Original Article

Effects of Original Crystalloid Cardioplegia Followed by Additional Blood Cardioplegia: Treatments for Prolonged Cardiac Arrest

Susumu Ishikawa, MD,[1] Keisuke Ueda, MD,[1] Kazuo Neya, MD,[1] Keiko Abe, MD,[1] Satoshi Kugawa, MD,[1] Akio Kawasaki, MD,[1] Satoru Nishizawa,[2] and Keiko Yamaoka, PhD[2]

Purpose: The efficacy of combination treatment of original cold crystalloid cardioplegia (SHA solution; St. Thomas + Histidine + ATP + oxygen) and additional blood cardioplegia was studied in patients who required cardiac arrest time of 120 minutes or longer.

Methods: One hundred and thirty-six patients were included in this study. Patients were divided into two groups according to the cardiac arrest time: S group (cardiac arrest time: 120–149 minutes, n = 81); L group (150–180 minutes, n = 55). Just after cross-clamping of the ascending aorta, 800 ml of SHA solution was infused in an antegrade fashion. Cold-blood cardioplegia was initiated after two hours of cardiac arrest.

Results: Six (4%) of the 136 patients died after surgery, 3 in each group. Two critical patients with ischemic cardiomyopathy died of cardiac failure after coronary artery bypass grafting (CABG), and 4 died of noncardiac morbidity. The mean value of postoperative maximum creatine phosphokinase-MB (CPK-MB) in dead patients was 47 IU/L in the S group and 75 IU/L in the L group. The peak CPK-MB values exceeded 100 IU/L in one out of 6 patients who died after surgery.

Conclusions: Combination treatment using original SHA solution and additional blood cardioplegia was effective in patients who required prolonged cardiac arrest. (Ann Thorac Cardiovasc Surg 2010; 16: 335–339)

Key words: crystalloid cardioplegia, blood cardioplegia, St. Thomas' Hospital cardioplegic solution, cardiac surgery, prolonged cardiac arrest

Introduction

St. Thomas' Hospital solution is the most popular crystalloid cardioplegia available and has been used worldwide.[1)] We compounded conventional St. Thomas' Hospital cardioplegia solution with histidine, adenosine triphosphate (ATP), and oxygen. This new solution (SHA solution) was applied to clinical use after experimental studies, and we had already reported the excellent effect of this cardioplegia in preliminary clinical application.[2)] The application of SHA solution, however, in patients who required prolonged aortic cross-clamping time over 120 minutes is controversial. In this study, we examined the efficacy of the combination treatment of SHA solution and additional cold-blood cardioplegia.

From [1]Department of Surgery, Cardiovascular Division, and [2]Department of Pharmacy, Teikyo University School of Medicine, Tokyo, Japan

Received November 26, 2008; accepted for publication June 14, 2009
Address reprint requests to Susumu Ishikawa, MD: Department of Surgery, Cardiovascular Division, Teikyo University School of Medicine, 2–11–1 Kaga, Itabashi, Tokyo 173–8605, Japan.

Materials and Methods

A total of 866 patients have undergone cardiac surgery in Teikyo University Hospital for six years since 2000, and 136 (16%) of them required long cardiac arrest time (120–180 minutes). This study includes these patients; 86 were males and 50 were females. Their mean age was 64, ranging from 17 to 84. Elective (EL) and urgent/emergency

Table 1. Demographics of patients

		S Group	L Group	p
Number of patients		81	55	
Age		64 ± 12	65 ± 12	NS
Male/Female		51/ 30	35/ 20	NS
Cardiothoracic ratio (%)		54 ± 10	57 ± 6	NS
Disease	Valvular	46	35	NS
	Ischemic	35	20	
Operation	Elective	71	52	NS
	Urgent/Emergency	10	3	
Cardioplegia	SHA	6	3	NS
	SHA + blood	75	52	
Operation time (min.)		355 ± 71	402 ± 76	< 0.01
CPB time (min.)		166 ± 28	202 ± 37	< 0.01
Aortic cross-clamp time (min.)		132 ± 8	165 ± 8	< 0.01

CPB, cardiopulmonary bypass.

(UR/EM) operations were performed on 123 and 13 patients, respectively. The patients were divided into two groups according to cardiac arrest time: S Group (120–149 minutes, n = 81) and L Group (150–180 minutes, n = 55). In the S group, the predominant heart disease was valvular in 46 patients and ischemic in 35. In the L group, it was valvular in 35 patients and ischemic in 20. There were no significant differences between the groups in age, male/female ratio, cardiothoracic ratio, cardiac diseases, operative timing, or cardioplegia. Operation time, cardiopulmonary bypass time, and aortic cross-clamp time were significantly longer in the L group than in the S group (Table 1).

SHA solution was compounded by a pharmacist in an aseptic room of the pharmacy department. It contains modified St. Thomas' Hospital cardioplegic solution, L-histidine (30 mmol/L), ATP (0.16 mmol/L), and oxygen (95% O_2 + 5% CO_2). The compound fluid is percolated using membrane filters (0.22μ) with compression. The SHA solution is preserved in a refrigerator, and its available period is five days. The constitution of SHA solution is presented in Table 2. Just after cross-clamping of the aorta, SHA solution (800 ml, 10˚C was infused in an antegrade fashion via an aortic root cardioplegic cannula or directly into coronary artery orifices. Cold-blood antegrade cardioplegia (500 ml, 15˚C, potassium 15 mmol/L) was added every 30 minutes after two hours of cardiac arrest by SHA solution in all but nine patients. Intraoperative topical cooling was not used in any patient.

Statistical analysis was conducted with SAS version 5.0 software (SAS Institute, Inc., Cary, NC). Continuous data are expressed as the mean ± standard deviation (SD). The Student's t-test and the chi-square test were used for statistical analysis, and a p value of less than 0.05 was considered significant.

Results

Six (4%) out of the 136 patients died after surgery, including 3 (4%) of the S group and 3 (5%) of the L group. In elective surgery, the operative mortality rate of the S group was lower than that of the L group; however, there was no significant difference (1% vs. 6%). Two patients of the S group died after UR/EM surgery. In total patients, the operative mortality of UR/EM surgery was significantly ($p<0.05$) higher than that of elective surgery (3% vs. 15%). In the S group, 3 with ischemic heart disease died after surgery. In the L group, 3 with valvular heart disease died.

Causes of death were cardiac events in 2 patients and noncardiac events in 4. In the S group, 2 patients with ischemic cardiomyopathy died of cardiac failure after UR/EM surgery. One dead patient was assisted by percutaneous cardiopulmonary support preoperatively and underwent CABG (5 grafts) plus Dor's left ventriciular plasty. The other was assisted by high-dose catecholamine-dependent preoperatively and underwent CABG (4 grafts), left ventricular volume reduction (Batista), and mitral valve plasty. In the L group, all 3 patients died of noncardiac morbidity. Causes of noncardiac death were ischemic colitis, sepsis, mediastinitis, and cerebral infarction, respectively. There were no significant differences in operating time between the dead and live patients. However, the cardiopulmonary bypass time and the aortic cross-clamp time were significantly ($p <0.01$) longer in the dead patients than in the live patients (277 ± 36 vs.

Table 2. Constitution of SHA solution

Modified St. Thomas' solution		
Sodium chloride	(NaCl)	97.5 mM
Sodium bicarbonate	($NaHCO_3$)	12.5
Potassium chloride	(KCl)	14.8
Potassium phosphate	(KH_2PO_4)	1.2
Magnesium chloride	($MgCl_2$)	15.5
Magnesium sulfate	($MgSO_4$)	1.3
Calcium chloride	($CaCl_2$)	0.6
Procaine hydrochloride		0.98
Additions for SHA solution		
Glucose		11.1
Histidine		30.0
Adenosine triphosphate (ATP)		0.16
7% $NaHCO_3$		8.3
95% O_2 + 5% CO_2		saturated
Osmolality: 330 mOsm/L		
PH : 7.8 (nonoxygenation), 6.9 (oxygenation)		

Table 3. Operative Mortality and Cause of Death

	S Group (n = 81)	L Group (n = 55)	Total
Total	3 cases (4%)	3 cases (5%)	6/136 (4%)
Operative timing			
Elective	1/71 (1%)	3/52 (6%)	4/123 (3%)*
Urgent/Emergency	2/10 (20%)	0/3	2/13 (15%)*
Disease			
Ischemic	3	0	3
Valvular	0	3	3
Cause of Death (n = 6)			
Cardiac	2 PCPS 1 Batista 1	0	2
Noncardiac	1	3	4
Ischemic colitis	0	1	
Sepsis	1	0	
Mediastinitis	0	1	
Cerebral infarction	0	1	

*$p < 0.05$

PCPS, percutaneous cardiopulmonary support.

179 ± 37 minutes, 167 ± 46 vs. 144 ± 18 minutes, respectively). The mean value of postoperative maximum CPK-MB in dead patients was 47 IU/L (range 31–63) in the S group and 75 IU/L (range 32–118) in the L group. The peak CPK-MB values exceeded 100 IU/L in a dead patient of the L group.

Discussion

In cardiac surgery, the quality of cardioplegic solution influences the operative results, especially in patients with major cardiac surgery. Cardioplegic solution was developed together with the experimental study of heart preservation for heart transplantation. In the 1980s, myocardial protection during open heart surgery had been the focus of many surgical interventions, and debate continued regarding the ideal cardioplegic solution. But a review of laboratory and clinical studies shows no conclusive advantage of one solution over the others. Among many cardioplegic solutions, St. Thomas' Hospital solution has been the most popular crystalloid cardioplegia. However, the compound components in addition to St. Thomas'

Hospital solution was considered necessary to obtain longer and safer cardioplegic effects in clinical use.[3)]

Oxygenated cardioplegic solutions can deliver sufficient oxygen to support aerobic metabolism of heart tissue during cardiac arrest,[4,5)] Oppell and his colleagues reported that modified St. Thomas' Hospital solution should be oxygenated, but with 95% oxygen: 5% carbon dioxide rather than 100% oxygen because of the additive effect of a relatively "acidotic" pH.[6)] Intramyocardial pH is an important determinant in the functional recovery of the heart, and acidic conditions during normothermic ischemia optimize preservation of myocardial function. For this purpose, histidine was reported to be an effective buffer.[7)] High-energy phosphates such as ATP and creatine phosphate improve the cardioprotective properties of the St. Thomas' Hospital cardioplegic solution during prolonged hypothermic ischemic arrest.[8,9)] After sufficient basic animal studies, we compounded a cardioplegia of St. Thomas' Hospital solution by adding histidine (30 mmol/L), ATP (0.16 mmol/L), and oxygen (95% O_2 + 5% CO_2).

We maintained temperature of the SHA solution at 10˚C and infused it in an intermittent antegrade fashion in clinical use. Some authors reported that tepid-blood cardioplegia was superior to cold-blood cardioplegia[10,11)] for heart protection. However, Lajos and colleagues[12)] reported that cold crystalloid cardioplegia and cold retrograde blood cardioplegia was safe under hypothermic conditions, whereas warm cardioplegia required continuous uninterrupted technique with oxygen delivery.

The clinical results of SHA solution in patients who required aortic cross-clamping time of less than 120 minutes were favorable in the previous clinical series.[2)] However, the effect of SHA solution was not sufficient in prolonged cardiac arrest of more than 120 minutes, probably because of tissue edema. Thus since 2000 we have adapted additional cold-blood cardioplegia after two hours of cardiac arrest by SHA solution. Six out of a total of 136 patients died after surgery, and there were no significant differences in hospital mortality rates between two groups divided by aortic cross-clamping time. Only 2 patients died of cardiac failure, and another 4 died of noncardiac morbidity. The peak CPK-MB values exceeded 100 IU/L in 1 of the 8 patients who died after surgery. The cardiopulmonary bypass and aortic cross-clamp times were significantly longer in the dead patients than in the live ones; thus prolonged cardiopulmonary bypass might influence the onset of postoperative complications. In cardiac surgery that used typical crystalloid or blood cardioplegia, repetitive infusion of cardioplegia every 30–60 minutes is required, which is sometimes troublesome. By comparison, SHA solution has almost two hours of lasting effect and provides a clearer operative field. Thus operative procedures can be continued without interruption for two hours after the initial infusion of SHA solution. This report is not a comparative study; so we cannot verify the evidence of superiority of our method in comparison with others. Buckberg[13)] reported that a combination of antegrade/retrograde cardioplegia was the preferred method of myocardial protection in all adult operations and in many pediatric cardiac procedures. According to the reports by Partington et al.,[14)] antegrade/retrograde cardioplegia provides better myocardial protection than either technique alone, it ensures good cardioplegic distribution to the left and right ventricles, and it allows regional delivery of cardioplegic flow to segments supplied by occluded arteries. We generally infuse cardioplegia in an antegrade fashion; however, we use early additional cardioplegia in the jeopardized areas with operative resources. We believe that our method is at least clinically acceptable and reliable. In conclusion, combination treatment using original SHA solution and additional blood cardioplegia was effective in patients who required prolonged cardiac arrest time within 180 minutes.

References

1. Jynge P, Hearse DJ, Feuvray D, Mahalu W, Canković Darracott S, et al. The St. Thomas' hospital cardioplegic solution: a characterization in two species. *Scand J Thorac Cardiovasc Surg Suppl* 1981; **30**: 1–28.
2. Ueda K, Kitazawa T, Nakajima Y, Yamaoka K. The concept of newly development of the St. Thomas cardioplegic solution adapting to advanced surgery for critical cardiovascular diseases. (in Japanese with English abstract) *Low Temp. Med* 2000; **26**: 112–8.
3. Ueda K, Genda T, Hirata I, Shimada M, Shibata T, et al. Beneficial effect of fluorocarbon reperfusion on postoperative cardiac dysfunction of transplanted heart. *J Heart Lung Transplant* 1992; **11**: 646–55.
4. Ledingham SJ, Braimbridge MV, Hearse DJ. Improved myocardial protection by oxygenation of St. Thomas' Hospital cardioplegic solutions. Studies in the rat. *J Thorac Cardiovasc Surg* 1988; **95**: 103–11.
5. DeBoer LW, Rabjohns RR, Nutt MP, Swanson DK. Effects of oxygenated cardioplegic solutions on myocardial aerobic metabolism. *J Thorac Cardiovasc Surg* 1992; **104**: 632–6.
6. von Oppell UO, King LM, Du Toit EF, Owen P, Reichart B, et al. Effect of oxygenation and consequent pH changes on the efficacy of St. Thomas' Hospital cardioplegic solution. *J Thorac Cardiovasc Surg* 1991;

102: 396–404.
7. Iannettoni MD, Bove EL, Fox MH, Groh MA, Bolling SF, et al. The effect of intramyocardial pH on functional recovery in neonatal hearts receiving St. Thomas' Hospital cardioplegic solution during global ischemia. *J Thorac Cardiovasc Surg* 1992; **104**: 333–43.
8. Robinson LA, Braimbridge MV, Hearse DJ. Enhanced myocardial protection with high-energy phosphates in St. Thomas' Hospital cardioplegic solution. Synergism of adenosine triphosphate and creatine phosphate. *J Thorac Cardiovasc Surg* 1987; **93**: 415–27.
9. McDonagh PF, Laks H, Chaudry IH, Baue AE. Improved myocardial recovery from ischemia. Treatment with low-dose adenosine triphosphate-magnesium chloride. *Arch Surg* 1984; **119**: 1379–84.
10. Fiore AC, Swartz MT, Nevett R, Vieth PJ, Magrath RA, et al. Intermittent antegrade tepid versus cold blood cardioplegia in elective myocardial revascularization. *Ann Thorac Surg* 1998; **65**: 1559–64.
11. Badak MI, Gurcun U, Discigil B, Boga M, Ozkisacik EA, et al. Myocardium utilizes more oxygen and glucose during tepid blood cardioplegic infusion in arrested heart. *Int Heart J* 2005; **46**: 219–29.
12. Lajos TZ, Espersen CC, Lajos PS, Fiedler RC, Bergsland J, et al.Comparison of cold versus warm cardioplegia. Crystalloid antegrade or retrograde blood? *Circulation* 1993; **88**: II 344–9.
13. Buckberg GD. Antegrade/retrograde blood cardioplegia to ensure cardioplegic distribution: operative technique and objectives. *J Card Surg* 1989; **4**: 216–38.
14. Partington MT, Acar C, Buckberg GD, Julia PL. Studies of retrograde cardioplegia. II. Advantages of antegrade/ retrograde blood cardioplegia to optimize distribution in jeopardized myocardium. *J Thorac Cardiovasc Surg* 1989; **97**: 613–22.