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# Myocardial buffering capacity and high-energy phosphate utilization during hypothermic circulatory arrest and recovery in the newborn lamb in vivo

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## Abstract

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**The purpose of this study was to measure myocardial buffering capacity and adenosine triphosphate utilization rates in the newborn animal in vivo during hypothermic circulatory arrest and recovery. *Methods*: These studies were performed with $^{31}P$ magnetic resonance spectroscopic techniques, which supplied a 12- to 16-second time resolution, to monitor intracellular pH and phosphocreatine and adenosine triphosphate levels. All experiments were performed with a radiofrequency surface coil on the pericardium with the sheep centered inside a 4.7 T magnet. Newborn sheep (*n* = 5, aged 16 days ± 2.4 standard error) were supported by cardiopulmonary bypass, cooled to 20° C, and subjected to 20 minutes of circulatory arrest. *Results*: During early ischemia, phosphocreatine hydrolysis progressed at a linear rate, 1.2 ± 0.05 μmol/gm per minute, and was accompanied by intracellular alkalinization. Myocardial buffering capacity calculated from ΔpH/Δ phosphocreatine equals 25 ± 3 μeq $gm^{-1}$ $\Delta pH^{-1}$, a value similar to that obtained from perfused heart studies. After the initial 4 minutes in ischemia, the decrease in phosphocreatine hydrolysis was accompanied by intracellular acidification, which is likely**

**due to late induction of anaerobic metabolism. *Conclusions*: In these studies, early phosphocreatine hydrolysis rate is nearly equivalent to adenosine triphosphate utilization rate. During the early period of ischemia phosphocreatine hydrolysis serves a buffering function and is associated with intracellular alkalinization. These techniques and measurements can be used to compare effects of myocardial preservation techniques on intracellular pH and adenosine triphosphate kinetics. (J THORAC CARDIOVASC SURG 1994;108:946-52)**

Hypothermia currently provides the primary myocardial protection in the infant during circulatory arrest.[1,2] Although cooling clearly decreases rates of myocardial adenosine triphosphate (ATP) expenditure, the cellular energy processes during hypothermic circulatory arrest are incompletely understood. Measurements of ATP utilization and high-energy phosphate kinetics during hypothermic ischemia have been limited by methods providing temporal resolution, which is inadequate for reaction rate determination.[3,4] Similarly, the interaction between energy metabolism and pH during circulatory arrest has been incompletely described. Manipulation of extracellular pH and possibly intracellular pH has been advocated as an adjunctive method of myocardial protection in the neonate.[2,5] However, myocardial buffering capacity in an intact animal model has not been measured. The purpose of this study was to use magnetic resonance techniques that have been previously used in skeletal muscle[6] to measure ATP utilization rates and myocardial buffering capacity during hypothermic circulatory arrest in a neonatal model in vivo. This study provides a basis for further experiments that can analyze the effects of various manipulations on these processes.

## MATERIALS AND METHODS

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### Surgical procedures

All sheep used 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 (NIH Publication No. 86-23, revised, 1985). Neonatal sheep ($n$ = 5, aged 16 days ± 2.4, standard error) were anesthetized with a 1% halothane and oxygen mixture after presedation with ketamine 10 mg/kg and xylazine 0.2 to 0.4 mg/kg. The sheep were completely shorn, wrapped in a rubber water-circulating blanket to maintain temperature, and then placed into a cradle specially designed for the 26 cm clear bore magnet. Femoral venous and arterial catheters were placed and systemic arterial pressure was monitored. A 4 mm cannula was inserted in the other femoral artery for perfusion during cardiopulmonary bypass. A median sternotomy was performed, followed by removal of the pericardial fat pad. The hemiazygos vein, which empties into the coronary sinus in sheep, and the ductus arteriosus were ligated. After heparin was administered in a dose of 350 units/kg, the venae cavae were cannulated and connected to the venous return line of a Sarns heart-lung machine (Sarns Inc./3M Health Care, Ann Arbor, Mich.) with a Bentley infant oxygenator (Bentley Laboratories Division, Irvine, Calif.) that was primed with 1 L of adult sheep blood augmented with lactated Ringer's solution. The femoral artery return cannula was attached to the arterial line of the pump-oxygenator. An additional cannula was placed through the atrial appendage for coronary sinus cannulation to direct coronary venous drainage to the return of the heart-lung machine. A Transonics cannulating flow probe (Transonic System, Inc., Ithaca, N.Y.) was placed in this line for continuous flow monitoring. A sump line was placed into the left ventricular chamber. A 2 cm ellipsoid surface coil that conforms to the general shape of the sheep heart was sutured to the pericardium overlying the left ventricle. Normothermic bypass (37° C) was begun and the animal was then placed in the magnet. The large amount of blood used for priming the pump served to compensate for the decrease in volume caused by long drainage and perfusion

lines necessary for working within the magnet. Temperature was monitored via a thermistor in the esophagus.

## Magnetic resonance spectroscopy techniques

All studies were performed with a General Electric CSI system (General Electric Company, Fairfield, Conn.) with Omega software, and a 4.7 T Oxford magnet with a 26 cm clear bore. Before the studies were done, the surface coil was tuned within the magnet to 81 MHz, the operative frequency for phosphorus 31. Shimming was performed with the proton signal as previously described.[7,8] Proton line widths were generally less than 40 Hz, which affords high resolution of phosphorus spectra at 4.7 T. $^{31}$P spectroscopy was performed by means of a simple one-pulse technique with a 2-second interpulse delay. Six to eight acquisitions were averaged into consecutive blocks, depending on signal-to-noise ratio in individual experiments and therefore providing 12- to 16-second time resolution. Spectra were acquired with 5000 Hz spectra width and 2048 data block size. Zero filling was applied once to increase block size and enhance resolution before analysis.

## Protocol

$^{31}$P spectra were acquired at 37° C for 10 minutes. Subsequently, central cooling to 18° to 20° C over approximately 20 minutes was performed. Spectra were obtained at baseline and during subsequent 20-minute periods of circulatory arrest followed by a 10-minute reperfusion. Arterial pH was maintained at 7.35 to 7.45 with temperature correction by adjusting perfusion carbon dioxide tension.

## Data analysis

Peak areas were measured by Lorentzian deconvolution fitting of individual peaks[7] and by least squares analysis asdescribed by Heineman and associates.[9] Initial ATP levels were assumed to be at 8.6 mmol/L as shown by published freeze clamp extraction studies.[10] This value in conjunction with the inorganic phosphate ($P_i$)/ATP and phosphocreatine (PCr)/ATP ratios corrected for saturation through comparison with fully relaxed spectra was used for calculation of absolute PCr and $P_i$ concentrations. Changes in ATP concentration were calculated from alterations in the area of the ß-ATP peak and were confirmed with difference spectra.

Intracellular pH was calculated from the chemical shift of the intracellular $P_i$ peak relative to PCr, as described by Portman and Ning.[7] Calibration curves for the different temperatures have been adapted from Swain and associates[11] and confirmed in our laboratory in Seattle.

20° C pH = 6.9602 + Log([$\delta$ - 3.412218]/[5.685908 - $\delta$])

37° C pH = 6.7698 + Log([$\delta$ - 3.236025]/[5.685646 - $\delta$])

where $\delta$is the chemical shift of $P_i$ in parts per million from PCr.

Curve fitting to data was performed with linear and multiple order polynomial functions calculated by means of Axum commercial software graphics program (Trimetrics Co., Seattle, Wash.).

# RESULTS

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Typical $^{31}$P spectra are illustrated in Figs. 1 to 3.

**Fig. 1.** $^{31}$P spectra obtained from the heart of an open-chest lamb. **A,** Sum of eight 12-second blocks acquired during the initial phase of hypothermic circulatory arrest. Spectra were obtained by means of 5000 Hz spectral width and

2000 data points. Ten-hertz line broadening was applied before Fourier transformation. Labeled peaks are as follows: $P_i$, intracellular phosphate; *PCr*, phosphocreatine, *ATP*; γ, α, and ß. **B,** Spectra from the final eight blocks obtained during ischemia. Note that the $P_i$ peak has shifted slightly downfield (lower ppm), as well as increasing in intensity. This shift corresponds to an acidic change in pH, which is related to the chemical shift difference between $P_i$ and PCr. **C,** Difference spectra **B** minus **A.** The increase in $P_i$ is stoichiometrically equivalent to the PCr decrease. There is no observable change in ATP.

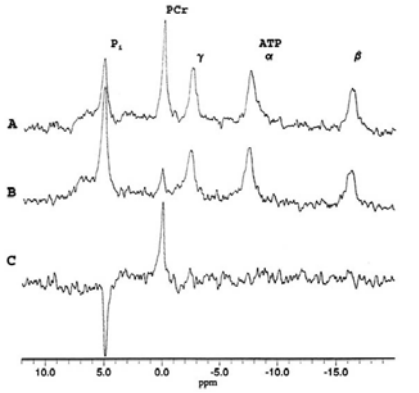


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**Fig. 2.** Full-spectrum stack plot obtained during a protocol. Each spectrum represents a 16-second period. Every third acquisition block is shown. The chronologic order is noted by the data file name on the right border. Peak identification is the same as in Fig. 1. A, Initiation of circulatory arrest. **B,** First spectrum obtained during reperfusion. **C,** Completion of recovery.

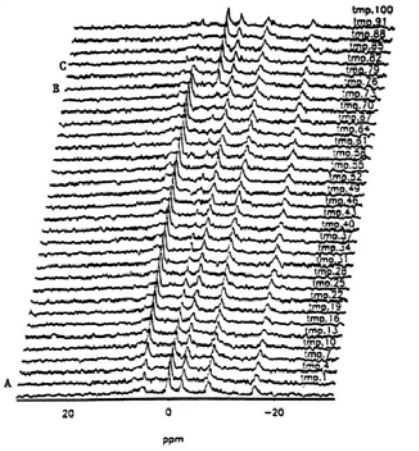


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**Fig. 3.** Enlargement of Fig. 2 to emphasize change in the predominant peaks, Pi and PCr (at 0 ppm). **A** denotes reperfusion. Note that $P_i$ initially shifts slightly away from PCr, but then moves toward it during late ischemia, just before **A.** A decrease in the chemical shift difference between PCr and $P_i$ corresponds to a decrease in pH.

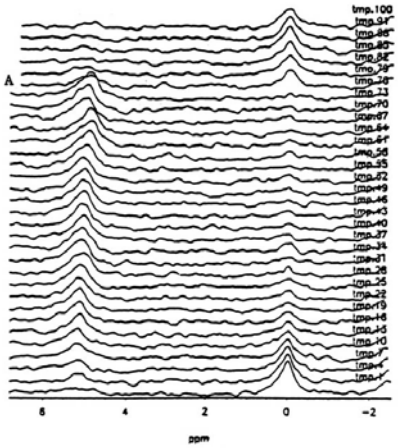


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Fig. 1 illustrates spectra from baseline and ischemia. The difference spectrum illustrates that PCr loss corresponds to a fairly equivalent amount of $P_i$ gain with a small discrepancy caused by differential saturation effect. ATP remains stable. Figs. 2 and 3 illustrate stack plots of spectra extending from before ischemia through circulatory arrest to recovery. Resolution allows analyses of peak area and chemical shift. Retention of some PCr even at 20 minutes allows these measurements to be performed. Longer periods of ischemia with resulting decrease in PCr would prevent measurement of chemical shift and pH.

## pH during ischemia

Intracellular pH increased from 7.19 ± 0.03 to 7.43 ± 0.03 during the temperature transition from 37° to 20° C. Typical data curves obtained during hypothermic circulatory arrest and reperfusion are illustrated in Figs. 4 and 5.

**Fig. 4.** Typical scatter plot for an individual experiment relating PCr concentration to time during hypothermic circulatory arrest, which begins a time 0. The regression line is drawn during the initial 4 minutes of rapid of PCr hydrolysis. The reaction rate is equivalent to the slope of this line. This period is followed by a slowing of PCr hydrolysis. Recovery begins at 20 minutes. This rapid phase is also described as a linear function.

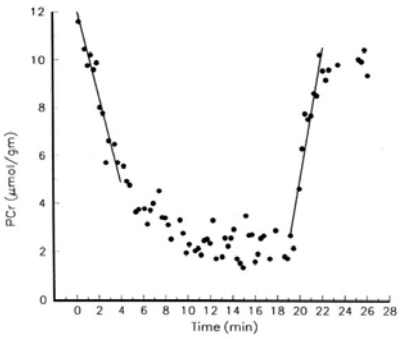


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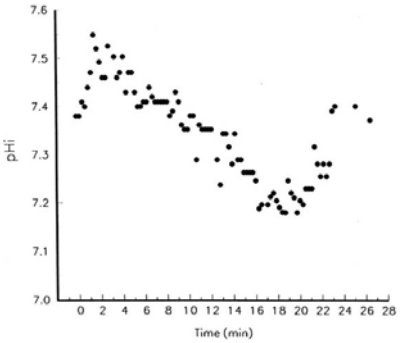
**Fig. 5.** Intracellular pH is shown as a function of time. These data parallel those shown in Fig. 4. During the initial 4 minutes of circulatory arrest, pH increases because of the rapid phase of PCr hydrolysis. This initial phase is followed by acidification, probably the result of induction of anaerobic ATP-producing pathways. During recovery pH increases rapidly. Signal to noise is then markedly reduced because of a rapid decrease in the intracellular phosphate peak. This decreases the accuracy of the pH measurement, which is determined from the chemical shift difference between the intracellular phosphate peak and PCr.

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Polynomial curve analyses reveal that pH increases in the initial 4.0 ± 0.09 minutes. During this initial ischemic period, pH increased to 7.52 ± 0.04 because of proton consumption associated with creatine formation. After this initial alkalinization, pH decreased nearly linearly over the remaining ischemic period to a nadir 7.35 ± 0.09. Analysis of variance and paired *t* tests were used to confirm the significance of pH changes ($p < 0.05$) as noted earlier.

## PCr during ischemia

PCr hydrolysis approximates a linear function during the initial 4 minutes as assessed by regression analysis ($R = 0.90$). Slope ΔPCr/Δtime, the initial hydrolysis rate, equals 1.2 ± 0.05 μmol/gm per minute. This initial rapid PCr hydrolysis is consistently followed by slowing coincidental with the linear drop in pH.

## Recovery

pH and PCr recovery is extremely rapid and is completed in less than 3 minutes. The initial recovery rate determined by linear regression and using the recovery data points is 2.3 ± 0.2 μmol/gm per minute. This value represents the maximal phosphorylation rate. During these studies no significant changes occurred in ATP levels.

## DISCUSSION

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### Myocardial buffering capacity

Total myocardial buffering capacity can be defined as the resistance to pH change when an acid load is delivered to or removed from the cell. There are two major components: (1) intrinsic buffering capacity and (2) the capability of the cell to extrude hydrogen ions or import bicarbonate. Anaerobic glycolysis with resulting lactate and proton production has often been implicated as the primary process that influences pH during ischemia. However, numerous complex reactions both generate and consume protons during myocardial ischemia (for review see Gevers,[12] 1977). PCr hydrolysis is the dominant pH altering reaction in the initial early period of ischemia. The reaction PCr + ADP + $H^+$ ⟷ Creatine + ATP, catalyzed by creatine kinase, provides an energy buffering function and not only delays ATP depletion during ischemia but also moves intracellular pH in the alkaline direction. This initial alkalinization has been well documented in skeletal muscle.[6] Methods that provide relatively poor temporal resolution are inadequate to delineate this early ischemic phenomenon in myocardium because of the rapid development of subsequent acidosis. Slowing of metabolic processes during hypothermia paired with the improved time resolution measurement provided in these studies enables measurement of the linear PCr hydrolysis rate during early ischemia. Buffering capacity (BC) has been measured in skeletal muscle[6] by the formula BC = 0.43$\Delta$pH/$\Delta$PCr, where 0.43 accounts for the difference in the $H^+$ ionization constant between PCr and $P_i$ at pH 7. Similar calculations can be performed speculatively in the present model under study. With an initial PCr rate of 1.2 mmol/gm per minute and a corresponding $\delta$pH of 0.0225 pH per minute, a buffering capacity of 25 ± 3 meq $gm^{-1}\Delta pH^{-1}$ is calculated for hypothermic neonatal myocardium. This value is comparable with that determined in rat myocardium, 23 meq $gm^{-1}$ $\Delta pH^{-1}$, during ischemia at 37° C and at pH greater than 6.4.[13] Myocardial buffering capacity varies considerably with pH and has been shown to increase as pH drops below 6.4. At lower pH there is presumably an increasing proportion of cardiac buffering from intrinsic buffers such as intracellular proteins. Theoretically, the increased buffering capacity might limit the range of intracellular acidosis and possibly protect the heart from damage during ischemia. However, this effect has not been proved. The myocardial buffering capacity determined in this study provides a comparison for measurements that can be performed during various pH management strategies, such as alpha-stat, pH-stat, or modification of buffers in cardioplegic solution.

### ATP utilization rate

Presumably, a goal of myocardial protection is preservation of cellular high-energy phosphate stores through reduction of ATP utilization. The alkalinization of the cytosol in early ischemia indicates that PCr hydrolysis is probably the primary ATP-producing pathway. This is followed by acidification likely caused by later induction of other ATP-producing pathways, principally anaerobic glycolysis with resulting lactate formation.[14] However, because of late induction of these acidification processes and preservation of ATP levels in early hypothermic ischemia, the initial PCr hydrolysis rate is assumed to be equivalent to the ATP utilization rate. The value of 1.2 μmol/gm per minute can be compared to normoxic values between 10 and 50 in working lamb hearts in situ[8,10,15] (calculating 3 ATP/oxygen consumed).

Rephosphorylation approximates a monoexponential course in skeletal muscle.[6] However, only eight or nine points were usually available for analysis during the recovery time course in these experiments. Therefore a rate was approximated by means of linear regression analysis. The rephosphorylation rate has been used to calculate the maximal oxidative phosphorylation rate in skeletal muscle and may be considered a measure of oxidative capacity.[16,17] The assumption that

this rate isequivalent to $V_{max}$ is difficult to apply to myocardium, inasmuch as basal ATP requirements must be met in addition to rephosphorylation of creatine. However, because the ATP concentration is stable throughout recovery, the rephosphorylation rate represents oxidative phosphorylation in excess of basal requirements and should be dependent on the oxidative capacity of the mitochondria. Theoretically, this rate should be decreased if mitochondrial damage occurs during ischemia[18] and possibly increased if myocardial protection is applied. Determination of oxygen consumption directly through Fick type calculations is complicated and possibly misleading because a steady state does not occur in this early reperfusion period. For comparisons with the rephosphorylation rate, we did perform such calculations by cannulating the coronary sinus and measuring coronary venous return while sampling arterial and sinus oxygen content in three animals. As expected, the mean ATP synthesis value 3.8 ± 0.4 μmol/gm per minute does exceed the rephosphorylation rate calculated at 2.3 μmol/gm per minute.

## Glycolysis

Slowing of PCr hydrolysis occurs after the initial 4 minutes and is accompanied by acidification, presumably because of lactate formation. No significant change occurs in ATP levels, indicating that basal energy requirements are now being met by anaerobic pathways supplemented by the residual PCr hydrolysis. Glycolysis may be stimulated by increasing pH, adenosine diphosphate, and $P_i$ levels.[19] The glycolytic rate should therefore be less than one third the ATP utilization rate assuming that 3 mol ATP are produced per glycogen-derived glucose consumed.[19] If PCr hydrolysis is assumed to be negligible over the final 20 minutes of ischemia, then

$$\mathrm{MBC} = \Delta[\mathrm{H}^+]/\Delta\mathrm{pH} \qquad \text{and}$$
$$\mathrm{MBC} = \Delta[\text{lactate}]/\Delta\mathrm{pH}^{13}$$

(where MBC is myocardial buffering capacity) and the rate of lactate formation is calculated at 0.3 μmol/gm per minute, not substantially different from the value predicted from the stoichiometry (<1.2/3 = 0.4) according to the ATP utilization rate previously determined from the initial PCr hydrolysis. Calculation of glycolytic rate from $^{31}$P spectra during ischemia, when myocardial buffering capacity is known, has been previously described by Wolfe, Gilbert, and Brindle.[13] Glycolytic rates in ischemic perfused rat hearts were confirmed in those studies by using $^{1}$H spectroscopy to monitor lactate accumulation.

Values for myocardial buffering capacity and PCr hydrolysis and recovery rates obtained in an intact animal model during hypothermic circulatory arrest have not been previously reported. Evaluation of myocardial protection therapy that can be adjunctive to hypothermia in the neonate has been limited by lack of knowledge concerning these basic cellular processes during circulatory arrest. Certainly, the vast majority of surgical literature has focused on the evaluation of cardiac function after application of various myocardial protection modalities.[1,2,20] Unfortunately, functional assessment causes interpretative difficulties because prolonged periods of ischemia must usually be applied to achieve statistical significance in most studies. Heineman and Balaban[21] have previously demonstrated the use of time-resolved $^{31}$P spectra (15- to 16-second resolution) in the canine heart. Similar magnetic resonance techniques applied in the present study provide an alternate approach to analysis at the biochemical and cellular levels and yet can be performed during cardiopulmonary bypass in vivo. Furthermore, reaction rates can be measured as opposed to performing isolated determination of metabolite concentrations. The early PCr hydrolysis phase and concomitant alkalinization are not widely recognized or discussed in the surgical literature. The rapidity of these phenomena emphasizes the importance of adequate time resolution when metabolic studies are being analyzed. Conceivably, adjunctive myocardial protection may alter myocardial buffering capacity or high-energy phosphate reaction rates. The techniques described here can be used to compare the effect of various myocardial protection strategies on intracellular pH and reaction velocities during hypothermia. These

methods also offer a means for measuring these rates without prolonged periods of ischemia. In our model, rapid PCr depletion during normothermic circulatory arrest precludes measuring these reaction rates. Therefore a comparison between normothermic and hypothermic conditions is not provided in this study. Conceivably, a further increase in signal-to-noise ratio may enable attainment of adequate temporal resolution during normothermic ischemia in the future. However, because hypothermia is currently the mainstay of myocardial protection in the neonate, assessment of reaction rates under normothermic conditions is not clinically relevant.

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## Publishing and Reprint Information

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## Articles with References to this Article

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**This article is referenced by these articles:**

**Influence of the ph of cardioplegic solutions on cellular energy metabolism and hydrogen ion flux during neonatal hypothermic circulatory arrest and reperfusion: A dynamic $^{31}$p nuclear magnetic resonance study in a pig model**
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ABSTRACT FULL TEXT