Myocardial Preservation in Double Valve Replacement Surgery: Comparison of the Post-operative Clinical Outcome between Histidine-Triptophan-Ketoglutalate Solution and Cold Blood Cardioplegic Solution.

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Abstract:
Double valve replacement surgery is one of the open heart surgical procedures that require prolonged aortic cross-clamp times. This study was conducted to compare the postoperative clinical outcome of two cardioplegic solutions used for myocardial preservation in such procedures: histidine-triptophan-ketoglutalate solution (HTK), and cold blood cardioplegic solution (CBC).Sixty patients, ASA physical status III–IV, whose age between 25-45yr and body weight between 70–90 kg, who underwent double valve replacement, were enrolled in this study. All patients received a standardized fentanyl / pancuronium/ sevoflurane anaesthesia. Haemodynamic measurements were done using a Swan-Ganz catheter. For myocardial preservation during aortic cross-clamp time patients were randomized to two groups (n=30):
 Group I (HTK group)**:** Received a single high dose of HTK, and
Group II (CBC group)**:** Received the usual multidose format of CBC.
The clinical outcome was evaluated by examination of frequency of spontaneous defibrillation after releasing the aortic cross-clamp, and frequency of temporary pacing in each group, the dose of inotropic agent used at the end of cardiopulmonary bypass (CPB), and changes in cardiac index (CI) before and after the operation, Markers of myocardial injury (serum level of MB fraction of creatine phosphokinase (CK-MB) and cardiac troponin-I) were analyzed before the operation, at 7 hours and, 1, 2, and 3 days after surgery. The incidences of adverse events were also recorded.
Incidence of spontaneous defibrillation, and need for temporary pacing were statistically significant difference between the two groups ($p < 0.05$). The dose of inotropic support at the end of CPB was statistically non significant difference between the two groups ($p > 0.05$). No significant difference in the release of cardiac CK-MB and troponin-I between the two groups ($p > 0.05$), although there was more spontaneous ventricular defibrillation in the HTK group. It was concluded that in elective double valve replacement surgery, one single dose of cold HTK cardioplegia is as effective as repetitive CBC in protecting the myocardium, as measured by CK-MB and troponin-I. Patients in HTK group had more frequent spontaneous defibrillation and required less postoperative electrical pacing than in CBC group.

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INTRODUCTION

Myocardial protection is a complex process involving all the actors present in the surgical theatre: the anaesthesiologist, surgeon and perfusionist.

 Since its introduction, by Bigelow in 1950, hypothermia has been the gold standard for intra-operative organ protection. In open heart surgery, the major component of myocardial protection is the electromechanical arrest of the heart with a hyperkalaemic crystalloid solution , and as a result of cardiac arrest, there is a 90% reduction in myocardial oxygen consumption at normothermia (Buckberg et al, 1977). In the 1960s, the combination of these two principles was used to match myocardial oxygen supply with myocardial oxygen demand and protect the heart from a level of ischemia that leads to irreversible myocardial damage (Bretschneider et al, 1975) and (Baimbridge et al, 1977). Consequently, cold crystalloid cardioplegia was applied in cardiac surgery and remains the key method of myocardial protection for many centers.

In the 1980s, use of blood cardioplegia was suggested by Buckberg (Buckberg 1979). Blood is the natural liquid adapted for oxygen transport and release, and its composition (including buffering capacity, osmotic pressure, and rheology) is designed for vascular circulation. Reported beneficial effects were preservation of myocardial structure and adenosine triphosphate levels (Catinella et al, 1984).

The literature on comparison between crystalloid cardioplegia and blood cardioplegia is prolific. The conclusion from a 34-adult trial meta-analysis was that blood cardioplegia significantly decreased low-cardiac output syndrome incidence and creatinine kinase MB release (Guru et al, 2006).

 Recently, cardioplegia with histidine–tryptophan–ketoglutarate (HTK–Custodiol; Koehler Chemi, Alsbach-Haenlien, Germany) or Bretschneider solution for myocardial preservation during cardiac operations has been widely used clinically and reported in more than 700,000 cases of open cardiac surgery (Braathen et al, 2011) and (Salvador et al, 2008). It is simple to use, administered as one single dose, and it is claimed to give sufficient myocardial protection for more than 2 hours of cardiac arrest (Liu et al, 2008).

In our hospital, although we have attained favorable results with CBC, we are concerned by the fact that double valve replacement operations have to be suspended every time CBC is administered, to operate without interruption for 120 minutes.

No prospective randomized studies comparing the effects of HTK and cold blood cardioplegia on myocardial injury in patients having double valve replacement surgery have been reported.

Therefore, this study was designed to compare the postoperative clinical outcome of the two cardioplegic solutions HTK, and CBC used for myocardial preservation in such procedures.

PATIENTS AND METHODS

Patients:
The study was performed at National Heart Institute, Cairo, Egypt, and approved by the hospital ethics Committee and informed consent was obtained from each patient. Sixty male and female patients, ASA physical status III–IV, whose age between 25-45yr and body weight between 70–90 kg, who underwent double valve replacement between May2009 and June 2010, were enrolled in this study.

Exclusion criteria included: poor left ventricular (LV) function (ejection fraction <0.40), combined CABG and valvular replacement, patients requiring inotropic or mechanical support prior to surgery.
Also, patients with aortic cross-clamp time < 60minutes were excluded from this study.

Methods:
All usual cardiac medications required by the patient's underlying condition were continued until surgery. All patients received a standard premedication consisting of 1-3mg lorazepam, plus 150mg zantac orally on the evening of surgery and 0.15 mg/kg morphine intramuscular (I.M) given 30 min before the procedure. Prior to induction of anesthesia, pulse-oxymetry, ECG leads II and V5 were continuously recorded. After placement of peripheral intravenous (I.V) lines, and radial arterial line, anaesthesia was induced with propofol 0.5-1.5 mg/kg then, 3-5 µg/kg fentanyl was given in 5 min. During fentanyl infusion, ventilation was assisted manually with 100% oxygen supplemented with sevoflurane. Neuromuscular blockade was achieved with 0.1 mg/kg pancuronium at induction and prior to CPB.

After intubation, a continuous fentanyl infusion at 1-2µg/kg/hr was initiated and maintained until onset of CPB. Afterward, the fentanyl infusion was decreased to 0.5-1µg/kg/hr until the end of surgery. During CPB, propofol infusion 100µg/kg/min was substituted for sevoflurane. Controlled mechanical ventilation was adjusted to maintain end-tidal carbon dioxide between 35 and 40 mmHg.

 Becton Dickinson (Criticath ^{TM} SP 5107HTD) pulmonary artery catheter was positioned for readings of cardiac output (HP Component Monitoring system M1094A (Hewlett Packard, Palo Alto, CA).

All baseline haemodynamic measurements were taken after a 5-min stabilization period after intubation. They **included:** heart rate (HR), mean arterial pressure [MAP], central venous pressure (CVP), mean pulmonary

arterial pressure [MPAP], pulmonary artery wedge pressure (PAWP), and cardiac output (CO).

Calculated indices included: Cardiac index (CI, L/min/m^2) = CO/BSA, where CO is cardiac output (L/min) and BSA is body surface area (m^2);Stroke volume (SV, mL/beat) = CO/HR, where HR is heart rate (bpm); Systemic vascular resistance (SVR, dyne.s.cm^{-5}) = (MAP-CVP)/CO x 80; and Pulmonary vascular resistance (PVR, dyne.s.cm^{-5}) = (MPAP-PAWP)/CO x 80.

All patients were operated on by the same surgeons. Cardiopulmonary bypass was performed under mild hypothermia (32–34°C) with a membrane oxygenator.

For myocardial preservation during aortic cross-clamp time patients were randomly allocated by means of (closed envelope) to one of two groups (n=30):
 Group I (HTK group)**:** Received a single high dose of HTK (Bretschneider's HTK-   Solution CUSTODIOL®), and
Group II (CBC group)**:** Received the usual multidose format of CBC.

HTK 1000 mL was cooled to 4°C and infused for 10 minutes at a perfusion pressure of 40-50 mmHg. The HTK doses did not contain glucose as the source of energy but had a strong buffering action due to its histidine content. Preparation of CBC was done by mixing crystalloid solution with blood at a ratio of 1: 1. The temperature of the blood solution was lowered to 15°C and infused at an initial dose of 15 ml/kg after the aortic cross-clamp was applied. After this initial dose, CBC was infused antegrade every 30 minutes at a dose of 7 ml/kg.
The constitution of each solution is given in table (1).

(Table 1) Constitution of Cardioplegic Solutions:

	CBC	HTK
Potassium (mEq/L)	40	10
Sodium (mEq/L)	70	15
Calcium (mEq/L)	1	0
Magnesium (mEq/L)	19	8
Glucose (g/L)	25	0
Tryptophan (mEq/L)	0	2
K-ketoglutarate (mEq/L)	0	1
Histidine (mEq/L)	0	180
Histidine-HCl (mEq/L)	0	15
Mannitol (mEq/L)	0	30
pH	7.6-7.8	7.2
Osmolality (rnOsm/kg)	374	310

CBC = cold blood cardioplegia; HTK = histidine-triptophan ketoglutalate.

Both cardioplegic solutions were infused into the aortic root using a roller pump. In the HTK group, excessive hemodilution was avoided by aspirating the solution directly from the coronary sinus.

All patients were rewarmed till bladder temperature returned to 36°C. During CPB, mean arterial pressure was maintained between 40 and 80 mmHg with changes in anesthesia (propofol and/or fentanyl infusion), and/or administration of fluids and phenylephrine or sodium nitroprusside as necessary.

After CPB, **the limits for use of inotropic support were:**
(1) Persistent hypotension (systolic blood pressure <90 mmHg), in the presence of
(2) Central venous pressure (CVP) >12 mmHg,
(3) Mean pulmonary arterial pressure [MPAP] >30 mmHg,
(4) Pulmonary capillary wedge pressure (PCWP) >16 mmHg, and
(5) The cardiac index (CI) <2.2 L/min/m^2, with
(6) The presence of generalized hypokinesia through direct visualization of the heart.

In this study, the inotropic support was in the form of Dobutamine (Dobutamine Hydrochloride, Mayne Pharma, Pty Ltd. Mulgrave, Australia) as a continuous infusion of 5-10μg/kg/min.
The clinical outcome was evaluated by examination of frequency of spontaneous defibrillation after releasing the aortic cross-clamp, and frequency of temporary pacing in each group, changes in cardiac index (CI) before and after the operation, and the dose of inotropic agent used at the end of CPB.
Markers of myocardial injury:
Serum level of MB fraction of creatine phosphokinase (CK-MB) and cardiac troponin-I (cTnI) were analyzed in venous blood samples before the operation, at 7 hours and, 1 day, 2 days, and 3 days after surgery.
Serum CK-MB levels were studied by enzymatic immunoassay, cardiac troponin-I levels was assessed by electrochemiluminescence in immunoassay analysis. Serum CK-MB upper normal reference limit (99th percentile) is < 5 (ng/mL or μg/L); while serum cTnI upper normal reference limit (99th percentile) is < 0.2 (ng/mL or μg/L).
Release of cardiac troponin-I and CK-MB were considered as the most sensitive and specific markers of myocardial injury in clinical use (Bonnefoy et al, .1998), and in this study, they were used as markers for the effectiveness of myocardial protection.
The incidences of adverse events were also recorded.

Statistical analysis:
The results are reported as mean values ± standard deviations (SD).
Unpaired Student's *t* test was used to determine the statistical significance of difference between the two groups. To evaluate the myocardial protective effects, preoperative and postoperative data were compared using paired

Student's t-test. The Chi-square test or Fisher's Exact Test when appropriate was used to compare observed frequencies in each group. All differences were regarded as statistically significant (p < 0.05).

RESULTS

The demographic data were similar in both groups with respect to age, weight, height, sex distribution, and ASA physical status. There were no significant differences in the preoperative physical examination variables and cardiac function (ejection fraction).
 Four patients in CBC group and five patients in HTK group had undergone mitral valve repair with aortic valve replacement, but, otherwise, all patients in both groups had undergone double (mitral and aortic) valve replacement.

The aortic cross clamp time, bypass time, duration of surgery, and anaesthesia were also similar in both groups as seen in table (2).

Spontaneous defibrillation occurred in 8 patients in CBC group while it occurred in 26 patients in HTK group which was statistically significant difference between the two groups (p < 0.05) as seen in table (3).

 Temporary pacing was used in 13 patients in CBC group while it was used in only 5patients in HTK group which was also statistically significant difference between the two groups (p < 0.05) as seen in table (3).

Although the cardiac index increased in HTK group, the difference was not significant between the cardiac index on anaesthesia induction and at the end of CPB as seen in table (3).

The dose of inotropic support (Dobutamine) at the end of CPB was 8.72 ± 0.99 in CBC group and 7.45 ± 1.35 in HTK group which was statistically non significant difference between the two groups (p >0.05) as seen in table (3).

Markers of myocardial injury:

CK-MB:
The peak level of CK-MB found in the first blood sample 7 hours after the operation, was not significantly different between the HTK group and the CBC group
 (11.90 ± 4.30 vs 13.60 ± 3.40 ng/mL; P >0.05; Table 4 and Figure 1). There were no significant differences in CK-MB levels between the two groups at any postoperative time point (P >0.05; Table 4 and Figure 1).

Troponin-I
The peak level of cardiac troponin-I was not significantly different between the HTK group and the CBC group (0.68 ± 0.24 vs 0.73 ± 0.30 ng/mL; P >0.05; Table 4 and Figure 1). In accordance with CK-MB, the highest troponin-I value was found in the first blood sample 7 hours after the operation (Table 4 and Figure 1). Furthermore, there were no significant differences in troponin-I levels between the two groups at any postoperative time point (P >0.05; Table 4 and Figure 1).

(Table 2): Demographic data of both groups (Mean±SD):

Parameter	CBC group (n=30)	HTK group (n=30)	P value
Age (yr)	36.06±6.22	33.03±7.00	>0.05
Weight(kg)	78.41±5.51	77.55±6.47	>0.05
Height(cm)	175.65±6.57	176.86±7.12	>0.05
Male/female	16/14	15/15	>0.05
ASA class III/IV	17/13	16/14	>0.05
Preoperative ejection fraction (%)	51.58±3.43	52.72±2.57	>0.05
Aortic cross clamp time (min)	91.96±7.80	88.75±8.54	>0.05
Cardiopulmonary bypass time (min)	142.79±11.82	140.65±6.66	>0.05
Duration of surgery(min)	173.62±21.87	170.37±7.14	>0.05
Duration of anaesthesia (min)	255.58±21.56	251.24±10.93	>0.05

No significant difference between the two groups. CBC = cold blood cardioplegia; HTK = histidine-triptophan ketoglutalate.

(Table 3): Post-operative data of both groups (Mean±SD or percentage):

Parameter	CBC group (n=30)	HTK group (n=30)	P value
Spontaneous defibrillation	8(26.6%)	26(86.6%)*	<0.05
Temporary Pacing	13(43.3%)	5(16.6%)*	<0.05
Preoperative CI (L/min/m^2)	2.69 ± 0.70	2.71 ± 0.65	>0.05
Postoperative CI (L/min/m^2)	2.44 ± 0.47	2.73 ± 0.58	>0.05
Dobutamine dose (µg/kg/min.)	8.72 ± 0.99	7.45 ± 1.35	>0.05

* P value <0.05 = Statistical significance,   CBC = cold blood cardioplegia;
   HTK = histidine-triptophan ketoglutalate.

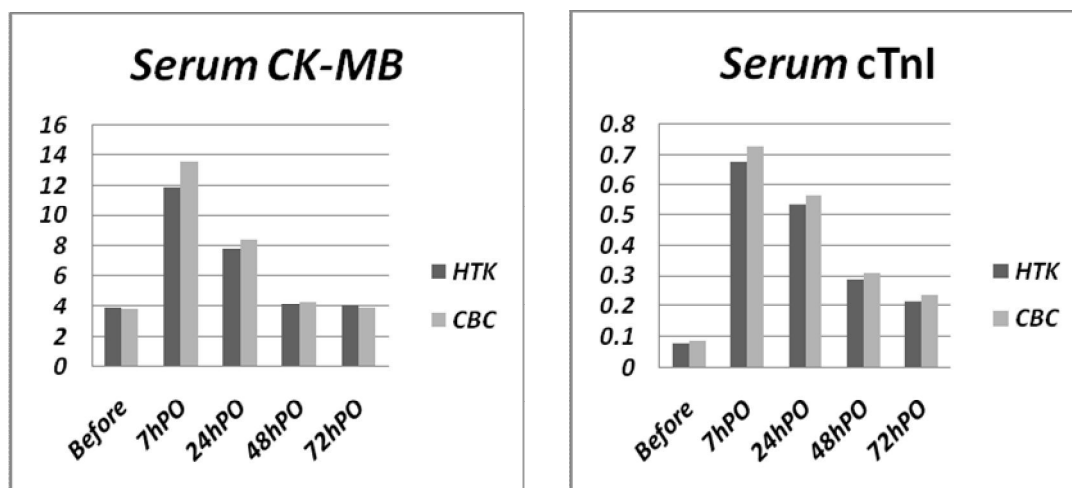**(Table 4): Post-operative Markers of Myocardial Injury of both groups**
(Mean±SD):

Parameter	CBC group (n=30)	HTK group (n=30)	P value
CK-MB(ng/mL or µg/L)			
CK- MB before operation	3.80 ± 0.60	3.90 ± 0.80	>0.05
CK- MB at 7 hours	13.60 ± 3.40	11.90 ± 4.30	>0.05
CK - MB at 24 hours	8.40 ± 2.70	7.80 ± 3.50	>0.05
CK - MB at 48 hours	4.30 ± 1.40	4.20 ± 1.30	>0.05
CK - MB at 72 hours	3.90 ± 0.80	4.10 ± 0.40	>0.05
cTnI(ng/mL or µg/L)			
cTnI before operation	0.09 ± 0.04	0.08 ± 0.06	>0.05
cTnI at 7 hours	0.73 ± 0.30	0.68 ± 0.24	>0.05
cTnI at 24 hours	0.57 ± 0.16	0.54 ± 0.28	>0.05
cTnI at 48 hours	0.31 ± 0.16	0.29 ± 0.18	>0.05
cTnI at 72 hours	0.24 ± 0.14	0.22 ± 0.17	>0.05

No significant difference between the two groups.
 CBC = cold blood cardioplegia; HTK = histidine-triptophan ketoglutalate.
 CK-MB= MB fraction of creatine phosphokinase, cTnI= cardiac Troponin-I.

(Figure 1): Markers of Myocardial Injury of both groups (Mean values): Left: CK-MB= MB fraction of creatine phosphokinase, Right: cTnI=

cardiac troponin-I, CBC = cold blood cardioplegia; HTK = histidine-triptophan ketoglutalate, PO= postoperatively.

DISCUSSION

The aim of this prospective, randomized study was to compare the postoperative clinical outcome of two cardioplegic solutions used for myocardial preservation in double valve replacement surgery: HTK and CBC.

Double valve replacement surgery is a long procedure, and CBC must be administered every 30 minutes and the surgical procedure has to be suspended during infusion which may increase cross clamp time with prolongation of myocardial ischemic time. A single high dose of HTK was apparently adequate to protect the myocardium for an extended period. However, cross clamp time was not significantly different between the 2 groups. The reason for this finding, although HTK is only given as one single dose, is most likely that the initial time of HTK administration is about 10 minutes and thus longer than for blood cardioplegia.

Postoperatively, our results showed that doses of inotropic agent in the HTK group and in the CBC group during the weaning of the extracorporeal circulation were almost equal and statistically non significant. Although the cardiac index increased in HTK group, the difference was not significant between the cardiac index on anaesthesia induction and at the end of CPB.

In contrast, spontaneous defibrillation occurred in more patients in the HTK group (26 patients in HTK group, while it occurred in 8 patients in CBC group), which was statistically significant difference. Also, the frequency with which temporary pacing was used after extracorporeal circulation was also different between the two groups (5patients in HTK group while it was used in 13 patients in CBC group) which was also statistically significant difference.

Generally, it is believed that postoperative conduction disturbances are associated with inadequate intraoperative myocardial protection and hearts with good myocardial protection usually spontaneously defibrillate. Thus, these results suggest that HTK contributed to favorable myocardial protection.

Kerber and associate (1980) demonstrated that high-energy shocks applied directly to the heart cause subepicardial necrosis and are therefore undesirable. Jones et al. (1980) and Doherty et al. (1979) also indicated that structural and functional alterations occur in the human heart following high-intensity electric counter shock and that these alterations may result in myocardial necrosis and arrhythmias. In this sense, HTK seems to provide better myocardial protection than CBC.

The mechanism of blood cardioplegia's protective effect is still a matter of debate however. A direct effect on the myocardial microvasculature is suggested in an experimental study. Crystalloid cardioplegia is associated with temporary loss of myocardial capillaries and significantly higher troponin-I

release while blood cardioplegia caused no capillary-density modification (Mubarak et al, 2003).

Heat shock proteins are produced by cardiomyocytes in response to stress stimuli. Protective effects of these proteins against myocardial cell damage and ischemia have been suggested and could be involved in the positive effects of preconditioning. Heat shock protein 70-1 gene (hsp70-1 gene) expression was assessed on right atrium biopsies in 59 pediatric patients during blood cardioplegia arrest. An upregulation of heat shock protein 70-1 correlated with aortic crossclamping time was observed during blood cardioplegia. This could also be a mechanism behind the protective effects of blood cardioplegia (Vittorini et al, 2007).

On the other hand, HTK is an intracellular cardioplegic solution containing low sodium concentration to arrest the heart by inhibiting the rapid phase of the action potential, histidine as buffer, ketoglutarate to improve the ATP energy production during reperfusion, tryptophan to stabilize the cell membrane, and mannitol to decrease the cellular edema (Aarsæther et al, 2009) and (Bretschneider 1980).

Kresh and colleagues (1987) noted that protein buffers such as histidine might be superior to bicarbonate in stabilizing intracellular pH and the recovery of post ischemic biochemical and mechanical parameters.

HTK contains the basic amino acid histidine that buffers H+, α-ketoglutarate (KG) as a substrate, and low sodium and calcium concentrations to mimic the intracellular ionic environment. del Nido and associates (1985) also demonstrated that the significant buffering capacity (similar to that of blood) in a crystalloid solution can be effective in preserving myocardial adenosine triphosphate stores, improving post arrest contractile function, and minimizing myocardial necrosis, provided a combination of high extracellular potassium and high pH levels are avoided.

Kjellman and associates (1997)   demonstrated that the administration of α-KG during blood cardioplegia improved myocardial protection, and this may be linked to enhanced oxidation.

Ohkado and colleagues (1994) indicated that promoting anaerobic glycolysis during ischemia by HTK results in superior prolonged preservation of the energetic and contractile functions of the heart.

Takeuchi and associates (1995) also demonstrated that administration of histidine containing cardioplegia solution promotes anaerobic glycolysis and improves recovery of high-energy phosphates and contractile function in hypertrophied myocardium.

Because of these qualities and the high buffer capacity, it has been demonstrated that one single dose of HTK is sufficient for myocardial protection up to more than 2 hours of ischemia (Liu et al, 2008).

Patients undergoing double valve replacement surgery frequently have dilated myocardium, and generally, myocardial protection in the dilated heart might be difficult during ischemia. However, (Hachida et al, 1997) indicated that histidine-tryptophan-potassium solution is superior to glucose-insulin-potassium solution for protecting the dilated heart during prolonged ischemia during open heart surgery.

In the present study, there was no significant difference in the release of the cardiac enzymes CK-MB and troponin-I between the two groups (p >0.05), although there was more spontaneous ventricular defibrillation in the HTK group.

However, experimental studies comparing one single dose of cold HTK with multidose cold blood cardioplegia (Fanneløp et al, 2009), or multidose cold St Thomas'Hospital solution (Aarsæther et al, 2009), have reported that HTK provides less adequate cardioprotection. Both studies applied 60 minutes of crossclamping, and they reported almost double values of troponin-T in the groups receiving HTK, and in the study by Aarsæther and coworkers (Aarsæther et al, 2009), 5 of 12 pigs could not be weaned from cardiopulmonary bypass. In the study by Fanneløp and coworkers (Fanneløp et al, 2009), 4 animals were excluded owing to persistent therapy-resistant arrhythmias. This was clearly not the result in human patients in the present study and in the study of (Braathen et al 2011), leading us to speculate that species differences and the known fragility of the pig model might explain the differences between those studies and our studies.

Most of the clinical studies of the cardio protective effect of HTK solution have been performed on patients undergoing coronary artery bypass grafting and only a relatively small number of patients have been included.

One retrospective study with a total of 46 patients undergoing mitral valve replacement with various additional procedures (bypass grafting, maze, tricuspid valve surgery) (Sakata et al, 1998), reported in accordance with the present study more spontaneous ventricular fibrillation after removal of the cross clamp in patients receiving HTK.

HTK solution may be associated with some disadvantages, one of which is excessive hemodilution due to infusion of a high-volume solution. By aspirating the solution directly from the coronary sinus, the problem can be solved. However, this method requires bicaval cannulation (Sakata et al, 1998).

This study has some potential limitations. First, double valve replacement might play a potential role regarding release of cardiac enzymes. These procedures were also equally distributed between groups and should therefore not influence the conclusion. Second, the temperature of the cardioplegic solution given was 15°C in blood compared with 4°C in the HTK solution, making a comparison of the 2 cardioplegic solutions difficult. The temperature of the cardioplegic solution is an important factor in determining myocardial protection. Simply, low temperature reduces the myocardial oxygen requirement. Therefore, an 11°C difference between the two forms of cardioplegia may affect myocardial protection. However, CBC and HTK are based on different concepts as discussed before.

CONCLUSION

In conclusion, in elective double valve replacement surgery, one single dose of cold HTK cardioplegia is as effective as repetitive CBC in protecting the myocardium, as measured by CK-MB and troponin-I. Patients in HTK group

had more frequent spontaneous defibrillation and required less postoperative electrical pacing than in the CBC group, although the level of cardiac enzymes was not significantly different between groups. Further studies are needed to document the safety of one dose of HTK in cross clamp times exceeding those of the present study.

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