Transplant Int (1992) 5 [Suppl 1]: S411–S416

TRANSPLANT
International

The significant role of membrane stabilization in hypothermic cardioplegic cardiac preservation in a canine experimental model

Makoto Sunamori, Imad Sultan, Toshizumi Shirai, and Akio Suzuki

From the Department of Thoracic-Cardiovascular Surgery, Tokyo Medical and Dental University, School of Medicine, Tokyo, Japan

Abstract. Isolated mongrel hearts were preserved for 6 h at 5 °C followed by normothermic reperfusion for 2 h. The dogs were divided into three groups; K^+-cardioplegic solution alone, group C, $n = 7$; K^+-cardioplegic solution with lidocaine 200 mg/l, group L, $n = 7$; and K^+-cardioplegic solution with betamethasone 250 mg/l and lidocaine 200 mg/l, group B + L, $n = 7$. Ventricular fibrillation occurred early during reperfusion in all dogs in group C, in one of seven in group L, and in two of seven dogs in group B + L. The serum MB fraction of creatinine kinase (MB-CK), mitochondrial aspartate aminotransferase (m-AAT) and calcium overload were suppressed to a greater extent in both groups L and B + L during reperfusion compared to group C. Myocardial ATP, total adenine nucleotide, and creatine phosphate did not differ between the three groups at the end of reperfusion. Myocardial ADP and AMP declined significantly during reperfusion in group C, however, they remained unchanged in group B + L and increased in group L which showed significantly higher levels compared to group C. Left ventricular functional recovery during reperfusion was consistently better in both group L and B + L compared to group C. These results suggested that membrane stabilization prevents myocardial damage from hypothermia and cardioplegia and provides better myocardial viability and functional recovery in donor heart preservation.

Key words: Heart transplantation – Cardioplegic solution – Lidocaine – Betamethasone

The preservation of the donor heart is a major issue in cardiac transplantation. This falls within two objectives: to improve the early operative results and to increase the supply of donor hearts. Hypothermia has been widely accepted as a means of myocardial preservation since it reduces myocardial consumption of oxygen and metabolic demand. However, hypothermia below 15 °C inhibits the activity of membrane-bound ATPase resulting in ionic shifts across the sarcolemma [14] and inducing a change in the fluidity of the phospholipid layers of the membrane [7, 15].

The current method of cardioplegia is based largely on depolarization of the membrane of the myocyte. Under depolarized conditions, myocardial cells are exposed to unfavorable phenomena such as increased permeability and the accumulation of sodium and calcium, with subsequent cellular swelling. Calcium overload is thought to be one of the major causes of reperfusion injury [18]. The function of the myocardial membranes is severely modified under conditions of prolonged ischemia followed by reperfusion. The major problems during reperfusion include dysrrhythmias, depletion of high energy phosphate (HEP), ventricular dysfunction, and myocardial necrosis.

Lidocaine hydrochloride [2, 6, 10, 13, 17, 19, 22–24, 33] and betamethasone [9, 25, 29], one of the glucocorticoids, have been reported to have a significant effect on membrane stabilization in the myocardium via different mechanisms. Thus, our objective was to elucidate the effects of membrane stabilization with lidocaine alone or lidocaine plus betamethasone in preservation of the donor heart. We evaluated myocardial viability by assessing biochemical findings, cell ultrastructure, and left ventricular function in experimental hypothermic cardioplegic cardiac preservation.

Materials and methods

Twenty-one mogrel dogs weighing between 8 and 21 kg were used in this experiment. All dogs were anesthetized with pentobarbital (approximately 30 mg/kg intravenously) to the suppression of corneal reflexes. Respiration was controlled with a positive-pressure ventilator. Ringer's lactate solution was infused intravenously to maintain a physiologic hemodynamic status. These animals received humane care as described in "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 Na-

Offprint requests to: Makoto Sunamori, M.D., Department of Thoracic-Cardiovascular Surgery, Tokyo Medical and Dental University, School of Medicine, 1-5-45, Yushima, Bunkyo-ku, Tokyo, 113, Japan

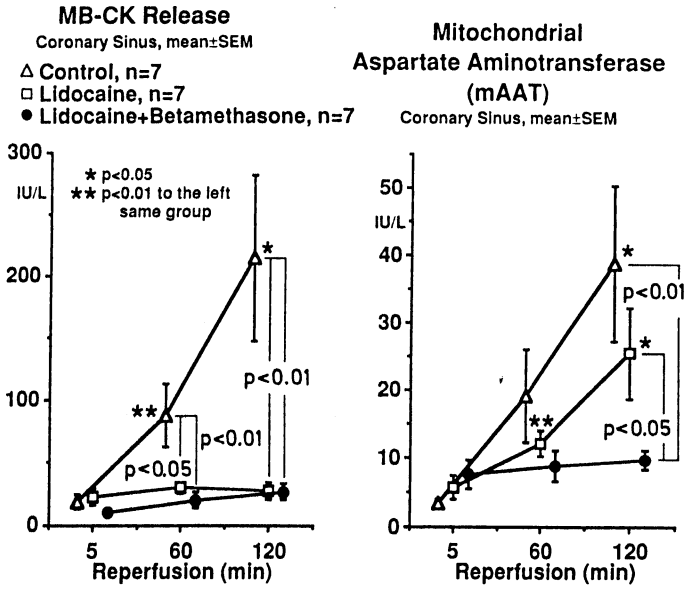

Fig. 1. Myocardial enzyme release into coronary sinus. MB-CK during reperfusion was significantly suppressed in both groups L and B + L as compared to group C. mAAT remained unchanged in group B + L however, it increased significantly during the course of reperfusion in groups C and L

tional Academy of Sciences and published by the National Institutes of Health.

Procurement of the heart. After median sternotomy, the superior and inferior vena cava were encircled with 2–0 silk sutures at both proximal and distal ends for future ligation and division. The azygous vein was ligated and divided. Both common carotid arteries, the left subclavian artery, and the descending aorta were encircled with 2–0 silk both proximally and distally. The hili of the lungs were encircled with 00 silk bilaterally in each animal. An arterial canula (Fr # 10) was inserted through the proximal right subclavian artery. A venous canula (Fr # 24) was placed in the right ventricle through the right atrial appendage. Approximately 500 ml of blood was withdrawn from the venous canula. This blood was saved with adequate heparinization for transfusion during reperfusion. The encircled arteries were ligated. The pulmonary hili were also ligated after ventilation was terminated. Immediately after aortic occlusion, cardioplegia was induced by infusion of cold (4 °C) cardioplegic solution via the arterial canula. The initial amount infused was 10 ml/kg. The superior and inferior vena cava were subsequently ligated and divided, and the heart was harvested.

Preservation of the heart. The heart was immersed in cold (4 °C) saline solution for 6 h. The cardioplegic solution (3 ml/kg) was infused every 60 min. The cardioplegic solution consisted of K^+ 20 mEq, Mg^{2+} 16 mM, Ca^{2+} 1 mM, mannitol 100 mM, and glucose 245 mM, per liter, osmolarity 450 mOsm, pH 7.50, adjusted by bicarbonate. One hour prior to reperfusion, a latex-balloon was placed in the left ventricle with a holding apparatus sutured in the mitral position. This balloon was connected to a transducer (Statham P23DB, Statham Instruments, Los Angeles, Calif.) to measure left ventricular pressure during reperfusion with a polygraph (Nihon Kohden, Tokyo). Special care was taken not to induce mechanical aortic regurgitation. For 30 min prior to reperfusion, the heart was exposed to room temperature without cold saline immersion.

Reperfusion. An additional mongrel dog was anesthetized and ventilated in the manner described earlier. The dog was maintained in physiologic cardio-pulmonary status with an infusion of Ringer's lactate solution. Both carotid arteries were canulated (Fr # 10), and these arterial lines were connected to the arterial canula placed in the preserved heart. A pressure transducer (Statham P23DB, Statham Instruments, Los Angeles, Calif.) and a magnetic flow meter (Nihon Kohden, Tokyo) for measurement of perfusion pressure and perfusion flow, respectively, were connected to the circulation. Coronary sinus blood flow was measured by a magnetic flow meter (Nihon Kohden, Tokyo) to obtain a close approximation of coronary blood flow. Blood from the canula placed in the right ventricle, and from the left ventricle vented at the apex was collected in a reservoir. This blood was infused back into a supporting dog by a pump and normothermia was maintained by a heat exchanger. Reperfusion was continued for 2 h. Defibrillation was applied when the heart developed ventricular fibrillation during early reperfusion. After 5 min

Table 1. Myocardial high energy phosphate

		Control $n=7$	Lidocaine $n=7$	Lidocaine + Betamethasone $n=7$
Adenosine Triphosphate (ATP) μg/mg protein	Preservation 6 h	14.34 ± 1.50	8.67 ± 1.09*[1]	10.06 ± 5.20
	Reperfusion 2 h	13.28 ± 4.10	13.34 ± 1.58*[3]	14.29 ± 0.99
Adenosine Diphosphate (ADP) μg/mg protein	Preservation 6 h	4.51 ± 0.31	2.34 ± 0.36*[2]	2.86 ± 0.28*[1]
	Reperfusion 2 h	2.58 ± 0.31*[3]	3.56 ± 0.17*[3]	3.06 ± 0.34
Adenosine Monophosphate (AMP) μg/mg protein	Preservation 6 h	0.82 ± 0.11	0.55 ± 0.13	0.74 ± 0.12
	Reperfusion 2 h	0.36 ± 0.08*[3]	0.71 ± 0.09*[1]	0.56 ± 0.09
Total Adenine Nucleotide (TAN) μg/mg protein	Preservation 6 h	20.11 ± 1.61	11.23 ± 1.22*[2]	13.49 ± 2.24*[1]
	Reperfusion 2 h	16.32 ± 4.24	17.52 ± 1.22*[3]	17.99 ± 1.18
Creatine Phosphate (CP) μg/mg protein	Preservation 6 h	3.58 ± 0.64	2.85 ± 0.93	3.98 ± 0.77
	Reperfusion 2 h	16.67 ± 5.31*[4]	16.14 ± 3.40*[3]	17.14 ± 2.60*[3]

Mean ± SEM *[1] $P < 0.05$, *[2] $P < 0.01$ indicate significance vs control group, *[3] $P < 0.01$, *[4] $P < 0.05$ indicate significance vs preservation 6 h group

of reperfusion, all dogs were paced at 130 beats/minute. No cardiotonic drug was administered to any dog.

The 21 dogs were grouped as follows: group C (control, 7 dogs) received cardioplegic solution alone, group L (7 dogs) received cardioplegic solution together with lidocaine hydrochloride 200 mg/l, and group B + L (7 dogs) received cardioplegic solution together with both betamethasone 250 mg/l and lidocaine 200 mg/l.

At the end of both preservation and during reperfusion while the heart was beating and oxygenated, tissue was biopsied from the subendocardium of the left ventricle. These tissues were analyzed for myocardial content of adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), creatine phosphate (CP), cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP) and calcium (Ca) by methods described elsewhere [30]. These tissues were also examined by electron microscopy to evaluate ultrastructural changes.

At 5, 60 and 120 min of reperfusion, coronary sinus venous blood was withdrawn through a venous canula. The serum MB fraction of creatine kinase (MB-CK) and mitochondrial aspartate aminotransferase (m-AAT) were measured. Left ventricular (LV) end-systolic pressure was measured with a balloon inflated with saline, using volumes of 10, 15, and 20 ml. The left ventricular end-systolic pressure-volume relation (ESPVR) was studied to evaluate the functional recovery of the left ventricle.

Data within each group was analyzed by the Student's paired *t*-test, and between groups by the Mann-Whitney test. A level of $P < 0.05$ was accepted as statistically significant.

Results

Basic data such as perfusion pressure and flow during reperfusion, coronary flow, hematocrit, temperature and weight of the LV were well matched between the groups. Defibrillation was performed in all seven dogs in group C (2.43 times/dog), while one of the seven dogs in group L (0.29 times/dog), and two of the seven dogs in group B + L (0.29 times/dog) were defibrillated. All the dogs in each of the three groups survived 2 h of reperfusion.

Myocardial high-energy phosphate (HEP)

As shown in Table 1, myocardial ATP content in group L was significantly lower at the end of preservation than that of group C. Myocardial ATP in group L increased significantly during reperfusion, and its level was not significantly different from the other two groups. No significant difference in myocardial ATP was observed at the end of both preservation and reperfusion between group L and group B + L. Myocardial ADP in group L was significantly lower at the end of preservation and significantly higher at the end of reperfusion as compared to those in group C. Depletion of myocardial AMP in group C was significant, while myocardial AMP did not decline during reperfusion in both group L and group B + L. Myocardial AMP at the end of reperfusion in group L was significantly higher than that of group C. Myocardial total adenine nucleotide (TAN) in group C was significantly better maintained during preservation than that of group L. However, myocardial TAN did not differ at the end of reperfusion between the three groups. Myocardial CP increased significantly during reperfusion in all groups. However, no significant difference in CP was observed between the three groups at the end of either preservation or reperfusion.

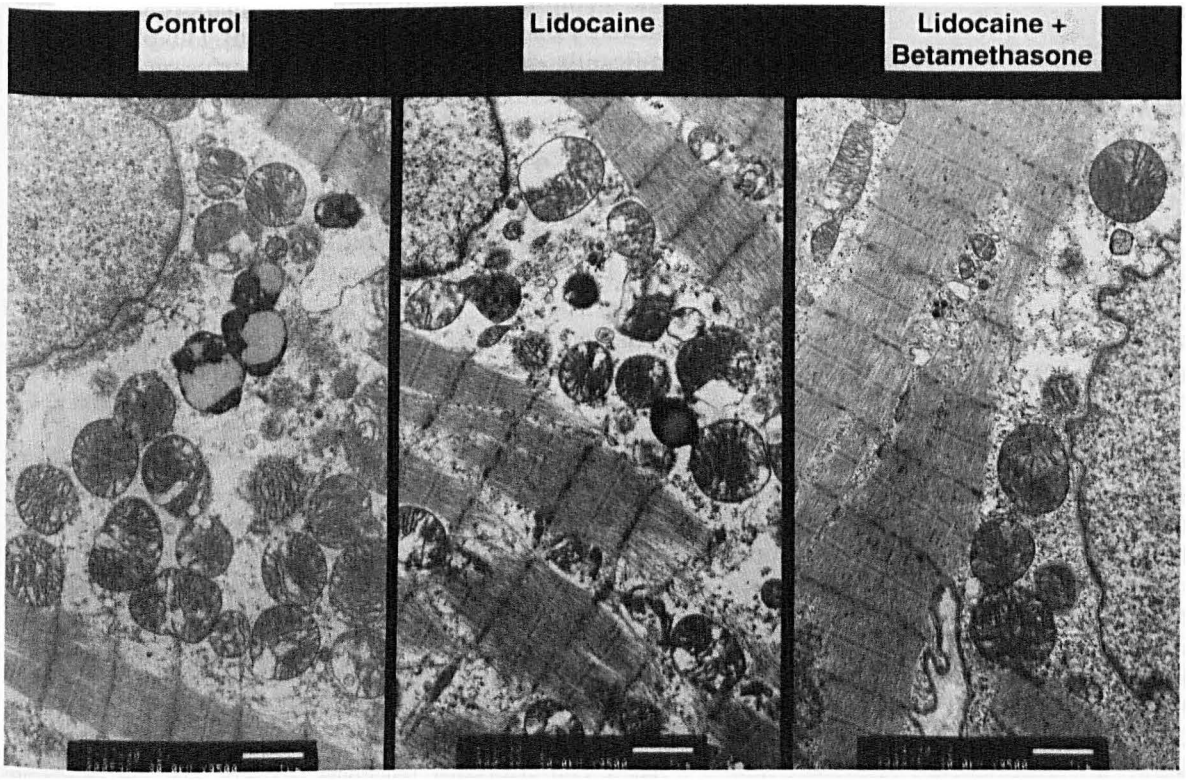

Fig. 2. Ultrastructure of the subendocardial layer of the left ventricle: *left,* group C; *middle,* group L; and *right,* group B + L. Mitochondrial disruption and swelling are observed in addition to interstitial edema in group C. Ultrastructure is well preserved in group B + L

Table 2. Myocardial cyclic monophosphate

		Control $n=7$	Lidocaine $n=7$	Lidocaine + Betamethasone $n=7$
Cyclic Adenosine Monophosphate (cAMP) pmol/g	Preservation 6 h	2604 ± 137	2770 ± 154	2523 ± 389
	Reperfusion 2 h	1161 ± 338*	1033 ± 84*	1099 ± 435**
Cyclic Guanosine Monophosphate (cGMP) pmol/g	Preservation 6 h	15.0 ± 2.7	13.5 ± 2.8	15.8 ± 2.2
	Reperfusion 2 h	10.0 ± 2.0	5.8 ± 0.4**	5.0 ± 1.3* **

Mean ± SEM * $P < 0.01$, ** $P < 0.05$ indicates significance vs preservation 6 h group, *** $P < 0.05$ indicates significance vs control group

Table 3. Myocardial tissue calcium content, μg/g tissue, mean ± – SEM

	Control $n=7$	Lidocaine $n=7$	Lidocaine + Betamethasone $n=7$
Preservation 6 h	50.7 ± 4.7	46.7 ± 5.4	39.6 ± 2.6*
Reperfusion 2 h	83.7 ± 13.2**	58.6 ± 4.2 **	50.5 ± 2.9 **

* $P < 0.05$ indicates significance vs control group, ** $P < 0.05$ indicates significance vs preservation 6 h group

Cyclic monophosphate. Tissue content of cyclic monophosphates is shown in Table 2. Tissue cAMP declined significantly during reperfusion in all three groups, and no significant difference in tissue cAMP was observed between the three groups at the end of either preservation or reperfusion. Tissue cGMP in both groups L and B + L declined significantly during reperfusion. Their levels at the end of reperfusion tended to be lower than those of group C.

Myocardial isoenzymes. As shown in Fig. 1, MB-CK and m-AAT in group C increased remarkably during the course of reperfusion, while MB-CK and m-AAT in both groups L and B + L remained unchanged or increased only slightly.

Tissue Ca. As shown in Table 3, tissue Ca increased significantly during reperfusion in all groups. Tissue Ca at the end of preservation tended to be lower in group L and was significantly lower in group B + L as compared to that in group C.

Ultrastructural change. Mitochondrial changes were minimal in both groups L and B + L at the end of reperfusion. On the other hand, moderate damage was observed in the cristae and membranes of mitochondria in group C. Myofibrils were well preserved in all groups. Representative pictures are shown in Fig. 2.

Left ventricular functional recovery. As shown in Fig. 3, the ESPVR at 2 h of reperfusion demonstrated satisfactory functional recovery in all groups. Better functional recovery of the left ventricle was observed in both groups L and B + L in the range of 5 to 20 ml of LV volume as compared to group C.

Discussion

The major myocardial problems encountered during reperfusion following ischemia are arrhythmia, depletion of HEP and substrates for myocardial metabolism, myocardial necrosis, and ventricular dysfunction. Hypothermic cardioplegia has become the standard procedure for myocardial protection of the donor heart. Cardiac arrest under hypothermia serves to reduce dramatically the rate of oxygen consumption and metabolic demand, and consequently slows various degradative processes within the myocardium [20]. However, hypothermia has deleterious effects on the myocardium: firstly, there is an alteration of membrane lipid bilayer structures, and secondly, there is an increase in ion permeability across the cell membranes. The cell membrane undergoes phase transition as the temperature is lowered [7, 15]: at 18 °C, membrane lipids undergo a stabilizing phase change, but below 10 °C, lipid crystallization can occur resulting in rupture of the membranes and an increase in ion permeability, particularly for sodium and calcium [1, 16]. This process is significantly modified in ischemia-reperfusion. As for the mechanism of the increase in membrane permeability during hypothermia, it is well documented that hypothermia

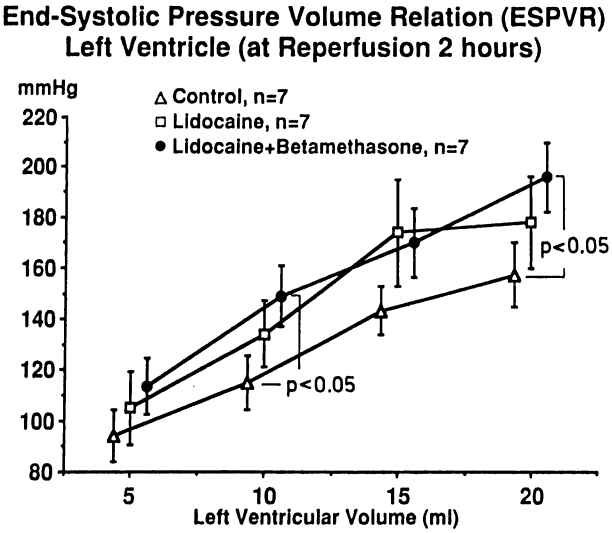

Fig. 3. Left ventricular functional recovery. This Fig. represents values at 2 h of reperfusion. ESPVR in group B + L is consistently better compared to group C

inactivates both enzyme systems of the Na-K ATPase and Ca ATPase located in the sarcolemma and sarcoplasmic reticulum, leading to possible loss of cell volume regulation and swelling [12]. Other ion pumps are probably also temperature-sensitive. The cardiac sarcolemma has, in addition to the Na-Ca exchange system, an ATP-dependent Ca transport system [4]. This system seems to have a higher affinity for Ca than does the Na-Ca exchange system, but a lower transport rate. Hypothermia depresses ATPase activity in tissues, and membrane-bound ATPase is inhibited at temperatures below 15 °C [14], thereby inactivating the Na-K pump so that sodium and water enter the cell and potassium moves out [12]. Through the Na-Ca exchange system, calcium influx is accelerated.

The current method of cardioplegia is based largely on depolarization of the membranes. When depolarized, myocardial cells are exposed to unfavorable phenomena such as increased permeability, the accumulation of sodium and calcium with subsequent cellular swelling, Ca overload, damage to subcellular organelles and ventricular fibrillation during reperfusion after ischemia. Calcium overload is thought to be one of the major causes of reperfusion injury [18]. The fundamental composition of our solution for cardiac preservation in this study is classified as a depolarizing type of solution. The resting membrane potential was estimated to be around −50 mV at 15 °C given the concentration of potassium in the solution of the control group. However, the hearts in the other two groups were preserved with the solution which contained lidocaine, 200 mg/l (approximately 1 mM/l) in addition to the solution administered to the hearts in the control group. Therefore, the hearts in both groups L and B + L may have had a slightly lower resting membrane potential, i.e. be more repolarized than the hearts in the control group. This electrophysiological difference in membrane potential between the groups suggests that the hearts in the former two groups are more resistant to ischemia than those of the latter. It is interesting to note that the hearts in the control group experienced a significantly higher incidence of ventricular fibrillation during early reperfusion than did the other two groups. Ventricular fibrillation is the most typical arrhythmia in early reperfusion following ischemia. It is proposed that the arrhythmia of early reperfusion results from an alteration of the Na^+-H^+-Ca^{2+}-exchange system [32]. Our results demonstrating inhibition of Ca overload and suppression of ventricular fibrillation during early reperfusion may be explained by these mechanisms.

Betamethasone protects ischemic myocardium by increasing coronary blood flow [29], and suppressing myocardial edema in an open heart model [28]. Furthermore, steroids stabilize lysosomal membranes [9, 25]. Lidocaine preserves mitochondrial oxidative phosphorylation [2], and inhibits cellular and subcellular damage from ischemia followed by reperfusion by stabilizing the membranes [17, 21]. Our previous investigations have suggested that combined pharmacological protection similar to that utilized in this investigation provides significant protection from prolonged cardioplegia followed by reperfusion [31].

The method of myocardial protection utilized in this investigation differed from the common method in clinical practice with respect to both the formula and frequency of injection of the cardioplegic solution. This study was conducted as a prospective animal experiment, and did include the use of a placebo; however, the data were analyzed in a blind fashion, particularly with regard to biochemical and ultrastructural changes.

Regarding the adenine nucleotide pool, HEP is catabolized during ischemia. The depletion of HEP and its intermediates leads to irreversible myocyte damage during reperfusion. Sukehiro et al. [27] have reported that ATP decreases to a level that is 50–60 % of normal during the first 6 h of preservation. Our results with myocardial ATP in this study were slightly lower than predicted by that observation. Those authors have also reported that ATP catabolism is less pronounced when the Bretschneider solution is used instead of the extracellular fluid-type hyperkalemic cardioplegic solution. Our results suggested that myocardial ATP and TAN did not differ within the three groups. During reperfusion, however, myocardial ADP and AMP did not decline, but either remained unchanged or rose significantly higher in hearts treated with membrane stabilization. This finding suggested that unfavorable leakage of AMP from cytosol could be prevented during reperfusion of the preserved heart with membrane stabilization. Coronary sinus plasma concentration of MB-CK in this study was significantly suppressed during reperfusion in the hearts treated with lidocaine or lidocaine + betamethasone. This finding clearly suggested that the hearts preserved with the aid of membrane stabilization experienced less injury during reperfusion following hypothermic cardioplegia than did hearts preserved with hypothermic cardioplegia alone. These data were further corroborated by the finding that the ultrastructure of the hearts treated with membrane stabilization was better preserved compared to hearts undergoing cardioplegia alone.

Ignarro et al. [8] and others [5] report that cGMP destabilizes lysosomal membranes while cAMP stabilizes them. In our study, tissue cAMP in all groups decreased slightly during the 6 h of preservation, and decreased significantly during reperfusion; however, no significant difference was observed between the three groups at the end of 2 h reperfusion. Tissue cGMP declined significantly during reperfusion in hearts treated with either lidocaine or lidocaine + betamethasone as compared to hearts of the control group. In addition, tissue levels of cGMP at the end of reperfusion in the former two groups tended to be lower than that of the control group. It has been reported that glucocorticoids inhibit the activity of guanylate cyclase [26] that catalyzes cGMP synthesis. Kuehl [11] has reviewed the meticulous interrelation between cyclic nucleotides and endogenous prostaglandins involving adenylate cyclase, phosphodiesterase, adenylate kinase and ATPase, which all influence intracellular cAMP levels. In this study, the addition of glucocorticoid to lidocaine did not demonstrate additional protection with regards to myocardial adenine nucleotide metabolism, but added significant protection in terms of mAAT and myocardial ultrastructure. Furthermore, the present study demonstrated better functional recovery of the left ventricle with the addition of lidocaine and betamethasone for mem-

brane stabilization together with a lower content of myocardial cGMP, suggesting that further study of these phenomena is required.

Acknowledgements. The authors wish to express our gratitude to Mr. Tatsuyuki Nakamura for his excellent technical assistance.

References

1. Alto LE and Dhalla NS (1979) Myocardial cation contents during induction of calcium paradox. Am J Physiol 237: H13–H19
2. Baron DW, Sunamori M, Harrison CE Jr (1983) Preservation of oxidative phosphorylation by lidocaine in ischemic and reperfused myocardium. Adv Myocardiol 4: 567–573
3. Busuttil RW, George WJ (1978) Myocardial ischemia, cyclic nucleotides and lysosomal enzymes. Adv Cyclic Nucleotide Res 9: 629–645
4. Caroni P, Carafoli E (1980) An ATP-dependent Ca^{2+}-pumping system in dog heart sarcolemma. Nature 283: 765–767
5. Carr FK, Goldfarb RD (1980) Ischemia-induced canine myocardial lysosome labilization: the role of endogenous prostaglandins and cyclic nucleotides. Exp Mol Pathol 33: 36–42
6. Chance B, Mela L, Harris EJ (1968) Interraction of ion movements and local anesthetics in mitochondrial membranes. Fed Proc 27: 902–906
7. Flaherty FT, Schaff HV, Goldman RA, Gott VL (1979) Metabolic and functional effects of progresive degrees of hypothermia during global ischemia. Am J Physiol 236: H839–H845
8. Ignarro LJ, Krassikoff N, Slywka J (1973) Release of enzymes from a rat liver lysosome fraction: Inhibition by catecholamines and cyclic 3', 5'-adenosine monophosphate, stimulation by cholinergic agents and cyclic 3', 5'-guanosine monophosphate. J Pharmacol Exp Ther 186: 86–99
9. Jefferson TA, Glenn TM, Martin JB, Lefer AM (1971) Cardiovascular and lysosomal actions of corticosteroids in the intact dog. Proc Soc Exp Biol Med 136: 276–280
10. Johnson CL, Schwartz A (1969) Some effects of local anesthetics on isolated mitochondria. J Pharmacol Exp Ther 167: 365–373
11. Kuehl FA Jr (1974) Prostaglandins, cyclic nucleotides and cell function. Prostaglandins 5: 325–340
12. Leaf A (1973) Cell swelling. A factor in ischemic tissue injury. Circulation 48: 455–458
13. Lesnefsky EJ, van Benthuysen KM, McMurtry IF, Shikes RH, Johnston RB Jr, Horwitz LD (1989) Lidocaine reduces canine infarct size and decreases release of a lipid peroxidation product. J Cardiovasc Pharmacol 13: 895–901
14. Martin DR, Scott DF, Downer GL, Belzer FO (1972) Primary causes of unsuccessful liver and heart preservation: Cold sensitivity of the ATPase system. Ann Surg 175: 111–117
15. McMurchie EJ, Raison JK, Cairncross KD (1973) Temperature-induced phase changes in membranes of hearts: A contrast between the thermal responses of poikilotherms and homeotherms. Comp Biochem Physiol 44: 1017–1026
16. Mattiazi A, Nilson E (1976) The influence of temperature on the tissue course of the mechanical activity in rabbit papillary muscle. Acta Physiol 97: 310–318
17. Okamura T, Sunamori M, Suzuki A (1982) Protective effect of lidocaine in reperfused ischemic myocardium. Evaluation by hemodynamic and biochemical study. Jpn Circ J 46: 657–662
18. Opie LH (1991) Role of calcium and other ions in reperfusion injury. Cardiovasc Drug Ther 5: 237–248
19. Peck SL, Johnston RB, Horwitz LD (1985) Reduced neutrophil superoxide anion release after prolonged injusions of lidocaine. J Pharmacol Exp Ther 235: 418–422
20. Rosenfeldt FL, Hearse DJ, Cankovic-Darracott S, Braimbridge MV (1980) The additive protective effects of hypothermia and chemical cardioplegia during ischemic cardiac arrest in the dog. J Thorac Cardiovasc Surg 79: 29–38
21. Schaub RG, Lemole GM, Pinder GC, Black P, Stewart GJ (1977) Effects of lidocaine and epinephrine on myocardial preservation following cardiopulmonary bypass in the dog. J Thorac Cardiovasc Surg 74: 571–576
22. Schaub RG, Stewart G, Strong M, Ruotolo R, Lemole G (1977) Reduction of ischemic myocardial damage in the dog by lidocaine infusion. Am J Pathol 87: 399–414
23. Seeman P (1972) The membrane actions of anesthetics and tranquilizers. Pharmacol Rev 24: 583–655
24. Seppala AJ, Saris NEL, Gauffin ML (1971) Inhibition of phospholipase A-induced swelling of mitochondria by local anesthetics and related agents. Biochem Pharmacol 20: 305–313
25. Spath JA Jr, Lane DL, Lefer AM (1974) Protective action of methyprednisolone on the myocardium during experimental myocardial ischemia in the cat. Cir Res 35: 44–51
26. Steiner AL, Pagliara EA, Chase LR, Kipnis DM (1972) Radioimmunoassay for cyclic nucleotides. II. cAMP and cGMP in mammalian tissues and body fluids. J Biol Chem 247: 1114–1120
27. Sukehiro S, Dyszliewics W, Minten J, Wynants J, van Belle H, Flameng W (1991) Catabolism of high energy phosphates during long-term cold storage of donor hearts: effects of extra- and intracellular fluid-type cardioplegic solutions and calcium channel blockers. J Heart Lung Transplant 10: 387–393
28. Sunamori M (1978) Protective effect of betamethasone on the subendocardial ischemia after the cardiopulmonary bypass. J Cardiovasc Surg (Torino) 19: 291–310
29. Sunamori M, Harrison CE Jr (1980) Effect of betamethasone on mitochondrial oxidative phosphorylation in ischemic canine myocardium. Mayo Clin Proc 55: 377–382
30. Sunamori M, Amano J, Okamura T, Suzuki A (1982) Superior action of magnesium-lidocaine-l-aspartate cardioplegia to glucose-insulin-potassium cardioplegia in experimental myocardial protection. Jpn J Surg 12: 372–380
31. Sunamori M, Innami R, Amano J, Suzuki A, Harrison CE Jr (1988) Role of protease inhibition in myocardial preservation in prolonged hypothermic cardioplegia followed by reperfusion. J Thorac Cardiovasc Surg 96: 314–320
32. Tani M, Neeley JR (1989) Role of intracellular Na^+ in Ca^{2+} overload and depressed recovery of ventricular function of reperfused ischemic rat hearts. Possible involvement of H^+-Na^+ and Na^+-Ca^{2+} exchange. Circ Res 65: 1045–1056
33. Tosaki A, Balint S, Szekeres L (1988) Protective effect of lidocaine against ischemia and reperfusion-induced arrhythmia and shifts of myocardial Na, K, and Ca content. J Cardiovasc Pharmacol 12: 621–628