

**Preservation of Neonatal Myocardial Function Following Ischemic Arrest**

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**ABSTRACT**

The protection of the ischemic neonatal myocardium was studied utilizing both cardioplegic and noncardioplegic solutions. Six groups of seven-day-old isolated working rabbit hearts, exposed to 120 minutes of hypothermic (30°C) arrest, were treated with either an oxygenated or nonoxygenated cardioplegic or physiologic saline solution. The results indicated that postischemic aortic flow, stroke volume and cardiac output were significantly depressed in all oxygenated groups, but not in the nonoxygenated cardioplegic groups. Recovery of cardiac output remained near baseline in hearts treated with either single dose ( $94.4 \pm 2.5\%$  mean  $\pm$  SEM) or multidose ( $94.3 \pm 2.3\%$ ) nonoxygenated cardioplegia, but was significantly depressed in multidose oxygenated cardioplegia ( $76.2 \pm 6.2\%$ ), multidose oxygenated physiological saline ( $74.8 \pm 3.0\%$ ), and single dose physiological saline ( $74.8 \pm 3.0\%$ ), all at  $p < 0.05$ . Coronary sinus creatine kinase was significantly elevated during ischemia in all physiological saline groups as well as the multidose oxygenated cardioplegia group, and remained elevated following reperfusion. In the nonoxygenated cardioplegic groups, creatine kinase was not elevated. This study has demonstrated that the addition of oxygen to either cardioplegic or noncardioplegic physiological saline solutions failed to protect the neonatal myocardium from ischemic or reperfusion related injury.

**INTRODUCTION**

The underlying goal of myocardial protection is the preservation of cellular and mechanical function following ischemia. Due to the normally aerobic nature of the myocardium, various methods of cardioplegic arrest have included the addition of oxygen to hemoglobin in sanguineous solutions<sup>1,2</sup> to perfluorocarbon emulsions<sup>3,4</sup> or in the dissolved state in crystalloid solutions.<sup>5</sup> However, oxygen may not be totally innocuous and has been implicated in the etiology of

myocardial injury.<sup>6,7</sup> It has been shown that certain toxic intermediates, free oxygen radicals, are generated during reperfusion/reoxygenation and participate in cellular and subcellular injury.<sup>8</sup> The generation of these metabolites during reperfusion of ischemic muscle can exacerbate tissue damage altering compromised areas from reversible to irreversible injury. Recently several investigators have been able to identify the injury created during ischemia from that occurring during the reperfusion period.<sup>8,9,10</sup>

The majority of work evaluating the efficacy of oxygenated cardioplegia has thus far been completed utilizing the mature myocardium as a model, with few studies examining immature hearts. Known ontogenic differences, however, do exist which include cardiac ultrastructure,<sup>11,12</sup> metabolic activity<sup>13</sup> and calcium homeostasis,<sup>2,10</sup> all of which may influence differential response to ischemic arrest. In this study, we have examined the neonatal rabbit myocardium in an isolated working heart preparation to evaluate myocardial protection established with either: 1) oxygenated and nonoxygenated physiologic saline solutions, or 2) oxygenated and nonoxygenated St. Thomas' cardioplegic solutions.

**MATERIALS AND METHODS**

An isolated working heart preparation was utilized in all experiments and has been previously described.<sup>14,15</sup> All animals received care according to the "Principles of Laboratory Animal Care of the National Society of Medical Research" and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences (NIH Publication No. 80-23, revised 1978). Neonatal (6 to 8 days old) New Zealand white rabbits of either sex were utilized in all experiments. Following anesthesia with Ketamine<sup>a</sup> (100 mg/kg) and Xylazine<sup>b</sup> (5mg/kg) all animals were intubated and ventilated with a small animal respirator<sup>c</sup>. The chest was opened via a median sternotomy and the pericardium incised. The thymus was removed exposing the great vessels and the heart was rapidly excised and placed in 4°C

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<sup>a</sup> Ketamine, Parke-Davis, Morris Plains, NJ

<sup>b</sup> Xylazine, Mobay Co., Shawnee, KA

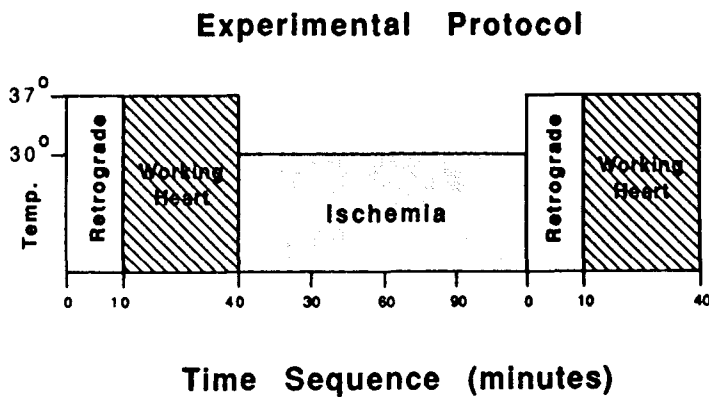
<sup>c</sup> Harvard Apparatus Co. Inc., Millis, MA

Krebs-Henseleit solution. The heart was immediately fitted with an 18 gauge blunt tipped needle which served as an aortic cannula, and retrograde perfusion begun. The time from excision to perfusion never exceeded 30 seconds. A polyethylene cannula was then inserted through the left atrial appendage and secured just above the mitral valve via a purse string suture. The pulmonary veins were ligated and the pulmonary artery transected to assure adequate coronary sinus drainage. The heart was then placed in the water jacketed chamber and maintained at 37°C.

Thirty hearts were randomly assigned to one of the following treatments, with 5 hearts in each group: single dose oxygenated Krebs-Henseleit (SDOKH), multidose nonoxygenated KH (MDNOKH), multidose oxygenated KH (MDOKH), multidose nonoxygenated cardioplegia (MDNOCP), multidose oxygenated cardioplegia (MDOCP), or single dose nonoxygenated cardioplegia (SDNOCP). Nonoxygenated solutions are arbitrarily defined as oxygen poor and reflect the normal solubility of gas at room temperature with O<sub>2</sub> tensions of approximately 160 torr. Oxygenated solutions were created by bubbling in 95% O<sub>2</sub> and 5% CO<sub>2</sub> creating O<sub>2</sub> tensions greater than 650 torr and CO<sub>2</sub> tensions between 30 and 40 torr.

The experimental time course (Figure 1) consisted of a 10 minute retrograde perfusion period at 55 cm H<sub>2</sub>O with the coronary sinus effluent discarded. The hearts were then switched to the working mode and perfused at left atrial filling pressures of 20 cm H<sub>2</sub>O, spontaneously ejecting against an afterload of 55 cm H<sub>2</sub>O. During this time the stability of the model was ascertained and baseline values recorded. All groups received an initial 3 minute dose of either KH or CP prior to the onset of ischemia,

FIGURE 1- Experimental Time Course



with the multidose groups treated with additional 3 minute washout periods at 30 minute intervals. After a 120 minute ischemic period, all hearts were reperfused in the retrograde fashion for 10 minutes before being converted to the working heart mode for an additional 30 minutes. Functional recovery was assessed by recording hemodynamic function at the end of a 30 minute postischemic working heart period. The hearts were then removed from the apparatus, weighed and placed in a 120°C oven, and dried to constant weight for the analysis of water content by the equation:

$$\% \text{ Water Content} = \frac{(\text{wet weight} - \text{dry weight})}{\text{wet weight}} \times 100$$

The solutions utilized were a standard glucose enriched Krebs-Henseleit (KH) perfusate with the following composition: NaCl 120 mmol/L, KCl 4.7 mmol/L, CaCl<sub>2</sub> 2.5 mmol/L, MgSO<sub>4</sub> 1.2 mmol/L, KH<sub>2</sub>PO<sub>4</sub> 1.2 mmol/L, NaHCO<sub>3</sub> 25 mmol/L and glucose 11.1 mmol/L with a pH of 7.4 at 37°C, and calculated osmolality of 323 mOsm/L. The cardioplegia was St. Thomas' #2 and consisted of: NaCl 110 mmol/L, KCl 16 mmol/L, CaCl<sub>2</sub> 1.2 mmol/L, MgCl<sub>2</sub> 16 mmol/L, NaHCO<sub>3</sub> 10 mmol/L with a pH of 7.9 at 37°C, and calculated osmolality of 325 mOsm/L. Both the KH and CP solutions were equilibrated with 95% O<sub>2</sub> and 5% CO<sub>2</sub> through a sintered glass filter to facilitate bubble dispersion. All solutions were double filtered through 5 micron filters and passed through in-line bubble traps prior to perfusion.

### MEASURED PARAMETERS

Hemodynamic function was assessed by making timed collections of aortic flow and coronary flow with the summation being cardiac output. Heart rate was recorded and stroke volume calculated by dividing the cardiac output by the heart rate. Left ventricular pressure was measured by an high fidelity ultraminiature pressure transducer<sup>a</sup> inserted via a side arm off the left atrial cannula. The signal was then interfaced into a pressure conditioner<sup>b</sup> and a medium gain amplifier for the determination of the rise (+dP/dt) and fall (-dP/dt) of left ventricular pressure with respect to time.

Serial perfusate samples were collected from the coronary sinus, placed on ice, and assayed within 48 hours of collection. Creatine kinase, an enzymatic indicator of cellular damage which has been shown to correlate with ischemic injury, was measured<sup>c</sup> and expressed in IU L<sup>-1</sup> gm dry weight. Additional specimens were collected in 7% perchloric acid and assayed for lactic acid<sup>c</sup>, an end product of anaerobic metabolism, and expressed in mmol/L gm dry weight<sup>-1</sup>.

### STATISTICAL ANALYSIS

All results are expressed as mean ± standard error of the mean (SEM). Data were analyzed with the statistical program ABstat<sup>a</sup> and an IBM microprocessor. Student's paired t test was utilized only to compare values within the same group. Percent recovery for hemodynamic parameters was determined for each

<sup>a</sup> PR-249, Millar Instruments, Houston, TX

<sup>b</sup> Hewlett-Packard Co., Andover, MA

<sup>c</sup> Sigma Diagnostics Inc., Kits CK47-UV and 726-UV, St. Louis, MO

<sup>a</sup> Anderson-Bell Co., Cannon City, CO

heart, and the mean and SEM calculated for each group. Sample means were compared among groups by the use of one way ANOVA. Where significance was found the multiple comparison test Neuman-Keuls was performed to determine differences among groups. Dunnett's two tailed test of significance was used to compare baseline values (preischemia) to multiple postischemic values. Statistical significance was accepted at the  $p < 0.05$  level.

## RESULTS

A total of 30 neonatal hearts were utilized throughout the study with 5 hearts assigned to each group. There were no significant differences for age and weight among groups (Table 1). All hemodynamic data are expressed in tables 2 through 4 and are discussed below.

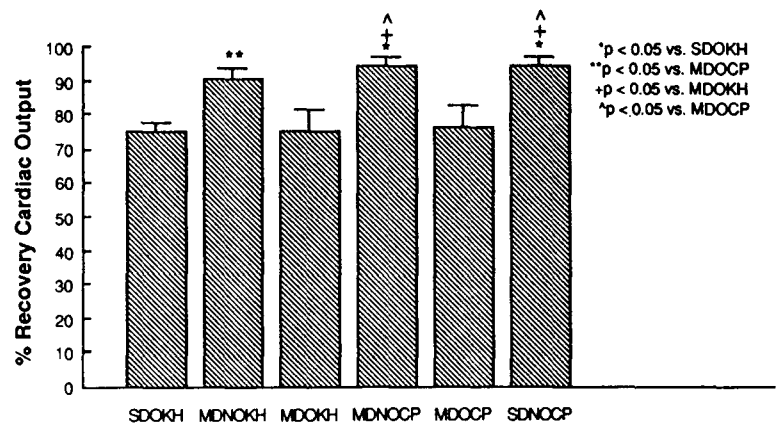
Recovery of aortic flow was depressed across all groups at 30 minutes postischemia. MDNOKH had significantly better recovery of aortic flow than either SDOKH, MDOKH or MDOCP ( $p < 0.05$ ). Cardiac output (Figure 2) was only depressed in the SDOKH ( $74.8 \pm 3.0\%$ ), MDOKH ( $74.8 \pm 6.6\%$ ) and the MDOCP ( $76.2 \pm 6.2\%$ ) groups, while MDNOKH ( $90.1 \pm 3.4\%$ ), MDNOCP ( $94.3 \pm 2.3\%$ ) and SDNOCP ( $94.4 \pm 2.5\%$ ) all recovered to near their baseline values.

Postischemic recovery of coronary flow was similar to that previously reported<sup>7</sup> with all groups displaying some level of reactive hyperemia. A significant difference was only seen in the SDNOCP group ( $3.1 \pm 0.2$  ml min<sup>-1</sup> to  $4.9 \pm 0.7$  ml min<sup>-1</sup>,  $p < 0.05$ ), although the SDOKH was also elevated from  $3.0 \pm 0.3$  ml min<sup>-1</sup> to  $4.3 \pm 0.6$  ml min<sup>-1</sup>,  $p = ns$ .

Heart rate did not vary from preischemic values with all groups recovering at least 96% of control levels.

Stroke volume fell significantly in SDOKH, MDOKH and MDOCP but was not depressed in any nonoxygenated group (Figure 3).

The first derivative of developed pressure has been used as both an indicator of myocardial contractility and relaxation. Although there were no significant differences seen in either +dP/dt or -dP/dt, interesting trends were observed. Recovery of



**FIGURE 2** Percent recovery of preischemic cardiac output. SDOKH, single dose oxygenated Krebs-Henseleit (KH). MDNOKH, multidose, non-oxygenated KH. MDOKH, multidose oxygenated KH. MDNOCP, multidose nonoxygenated cardioplegia (CP). MDOCP, multidose oxygenated CP. SDNOCP, single dose nonoxygenated CP.  $n = 5$  for each group. All data are mean  $\pm$  SEM.

control +dP/dt was near or at baseline for all groups, yet -dP/dt declined throughout all experiments. The neonate is known to contain less contractile mass than adult myocardium which is associated with inherent differences in relaxation indices<sup>12</sup>. Although all groups did display some level of depressed mechanical function, the decline in -dP/dt may reflect subtle alterations in compliance further defining developmental variations.

Lactic acid production was elevated during ischemia in all multidose groups which indicated a shift from aerobic to anaerobic metabolism. Peak lactic acid values were measured at 30 minutes during ischemia and steadily declined throughout the remainder of the ischemic period (Figure 4). The greatest increase in lactic acid was seen at all times in the KH protected hearts, with the MDNOKH increasing from 0.14 mmol L<sup>-1</sup> gm

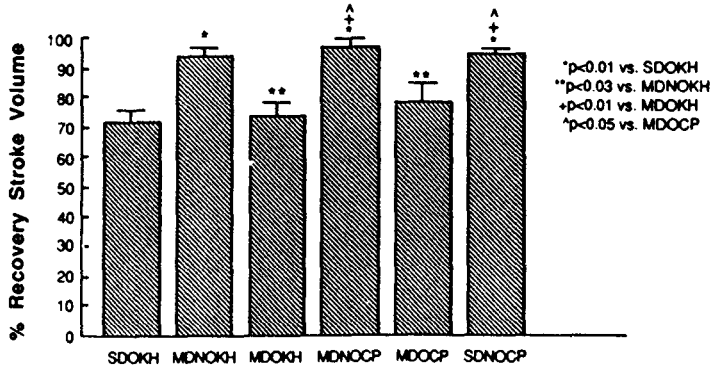
TABLE 1. Age, Weight and % H<sub>2</sub>O Content of Individual Groups.

Group	Rabbit		Heart		% H <sub>2</sub> O Content
	Age(days)	Weight(gms)	Wet Wt.(gms)	Dry Wt.(gms)	
SDOKH	8.8 ± 4	130 ± 3.6	1.20 ± 1	0.48 ± 0.1	59.8 ± 1.1
MDNOKH	7.8 ± 4	136 ± 12.1	1.28 ± 1	0.49 ± 0.1	61.6 ± 1.5
MDOKH	8.0 ± 5	129 ± 7.2	1.30 ± 1	0.50 ± 0.1	61.2 ± 0.4
MDNOCP	7.0 ± 3	131 ± 7.8	1.25 ± 1	0.50 ± 0.1	60.0 ± 1.1
MDOCP	7.2 ± 4	124 ± 12.2	1.18 ± 1	0.49 ± 0.1	58.6 ± 1.6
SDNOCP	7.4 ± 5	131 ± 12.2	1.23 ± 1	0.49 ± 0.1	59.8 ± 1.5

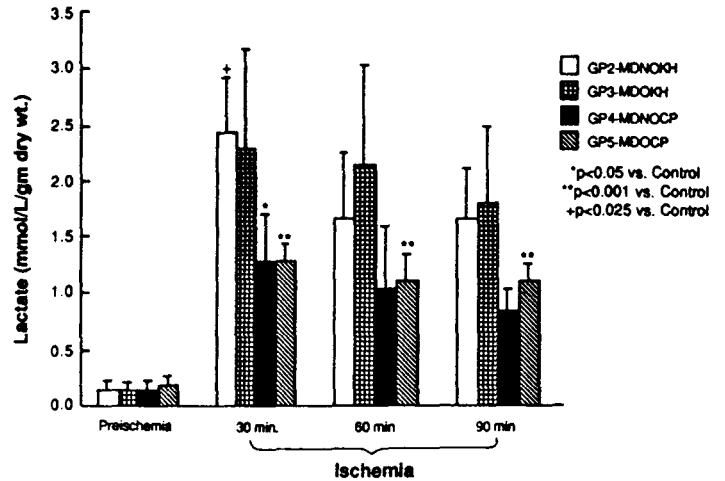
Legend: Values are Mean  $\pm$  SEM; SDOKH - single dose oxygenated Krebs-Henseleit; MDNOKH - multidose non-oxygenated Krebs-Henseleit; MDNOCP - multidose non-oxygenated cardioplegia; MDOCP - Multidose oxygenated cardioplegia; SDNOCP - single dose non-oxygenated cardioplegia; MDOKH - multidose oxygenated Krebs-Henseleit.

$$\% \text{ H}_2\text{O Content} = \frac{\text{wet weight} - \text{dry weight}}{\text{wet weight}} \times 100$$

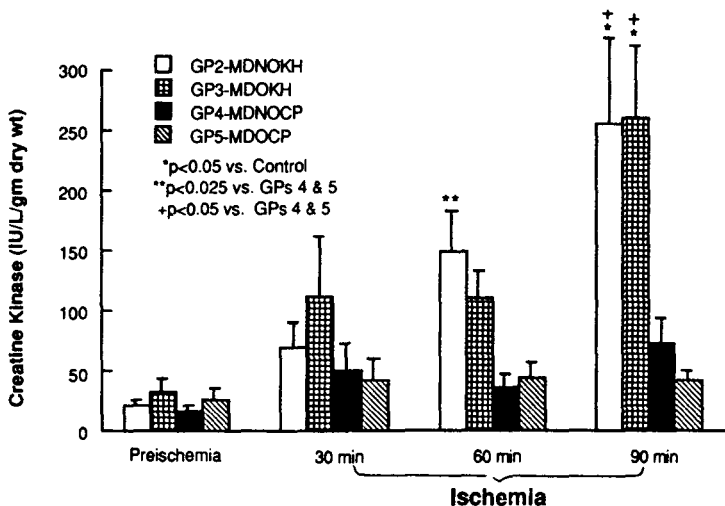
**FIGURE 3 - Percent recovery of preischemic stroke volume.** SDOKH, single dose oxygenated Krebs-Henseleit (KH). MDNOKH, multidose nonoxygenated KH. MDOKH, multidose oxygenated KH. MDNOKH, multidose nonoxygenated KH. MDNOCP, multidose nonoxygenated cardioplegia (CP). MDOCP, multidose oxygenated CP. SDNOCP, single dose nonoxygenated CP. n=5 for each group. All data are mean  $\pm$  SEM.



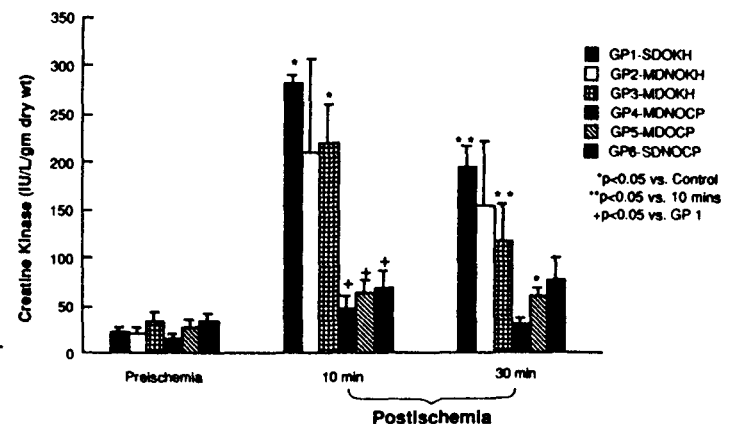
**FIGURE 4 - Coronary sinus lactate release.** MDNOKH, multidose nonoxygenated KH. MDOKH, multidose oxygenated KH. MDNOCP, multidose nonoxygenated cardioplegia (CP). MDOCP, multidose oxygenated CP. n=5 for each group. All data are mean  $\pm$  SEM.



**FIGURE 5 - Coronary sinus creatine kinase release during ischemia.** MDNOKH, multidose nonoxygenated KH. MDOKH, multidose oxygenated KH. MDNOCP, multidose nonoxygenated cardioplegia (CP). MDOCP, multidose oxygenated CP. n=5 for each group. All data are mean  $\pm$  SEM.



**FIGURE 6 - Coronary sinus creatine kinase release postischemia.** SDOKH, single dose oxygenated Krebs-Henseleit (KH). MDNOKH, multidose nonoxygenated KH. MDOKH, multidose oxygenated KH. MDNOCP, multidose nonoxygenated cardioplegia (CP). MDOCP, multidose oxygenated CP. SDNOCP, single dose nonoxygenated CP. n=5 for each group. All data are mean  $\pm$  SEM.



dry weight<sup>-1</sup> to 2.42 mmol L<sup>-1</sup> gm dry weight<sup>-1</sup>,  $p > 0.05$ . The greater lactic acid production may coincide with decreased protection associated with the inability of the KH perfusate to achieve electromechanical uncoupling at the onset of ischemia. Nevertheless, direct correlation of increased lactic acid levels with decreased hemodynamic indices was not evident. During reperfusion lactic acid fell back to preischemic control levels across all groups.

Creatine kinase is an enzymatic indicator of cellular injury when found in elevated levels in extracellular fluid. Its presence in coronary sinus effluent samples corresponds to depressed functional recovery. Baseline values for CK were similar across all groups (Figure 5).

During ischemia CK levels in the multidose KH groups increased in a linear fashion with time (Figure 6), indicating inadequate protection with noncardioplegic solutions. Conversely the cardioplegia protected hearts remained at or near baseline values throughout the ischemic period. During reperfusion the greatest CK leakage was again seen in the KH hearts. All CP protected hearts had significantly less CK efflux than the SDOKH group, and at 30 minutes, the MDNOC hearts had returned to baseline levels.

## **DISCUSSION**

Maintenance of cellular integrity during ischemia is the primary goal of cardioplegic arrest which is fundamental in providing mechanical recovery upon reperfusion. The extreme aerobic demands of the myocyte has led investigators to include some form of oxygenation within the myoprotective agents applied during ischemia. Oxygenated sanguineous, perflurocarbon emulsions and crystalloid solutions have all been used with varying success.<sup>1,2,3,5</sup> Aerobic metabolism without substrate limitation increases production of high energy phosphates through oxidative pathways when compared to substrate level phosphorylation active during ischemia. The increased oxygen carrying capacity seen with blood enriched cardioplegia is confounded by the leftward shift in the oxygen dissociation curve due to decreased temperatures, hypocarbia and alkalosis. The viscosity changes seen with lowered delivery temperatures also compromise distribution to subendocardial areas. Perflurocarbon compounds are agents with high oxygen solubilities that when used clinically, have been shown to promote adverse reactions, such as complement activation.<sup>3</sup> Crystalloid cardioplegic solutions with increased oxygen tensions can provide 100% oxygen availability but can deliver only a finite quantity of dissolved oxygen, and may illicit hyperoxic injury during the reperfusion period.<sup>6,7</sup> Indeed, in the present study, hyperoxygenation of a commercially available cardioplegic solution failed to provide adequate protection during myocardial ischemia and reperfusion in the neonatal rabbit heart.

Although it is generally accepted that the newborn myocardium is more tolerant of hypoxia than the adult,<sup>16,17</sup> whether or not this effect is contiguous with ischemic resistance remains to be shown. The lack of agreement among investigators<sup>7-9,16,18-20</sup> further emphasizes the need to elucidate age related responses to ischemic arrest.

The decline in hemodynamic function was directly related to the oxygen content of the solutions used during the ischemic period. All hearts were exposed to similar reperfusion sequelae at the termination of ischemia, so that the differences in mechanical recovery could only be explained by the cellular changes which occurred during ischemia. The multiple administration of solutions containing high levels of oxygen during ischemia may have predisposed the myocardium to reperfusion injury in the postischemic period. Recently several investigators have shown that neonatal rabbit hearts exposed to multidose cardioplegia had depressed hemodynamic recovery when compared to singledose administration.<sup>21,22</sup> Baker et.al.<sup>21</sup> believed this to be a function of inadequate formulation of the St. Thomas' cardioplegia and not the administration technique itself, because multidose KH did not depress myocardial recovery. Magovern, Pae, and Waldhausen<sup>22</sup> felt that multidose cardioplegia was toxic to hypothermic ischemic immature hearts and that the total dose of solutions should be restricted. Our study did not support their data; however, for hearts protected with either single or multidose nonoxygenated cardioplegia had similar mechanical recovery. Both groups did utilize deep hypothermia (10 and 14°C) which may obviate the inherent benefits of hyperkalemia in providing electromechanical uncoupling, and neither compared the effects of oxygenated St. Thomas' solution.<sup>21,22</sup>

Sadeghi et. al.,<sup>23</sup> in a neonatal blood perfused pig model, have shown that newborns exposed to hypoxia and reoxygenation displayed more myocardial injury than control hearts. Reperfusion with reoxygenation is a necessary phenomenon that cannot be avoided in open heart surgery. However, the modification of reperfusates can be achieved especially if reperfusion/reoxygenation damage may be occurring during multiple cardioplegic washouts. The role of oxygen in cardioplegic solutions was recently examined by Krukenkamp, Silverman and Levitsky in crystalloid and blood perfusates.<sup>2</sup> Although they found superior recovery in the blood perfused group, they were unable to correlate this with overall oxygen delivery, and stated that adjuvant oxygenation is not an important myoprotective strategy.<sup>2</sup>

Lynch et. al.<sup>18</sup> utilized isolated neonatal rabbit hearts exposed to normothermic arrest, and failed to show an added benefit when cardioplegic solutions were oxygenated. Additionally, intermittent perfusion with a physiologic saline solution resulted in similar protection to cardioplegic hearts. These data support our findings of excellent myocardial preservation with nonoxygenated KH solutions. Hendren and associates have shown that oxygenation of a cardioplegic solution with 100% O<sub>2</sub> can illicit the calcium paradox as evidenced by enzyme leakage, sustained contracture and increased diastolic pressures.<sup>6</sup> They further stated that the rise in pH caused by the displacement of CO<sub>2</sub> may have accentuated the effects of calcium influx because hydrogen ions oppose the inward movement of calcium at the sarcolemma.<sup>6</sup>

Newborn hearts have been shown to be more susceptible to reperfusion injury and this can be related to enhanced generation of free oxygen radicals (FOR) with

associated oxidative injury.<sup>7,8</sup> Otani et. al. have shown that the newborn myocardium is more susceptible to FOR injury because of lower concentrations of intrinsic antioxidants (glutathione), slower synthesis of membrane phospholipids and increased generation of FOR.<sup>8</sup> Other investigators have shown that the newborn heart is more susceptible to the effects of ischemia and reperfusion than either juvenile or adults, because 1) they are devoid of the antioxidant enzymes needed to detoxify FOR, and 2) that their membrane systems contain greater quantities of polyunsaturated fatty acids which are the prime targets of lipid peroxidation.<sup>20</sup> We have previously shown that neonates exposed to high dose oxygen in cardioplegic solutions had elevated levels of the lipid peroxidation indicator malondialdehyde<sup>7</sup> which correlates with oxidant injury.

The failure of oxygenated cardioplegia to preserve neonatal function and the efficacy of nonoxygenated KH to protect the ischemic myocardium question the need of cardioplegic protection of the developing heart. Fujiwara et. al., in a neonatal lamb model, have shown that cardioplegia is only effective in treating cyanotic hearts and not normoxic hearts.<sup>24</sup> They stated that the mitochondria from cyanotic animals have an increased oxidative capacity, so although oxygen tensions were decreased, aerobic metabolism was maintained.<sup>24</sup> Grice, Konishi, and Apstein<sup>9</sup> have stated that cardioplegia may not be as beneficial to the neonatal heart as to the mature myocardium exposed to either hypothermic or normothermic ischemia. In two recent studies<sup>25,26</sup>, neonatal guinea pigs exposed to 180 minutes of 20°C ischemia protected with a cardioplegic solution showed poorer functional recovery than when not given cardioplegia. They believe that this may be a function of the formulation of the cardioplegic solution, and hence, advocate re-evaluating adult clinical myoprotective techniques for the immature heart.

Coronary blood flow was elevated in all groups following ischemia reflecting a reactive hyperemia which facilitates a rapid repayment of oxygen debt. This is in good corroboration with our previous study<sup>7</sup> and of others.<sup>24,26</sup> Adenosine Triphosphate (ATP) degradation leads to the generation of nucleoside intermediates which include adenosine. Adenosine, although not measured in the present study, is one of the most powerful vasodilators known and may be an important mediator of the hyperemic response. Portman et. al. have looked at developmental myocardial energy metabolism and believe that ATP hydrolysis products are more important in the regulation of myocardial energetics in the newborn than the adult.<sup>27</sup> During reperfusion the increased delivery of nutritive solution to the compromised myocardium may provide necessary metabolites for reparative processes, aiding in the neonates ability to recover from ischemic insult.

In conclusion, our results question the efficacy of hyperoxygenated crystalloid solutions in preserving the neonatal heart during ischemia. Reperfusion with oxygen rich solutions failed to provide additional protection during moderate hypothermic ischemic arrest. Single dose administration of nonoxygenated cardioplegia was just as effective in preserving mechanical function as was multidose nonoxygenated cardioplegia. Furthermore, a low dose nonoxygenated physiologic saline solution provided excellent myocardial preservation, although indicators of cellular injury were elevated.

The substantial differences that exist between developmental states of the heart question the efficacy of current myoprotective techniques established for the mature myocardium, and need to be re-evaluated as protective strategies for the neonatal population.

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TABLE 2.

Baseline and 30 Minute Postischemic Recovery For Krebs-Henseleit Groups

	SDOKH Group 1			MDNOKH Group 2			MDOKH Group 3		
	Baseline	30 Minute PI	pValue	Baseline	30 Minute PI	pValue	Baseline	30 Minute PI	pValue
Aortic Flow (ml/min)	13.2±.8	7.90±.6	<.001	13.7±2.2	11.2±2.0	<.005	13.0±1.4	7.6±.9	<.01
Coronary Flow (ml/min)	3.0±.3	4.3±.6	NS	4.1±.6	4.7±.9	<NS	3.7±.6	4.6±.7	NS
Cardiac Output (ml/min)	16.2±.7	12.2±.4	<.01	17.7±2.2	15.9±1.9	<.05	16.7±1.2	12.2±.7	<.05
Heart Rate (beats/min)	209.2±13.3	201.6±16.5	NS	215.2±5.6	208.0±8.1	NS	221.6±5.6	216.0±5.2	NS
Stroke Volume (ml)	.08±.01	.06±.01	<.05	.08±.01	.08±.01	NS	.08±.01	.06±.0	<.05
Peak LVP (mmHg)	66.5±18.8	54.5±9.5	NS	54.4±6.8	51.2±7.7	NS	49.3±7.7	55.3±5.3	NS
LVEDP (mmHg)	7.8±1.4	11.9±2.4	NS	4.1±.8	5.2±.7	NS	6.3±1.0	7.8±.0	NS
+dp/dt (mmHg/sec)	906.3±152.9	825.0±197.4	NS	718.8±91.3	672.6±87.9	NS	625.0±84.8	645.0±111.4	NS
-dp/dt (mmHg/sec)	793.8±199.6	490.8±81.3	NS	547.6±125.4	455.0±75.2	NS	470.0±51.4	397.6±56.8	.05

Legends: Values are mean±SEM. SDOKH - single dose oxygenated Krebs-Henseleit; MDNOKH - multidose non-oxygenated Krebs-Henseleit; MDOKH - multidose oxygenated Krebs-Henseleit; LVP - left ventricular pressure; LVEDP - left ventricular end diastolic pressure.

TABLE 3.

Baseline and 30 Minute Postischemic Recovery For Cardioplegic Group

	MDNOCP Group 4			MDOCP Group 5			SDNOCP Group 6		
	Baseline	30 Minute PI	pValue	Baseline	30 Minute PI	pValue	Baseline	30 Minute PI	pValue
Aortic Flow (ml/min)	12.2±.5	10.0±.5	<.01	11.9±.3	7.8±.6	<.005	12.9±.6	10.2±.2	<.01
Coronary Flow (ml/min)	4.8±.8	6.1±.8	NS	4.1±.5	4.5±.7	NS	3.1±.2	4.9±.7	<.05
Cardiac Output (ml/min)	16.9±.9	15.9±.8	NS	16.0±.9	12.3±1.6	<.05	16.0±.5	15.1±.7	NS
Heart Rate (beats/min)	228.0±9.3	222.4±4.8	NS	208.0±.4	203.2±12.8	NS	216.8±7.3	216.8±8.6	NS
Stroke Volume (ml)	.08±.1	.07±.01	NS	.08±.01	.06±.01	<.05	.07±.01	.07±.01	NS
Peak LVP (mmHg)	57.8±7.6	53.8±7.2	NS	59.5±5.1	49.0±8.5	<.05	62.8±4.1	61.6±2.8	NS
LVEDP (mmHg)	4.5±.5	7.0±1.7	NS	6.5±1.4	6.0±.9	NS	7.4±1.9	5.6±.9	NS
+dp/dt (mmHg/sec)	1037.5±94.4	1012.5±71.8	NS	986.2±38.8	990.0±58.4	NS	896.1±120.7	977.4±114.4	NS
-dp/dt (mmHg/sec)	761.5±80.6	628.3±54.1	NS	771.2±96.0	695.2±62.1	NS	803.0±87.2	698.8±92.4	NS

Legend: All values are mean±SEM. MDNOCP - multidose non-oxygenated cardioplegia; MDOCP - multidose oxygenated cardioplegia; SDNOCP - single dose non-oxygenated cardioplegia; LVP - left ventricular pressure; LVEDP - left ventricular end diastolic pressure.

TABLE 4.

Percent Recovery of Preischemic Control Values

	SDOKH Group 1	MDNOKH Group 2	MDOKH Group 3	MDNOCP Group 4	MDOCP Group 5	SDNOCP Group 6
Aortic Flow	59.9±1.8	81.3±2.4	59.2±6.6	82.2±3.6	63.7±6.7	78.0±5.9
Coronary Flow	146.2±18.9	111.0±6.7	127.6±10.0	135.2±20.1	114.4±18.0	156.4±11.1
Cardiac Output	74.8±3.0	90.1±3.4	74.8±6.6	94.3±2.3	76.2±6.2	94.4±2.5
Heart Rate	96.4±4.9	96.6±2.3	97.6±2.1	97.8±1.8	97.4±3.2	99.2±1.0
Stroke Volume	71.7±4.1	93.8±3.2	73.4±4.7	96.6±2.5	78.2±6.7	94.2±1.9

Legend: All values are mean percent recovery±SEM. SDOKH - single dose oxygenated Krebs-Henseleit; MDNOKH - multidose non-oxygenated Krebs-Henseleit; MDOKH - multidose oxygenated Krebs-Henseleit; MDNOCP - multidose non-oxygenated cardioplegia; MDOCP - multidose oxygenated cardioplegia; SDNOCP - single dose non-oxygenated cardioplegia.

\* p<.05 vs group 1; \*\* p<.05 vs group 2; † p<.05 vs group 3; †† p<.05 vs group 4; Δ p<.05 vs group 5

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