

# Ventricular Fibrillation after Aortic Cross-Clamp Removal in Patients Undergoing Heart Valve Surgery: HTK Solution vs. Blood Cardioplegia

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**Objective:** Single-dose cardioplegia for myocardial protection is non-interrupting option for a cardiac procedure. Histidine-Tryptophan-Ketoglutarate (HTK) solution has been used for cardioplegia in many cardiac centers; but the incidence of associated intraoperative ventricular fibrillation has been frequently observed. The current study determined the outcomes of HTK cardioplegia for simple cardiac operations compared to conventional blood cardioplegia.

**Materials and Methods:** A retrospective study was conducted among patients who underwent heart valve operations between January 2014 and December 2014. Sixty-four patients were included into the study. The medical records were source for detailed demographics, preoperative status, operative technique, and post-operative hospital course.

**Results:** Sixty-four patients were included in the study; 31 patients received HTK solution. Ventricular fibrillation after aortic cross-clamp removal occurred in 26 patients (40%), 14 in the HTK group (45%). There was no perioperative myocardial infarction. Ventricular fibrillation after aortic cross clamp removal occurred more frequently in patients receiving HTK solution, albeit the difference was not statistically different.

**Conclusion:** The use of HTK solution has no significant different outcomes compare to conventional cold blood cardioplegia in heart valve operation. Ventricular fibrillation occurred after aortic cross clamp removal tends to be temporary and there was no evidence of postoperative myocardial infarction.

**Keywords:** Cardioplegia, HTK, Custodiol, Ventricular fibrillation

**J Med Assoc Thai 2019;102(Suppl5): 122-7**

**Website:** <http://www.jmatonline.com>

Myocardial protection is an important issue in cardiac surgery, which involves a period of ischemia followed by reperfusion. Inadequate myocardial preservation may result in devastating events following the cardiac procedure. Ventricular fibrillation is one of the manifestation of myocardial ischemia, resulting from metabolic disturbance, decreased ATP production, accumulation of free radicals, release of catecholamine, and altered mechanical properties of the ischemic tissue.

Single-dose cardioplegia is an option in cardiac procedures as re-administration of cardioplegia may interrupt the technical flow of the surgery. Bretschneider's histidine-tryptophan-ketoglutarate (HTK) solution can preserve the myocardium for up to 4 hours without re-administration.

The safety of the HTK solution has been assessed, and a higher incidence of ventricular fibrillation was documented compared to standard cold blood cardioplegia<sup>(1-8)</sup>.

Thus, the purposes of the current study were to compare the incidence of ventricular fibrillation after aortic cross clamp removal between two types of cardioplegia, and to assess the postoperative outcomes of each solution.

## Materials and Methods

We performed a retrospective review of in-patient charts, all patients who underwent valvular heart surgery between January and December 2014 were enrolled. Exclusion criteria included decompensated congestive heart failure, concomitant coronary artery disease, concomitant coronary bypass surgery, MAZE procedure, and chronic renal failure. Inpatient data records also resulted in inclusion.

The database records detailed patient demographics, pre-operative status, operative technique, post-operative hospital course. Thirty-day mortality information was obtained. The current study was approved by the Khon Kaen University Ethics Committee for Human Research.

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**How to cite this article:** Rimphanitchayakit J, MD<sup>1</sup>, Chanmayka T, MD<sup>2</sup>, Wongbuddha C, MD<sup>2</sup>, Karunasumetta C, MD<sup>2</sup>, Prathanee S, MD<sup>2</sup>, Kuptarnond C. Ventricular Fibrillation After Aortic Cross-clamp Removal in Patients Undergoing Heart Valve Surgery: HTK Solution vs. Blood Cardioplegia. J Med Assoc Thai 2019;102(Suppl5): 122-7.

### **Surgical technique**

Hemodynamic monitoring was carried out via a radial arterial line, and central venous pressure monitoring via the internal jugular vein or subclavian vein. Other monitoring included end-tidal CO<sub>2</sub>, ECG, and urinary catheter volume. Conventional general anesthesia was used for all patients.

The surgical approach was via standard median sternotomy. The cardiopulmonary bypass was established by an arterial cannula in the ascending aorta. Venous drainage was obtained either from bicaval cannulation or 2-stage venous cannulation. The selection of the optimum cardioplegia route depends upon aortic valve regurgitation and surgeon preference.

In both groups, the cardioplegia was given after aortic cross-clamping according to the route the surgeon decision. Cold HTK solution (4°C) was administered once with an initial perfusion pressure of 120 mmHg. After onset of cardiac arrest, the pressure was then reduced to 60 mmHg for 6 to 8 minutes. In another group, mixing oxygenated blood with cold crystalloid cardioplegia (4°C) at a ratio of 4 to 1 was administered at 20 ml/kg, with a repeat dose of 10 mg/kg every 20 to 25 minutes.

### **Study endpoints**

The primary study endpoint in both group was the incidence of ventricular fibrillation after removal of the aortic cross-clamp presented at ECG monitoring and interpreted by surgeons and anesthesiologist. The secondary outcomes were myocardial infarction (MI), stroke, acute renal failure, and 30-day mortality.

The definition of post-operative myocardial infarction was fulfilled if there were at least two of the followings: (a) an increase in cardiac biomarker more than 10-fold of the 99<sup>th</sup> percentile of a normal reference range at Queen Sirikit Heart Center of the Northeast laboratory (Troponin T >30 ng/ml in association with elevated CK-MB), (b) new post-operative Q wave on at least two serial electrocardiograms, or (c) new wall motion abnormalities.

The definition of acute renal failure was fulfilled when any of the followings were present: (a) serum creatinine increased more than 0.3 mg/dl from baseline within 48 hour post-operatively, or (b) urine output less than 0.5 ml/kg/h for 6 hours or more.

### **Statistical analysis**

Patient demographic data, operative variables, and post-operative outcomes were compared between the HTK and blood cardioplegia groups. Categorical variables were expressed as frequencies and compared using Pearson Chi-squared tests. Continuous variables were expressed as the mean  $\pm$  standard deviation (SD) and compared using the unpaired t-test. Comparison of ventricular fibrillation in both group was expressed as the odds ratio (OR) and the 95% confidence interval (CI). A *p*-value <0.05 was considered statistically significant. The analyses were carried out by IBM SPSS version 19.0.

### **Results**

Sixty-four patients were included in the study; 31 received HTK solution, and 33 patients received blood cardioplegia. Demographic data are presented in Table 1, and the groups were not statistically different from one another.

The analysis of the intra-operative data revealed no statistical difference between the two groups. Total cardiopulmonary bypass time was indifferent between groups, but the aortic cross clamp time in the HTK group was insignificant longer than in the blood cardioplegia group. This may be due to more single valve procedures having been done in blood cardioplegia group. Intra-operative patient urine output and dialysis during cardiopulmonary bypass were statistically higher in the HTK group (Table 1).

Ventricular fibrillation after aortic cross-clamp removal occurred in 26 patients (40%); insignificantly more in the HTK group than the blood cardioplegia group (45% vs. 36%, *p* = 0.474). The average body temperature at the time ventricular fibrillation occurred was 36.1°C in both groups (*p* = 0.925) (Table 2).

Seven patients from the HTK group and 7 from the blood cardioplegia group had a temporary pacemaker, while only 1 patient from the blood cardioplegia group needed a permanent pacemaker due to third degree atrioventricular blockage.

There was no case of post-operative myocardial infarction in the current study. Two patients (1 from each group) had acute kidney injury in the 1 to 2 days after surgery, but the creatinine level declined in the following day and urine output was satisfactory. One patient who received blood cardioplegia has transient left hemiparesis on the fifth day after surgery, which was completely resolved in 12 hours and a CT brain showed no intracranial lesion. One patient from the HTK group had abrupt bleeding from the aorta on the fifth day after surgery and passed away. The length of intensive care unit stay was not different between the two groups (Table 3).

Cardiac enzyme (Troponin-T and CK-MB) was examined in 19 patients immediately after surgery and once daily on the first to third day post-operatively. Cardiac enzymes were elevated on the first day after surgery, but did not reach the diagnostic criteria for post-operative myocardial infarction and moreover, gradually decreased on the following days (Figure 1 and 2).

Pre and post-operative creatinine levels were investigated in all patients, and followed for 3 days after the operation. The creatinine levels were slightly higher in the blood cardioplegia group albeit the difference was not statistically significant (*p* = 0.195) (Figure 3). Patients' urine output on the first operative day was slightly higher in the HTK group (1.21 vs. 1.09 ml/kg/hr, *p* = 0.404).

The results of the multiple logistic regression analysis for controlling the influence of a variety of independent variables showed that female sex and patients who had atrial fibrillation had a decreased risk of ventricular fibrillation (Table 4).

In the subgroup analysis, males who received the

**Table 1.** Pre-operative demographic and operative data

Characteristics	HTK (n = 31)	Blood cardioplegia (n = 33)	p-value
Age (years)	47±11	47±11	0.905
Males	15 (48)	19 (57)	0.462
Rheumatic heart disease	20 (64)	21 (63)	0.717
NYHA functional class			0.622
I	4 (13)	3 (9)	
II	19 (61)	24 (73)	
III	8 (26)	6 (18)	
LVEF (%)	60±11	59±12	0.562
ECG normal sinus rhythm	16 (52)	18 (54)	0.840
Procedure involving mitral valve	26 (84)	25 (76)	0.620
Procedure involving aortic valve	16 (51)	13 (45)	0.465
Procedure involving tricuspid valve	13 (42)	11 (33)	0.651
Clamp time (min)	76±25	65±28	0.101
Bypass time (min)	95±30	92±35	0.730
Route of cardioplegic administration			0.050
Antegrade	20 (64)	20 (61)	
Retrograde	4 (13)	11 (33)	
Combined	7 (23)	2 (6)	
Single valve procedure	13 (42)	19 (58)	0.211
Double valve procedure	12 (38)	12 (36)	0.846
Triple valve procedure	6 (20)	2 (6)	0.108
Intraoperative urine output	1,064±130	699±101	0.030
Intraoperative dialysis	482±153	81±81	0.022

HTK = Histidine-Tryptophan-Ketoglutarate, NYHA = New York Heart Association, LVEF = Left ventricular ejection fraction, ECG = Electrocardiogram  
Value present as mean ± SD, n (%).

**Table 2.** Incidence of ventricular fibrillation after aortic cross-clamp removal and need for a pacemaker

Outcomes	HTK (n = 31)	Blood cardioplegia (n = 33)	p-value
Ventricular fibrillation	14 (45)	12 (36)	0.474
Body temperature when fibrillation	36.1±1	36.1±1.2	0.925
Pacemaker required	7 (22)	7 (21)	0.100

HTK = Histidine-Tryptophan-Ketoglutarate  
Value present as mean ± SD, n (%).

**Table 3.** Postoperative outcomes

	HTK (n = 31)	Blood cardioplegia (n = 33)	p-value
Myocardial infarction	0	0	
Acute kidney injury	1 (3.2)	1 (3)	0.964
Stroke	0	1 (3)	0.329
Death	1 (3.2)	0	0.298
ICU stay (days)	2.61±1.4	2.85±1.8	0.573
New onset atrial fibrillation	1 (3)	4 (11)	0.632
30 day mortality	0 (0)	0 (0)	

HTK = Histidine-Tryptophan-Ketoglutarate  
Value present as mean ± SD, n (%).

HTK solution had an increased risk for ventricular fibrillation compared to cold blood cardioplegia (OR 2.06, 95% CI 0.520 to 8.174,  $p = 0.303$ ) but not statistical significant also for females the risk was not different between groups (OR 1.13,

95% CI 0.236 to 5.457,  $p = 0.873$ ). Ventricular fibrillation occurred more often in patients with a normal sinus rhythm, but the risk between the solutions was not different (OR 1.06, CI 0.265 to 4.243,  $p = 0.934$ ). Patients who had preoperative atrial fibrillation, by contrast, had an increased risk when using HTK solution (OR 5.090, CI 0.495 to 52.285,

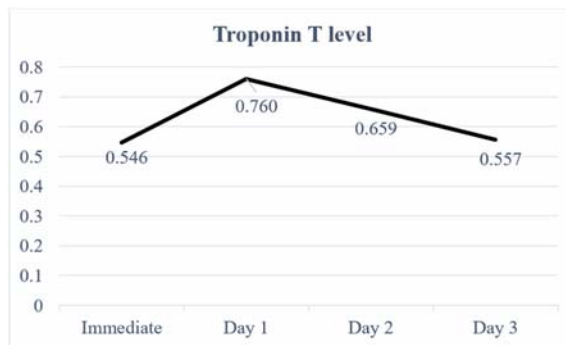
$p = 0.171$ ).

## Discussion

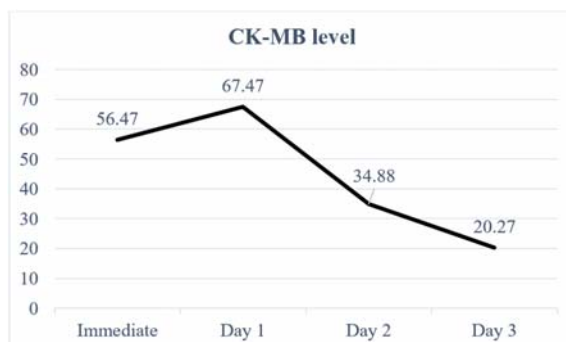
Bretschneider's histidine-tryptophan-ketoglutarate (HTK) is a solution based on the intracellular level of electrolytes, proposed by Bretschneider in the 1970s. Histidine acts as a buffer; potassium hydrogen 2-ketoglutarate helps to increase ATP production during reperfusion, and tryptophan helps stabilize the cell membrane<sup>(1,2)</sup>.

In the current study, the incidence of ventricular fibrillation after aortic cross-clamp removal was higher in the HTK group but not statistically significant, which is consistent with other studies<sup>(3,4,5)</sup>. Suparit et al studied the incidence of ventricular fibrillation in mitral valve repair patients and hypothesized that the HTK solution does not contain procaine, an anti-arrhythmic medication found in the preparation for cold blood cardioplegia<sup>(6)</sup>.

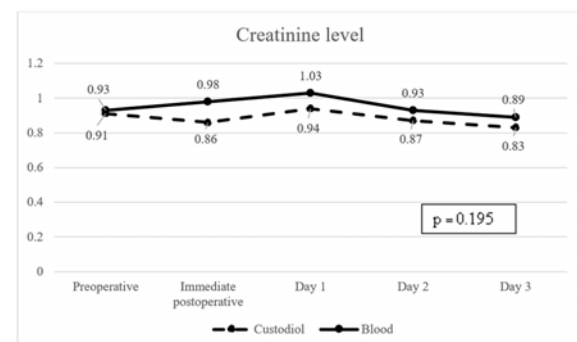
There was greater risk of ventricular fibrillation in patients undergoing an aortic valve procedure; with the majority receiving cardioplegia via the retrograde route (14 of 29 patients, 48%). When performing the subgroup analysis, patients who received the HTK solution via the retrograde



**Figure 1.** Troponin level of patients in the HTK group. HTK = Histidine-Tryptophan-Ketoglutarate



**Figure 2.** CK-MB level of patients in the HTK group. HTK = Histidine-Tryptophan-Ketoglutarate



**Figure 3.** Comparison of creatinine levels between the HTK and blood cardioplegia groups. HTK = Histidine-Tryptophan-Ketoglutarate

**Table 4.** Multiple logistic regression analysis showing the association of factors with incidence of ventricular fibrillation

	Adjusted OR	95% CI	p-value
HTK solution versus blood cardioplegia	1.908	0.521 to 6.988	0.329
Age (years)	1.000	0.939 to 1.066	0.978
Female	0.247	0.066 to 0.925	0.038
Preoperative atrial fibrillation	0.069	0.013 to 0.348	0.001
NYHA class III	1.451	0.299 to 7.041	0.644
Preoperative LVEF (%)	1.003	0.939 to 1.071	0.923
Procedure involving mitral valve	0.585	0.074 to 4.586	0.610
Procedure involving aortic valve	2.797	0.570 to 13.731	0.205
Procedure involving tricuspid valve	2.211	0.466 to 10.478	0.317

HTK = Histidine-Tryptophan-Ketoglutarate, NYHA = New York Heart Association, LVEF = Left ventricular ejection fraction, OR = Odds ratio, CI = confidence interval.

route and undergoing aortic valve procedure had an increased risk of ventricular fibrillation (OR 1.582, CI 0.282 to 8.877,  $p = 0.602$ ) but not statistically significant. Our surgical technique in retrograde cardioplegia administration includes (a) placement of a cardioplegia catheter in the most proximal to the coronary sinus, (b) monitoring pressure during cardioplegia administration, and (c) aortotomy to inspect the retrograde cardioplegia flow from the coronary ostia. Some surgeons cannulate the retrograde catheter under direct vision. In the subgroup analysis of the patients undergoing the tricuspid valve procedure, the risk of ventricular fibrillation was not significantly different between groups (OR 1.09, CI 0.207 to 5.755,  $p = 0.916$ ).

The other operative outcomes were not statistically different between groups. The ICU length of stay was not different between groups. The cardiac enzyme level was elevated on the first day after surgery, but this decreased on the following day which is similar with the study of Braathen et al. who studied the use of single-dose HTK solution over against repeated cold blood cardioplegia in elective mitral valve surgery<sup>(4)</sup>. They documented the troponin T and CK-MB levels of both groups and found no significant difference. They also noted that spontaneous ventricular fibrillation after aortic cross-clamp removal was observed more often in the HTK group, suggesting that the ventricular fibrillation observed may not have catastrophic consequences.

The aortic cross-clamped time and cardiopulmonary bypass duration was not statistically different. In a study by Prathanee et al, the use of HTK solution in CABG patients revealed that patients in the HTK group required less time for the cardiopulmonary bypass, which suggests a benefit of single-dose cardioplegia<sup>(7)</sup>. In the current study, the cardiac procedure was not complex, so there was less need for repeated blood cardioplegia. The longer aortic cross-clamp time in the HTK group may be an artifact of the greater numbers of patients undergoing surgery involving 3 valves which requires more time.

At Srinagarind Hospital, cold blood cardioplegia and HTK solution has the same cost; both solutions are covered by the National Health Policy. In procedures involving heart valves, both cardioplegia and HTK can be used without any difference in cost-effectiveness.

A main limitation of the study was its retrospective nature. We were unable to analyze the cardiac enzyme levels as these data were not routinely collected at our center. At the time, there was a lack of protocol for echocardiographic evaluation of post-operative LV function, and there was no definite protocol for cardiac enzyme study after a heart valve operation. There was also no clear record of volume of cardioplegia delivered. Moreover, intra-operative transesophageal echocardiography was not routinely used, nor were laboratory results routinely collected at the time of cross-clamp removal. A final limitation was that the number of patients undergoing each operation was quite small thus affecting the power of the subgroup analysis.

Future research might include a prospective randomized study using an established protocol for evaluation

of cardiac function prior to surgery, and a standard protocol for post-operative care to compare the safety and effectiveness of cardioplegia used for myocardial protection.

## Conclusion

The outcomes for heart valve surgery were not significantly different between HTK solution and cold blood cardioplegia. The ventricular fibrillation that occurred after aortic cross-clamp removal tended to be temporary and there was no evidence of peri-operative myocardial infarction related to the use of cardioplegia. Internal cardiac defibrillation should be prompt in case that it occurs. A prospective randomized study with a larger group of patients and well-established protocol would clarify its efficacy.

## What is already known on this topic?

Myocardial protection is an important issue in cardiac surgery, which involves a period of ischemia followed by reperfusion. Inadequate myocardial preservation may result in devastating events following the cardiac procedure.

## What this study adds?

The use of HTK solution has no significant different outcomes compare to conventional cold blood cardioplegia in heart valve operation. Ventricular fibrillation occurred after aortic cross clamp removal tends to be temporary and there was no evidence of postoperative myocardial infarction.

## Acknowledgements

The authors thank the Cardiovascular and Thoracic Surgery Research Group, Faculty of Medicine, Khon Kaen University, Thailand for support, Mr. Bryan Roderick Hamman for assistance with the English-language presentation of the manuscript and The Center of Cleft Lip-Cleft Palate and Craniofacial Deformities, Khon Kaen University under Tawanchai Royal Grant Project (Tawanchai Center) for Publication.

## Potential conflicts of interest

The authors declare no conflicts of interest.

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