with prolonged myocardial ischemia, we conducted a subgroup analysis on patients with a duration of myocardial blockade exceeding 150 min. Subgroup analysis showed that patients with more than 150 min of cross-clamp time had higher cTnI peaks in the BC group ($p=0.01$), less mechanical ventilation time ($p=0.002$) and intensive care unit stay ($p<0.001$) in HTK group (Fig. 2; Table 8).

The follow-up data

Clinical follow-up was performed for 1–24 months postoperatively. 12-lead ECG or 24-h Holter ECG were taken during each follow-up visit in all survivor patients (53 patients each group) at hospital discharge, in 50(94.34%)

Table 6 Comparison of patient characteristics before and after surgery in two groups

	HTK(*n* = 53)		BC(*n* = 53)		Mean difference (95% CI)	*P*
	mean	sd	mean	sd		
Discharge EF	55.13	8.52	54.43	4.52		0.59
Discharge LAD	45.64	7.38	47.81	5.29		0.09
Discharge LVD	49.98	5.67	47.79	6.56		0.07
Preoperative and postoperative difference of EF	0.377	9.89	0.415	5.48		0.98
Preoperative and postoperative ratio of EF	1.032	0.24	1.003	0.1		0.42
Preoperative and postoperative difference of LAD	7.774	7.55	5.642	2.19		0.05
Preoperative and postoperative ratio of LAD	1.19	0.19	1.117	0.04	0.07 (0.02–0.12)	0.01
Preoperative and postoperative difference of LVD	3.717	6	4.226	2.62		0.57
Preoperative and postoperative ratio of LVD	1.076	0.12	1.086	0.05		0.59
Mechanical ventilation time(h)	10.84	6.22	22.53	12.58	-11.69 (-15.46 to -7.91)	<0.001
ICU time(d)	2.32	0.87	3.32	4.31		0.1
Postoperative hospital stay(d)	11.28	2.81	13.42	6.67	-2.14 (-4.09 to -0.19)	0.03

EF represents the left ventricular ejection fraction, while LAD stands for the left atrial diameter, and LVD refers to the left ventricular diameter. Patients may be transferred to the intensive care unit (ICU) for further monitoring and treatment

Table 7 Comparison of postoperative traits in patients from two different groups

		HTK(*n* = 53)	BC (*n* = 53)	*P*
Postoperative KDIGO grades	0	28	29	0.59
	1	17	11	
	2	6	10	
	3	2	3	
AKI	no	28	29	0.85
	yes	25	24	
Need for inotropic	Low	45	35	0.02
	Moderate	6	13	
	High	2	5	
POAA (30 days) - no		1	2	-
Stroke- no		0	0	-
Reoperation for bleeding - no		1	1	-
SWI - no		1	1	-
Tracheostomy - no		0	1	-
Postoperative ventricular fibrillation- no		0	1	-
Renal failure (hemodialysis)- no		1	1	-
Cerebral infarction- no		0	1	-
Postoperative permanent pacemaker - no		1	1	-
Discharge status- no	Survival	53	53	1
	Died	0	0	
Hospital mortality (30 days)- no	Survival	53	53	1
	Died	0	0	

of HTK group and 49(92.45%) of BC group at 1month follow-up, in 49(92.45%)of HTK group and 48(90.57%) of BC group at 3 month follow-up, in 45(84.91%) of HTK group and 46(86.79%) of BC group at 6 month follow-up, in 41(77.36%) of HTK group and 38(71.70%) of BC group at 12 month follow-up, in 32(60.38%) of HTK

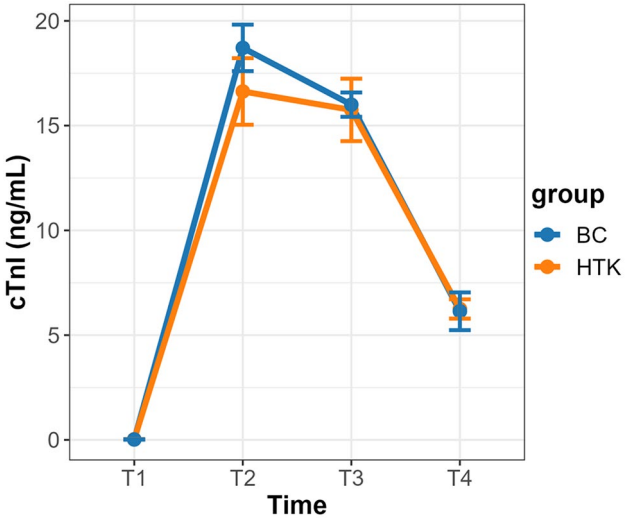

Fig. 2 Cardiac troponin I (cTnI) in perioperative patients with a cross-clamp time of more than 150 min. cTnI, Cardiac troponin I

Table 8 Postoperative characteristics of patients of more than 150 min of cross-clamp time

	HTK(*n* = 8)		BC(*n* = 7)		*P*
	mean	sd	mean	sd	
CPB time(min)	215.38	20.11	234.00	23.75	0.12
Aortic occlusion time(min)	159.50	3.55	156.40	3.59	0.12
Perfusion dose(ml)	2562.50	176.80	5200.00	931.33	< 0.001
Perfusion times	1.88	0.35	7.29	0.49	< 0.001
Mechanical ventilation time(h)	8.25	3.66	16.57	4.79	0.002
ICU time(d)	2.00	0.00	2.86	0.38	< 0.001
Postoperative hospital day(d)	9.88	1.46	13.00	4.00	0.06

CPB stands for Cardiopulmonary, while ICU stands for intensive care unit

group and 29(54.72%) of BC group at 24 month follow-up. Freedom from AF without anti-arrhythmia drugs (AADs) between the HTK and BC groups at the time of opening ascending aorta and the last follow-up point was 94.34% and 92.45%, 86.79% and 81.13%,92.0% and 91.84%, 93.88% and 93.75%, 95.56% and 93.48%, 92.68% and 92.11%, 90.63% and 89.66%, respectively (Fig. 3). The cardiac color ultrasound were taken during each follow-up visit in all patients (53 patients each group) at hospital discharge, in 49(92.45%)of HTK group and 48(90.57%) of BC group at 3 month follow-up, in 45(84.91%) of HTK group and 46(86.79%) of BC group at 6 month follow-up, in 41(77.36%) of HTK group and 38(71.70%) of BC group at 12 month follow-up, in 35(66.04%) of HTK group and 33(62.26%) of BC group at 18 month follow-up, in 32(60.38%) of HTK group and 29(54.72%) of BC group at 24 month follow-up. The LVEF(%) value in the HTK group 57.63±5.54 was higher compared to that in the BC group 55.23±4.25 in the 3-month follow-up data ($p=0.02$) (Tables 9 and 10; Fig. 3).

Discussion

Individuals diagnosed with atrial fibrillation (AF) have a significantly increased risk of stroke, with a 3 to 5-fold higher likelihood compared to those without the condition [8]. The latest recommendations from the American Heart Association and the American College of Cardiology indicate that patients exhibiting symptoms of atrial fibrillation (AF) should receive treatment for AF during heart surgery, in accordance with recent guidelines [6]. In recent years, advancements in technologies and methodologies for surgical atrial fibrillation ablation have led to simplified lesion sets and reduced procedural times. However, the challenge of achieving consistently transmural lesions remains unresolved. In a randomized multicenter trial, Gillinov AM et al. [9] reported the freedom from AF in the first year after surgery was 63.2% in the ablation procedures (biatrial maze or pulmonary-vein isolation procedure) group. Stulak et al. [10] reported the patients undergoing the Cox maze III procedure concurrent with isolated mitral valve surgery resulted in significantly greater freedom from AF without antiarrhythmic medication compared with any other procedure for AF ablation within 1 year postoperatively (87% vs. 70%, $P=0.04$) and after 5 years postoperatively (75% vs. 52%, $P=0.03$). In our follow-up data, we found that the rate of freedom from AF in 12 and 24 months after Cox maze III procedure (cut and sew) was 92.40% and 90.15%.

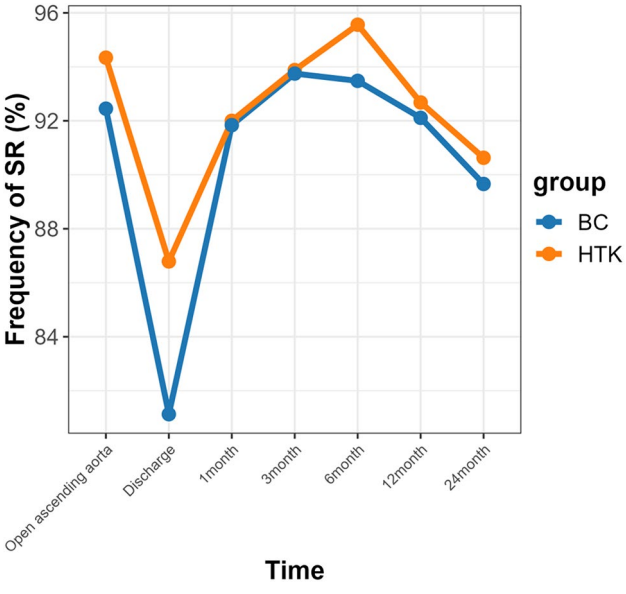

Fig. 3 Frequency of sinus rhythm (SR) during perioperative period and follow-up. SR, sinus rhythm

The inherent risk of ischemic injury persists during cardiac arrest, a frequently indispensable intervention to ensure the safe execution of surgical procedures within the field of cardiac surgery [11]. Notwithstanding this, the past two decades have observed no significant advancements in the development of cardioplegic solutions. Consequently, the perspective that the pursuit of an ideal cardioplegia solution remains unresolved has been substantiated by numerous scholarly reviews [12, 13]. HTK, known as an internal heart-stopping solution, contained important antioxidants and buffers, as well as a small amount of sodium meant to prepare the heart by slowing down the rapid action potential phase [14] Histidine present in HTK enhances anaerobic glycolysis, while tryptophan strengthens the structural integrity of the cellular membrane. Mannitol functions to reduce cellular edema. Unlike bicarbonate, histidine acts as a buffering agent with protein-like properties, providing superior capacity for maintaining intracellular pH balance and preserving adenosine triphosphate (ATP) reserves [15, 16]. Endorsed for its ability to provide myocardial protection for up to approximately 2–3 h through single-dose administration, HTK is favored by surgeons for the opportunity it presents in performing intricate surgical interventions uninterrupted [17]. Despite the long-standing history of cardioplegia in cardiac surgeries, the formulations of commonly used myocardial protective solutions have seen minimal changes since 1995 [18]. With the rising prevalence of aging populations and the accompanying multiple comorbidities, myocardial protection has become increasingly critical. The effectiveness of different types of cardioplegia in safeguarding the myocardium, particularly among patients with prolonged myocardial ischemic durations, remains a contentious subject.

In our investigation, we undertook a comparative analysis of perioperative parameters across patient cohorts. Despite our study encompassing extended durations

Table 9 The heart rhythm during perioperative period and follow-up

Time	Follow-up cases and follow-up rate (%)		Sinus rhythm		Atrial arrhythmia		Junctional rhythm		Frequency of SR (%)		*P*	Average
	HTK	BC	HTK	BC	HTK	BC	HTK	BC	HTK	BC		
Open ascending aorta	53(100)	53(100)	50	49	1	2	2	2	94.34	92.45	0.70	93.40
Discharge	53(100)	53(100)	46	43	3	5	4	5	86.79	81.13	0.43	83.96
1 month	50(94.34)	50(94.34)	46	45	2	3	2	2	92.0	91.84	0.73	91.92
3 month	49(92.45)	48(90.57)	46	45	1	2	2	1	93.88	93.75	0.97	93.82
6 month	45(84.91)	46(86.79)	43	43	1	2	1	1	95.56	93.48	0.66	94.52
12 month	41(77.36)	37(69.81)	38	35	2	1	1	1	92.68	92.11	0.73	92.40
24 month	32(60.38)	29(54.72)	29	26	2	2	1	1	90.63	89.66	0.90	90.15

Notes Data are presented as numbers (%) or as mean ± SD. SR Sinus rhythm

of aortic cross-clamping and cardiopulmonary bypass (CPB) relative to prior research, we observed comparable 30-day hospital mortality rates and postoperative complication frequencies between the HTK and BC groups. Notably, the HTK group exhibited significantly reduced times for weaning from mechanical ventilation and shorter postoperative hospital stays. Based on these findings, we discerned an association between the utilization of HTK and both expedited ventilator weaning and abbreviated postoperative hospitalization. The extension of these time periods within the BC group may be ascribed to an elevated necessity for inotropic support—a factor which inherently protracts durations among hemodynamically unstable patients. Similarly, according to the study by Nuri Utkan Tunca and colleagues, the BC cohort showed an increased need for inotropes(dopamine and epinephrine), resulting in prolonged weaning from mechanical ventilation, longer stays in the intensive care unit, and extended hospital stays overall [19]. In a randomized controlled and parallel group study, Ali, I [20] found that HTK was associated with significantly shorter cross-clamp time, bypass time, duration of mechanical ventilation, length of intensive care unit, and length of hospital stay. It was associated with lower incidence of postoperative segmental wall abnormalities and less need for inotropic support than BC. In the study by Bibevski [21] that juxtaposed BC and HTK solutions, notwithstanding an absence of substantive divergence in left ventricular ejection fractions deduced from postoperative echocardiography, it was noted that the HTK cohort necessitated lesser inotropes. All these observations were aligned with our results. Fang Y [22] reported that Del Nido cardioplegia resulted in longer cardiac relapse time and higher use of temporary pacemakers, the dose of vasoactive drugs used 15 min after weaning off CPB was also higher than that of HTK in patients with left ventricular hypertrophy (LVH) undergoing open heart surgery. Moreover, within our study, we observed that the peak values of post-operative cardiac cTnI in patients enduring longer cross-clamp intervals (> 150 min) remained significantly lower when treated with HTK solution and were akin to cTnI levels associated with shorter intervals of aortic occlusion across both cardioplegic solutions. Furthermore, G Scrascia [23] found that when aortic cross-clamping time exceeded 160 min during complicated aortic surgery, the reduced post-operative cTnI release seen with HTK use may suggest that in long cross-clamp time using HTK may be a better myocardial protection in these extreme conditions, which was similar to our research findings. A study used cultured cells in laboratory conditions showed that HTK could protect cardiomyocytes against oxidative stress by inducing superior iNOS and HSP27 expressions than plegisol [24]. Besides, in our study, the total perfusion volume of HTK and BC

Table 10 The follow-up data of cardiac color ultrasound

Time	Follow-up cases and follow-up rate (%)		LAD					LVEF (%)				
			HTK		BC		*P*	HTK		BC		*P*
	HTK	BC	mean	sd	mean	sd		mean	sd	mean	sd	
Discharge	53(100)	53(100)	45.64	7.38	47.81	5.29	0.09	55.13	8.52	54.43	4.52	0.59
3month	49(92.45)	48(90.57)	46.2	7.01	48.06	5.42	0.15	57.63	5.54	55.23	4.25	0.02
6month	45(84.91)	46(86.79)	46.36	6.48	48.76	5.55	0.06	59.13	4.99	57.33	4.21	0.07
12month	41(77.36)	38(71.70)	46.88	6.7	48.87	5.8	0.16	60.07	4.46	58.68	4.33	0.17
18month	35(66.04)	33(62.26)	46.89	6.55	48.85	5.28	0.18	60.86	3.67	59.33	4.01	0.11
24month	32(60.38)	29(54.72)	47.25	6.19	49.03	5.21	0.23	62.78	3.12	61.03	3.87	0.06

Notes Data are presented as numbers (%) or as mean±SD. LAD Left atrial diameter, LVEF Left ventricular ejection fraction

was 2141.51±247.60 ml and 3991.89±983.80 ml (crystal dose 798.38±196.76 ml) respectively and there was no difference in perioperative blood transfusion between the two groups. It might be attributed to our active and effective ultrafiltration techniques. However, in a study with the aortic clamping time over 120 min, Lian Duan [25] found that the transfusion-saving effect of Del Nido was weakened, suggesting that additional reinfusions of Del Nido resulted in a higher total cardioplegic volume, dilution and edema as a result of more transfusions during adult complex valve surgery. Although our analysis did not reveal a difference between the two groups regarding the rate of freedom from atrial fibrillation (AF) based on perioperative and follow-up data, we observed that the left ventricular ejection fraction (LVEF) percentage in the HTK group (57.63±5.54) was significantly higher than that in the BC group (55.23±4.25) at the 3-month follow-up ($p=0.02$). This finding suggests that HTK may offer superior short- to medium-term cardiac function compared to BC. Moreover, numerous studies have demonstrated that for both catheter and surgical ablation, enlargement of the left atrium serves as a predictor of procedural failure [26], and fortunately, our results showed that the LAD was significantly minished at discharge in all patients ($p<0.01$) and there was no significant enlargement of the LAD in both group during the follow-up.

The current research has its own constraints. Primarily, as a single-center retrospective analysis, it was inherently subject to selection bias and unmeasured confounding in the observational design. Secondly, the modest size of the sample precluded stratified subgroup analysis in relation to progressive 30-minute increments in aortic occlusion duration. Additionally, there was a scarcity of patients with occlusion times exceeding 150 min, rendering subgroup comparisons unfeasible. Consequently, this deficit has resulted in an absence of discourse regarding the myocardial protective efficacy in instances involving exceedingly prolonged aortic occlusions. Finally, our follow-up data were not available for all patients, and had a limited follow-up period and a small sample size. A larger sample and longer follow-up are required for a future study.

Conclusion

Both the HTK and 4:1 blood cardioplegia could be used safely in patients with atrial fibrillationAF who were subject to valvular replacement and Cox maze III procedure. However, the utilization of HTK conferred a greater advantage in diminishing the duration of mechanical ventilation weaning and the duration of postoperative hospitalization. HTK may be a better myocardial protection in patients with long cross-clamp time. The follow-up data indicated that HTK might be superior to 4:1 blood

cardioplegia blood cardioplegiaBC in the short-medium term cardiac function. The myocardial protection efficacy was found to be equivalent in both groups, however, the utilization of HTK conferred a greater advantage in diminishing the duration of mechanical ventilation weaning and the duration of postoperative hospitalization in patients afflicted with atrial fibrillation who were subject to valvular replacement and Cox maze III procedure. HTK may be a better myocardial protection in some extreme conditions. The follow-up data indicated that HTK might be superior to BC in the short-medium term cardiac function.

Abbreviations

AF	Atrial fibrillation
LVEF	Left ventricular ejection fraction
HTK	Histidine-tryptophan-ketoglutarate
CPB	Cardiopulmonary bypass
ACC	Aortic cross-clamping
ICU	Intensive care unit

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Author contributions
QBM and FSW participated in the conception and design of the study and were major contributors in writing the manuscript; WCT, ZL, SL and WHW completed the surgery; LQ, XZL and WAL sorted out the experimental data and performed the statistical analysis. All authors contributed to the interpretation of the results and critically reviewed the first draft. All authors read and approved the final manuscript. Wu Dan made great contribution in the revision of this manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
Approval for the study was obtained from the ethics review board of Jinling hospital (2018NZY-028-01).

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Competing interests
The authors declare no competing interests.

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