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Comparison of intermittent injection of nondepolarizing solution with a single flush of UW solution for donor heart preservation

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Abstract. Isolated canine hearts were preserved for 6 h at 5°C followed by normothermic reperfusion for 2 h. The dogs were divided into two groups of nine hearts each; group 1 received a nondepolarizing preservation solution in multidose, and group 2 received a single flush of University of Wisconsin (UW) solution. Serum MB-CK and mitochondrial aspartate aminotransferase (m-AAT) concentrations and calcium overload during reperfusion were lower in group 1 than in group 2. At the end of reperfusion, myocardial ATP and total adenine nucleotide concentrations were higher and mitochondrial morphology appeared more intact in group 1 than in group 2. Left ventricular diastolic function was preserved better in group 1 than in group 2. These results suggest that in 6-h heart preservation, a nondepolarizing solution applied in multidose fashion protects the myocardium from the deleterious effects of hypothermia and cardioplegia better than a single flush of UW solution.

Key words: Heart preservation, canine – UW solution, heart preservation – Nondepolarizing solution, heart preservation – Preservation, heart, canine

Introduction

Although great progress has been made in the field of cardiac transplantation, no fully satisfactory technique of donor heart preservation yet exists. Presently, hypothermia is commonly induced to aid preservation, but hypothermia causes enzyme dysfunction [16], decreased membrane stability [7, 17], and calcium sequestration [1, 20]. Cardioplegia with depolarizing solutions, such as University of Wisconsin (UW) solution, destabilizes the sarcolemma and allows increased intracellular accumulation of sodium and calcium, with subsequent cellular edema. Moreover, increased intracellular calcium itself is thought to be a major cause of reperfusion injury [20].

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Our group has developed a new nondepolarizing solution for use in cardiac preservation. This solution has an ionic composition that preserves the potential across the cell membrane. We have shown that the use of this solution improves cardiac viability, as assessed by biochemical, morphologic, and hemodynamic parameters [34, 35]. In the present study, we compare intermittent injection of this nondepolarizing solution with a single flush of UW solution in a canine model of cardiac preservation.

Materials and methods

Eighteen dogs weighing 8.2–17 kg (mean 11.7 kg) were anesthetized with intravenous pentobarbital (30 mg/kg) and maintained by mechanical ventilation. Animals received care according to the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences.

Procurement of the heart

A median sternotomy was performed, and the superior and inferior vena cavae were isolated with 2-0 silk sutures, both proximally and distally. The azygous vein was ligated and divided. Both common carotid arteries, the left subclavian artery, and the descending aorta were isolated with 2-0 silk, both proximally and distally, and the hila of the lungs were encircled bilaterally with 2-0 silk ligatures. A 10 Fr arterial cannula was inserted from the proximal right subclavian artery and a 24 Fr venous cannula was placed in the right ventricle through the right atrial appendage. Approximately 500 ml of blood was withdrawn from the venous cannula, heparinized, and saved for transfusion during reperfusion. The previously isolated arteries were ligated, as were the pulmonary hila after ventilation was terminated. Immediately after aortic occlusion, cardioplegia was induced by infusion of cold (5°C) cardioplegic solution via the arterial cannula. The volume of the initial infusion was 15 ml/kg in group 1 and 30 ml/kg in group 2. The superior and inferior vena cavae were ligated and divided, and the heart was removed.

Preservation of the heart

Each heart was immersed for 6 h in cold (5°C) saline in group 1 and in cold (5°C) UW solution in group 2. In group 1, cardioplegic solution (3 ml/kg) was infused every 60 min. The composition of this solution was Na^+ 60 mEq, Mg^{2+} 16 mM, Ca^{2+} 1 mM, mannitol 50 mM, lidocaine hydrochloride 2 mM, betamethasone 250 mg, and

Table 1. Myocardial concentrations of biochemical compounds after preservation (P) and reperfusion (R) of dog hearts with nondepolarizing or UW solution. Values given indicate mean ± SEM. * $P < 0.05$ versus group 2

		Group 1 ($n = 9$) Nondepolarizing solution	Group 2 ($n = 9$) UW solution
Adenosine triphosphate	P	13.51 ± 2.17	13.70 ± 1.18
(μg/mg protein)	R	18.77 ± 1.93*	13.45 ± 2.67
Adenosine diphosphate	P	4.10 ± 0.43	3.53 ± 0.32
(μg/mg protein)	R	4.03 ± 0.39	3.45 ± 0.27
Adenosine monophosphate	P	0.96 ± 0.13*	0.72 ± 0.16
(μg/mg protein)	R	0.49 ± 0.12	0.50 ± 0.08
Total adenine nucleotide	P	18.57 ± 2.17*	17.90 ± 1.42
(μg/mg protein)	R	23.28 ± 1.69*	17.40 ± 2.85
Creatine phosphate	P	3.33 ± 0.97	6.21 ± 1.14
(μg/mg protein)	R	20.45 ± 3.03	18.78 ± 4.96
Cyclic adenosine monophosphate	P	2618 ± 260	2704 ± 364
(pmol/g wet tissue)	R	1030 ± 117	929 ± 134
Cyclic guanosine monophosphate	P	13.3 ± 1.7	14.8 ± 1.3
(pmol/g wet tissue)	R	10.8 ± 1.1	9.7 ± 0.9
Calcium	P	40.4 ± 2.8	38.8 ± 3.8
(μg/g tissue)	R	64.0 ± 3.0	95.1 ± 17.8

glucose 245 mM per liter. The osmolarity was 450 mosmol and a pH of 7.50 was adjusted by the addition of 10 mM/l sodium bicarbonate. Commercially available UW solution was used (ViaSpan, E.I. du Pont de Nemours, Wilmington, Del., USA). One hour prior to reperfusion, a latex balloon was placed in the left ventricle and secured with a holding apparatus sutured in the mitral position. The balloon was connected to a transducer (Statham P23DB, Statham Instruments, Los Angeles, Calif., USA), and a polygraph (Nihon Kohden, Tokyo, Japan) was used to measure developed left ventricular pressure during reperfusion. Special care was taken to avoid mechanically induced aortic regurgitation. Thirty minutes prior to reperfusion, the heart was exposed to room temperature by discontinuing cold saline immersion.

Reperfusion

A second dog was anesthetized, ventilated, and maintained hemodynamically by the infusion of Ringer's lactate solution. Both carotid arteries were cannulated (10 Fr) and connected to the arterial cannula placed in the preserved heart. A second pressure transducer and a magnetic flow meter (Nihon Kohden, Tokyo, Japan) were connected to the circuit to measure the perfusion pressure and flow. Coronary sinus blood flow was also measured, using a magnetic flow meter to estimate coronary blood flow. Blood from the cannulae in the right and left ventricles was collected in a reservoir and infused back into the supporting dog by a pump; a heat exchanger maintained normothermia. Reperfusion was continued for 2 h. Defibrillation was performed when ventricular fibrillation developed during the early phase of reperfusion. After 5 min of reperfusion, all dogs were paced at 130 beats per minute. No cardiotonic drugs were administered to any of the dogs.

At the end of cardiac arrest and during reperfusion, while the heart was beating, a biopsy specimen of left ventricular subendocardium was obtained. Specimens were analyzed for concentrations of adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), and creatine phosphate (CP) using previously described methods [3]. The calcium concentration was determined using an atomic absorption spectrophotometry [10]. Electron microscopy was used to evaluate the myocardial mitochondrial ultrastructural changes by semiquantitative morphometry [30].

Samples of coronary sinus blood were collected after 5, 60, and 120 min of reperfusion and were analyzed for the serum MB fraction of creatine kinase (MB-CK) and mitochondrial aspartate aminotransferase (m-AAT) using an immunochemiluminometric technique [21]. Left ventricular (LV) end-systolic and diastolic pressures were measured by a balloon inflated with saline volumes of 5, 10, 15, and 20 ml. The left ventricular end-systolic pressure-volume relationship, the end-diastolic pressure volume relationship, and the -dp/dt were calculated to evaluate left ventricular function.

Data between groups were analyzed using the Mann-Whitney test. P values lower than 0.05 were considered statistically significant.

Results

Reperfusion pressure, aortic flow during reperfusion, coronary flow, hematocrit, temperature, and the weight of the LV were not different between groups 1 and 2. Defibrillation was performed in all nine dogs in group 2 (on the average, 2.4 times per dog), while only one dog in group 1 received defibrillation (0.3 times per dog). All animals in both groups survived reperfusion.

Myocardial ATP concentration was significantly higher at the end of reperfusion in group 1 than in group 2 (18.77 ± 1.93 vs 13.45 ± 2.67 μg/mg protein; $P < 0.05$) but not at the end of preservation. Myocardial AMP concentration was significantly higher at the end of preservation in group 1 than in group 2 but not at the end of reperfusion. Myocardial total adenine nucleotide concentration

Table 2. Serum concentrations of myocardial enzymes during reperfusion of dog hearts with nondepolarizing or UW solution. Values given indicate mean ± SEM

	Reperfusion (minutes)	Group 1 ($n = 9$)	Group 2 ($n = 9$)	Significance
MB-CK	5	4.7 ± 1.1	7.9 ± 1.7	
IU/l per 100 g LV	60	20.2 ± 5.7	64.8 ± 16.1	$P < 0.05$
	120	19.3 ± 4.9	83.4 ± 20.7	$P < 0.001$
Mitochondrial aspartate aminotransferase	5	3.8 ± 0.4	3.9 ± 0.5	
IU/l per 100 g LV	60	10.6 ± 2.0	10.4 ± 1.5	
	120	17.9 ± 3.0	29.3 ± 5.6	$P < 0.05$

[a] Coronary sinus blood

Table 3. Summary of mitochondrial ultrastructural alterations by semiquantitative morphometry. Values given indicate mean ± SEM. P, End of preservation; R, end of reperfusion. Scores indicate degree to which they are intact (100) or complete destruction (0)

		Group 1 ($n = 9$) Nondepolarizing solution	Group 2 ($n = 9$) UW solution	Significance
Mitochondrial membrane	P	73.5 ± 1.9	58.3 ± 1.1	$P < 0.001$
	R	73.6 ± 2.8	64.0 ± 2.1	$P < 0.05$
Mitochondrial cristae	P	63.5 ± 2.1	34.8 ± 1.5	$P < 0.001$
	R	57.3 ± 3.8	49.6 ± 4.0	

was significantly higher at the end of both preservation and reperfusion in group 1 than in group 2. No significant difference existed in myocardial content of ADP, creatine phosphate, cAMP, cGMP, or tissue calcium at the end of either preservation or reperfusion (Table 1).

Changes in serum myocardial enzyme concentrations were different between groups 1 and 2. The concentration of both MB-CK and m-AAT increased markedly during reperfusion in group 2 but only minimally in group 1. The MB-CK concentration was significantly higher at 60 and 120 min of reperfusion, and the m-AAT concentration was higher at 120 min ($P < 0.05$; Table 2).

Ultrastructurally, mitochondrial cristae and membranes were better preserved in group 1 than in group 2. Myofibrils were well preserved in both groups; however, contraction bands were observed more frequently in group 2 than in group 1 (Table 3, Fig. 1).

Left ventricular systolic function was satisfactory in both groups (Fig. 2). Left ventricular end-diastolic pressure was more significantly impaired at 60 and 120 min of reperfusion in group 2 than group 1 (Fig. 3). Group 1 also showed significantly better improvement in the -dp/dt (Fig. 4).

Discussion

Major problems encountered during myocardial reperfusion following ischemia include arrhythmias, depletion of high-energy compounds and metabolic substrates, myocardial necrosis, and ventricular dysfunction. At present, hypothermic cardioplegia is the standard technique for protection of donor hearts. Hypothermia dramatically reduces metabolic demands and oxygen consumption, thus slowing myocardial degradation [22]. However, hypothermia has its own deleterious effects on the myocardium, and both changes in membrane lipid bilayers and increased ion permeability across cell membranes have been observed.

Cell membranes undergo phase transition as the temperature is lowered [7, 20]. At 18 °C, membrane lipids undergo a stabilizing phase change, but below 10 °C lipid crystallization can result in membrane rupture and increased ion permeability, especially for sodium and calcium [1, 20]. Hypothermia also inactivates Na^+-K^+ and Ca^+ ATPase in the sarcolemma and sarcoplasmic reticulum, resulting in the loss of cell volume regulation and swelling [15]. Other ion pumps may also be temperature-sensitive. In addition to the Na^+-Ca^{2+} exchange system, the cardiac sarcolemma has an ATP-dependent Ca^{2+} transport system [5]. This system seems to have a higher affinity but lower transport rate for Ca^{2+} than does the Na^+-Ca^{2+} exchange system. Hypothermia depresses tissue ATPase activity, and membrane-bound ATPase in inhibited at temperatures below 15 °C [16]. This inactivates the Na^+-K^+ pump and allows sodium and water influx and potassium efflux [34]. This, in turn, increases intracellular Ca^{2+} concentrations via activation of the Na^+-Ca^{2+} exchange system.

The standard technique of cardioplegia causes membrane depolarization. Depolarized myocardial cells suffer increased permeability and intracellular sodium and cal-

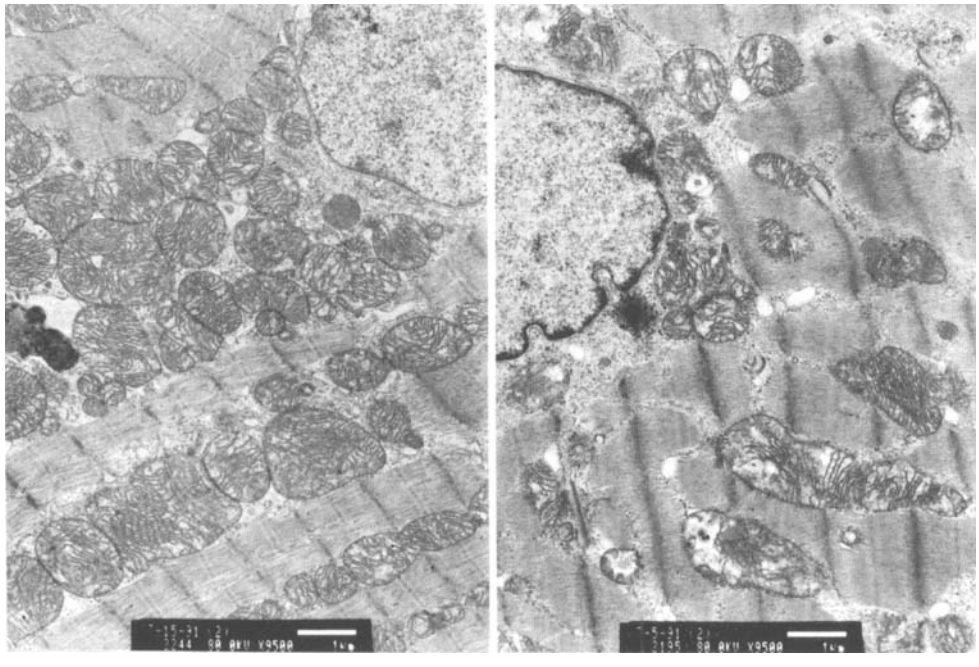

Fig. 1. Ultrastructure of the subendocardial layer of the left ventricle at 120 min of reperfusion in group 1 *(left panel)* and group 2 *(right panel)*. Mitochondrial disruption and swelling are observed in addition to contraction bands in group 2

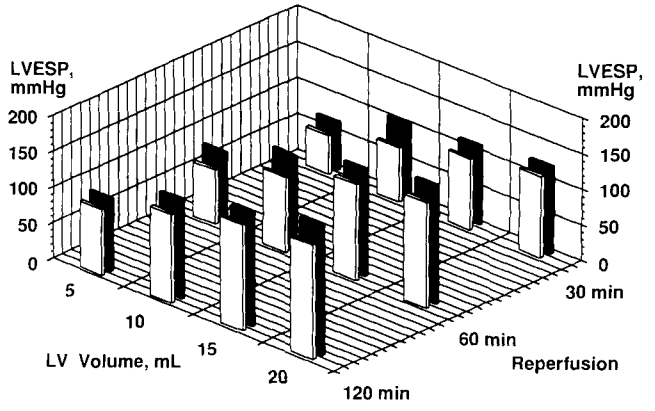

Fig. 2. End-systolic pressure volume relationship of the left ventricle during reperfusion in group 1 (■) nondepolarizing solution ($n = 9$) and in group 2 (□) UW solution ($n = 9$)

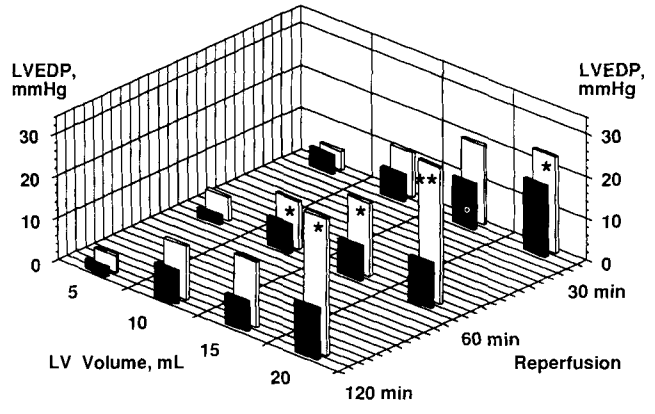

Fig. 3. End-diastolic pressure volume relationship of the left ventricle during reperfusion in group 1 (■) nondepolarizing solution ($n = 9$) and in group 2 (□) UW solution ($n = 9$). * $P < 0.05$, ** $P < 0.01$

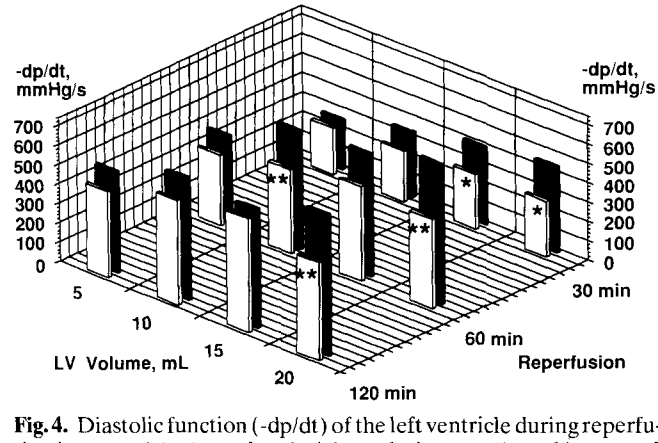

Fig. 4. Diastolic function (-dp/dt) of the left ventricle during reperfusion in group 1 (■) nondepolarizing solution ($n = 9$) and in group 2 (□) UW solution ($n = 9$). * $P < 0.05$, ** $P < 0.01$

cium concentrations. This is the primary cause of cellular swelling, Ca^{2+} overload, damage to cellular organelles, and ventricular fibrillation during reperfusion after ischemia. The resting potential is determined by a complicated mechanism involving ions, the structure of the membrane, its related enzymes, and an extracellular environment, such as pH and osmotic pressure [28]. Since we did not measure the membrane resting potential in situ in this study, we are unable to define the myocardium treated with our solution as being nondepolarized. However, the solution used in this study generates a resting membrane potential estimated to be approximately -80 mV at 15°C, according to the modified Nernst equation [25]. Furthermore, at 5°C, hearts preserved with this solution are believed to have a resting membrane potential lower than -80 mV [25]. Thus, this solution can be defined as a nondepolarizing solution.

In contrast, the resting membrane potential of hearts preserved with UW solution is estimated to be 0 mV at 15°C, according to the modified Nernst equation [25]. It has been reported that in the cultured cardiac cell, the membrane resting potential becomes markedly hyperpolarized at 10–15 mM of an extracellular K^+ concentration [26], and it changes depending upon the condition of the membrane. Therefore, it is argued that the solution used in group 1 did not contain K^+, and one questions whether this solution induces hyperpolarization of the membrane. However, we observed that coronary effluent contained K^+ and a trace of blood even when we infused the heart with our K^+-free solution. There are two possible causes: (1) the coronary bed contained blood including K^+ even after we had intermittently flushed the heart with K^+-free solution and (2) K^+ moved out from an intracellular space to an extracellular space. Our observation suggests that when we use the K^+-free solution, K^+ concentration in an extracellular space does not become zero. Further studies are needed to define the optimal concentration of K^+ in the nondepolarization solution. We have studied [33] the effect of the same solution as that used in group 1 on the myocardial biochemical and functional viability compared with a standard depolarizing solution that contained K^+ 20 mM. This showed that a nondepolarizing solution provided better myocardial preservation than a depolarizing solution.

Though there was no direct measurement of the membrane resting potential, and it is not known whether nondepolarization of the myocyte is better than depolarization for myocardial preservation, there are clear differences in the composition of the two solutions used in this study: K^+ 140 mM, Na^+ 30 mM in UW solution (group 2) and K^+ 0 mM, Na^+ 70 mM in the other solution (group 1). Although K^+ is the major determinant of the membrane resting potential and Na^+ the minor one, it has been reported that a high Na^+ in UW solution provides better myocardial preservation than a high K^+ in UW solution [19]. This report suggests that the better myocardial viability shown in group 1 in this study may have resulted from a higher concentration of Na^+ in group 1 than in group 2. It has been reported that both hypothermia and osmotic pressure lower the membrane resting potential [28]. Although the level of hypothermia was identical in both groups, an osmolarity of solution was higher in group 1 than in group 2. This factor might affect the heart in such a way as to show a different result with regard to myocardial viability.

Lidocaine was added to the cardioplegia in group 1 because it preserves mitochondrial oxidative phosphoryla-

tion [2] and inhibits cellular and subcellular damage from ischemia reperfusion by stabilizing membranes [18, 23, 33]. This accounts in part for why the incidence of ventricular fibrillation during early reperfusion was significantly higher in group 2. This arrhythmia has been attributed to changes in the Na^+-H^+-Ca^{2+} exchange system [34]. Local anesthetics increase the fluidity of the membrane, perhaps because they depress Na, K-ATPase activity [9] and the resting conductance of the membrane for K^+ and Na^+ [8]. This mechanism contributes to lowering the membrane resting potential and to stabilizing the membrane function [25]. It is obvious that the UW solution used in group 2 contained no lidocaine. Therefore, it is suggested that the cytoprotective effect of lidocaine is, in part, responsible for the better myocardial preservation shown in group 1.

Betamethasone protects ischemic myocardium by increasing coronary blood flow [29] and suppressing myocardial edema in an open heart model [28]. Furthermore, steroids have been shown to stabilize lysosomal membranes [14, 24]. In this study, both solutions contained a glucocorticoid: 250 mg/l betamethasone in group 1 and 16 mg/l dexamethasone in group 2. However, the pharmacological potential of each steroid seems to be identical. Therefore, the steroid does not seem to have been responsible for the different outcomes regarding myocardial viability observed in the two groups.

The technique of myocardial protection used in this study differs from standard practice, not only in the composition of the cardioplegic solution but also in its administration. Hearts in group 2 were preserved according to standard practice, i.e., immersion in cold UW solution. However, although the total volume of cardioplegic solution injected was 30 ml/kg in both groups, it was injected incrementally in group 1. In this study, differences in the technique used for preservation or in the methods of injecting solution in the two groups might have affected the quality of the myocardial preservation. A standard depolarizing cardioplegia injected in multidose fashion can ameliorate cardiac metabolism during prolonged ischemia but may cause myocardial edema and calcium overload. However, a nondepolarizing solution, if it exists in an ideal form, can increase myocardial tolerance to ischemia and can also prevent the myocardium from edema and calcium overload that result from multidose injection. Our previous study [33] and results from this study support a salutary effect of a nondepolarizing solution in an intermittent, multidose injection. Sukehiro et al. [27] have reported that the ATP concentration is 50 %–60 % its normal concentration after 6 h of preservation. Our results indicate that the myocardial ATP may be even lower. These same authors have also reported that ATP catabolism was less pronounced during the first 6 h of preservation when Bretschneider solution was used instead of an extracellular, fluid-type, hyperkalemic, cardioplegic solution. In contrast, when preservation lasted longer than 6 h, the intracellular concentration of high-energy compounds was higher when an intracellular type of solution like UWsolution was used. Although our study showed left ventricular functional deficits in group 2, the heart was in fact preserved with a single flush of UW solution for only 6 h, followed by 2 h of reperfusion. However, it is clear that UW solution provides excellent heart preservation for up to 10–15 h [12, 35] and possibly for 8 h clinically [13]. In this study of 6-h preservation, the myocardial concentrations of high-energy compounds in the two groups were the same at the end of preservation. However, during reperfusion, myocardial ATP, ADP, and TAN concentrations tended to be higher in hearts treated with a nondepolarizing solution (group 1). Elevation in coronary sinus plasma MB-CK concentration during reperfusion was significantly less in the hearts treated with nondepolarizing solution, as were ultrastructural changes.

Several groups have reported that cGMP destabilizes lysosomal membranes and that cAMP can stabilize them [6, 11]. In our study, tissue cAMP and cGMP declined slightly in both groups during preservation and were significantly lower than baseline during reperfusion. However, no significant intergroup difference was observed at the end of reperfusion. While no significant difference in left ventricular systolic function was present, the nondepolarizing solution afforded significant protection, as assessed by serum m-AAT and MB-CK concentrations and changes in myocardial ultrastructure. Furthermore, diastolic function was preserved better.

This study used two different types of solutions. The composition of UW solution was designed to minimize inflammation, particularly free-radical production in the myocardium, during ischemia-reperfusion, and contains allopurinol and glutatione. Bolli [4] has reported that free radicals are responsible for ventricular dysfunction during early reperfusion. This study did not demonstrate a salutary effect of UW solution on either inhibition of cellular damage or ventricular dysfunction, although heart preservation was limited to 6 h.

The etiology of elevated left ventricular pressure is multifactorial, but ventricular diastolic dysfunction has two main components: an increase in passive chamber stiffness and a decrease in relaxation. Acutely, both ischemia and abnormal cytosolic Ca^{2+} flux cause ventricular diastolic dysfunction. Left ventricular diastolic dysfunction was significantly greater in group 2 than in group 1, suggesting that when UW solution was used in 6-h preservation followed by 2-h reperfusion, it did not preserve ventricular diastolic function.

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