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The effect of sodium concentration on myocardial viability in donor heart preservation using a nondepolarizing solution

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Abstract This study examined the effect of different sodium concentrations in a nondepolarizing solution on myocardial viability and functional recovery of the canine donor heart. Isolated canine hearts were preserved for 6 h at 5 °C, followed by normothermic reperfusion for 2 h. Dogs were divided into two groups of nine dogs each: group 1 received a nondepolarizing solution with 70 mM Na^+ and group 2 with 30 mM Na^+. The myocardial Ca^{2+} concentration at the end of preservation was significantly higher in group 1 than in group 2 and increased after reperfusion in both groups without any intergroup difference. Myocardial concentrations of ATP, ADP, and total adenine nucleotide at the end of reperfusion were significantly higher in group 1 than in group 2. Myocardial cyclic adenosine monophosphate concentration was significantly higher in group 1 than in group 2 at the end of both preservation and reperfusion. The myocardial cyclic guanosine monophosphate concentration in group 1 increased and was higher than in group 2 at the end of preservation, but had returned to normal levels by the end of reperfusion. However, it remained unchanged through preservation and reperfusion in group 2. The left ventricular systolic and diastolic function, assessed by pressure-volume relationship, was better in group 1 than in group 2. Mitochondrial ultrastructural changes were similar. These results suggest that a nondepolarizing solution containing 70 mM Na^+ provides better myocardial protection than a solution containing 30 mM Na^+.

Key words Heart preservation, dog · Preservation, heart, dog Sodium, heart preservation

Introduction

Hypothermic cardioplegia is widely accepted as a means of myocardial preservation. However, current cardioplegic solutions depend upon depolarization of the myocyte, and both hypothermia and depolarization cause enzyme dysfunction [8], decreased membrane stability [5, 9], and Ca^{2+} sequestration [2].

A normal intracellular sodium concentration is second to potassium in importance with regard to the normal physiological functioning of myocytes, especially for the sarcolemma, just as sodium is second in importance to potassium in determining the resting membrane potential [15]. Sodium influx increases during ischemia followed by reperfusion because of Na^+-K^+ pump dysfunction which, in turn, leads to increased Ca^{2+} influx [4, 21]. These ion fluxes are attenuated during hypothermia. Our previous study showed that a nondepolarizing solution was better in preventing calcium overload and in preserving myocardial viability than UWsolution [10, 20]. However, the optimal Na^+ concentration during prolonged ischemia induced by a nondepolarizing solution has not yet been determined.

This study examines the effect of two different sodium concentrations in a nondepolarizing solution developed

Table 1 Comparison of hemodynamic conditions of canine hearts reperfused following 6 h of hypothermic preservation using high-sodium (group 1, 70 mM Na^+) or low-sodium (group 2, 30 mM Na^+) cardioplegia. Values given indicate mean ± SEM. LV, left ventricle

	Group 1 ($n = 9$)	Group 2 ($n = 9$)	Significance
Perfusion pressure (mm Hg)	100.1 ± 7.7	94.4 ± 6.1	NS
Reperfusion 30 min	81.9 ± 6.0	83.6 ± 6.1	NS
Reperfusion 60 min	69.7 ± 4.8	74.0 ± 3.3	NS
Reperfusion 120 min			
Aortic flow (ml/min per 100 g LV)			
Reperfusion 30 min	131 ± 13	132 ± 13	NS
Reperfusion 60 min	136 ± 12	119 ± 9	NS
Reperfusion 120 min	170 ± 14	156 ± 12	NS
Coronary flow (ml/min per 100 g LV)			
Reperfusion 30 min	113 ± 11	111 ± 16	NS
Reperfusion 60 min	117 ± 10	104 ± 13	NS
Reperfusion 120 min	144 ± 18	114 ± 10	NS
Temperature (°C)	35.6 ± 1.1	36.6 ± 0.1	NS
Hematocrit (%)	30.0 ± 1.3	32.1 ± 1.4	NS

for myocardial preservation in an experimental donor heart preservation model.

Materials and methods

Eighteen dogs weighing 12–21 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.

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 both groups. 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 (4°C) saline, and cardioplegic solution (5 ml/kg) was infused 10 min prior to starting reperfusion in both groups. In group 1, the composition of the cardioplegic solution was 60 mEq Na^+, 16 mM Mg^{2+}, 1 mM Ca^{2+}, 50 mM mannitol, 2 mM lidocaine hydrochloride, 250 mg/l betamethasone, and 245 mM glucose. The osmolarity was 450 mosmol/l, and the pH was adjusted to 7.50 by the addition of 10 mM sodium bicarbonate; thus, the final concentration of Na^+ was 70 mM. In group 2, the composition of the cardioplegic solution was the same as in group 1, except that 20 mM Na^+ was added, and the final Na^+ concentration was 30 mM with a pH of 7.50 and an osmolarity of 410 mosmol/l. 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) was used to measure left ventricular pressure during reperfusion. Special care was taken to avoid mechanically-induced aortic regurgitation.

Reperfusion

A second dog was anesthetized, ventilated, and maintained hemodynamically by the infusion of Ringer's lactate solution. Both carotid arteries were cannulated (Fr 10) and connected to the arterial cannula placed in the preserved heart. A second pressure transducer and a magnetic flow meter (Nihon Kohden, Tokyo) were connected to the circuit to measure the perfusion pressure and flow. Coronary sinus blood flow was also measured using a magnetic flow meter. 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, each dog was 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 the concentration of adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), total adenine nucleotide (TAN), and creatine phosphate (CP) using previously described methods [3]. Samples were also analyzed for cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) by radioimmunoassay [17]. The Ca^{2+} concentration was determined using atomic absorption spectrophotometry [7]. Electron microscopy was used to evaluate ultrastructural changes by semiquantitative morphometry [19].

Samples of coronary sinus blood were collected after 5, 60, and 120 min of reperfusion. The serum MB fraction of creatine kinase (MB-CK) and mitochondrial aspartate aminotransferase (m-AAT) were measured using an immunochemiluminometric technique [13]. Left ventricular end-systolic and diastolic pressures were measured by a balloon inflated with saline volumes of 0–20 ml. The left ven-

Table 2 Comparison of myocardial concentrations of biochemical compounds in canine hearts reperfused following 6 h of hypothermic preservation using high-sodium (group 1, 70 mM Na^+) or low-sodium (group 2, 30 mM Na^+) cardioplegia. Values given indicate mean ± SEM. p, Value at end of preservation; r, value at end of reperfusion

[a] Significance to P at end of preservation

	Group 1 ($n = 9$)	Group 2 ($n = 9$)	P value
Calcium	p 40.7 ± 2.8	30.2 ± 3.5	< 0.05
(μg/g)	r 61.5 ± 5.9[a]	65.1 ± 8.7[a]	
Adenosine triphosphate	p 33.63 ± 6.64	34.37 ± 5.45	
(μmol/g dry weight)	r 45.62 ± 2.80	31.76 ± 4.50	< 0.05
Adenosine diphosphate	p 8.31 ± 0.92	7.96 ± 0.66	
(μmol/g dry weight)	r 11.06 ± 1.13[a]	8.61 ± 1.19	< 0.05
Adenosine monophosphate	p 3.44 ± 0.63	4.77 ± 1.09	
(μmol/g dry weight)	r 4.18 ± 0.86	2.82 ± 0.82	
Total adenine nucleotide	p 45.38 ± 2.73	47.10 ± 2.40	
(μmol/g dry weight)	r 60.86 ± 1.60[a]	43.19 ± 2.17	< 0.05
Cyclic adenosine	p 2737 ± 200	2171 ± 154	< 0.05
monophosphate (pmol/g)	r 1360 ± 168[a]	510 ± 61[a]	< 0.001
Cyclic guanosine	p 16.2 ± 2.1	11.7 ± 2.5	< 0.05
monophosphate (pmol/g)	r 11.6 ± 2.4[a]	8.6 ± 1.0	
Creatine phosphate	p 14.64 ± 5.20	23.65 ± 5.24	
(μmol/g dry weight)	r 40.90 ± 4.30[a]	39.18 ± 3.78[a]	

Table 3 Comparison of coronary sinus plasma concentrations of biochemical compounds in canine hearts reperfused following 6 h of hypothermic preservation using high-sodium (group 1, 70 mM Na^+) or low-sodium (group 2, 30 mM Na^+) cardioplegia. Values given indicate mean ± SEM. MB-CK, MB-fraction of creatinine kinase

	Reperfusion (min)	Group 1 ($n = 9$)	Group 2 ($n = 9$)
MB-CK (IU/l per 100 g)	5	5.0 ± 2.1	6.7 ± 1.9
	60	27.8 ± 10.7	27.5 ± 6.4
	120	36.9 ± 13.2	34.6 ± 7.5
Mitochondrial aspartate aminotransferase	5	3.9 ± 0.5	4.1 ± 0.5
(IU/l per 100 g)	60	8.9 ± 1.6	8.5 ± 0.8
	120	19.9 ± 4.0	22.7 ± 3.0

tricular end-systolic pressure-volume relationship (ESPVR) and the end-diastolic pressure-volume relationship (EDPVR) were calculated to evaluate left ventricular function.

Data within each group were analyzed by Student's paired t-test and between groups by the Mann-Whitney test. P values lower than 0.05 were considered statistically significant.

Results

Perfusion pressure, flow during reperfusion, coronary flow, hematocrit, and temperature were matched between the two groups (Table 1). One of nine hearts in group 1 required defibrillation (average 0.22 times per heart) and five hearts in group 2 required defibrillation (average 1.00 times per heart). All animals in both gorups survived reperfusion.

The myocardial calcium concentration was slightly, but significantly, higher at the end of preservation in group 1 than in group 2 (40.7 ± 2.8 μg/g 30.2 ± 8.7 μg/g, $P < 0.05$), but not at the end of reperfusion (Table 2).

The myocardial ATP concentration was significantly higher at the end of reperfusion in group 1 than in group 2 (19.25 ± 1.18 μg/mg protein vs 13.40 ± 1.90 μg/mg protein, $P < 0.05$), but not at the end of preservation. Both the myocardial ADP and TAN concentrations were significantly higher at the end of reperfusion in group 1 than in group 2 ($P < 0.05$ and $P < 0.01$, respectively), but not at the end of preservation (Table 2). No significant difference existed in the myocardial concentration of AMP or CP at the end of either preservation or reperfusion. The myocardial cAMP concentration was significantly higher at the end of both preservation and reperfusion in group 1 than in group 2. The myocardial cGMP concentration was significantly higher at the end of preservation in group 1 than in group 2 ($P < 0.05$), but not at the end of reperfusion (Table 2).

The serum concentration of both MB-CK and mAAT increased during reperfusion, though the intergroup difference was not significant (Table 3).

Table 4 Comparison of changes in mitochondrial ultrastructure as determined by semiquantitative morphometry in canine hearts reperfused following 6 h of hypothermic preservation using high-sodium (group 1, 70 mM Na^+) or low-sodium (group 2, 30 mM Na^+) cardioplegia. Values given indicate mean ± SEM. Scores indicate range between "total destruction" (0) and "intact" (100)

		Group 1 ($n = 9$)	Group 2 ($n = 9$)
Membranes	Preservation	53.5 ± 1.5	54.3 ± 2.4
	Reperfusion	61.9 ± 2.0	62.9 ± 2.9
Cristae	Preservation	44.4 ± 1.2	44.2 ± 2.6
	Reperfusion	49.2 ± 2.9	53.1 ± 4.7

Table 5 Left ventricular end-systolic and diastolic pressure-volume relationship in canine hearts at 2 h of reperfusion following 6 h of hypothermic cardioplegia

	Group 1 ($n = 9$) Na^+ 70 mM	Group 2 ($n = 9$) Na^+ 30 mM
Left ventricular end-systolic pressure volume relationship (ESPVR) Slope	4.71 ($P < 0.001$)	4.07 ($P < 0.0001$)
Intercept (mm Hg)	66.3	75.0
Left venbtricular end-diastolic pressure volume relationship (EDPVR) Slope	1.24 ($P < 0.001$)	2.08 ($P < 0.0001$)
Intercept (mm Hg)	−4.49	−8.28

Morphometry of the mitochondrial ultrastructure did not demonstrate any significant difference between group 1 and group 2 in the structure of the mitochondrial membrane or cristae at the end of either preservation or reperfusion (Table 4).

Left ventricular systolic function was satisfactory in both groups but better in group 1 than in group 2 (Table 5). However, the left ventricular end-diastolic pressure was more significantly impaired during reperfusion in group 2 than in group 1 (Table 5).

Discussion

Our nondepolarizing solution showed better myocardial viability than a standard cardioplegic solution with 20 mM K^+ after 6 h of hypothermic preservation [20]. However, we have been criticized for not measuring the direct membrane resting potential (MRP) in situ. Although the Na^+ concentration in the preservation solution is believed to be of secondary importance compared to potassium in determining the MRP [15], the MRP in group 1 was likely to be lower than that in group 2. Furthermore, since hypertonicity reduces the MRP [1] because of cell shrinkage, the higher osmolarity in the solution used in group 1 probably reduced the MRP more than in group 2. Low temperature decreases membrane fluidity [9], resulting in a reduction in the MRP. It has been demonstrated that an acid pH markedly diminishes inward Ca^{2+} and Na^+ currents [22], as well as Na^+-K^+-ATPase activity in cardiac muscle [16]. However, in this study, temperature and acidosis due to ischemic preservation were most likely identical between the two groups because of this experimental design. Local anesthetics are known to depress the resting membrane conductance for K^+ and Na^+ and also to depress voltage-dependent slow channels [14]. These effects presumably represent a nonspecific effect of local anesthetics on the membrane fluidity. Furthermore, local anesthetics depress the Na^+-K^+-ATPase activity [6]. In this study, although both groups received 2 mM lidocaine, it is possible that lidocaine may have had a different effect on the sarcolemma because of the difference in the Na^+ concentration. This evidence suggests that the MRP in group 1 was more hyperpolarized than that in group 2. Although mechanisms are still unclear in 6-h preservation, the higher concentration of Na in a nondepolarizing solution improved cardiac preservation in adenine nucleotide compounds and left ventricular function.

Sukehiro et al. [18] have reported that in hearts rendered ischemic for more than 6 h, the use of an intracellular type of solution resulted in higher concentrations of myocardial ATP than an extracellular type of solution in hearts rendered ischemic for more than 6 h. They have also reported that the myocardial ATP concentration was better preserved with Bretschneider solution than with an extracellular hyperkalemic solution in hearts preserved for less than 6 h. The concept of depolarizing the myocyte with a K^+-containing solution developed from earlier studies. At present, no data is available on the optimal concentration of Na^+ in a nondepolarizing solution for preserving myocardial ATP. The depletion of adenine nucleotide compounds, which results from both a loss of membrane integrity and organelle dysfunction, is a critical factor that causes delayed left ventricular recovery during reperfusion. In this study, the myocardial concentration of ADP and TAN during reperfusion increased significantly in group 1 but remained unchanged in group 2. Furthermore, the myocardial ATP, ADP, and TAN concentrations at the end of reperfusion were significantly higher in group 1 than in group 2. These results suggest that a higher Na^+ concentration (70 mM) is superior to a lower one (30 mM) for preserving myocardial adenine nucleotide compounds.

After depolarization of the myocyte, in which most membrane-bound enzymes have been inactivated by deep hypothermia (5°C), massive Na^+ influx occurs as a result of the depth of the MRP and the Na^+ gradient across the sarcolemma, which induces Ca^{2+} influx. Pappano et al. [12] have reported that lowering $[Na^+]_0$ decreases Na^+ influx, which is a depolarizing current; hence, hyperpolarization should take place. In this regard, the solution used in group 2 with 30 mM Na^+ is superior to that in group 1 with 70 mM Na^+. This mechanism may account for the lower myocardial Ca^{2+} concentration at the end of preservation in group 2 than in group 1. Calcium overload in the ischemic myocardium occurs during reperfusion secondary to changes in the sarcoplasmic reticulum, adrenergic receptors related to cAMP, Ca^{2+} slow

channel, membrane structure, and depression of glycolysis and ATP [11]. The myocardial Ca^{2+} concentration at the end of preservation was slightly, but significantly, higher in group 1 than in group 2. However, although it rose significantly during reperfusion, the difference between groups was not significant. This finding suggests that a low Na^+ concentration (30 mM) may be more effective than a high Na^+ concentration in preventing Ca^{2+} overload during hypothermic preservation. Since there was no significant difference between groups in the Ca^{2+} concentration in the preservation solution, in the myocardial ATP concentration, or in the myocardial ultrastructure at the end of preservation, neither of these factors appeared to be responsible for the difference in the Ca^{2+} concentration. Moreover, the level of hypothermia during preservation was identical in the two groups, so its effect on membrane-bound enzymes can also be ignored. However, this study showed that the myocardial concentration of cAMP was higher in group 1 than in group 2. This result most likely involves calcium movement, which needs further investigation. The difference in osmolarity of solutions might have affected the myocardial water content at the end of preservation to a lesser degree in group 1 than in group 2. Then, the myocardial Ca concentration may have been lower in group 2 than in group 1, since we measured the myocardial Ca concentration per gram of the wet myocardium. The difference in the Na^+ concentration had no effect on the Ca^{2+} concentration at the end of reperfusion.

Left ventricular systolic function was preserved satisfactorily without any difference between groups. However, after both 60 and 120 min of reperfusion with left ventricular volume-loading, the left ventricular end-diastolic pressure was significantly lower in group 1 than in group 2. In an isovolumetric model like this study, an elevation of the end-diastolic pressure indicates an increase in left ventricular stiffness, which results from an accumulation of the myocardial Ca^{2+}. At the end of reperfusion, although the myocardial Ca^{2+} concentration was the same in both groups, the myocardial concentrations of ATP, ADP, TAN, and cAMP, which are essential for left ventricular relaxation, were higher in group 1 than in group 2. Therefore, the better diastolic function seen in group 1 may have been due to better relaxation rather than to decreased wall stiffness.

In summary, after 6 h of cold cardioplegic preservation of the canine heart, the higher concentration (70 mM) of Na in a nondepolarizing solution improved cardiac preservation in myocardial adenine nucleotide compounds and left ventricular functional recovery. Further study is needed to clarify biochemical and physiological mechanisms of these effects.

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