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SURGERY FOR CONGENITAL HEART DISEASE

CONTROLLED POSTCARDIOPLEGIA REPERFUSION: MECHANISM FOR ATTENUATION OF REPERFUSION INJURY

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Objective: Controlled reperfusion and secondary cardioplegia are used to minimize reperfusion injury. The mechanisms for their benefit are incompletely defined and may include attenuation of myocyte sodium uptake.

Methods: Pigs had 1 hour of cardioplegic arrest followed by reperfusion with blood (control) or warm cardioplegic solution followed by blood (test). Reperfusion injury in the control and test groups was quantified by measuring changes of intramyocyte ion content with atomic absorption spectrometry and by analyzing electrophysiologic recovery from recordings of reperfusion arrhythmias.

Results: Control animals had an increase in intramyocyte sodium content at 5 minutes after initiating reperfusion ($+20.2 \mu\text{mol/g}$ dry weight, $P < .04$), whereas the test group had an insignificant decrease ($-14.0 \mu\text{mol/g}$ dry weight, $P = .33$). The first rhythm after initiating reperfusion was more often ventricular fibrillation in the control group (100% vs 50%, $P < .02$), and the control group required more defibrillations to establish a nonfibrillating rhythm (4.5 ± 1.2 vs 1.1 ± 0.3 , $P < .03$).

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Conclusions: Controlled reperfusion eliminated the increase in intramyocyte sodium that was observed in the control group at 5 minutes after cardioplegic arrest. This improvement in myocyte ion homeostasis during postcardioplegia reperfusion was associated with fewer reperfusion arrhythmias. These data support the hypothesis that attenuation of myocyte sodium gain during postischemic reperfusion is a mechanism by which controlled reperfusion and secondary cardioplegia are beneficial. (*J Thorac Cardiovasc Surg* 2000;119:1093-101)

Creation of transient electromechanical arrest is a strategy that is fundamental to a variety of protocols to decrease ischemia-reperfusion injury with controlled postcardioplegia reperfusion and secondary cardioplegia.¹⁻⁶ It has been postulated that cessation of electromechanical activity during reperfusion allows myocytes to focus their metabolic activity on restoration of homeostasis and repair of ischemic injury.^{1,2,7,8} However, the precise mechanisms by which this occurs have not been fully elucidated.

The purpose of this study was to examine one possible mechanism for the beneficial effect of controlled postcardioplegia reperfusion and secondary cardioplegia. This mechanism is attenuation of the increase in intramyocyte sodium that occurs on reperfusion of ischemic myocardium. Alteration of intramyocyte ion homeostasis, specifically that caused by sodium influx, plays an important role in postischemic reperfusion injury.⁹⁻¹² Attenuating sodium influx appears to diminish ischemia-reperfusion injury,¹³⁻¹⁶ although the details of this process remain under investigation.

Work from this laboratory has shown that postcardioplegia reperfusion with unmodified blood in normal porcine hearts results in reperfusion arrhythmias and an increase in intramyocyte sodium content,¹⁷ both of which are markers for reperfusion injury. It was reasoned that a period of asystole during controlled postcardioplegia reperfusion would allow myocytes to restore ion homeostasis and thereby favorably affect these ionic and electrophysiologic markers for reperfusion injury. The hypothesis of this study is that controlled postcardioplegia reperfusion will diminish or abolish the reperfusion arrhythmias and the increase in intramyocyte sodium that otherwise occur on reperfusion of the heart with unmodified blood.

Methods

Postcardioplegia reperfusion injury was studied in an intact porcine model of cardiopulmonary bypass. All animals in this study received humane care in compliance with 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 Institute of Laboratory Animal Resources and published by the National Institutes of Health (National Institutes of Health publication No. 86-23, revised 1985).

Surgical protocol and biochemical data acquisition protocol. Twenty-two pigs of both sexes, weighing 25 to 30 kg, were anesthetized, intubated, and mechanically ventilated. After electrodes had been placed for electrophysiologic data acquisition (see details below), the pigs were given heparin and placed on cardiopulmonary bypass by using right atrial and aortic cannulation. Bypass was initiated at $2.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. The perfusion temperature was 37°C for the collection of control electrophysiologic data. The temperature was then decreased to 30°C , and the flow was decreased to $1.6 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ during cardioplegic arrest. The temperature and flow were increased to 37°C and $2.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ at 10 minutes before reperfusion and were maintained at this level during reperfusion.

Cardioplegia was initiated with a 3-minute infusion of a 4°C hyperkalemic-hypocalcemic blood cardioplegic solution (solution I, Table I). The cardioplegic solution was infused at a mean aortic root pressure of 70 mm Hg. Topical iced saline solution was placed around the ventricles. The left ventricle was decompressed by suction on a vent catheter in the pulmonary artery. Supplemental 1-minute infusions of blood cardioplegic solution (solution II) were given after 15, 30, and 45 minutes of arrest. After 60 minutes of arrest, reperfusion was initiated. Reperfusion in the control group ($n = 10$) was conducted with unmodified blood infused into the clamped aorta at a mean aortic root pressure of 70 mm Hg. Reperfusion in the test group ($n = 12$) was conducted with a 500-mL/m^2 dose of 37°C blood cardioplegic solution (solution II) infused into the clamped aorta at a mean aortic root pressure of 70 mm Hg. After infusion of the blood cardioplegic solution, unmodified blood at 70 mm Hg was infused in the aortic root until the termination of the study.

Method for tissue electrolyte measurements. Measurements of myocardial water and electrolyte (sodium and potassium) contents were made by using atomic absorption spectrometry.^{18,19} Two transmural left ventricular biopsy specimens (diameter of 5 mm) were obtained with the use of a custom trephine. The first was taken after loading the myocardium with a cobalt-ethylenediamine tetraacetic acid complex but before initiating cardioplegic arrest. The second biopsy specimen was taken after defibrillation of the heart after 5 minutes of postcardioplegia reperfusion. This time was chosen because (1) the duration of reperfusion was sufficient for equilibration of cobalt-ethylenediamine tetraacetic

acid in the blood and interstitial space and (2) harvesting of the biopsy specimen did not affect the recording of ventricular fibrillation before defibrillation.

Interstitial water content increased in both groups after cardioplegic arrest and reperfusion (mean change = +0.7 mL/g dry weight). For the purpose of comparing precardioplegia with postdefibrillation ion contents, the postdefibrillation interstitial ion content values were corrected to account for the ions carried into the interstitial space by this additional water. There were no significant changes in intracellular water content for either group (mean change = +0.02 mL/g dry weight); therefore no adjustments were made in the post-defibrillation intracellular ion content measurements.

An additional left ventricular biopsy specimen was obtained in the test group 10 minutes after successful defibrillation. This biopsy specimen was obtained to be certain that there was not a late increase in intramyocyte sodium content that was missed by the measurement taken after 5 minutes of reperfusion.

Statistical comparisons of precardioplegia and postcardioplegia ion content for each group were made by using a paired 2-tailed Student *t* test (SAS-PC; SAS Institute, Cary, NC). A plot of the change in ion content versus the precardioplegia measurement showed a pronounced linear relationship for sodium. Hence, the effect of between-group differences in ion measurements was adjusted by this covariate in the analysis of variance model, and comparisons of the group mean change scores were made on the adjusted means (LSMEANS statement in Proc GLM; SAS, SAS Institute). The adjusted means are noted in Table II.

Electrophysiologic data acquisition protocol. Surface electrodes were placed on the extremities to record limb lead electrocardiograms. A single unipolar atrial electrode was sewn to the left atrial appendage, and a mapping plaque measuring 2.2 × 2.3 cm with 504 unipolar electrode points (inter-electrode distance of 1 mm) was placed on the left ventricular epicardial surface.

Control electrophysiologic data included a recording of sinus rhythm followed by a precardioplegia recording of electrically induced (60-Hz burst of ventricular pacing) ventricular fibrillation and subsequent defibrillation while the pig was supported on cardiopulmonary bypass. Rapid gain switching, which refers to switching the entire amplifier bank from a high to a low gain and back to a high gain in synchrony with delivery of a shock to the heart, was used in this experiment. Rapid gain switching allows resumption of high-gain electrophysiologic data recording within 75 to 100 ms of the termination of a shock so that the initiating events of recurrent ventricular fibrillation can be captured.

Electrophysiologic data were collected continuously during postcardioplegia reperfusion. If spontaneous ventricular fibrillation occurred, it was allowed to continue until 5 minutes after the initiation of reperfusion. At 5 minutes after reperfusion, the fibrillating hearts were internally defibrillated with shocks (monophasic Edmark defibrillation waveform) delivered as often as every 20 seconds with handheld internal defibrillation paddles until a nonfibrillating rhythm was established. A 5-minute period of recovery after cardio-

Table I. Composition of blood cardioplegic solutions

Solution I	KCl (2 mmol/L per milliliter), 20 mL
	Tham (0.3 mol/L), 100 mL
	CPD, 25 mL
	D ₅ 1/4 normal saline solution, 275 mL
	CoEDTA, 5 mmol/L
	Blood cardioplegic solution
	Potassium, 22-25 mmol/L
	pH 7.7-7.8
	Calcium, 0.5-0.7 mmol/L
	Osmolarity, 340-360 mOsm/kg
Solution II	KCl (2 mmol/L per milliliter), 5 mL
	Tham (0.3 mol/L), 100 mL
	CPD, 25 mL
	D ₅ 1/4 normal saline, 275 mL
	CoEDTA, 5 mmol/L
	Blood cardioplegic solution
	Potassium, 8-10 mmol/L
	pH 7.7-7.8
	Calcium, 0.5-0.7 mmol/L
	Osmolarity, 340-360 mOsm/kg

Tham, Tris(hydroxymethyl)aminomethane; CPD, citrate-phosphate-dextrose; D₅, 5% dextrose; CoEDTA, cobalt-ethylenediamine tetraacetic acid.

plegic arrest was chosen on the basis of prior experience with this experimental model.²⁰

The 504 electrograms were bandpass filtered (0.5-500 Hz) and digitized at 2 kHz. Data analysis began with the extraction of 1-second data episodes at the following times: sinus rhythm before cardioplegic arrest; ventricular fibrillation before cardioplegic arrest; cardiac rhythm at 30 seconds and every minute during the initial 5 minutes of reperfusion; ventricular fibrillation (if it occurred) immediately before the final (ie, successful) defibrillation; and all episodes of recurrent ventricular fibrillation after defibrillation. Ventricular fibrillation and other rhythms were analyzed by computer-based algorithms that measure individual depolarizations and describe the propagation patterns of wave fronts.²¹ Other electrophysiologic variables measured in this study included the time of earliest electrical activity during postcardioplegia reperfusion, initial rhythm during reperfusion (ventricular fibrillation or a nonfibrillating rhythm), prevalence of ventricular fibrillation during reperfusion, the number of shocks needed to establish a nonfibrillating rhythm, and a description of recurrent ventricular fibrillation after defibrillation. Statistical comparisons of prevalence for electrophysiologic variables were made by means of the 2-tailed Fisher exact test, and comparisons of continuous variables were performed with an unpaired 2-tailed Student *t* test (SAS-PC, SAS Institute).

Results

Myocyte water and ion contents. Both the control group and the test group (Table II) had an increase in total myocardial water content after 5 minutes of postcardioplegia reperfusion. This increase was contained entirely in the extracellular (ie, interstitial) compart-

Table II. Atomic absorption spectroscopy data for the control and test groups

Atomic absorption measurement	Before cardioplegia	After defibrillation	P value
Control group			
Total water	4.6 ± 0.3	5.2 ± 0.4	<.001
Interstitial water	1.8 ± 0.4	2.5 ± 0.3	<.003
Intracellular water	2.8 ± 0.2	2.8 ± 0.4	<.84
Total sodium	297.6 ± 37.9	400.5 ± 39.2	<.002
Interstitial sodium	252.3 ± 48.7	244.1 ± 35.3	<.23
Intracellular sodium	45.3 ± 15.8	65.5 ± 22.5	<.04*
Total potassium	374.9 ± 34.6	358.7 ± 43.4	<.22
Interstitial potassium	5.9 ± 2.9	8.3 ± 1.5	<.04
Intracellular potassium	369.0 ± 31.8	347.3 ± 43.3	<.12
Test group			
Total water	4.5 ± 0.5	5.3 ± 0.6	<.001
Interstitial water	1.8 ± 0.3	2.8 ± 0.7	<.002
Intracellular water	2.7 ± 0.3	2.5 ± 0.5	<.18
Total sodium	306.1 ± 42.8	411.8 ± 56.0	<.002
Interstitial sodium	247.2 ± 54.0	237.8 ± 61.8	<.02
Intracellular sodium	58.9 ± 59.7	44.9 ± 26.8	<.33
Total potassium	395.5 ± 54.6	382.8 ± 60.8	<.22
Interstitial potassium	7.9 ± 2.3	11.9 ± 3.3	<.001
Intracellular potassium	388.4 ± 53.3	364.6 ± 60.9	<.04

Data listed are mean values ± SD. The measurement units are as follows: water content, milliliters per grams of dry weight; sodium content, micromoles per gram of dry weight; and potassium content, micromoles per gram of dry weight. The *P* values are given for before cardioplegic arrest versus after successful defibrillation measurements. Postdefibrillation measurements of interstitial ion content are corrected for the increase in interstitial water compared with the precardioplegia measurement.

*The means of the differences for intracellular sodium were adjusted for the observed linear relationship ($P < .001$) between the preobserved sodium content and the precardioplegia to postdefibrillation change in sodium content (least-squares estimate).

ment. The postreperfusion interstitial ion contents, after adjustment for the increase in interstitial water to provide an estimate of change in interstitial ion concentration, were insignificantly different from the paired precardioplegia measurements, with two exceptions as noted in the Table II.

The most important finding from the ion content comparisons was that the intracellular sodium content significantly increased after reperfusion in the control group, whereas in the test group the intracellular sodium content did not significantly change. The biopsy specimen taken at 10 minutes after successful defibrillation confirmed that there was no late increase in intramyocyte sodium content in the test group. The intramyocyte content of potassium was lower in the postdefibrillation measurement than in the precardioplegia measurement for both groups; however, in only the test group did this decrease attain statistical significance.

Electrophysiologic data. The earliest electrical activity was detected at 9.3 ± 2.6 seconds after starting reperfusion in the control group and was delayed by the infusion of warm cardioplegic solution in the test group until 126.6 ± 13.8 seconds after reperfusion ($P < .001$). The prevalence of ventricular fibrillation dur-

ing reperfusion was similar (100% for control group and 66% for test group, $P = .2$); however, the initial rhythm during reperfusion was organized (ie, nonfibrillating) in 50% of the test group and 0% of the control group ($P < .02$). The number of shocks required to establish a nonfibrillating rhythm was lower in the test group than in the control group (1.1 ± 0.3 vs 4.5 ± 1.2 , $P < .03$). At least one organized depolarization followed the first defibrillation attempt at 5 minutes after reperfusion in 60% of the control hearts compared with 83% of the test hearts ($P = .35$). However, one or more organized depolarizations developed after defibrillation in only 26% of all shocks in the control group, whereas 80% of all the shocks in the test group produced one or more organized depolarizations ($P < .001$).

Examination of the reperfusion rhythms that occurred during the initial 5 minutes of postcardioplegia reperfusion in the control group showed rapid restoration of the dV/dt of individual electrograms with insignificant changes in the organization of the wave fronts that constitute ventricular fibrillation. The electrograms recorded in the test hearts usually had a dV/dt (first derivative of voltage with respect to time) that was below the detection limits of the algorithms for fibrillation analysis until 4 to 5 minutes after reperfusion.

Fig 1. A, Data obtained in a control (blood reperfusion) animal. Electrograms from one half of one row of electrodes show a recurrence of ventricular fibrillation after defibrillation of postcardioplegia reperfusion ventricular fibrillation. **B,** Data from all electrode points are displayed as a function of time, depicting the progressive increase in heterogeneity that occurs in the conduction of accelerating wave fronts. These depolarizations eventually establish ventricular fibrillation. The SDs of activation times for electrograms from the first 6 beats in this illustration progressively increase (4.5, 9.5, 10, 30, 69, and 95 ms).

This precluded a quantitative description of changes that occurred in ventricular fibrillation during reperfusion in the test group.

Episodes of recurrent ventricular fibrillation after defibrillation were captured by rapid gain switching, and the electrophysiologic mechanism was similar for all of the episodes of recurrent fibrillation that were

successfully recorded. Accelerating depolarizations before the onset of fibrillation displayed increasingly disorganized propagation beneath the recording plaque (Fig 1). The increasing temporal dispersion of depolarization wave fronts eventually established continuous disorganized activity typical of ventricular fibrillation. The rhythms recorded during postcardioplegia reperfu-

Fig 2. A, Electrograms from one half of one row of electrodes show an organized postcardioplegia rhythm in a test (controlled reperfusion) animal. **B,** Data from all electrode points are displayed as functions of time for the rhythm shown in **A**. The SDs of activation times for the 3 beats in this illustration range from 1.0 to 2.1 ms.

sion in the controlled reperfusion group (Figs 2 and 3) had wave fronts with less temporal dispersion and more uniform patterns of propagation.

Discussion

Approximately 2 minutes of asystole produced by reperfusion with a warm blood cardioplegic solution diminished reperfusion arrhythmias and abolished the

increase in intramyocyte sodium that occurred in the control group after 1 hour of cardioplegic arrest. These findings support the hypothesis of this study and suggest that restoration of intramyocyte ion homeostasis and membrane function is a mechanism for the beneficial effects of controlled reperfusion and secondary cardioplegia.

There are at least two alternative explanations for the observed difference in intramyocyte sodium gain

Fig 3. A, Electrograms from one half of one row of electrodes in a test (controlled reperfusion) heart show recurrent ventricular fibrillation after defibrillation. Fibrillation results from an ectopic premature depolarization that initiates continuous electrical activity. **B,** Data from all electrode points are displayed as a function of time for the rhythm shown in **A**. The SDs of electrogram activation times for the two depolarizations before the ectopic beat are 7.0 and 4.6 ms, whereas the SD for the ectopic beat electrogram activation times is 18 ms.

between the test and control groups that cannot be excluded on the basis of the present study. One alternative explanation is that a longer cumulative duration of ventricular fibrillation in the control group was solely responsible for the increase in sodium at 5 minutes after reperfusion because of sodium entry from

myocyte action potentials. A second alternative explanation is that asystole in the test group improved microregional blood flow distribution during reperfusion. This could improve metabolic recovery by more rapid and homogeneous rewarming, which thereby could result in more rapid extrusion of sodium during

reperfusion. Regardless of the precise mechanism, it appears that ion homeostasis is improved with the use of controlled reperfusion.

Recently published information indicates that a net gain in myocyte sodium during postischemic reperfusion is pivotal to the deleterious effects of reperfusion.^{9-12,22,23} The precise mechanisms for reperfusion injury related to acute increases of intramyocyte sodium have not yet been completely defined^{9,10}; however, it is likely that attenuating the influx of sodium ions during reperfusion decreases calcium influx and limits the extent of necrosis that results from ischemia-reperfusion injury.

Experiments in animals have shown that postischemic increases in intramyocyte sodium are amenable to pharmacologic modulation, both in models of regional ischemia-reperfusion¹³⁻¹⁵ and in models of global ischemia associated with cardioplegic arrest.^{24,25} Our study examined a nonpharmacologic method (controlled reperfusion) for improving postischemic myocyte ion homeostasis and diminishing net sodium gain. Controlled reperfusion, which is unique from the pharmacologic methods because it is administered after the ischemic interval, provides its benefit by sparing the myocardium from electromechanical activity while ion homeostasis is restored. It is our hypothesis that asystole allows energy-dependent membrane transporters, such as Na⁺/K⁺ adenosinetriphosphatase, to extrude sodium from the cytosol at a relatively rapid rate, while a state of asystole limits sodium entry associated with action potentials.

The fact that the mechanisms by which controlled reperfusion and drugs (eg, Na⁺/H⁺ exchange inhibitors) attenuate net sodium gain are fundamentally different suggests that they could interact synergistically to diminish the effect of severe myocardial ischemia-reperfusion injury. Such synergism is potentially useful for treating evolving myocardial infarction, hearts subjected to prolonged periods of cardioplegic arrest, or hearts that are injured during a cardiac operation and fail to separate from cardiopulmonary bypass.

This study also examined reperfusion arrhythmias that are a manifestation of reperfusion injury.²⁶ To date, there have only been a few studies that pertain directly to postcardioplegia reperfusion arrhythmias. It has been shown that the conditions of reperfusion affect the prevalence of ventricular fibrillation after cardioplegic arrest²⁰ and that the most common mechanism for initiating postcardioplegia ventricular fibrillation is a non-reentrant accelerating ventricular tachycardia that degenerates into fibrillation.²⁷ Furthermore, a longer duration of asystolic reperfusion has been associated with fewer reperfusion arrhythmias, which provides support for the putative link between metabolic recovery and electrophysiologic recovery.²⁰

Rhythm analysis from the present study confirms the salutary effect of asystolic reperfusion on postcardioplegia myocardial wave front propagation and reperfusion arrhythmias. This study also provides new information documenting the electrophysiologic events that lead to recurrent postcardioplegia reperfusion ventricular fibrillation. Establishing an association between improved myocyte ion homeostasis and fewer reperfusion arrhythmias strengthens the case for using reperfusion arrhythmias as a means for monitoring the recovery of the myocardium during the first 10 to 15 minutes of postcardioplegia reperfusion and as an early indicator of important intraoperative ischemia-reperfusion injury.

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