Characterization of Cerebral Energetics and Brain pH by ³¹P Spectroscopy After Graded Canine Cardiac Arrest and Bypass Reperfusion

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Summary: Recovery of cerebral energy metabolism is used to indicate CNS viability after ischemia. This study utilized ³¹P nuclear magnetic resonance (NMR) spectroscopy to measure cerebral energy state and intracellular pH in dogs subjected to 8, 12, or 16 min of cardiac arrest and reperfusion using cardiopulmonary bypass. Spectra were obtained throughout ischemia and initial reperfusion and repeated at 30 and 144 h post ischemia. Neurologic deficit scoring was performed at 12 and 24 h post insult and then daily. High-energy phosphates were depleted by the end of all ischemic intervals. Recovery occurred within 60 min of reperfusion and persisted with no differences in the rate of return between groups (p > 0.05). Brain pH (pH_b) decreased by the end of ischemia in all

The perturbations in cerebral energy charge and pH that occur during cardiac arrest and reperfusion are not well understood. However, recent investigations (Hossmann et al., 1987; Martin et al., 1987; Pretto et al., 1987) have shown that the tolerance of the brain to complete ischemia is longer than the 4 min originally suggested by Weinberger et al. (1940), Kabat et al. (1941), and Grenell (1946) and may be as long as the 60 min suggested by Ames and Guarian (1963). Part of the difficulty in attempting to determine the tolerance limit results from the methodology used to define the return of neuronal

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Abbreviations used: CPB, cardiopulmonary bypass; NMR, nuclear magnetic resonance; PCr, phosphocreatine; VF, ventncular fibrillation.

groups (p < 0.0001). Neither the pH_b nadir nor its recovery differed between groups (p > 0.05). Although longterm neurologic outcome differed between groups, the spectra were similar. Assessment of cerebral energy state using ³¹P NMR spectroscopy does not appear to be a sensitive indicator of neurologic outcome after global ischemia in dogs. Return of high-energy phosphates may be a necessary but not sufficient condition for cerebral recovery after ischemia. The return of high-energy phosphates after a 16-min cardiac arrest, however, indicates a potential for neurological recovery. Key Words: Cardiac arrest—Cardiopulmonary bypass—Cerebral ischemia—³¹P nuclear magnetic resonance spectroscopy—Reperfusion.

function. Return of normal neurologic function by clinical assessment is the best determinant of cerebral recovery. Such survival studies are difficult and expensive and often fail to address the pathophysiology on **a** cellular level. Return **of** cerebral energy metabolism has been used as an indicator of CNS viability (Ljunggren et al., **1974**; Nordstrom et al., **1978**; Welsh et al., **1978**; Paschen et al., **1985**). The relationship between the return of cerebral energy metabolism and functional outcome was, until recently, impossible to directly determine without parallel studies, since metabolic measurement required physical brain sampling, precluding any correlation with clinical outcome.

Nuclear magnetic resonance (NMR) spectroscopy provides the methodology to measure cerebral energy metabolism (Thulborn et al., **1982**) and intracellular pH (Moon and Richards, **1973**; Petroff et al., **1985**) noninvasively as a function of time. The purpose of this experiment was to utilize NMR spectroscopy to investigate the changes in cerebral

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energy metabolism and pH that occur during graded cardiac arrest and reperfusion using fernorofemoral cardiopulmonary bypass (CPB). These changes were correlated with the clinical outcome **of** the animal.

METHODS

Fifteen adult conditioned mongrel dogs with mean weight of 32.3 ± 2.4 kg were utilized for this project. This study was approved by the institutional Care of Experimental Animals Committee. Two weeks prior to the actual experiment, a total of 2 units of packed red blood cells was obtained from each animal. This autologous blood was later used to prime the CPB circuit (see below).

Five days prior to the experiment, the animals were anesthetized with sodium thiamylal (17 mg/kg) and maintained with halothane. A scalp flap was made on the right side of the head and the right temporalis muscle excised. After closure of flap, the animals were allowed to recover.

On the day of the experiment, the animals were anesthetized with a single dose of pentobarbital (25 mg/kg) and intubated. The dogs were then transported to the NMR preparation room and placed on a nonferromagnetic animal holder. Mechanical ventilation was begun (room air) using an Ohio Medical Products CCV2 volume cycled ventilator at a rate of 15-20 min and tidal volume of 10-15 ml/kg. Specially adapted long tubing and valvular mechanisms enabled ventilation from a distance of 23 ft. Ventilation was adjusted to maintain $P_a co_2$ of 35-45 mm Hg and pH of 7.35-7.45. Meperidine (3 mg/kg) and pancuronium (0.1 mg/kg) were administered hourly to maintain anesthesia and paralysis throughout the experiment. Temperature was continuously monitored with a rectal probe. A heating/cooling blanket was used to maintain temperature between 36.5 and 38.5°C.

Bilateral femoral cutdowns were performed using sterile technique to expose both the femoral arteries and the femoral veins. A 60-cm, 6-French catheter was inserted into the left femoral artery and advanced to the thoracic aorta. This catheter was then connected to a pressure transducer (Gould P-50) and a Grass model 7D polygraph through 23 ft of pressure-monitoring tubing for continuous central arterial pressure recording. A 7-French Swan-Ganz catheter was inserted into the left femoral vein and advanced under pressure-tracing guidance into a branch of the pulmonary artery. Both proximal and distal ports were then connected as before, to enable continuous recordings of the central venous and pulmonary artery pressures. Five nonferromagnetic needle electrodes were placed subcutaneously to provide ECG monitoring. Defibrillator electrodes (R-2 Corp., Morton Grove, IL, U.S.A.) were attached to both the right and the left anterior chest.

A 7-French double-lumen catheter was then placed in a forelimb vein using sterile cutdown technique. This access was later used for medication administration. The scalp flap incision made **5** days previously was reopened to expose the skull of the animal. This area was draped in a sterile fashion in preparation for coil placement (see below). An 8-cm, 16-to 18-French (depending on vessel size) arterial bypass cannula was inserted into the right femoral artery. This was clamped until institution of CPB.

The animal was positioned in its portable holder and inserted into the magnet. The Bruker Biospec 1.89-T 60-

cm-bore superconducting magnet system utilized in this experiment is shielded and contained within a Faraday cage. Since no ferromagnetic objects are brought into the cage, all monitoring, ventilation, and CPB were conducted from outside the cage, a distance of -23 ft. A 4-cm-diameter single-turn copper surface coil embedded in plastic was immobilized on the exposed skull using a nonferromagnetic gantry. The animal was then advanced so as to position the coil in the center of the magnet. The homogeneity of the magnetic field was adjusted on the brain water proton resonance (80.3 MHz) and then the coil was tuned to the phosphorus frequency (32.5 MHz). For the phosphorus experiment, the following parameters were used: sweep width of 4,000 Hz, pulse length of 90 μ s, and 2-s relaxation delay. Phosphorus spectra were obtained at baseline (prior to the insult), during ischemia, during bypass, and during the subsequent 7 h of critical care monitoring. Before Fourier transformation of the data, the spectra were processed using a profile correction algorithm (Bruker) and multiplied by an exponential weighting function with a line broadening of 10-20 Hz. The relative concentrations of key metabolites can be compared from the areas beneath the signals of interest. Areas of individual phosphorus resonance were measured by triangulation. Baselines were reproducibly drawn to account for any residual broad intensity not removed by the mathematical correction (Gordon et al., 1982). The measurement of relative, rather than absolute, concentrations provides a sufficient basis for interpretation. The measurement of pH by ³¹P NMR is a standard technique (Crockard et al., 1987; Gadian et al., 1979; Gadian, 1983) that relies upon the chemical shift of the P_i signal with changes in pH.

After baseline spectra were collected, hemodynamic and physiologic measurements were obtained. The dog was then fibrillated with a transthoracic electric shock of 50 V AC and ventilation was terminated. The dogs remained in ventricular fibrillation (VF) for a period of 8 (n = 5), 12 (n = 5), or 16 (n = 5) min before the initiation of CPB.

During the period of VF, a 50-cm, 20-French venous bypass cannula (C.R. Bard Corp., Billerica, MA, U.S.A.) was inserted in the right femoral vein and its tip advanced to the right atrium. The arterial and venous cannulas were then connected to a Bard cardiopulmonary support system. This system is described in detail elsewhere (Martin et al., 1987) and was modified with an additional 18 ft of tubing to enable CPB from outside the Faraday cage. The system was primed with the 2 units of previously obtained autologous packed red blood cells and saline to minimize hemodilution. Heparin (1.5 mg/kg) and sodium bicarbonate (1 mEq/kg) were added to the prime. An additional 1.5 mg/kg heparin was given intravenously to the animal immediately preceding the institution of CPB.

CPB was begun after the predetermined VF time with flows between 80 and 120 ml/kg/min. Arterial pH (pH_a) was rapidly corrected using sodium bicarbonate. The animal was defibrillated 3 min later and CPB continued for an additional 2 h. The dog was then weaned from CPB over 10 min and allowed to resume its own spontaneous circulation. The venous bypass cannula was removed and the femoral vein clamped.

The animal was monitored continually by ³¹P NMR for an additional **7** h after termination of bypass. During this period it was monitored with therapy aimed at maximizing cardiac output. The animals were maintained within the following physiologic ranges: temperature, 36.5–39°C;

urine output, ≥ 1 ml/kg/h; central venous pressure, <20 mm Hg; PCWP, <20 mm Hg; MABP, 80-120 mm Hg; pH_a, 7.35-7.45;P_aco₂; 35-45 mm Hg; P_ao₂, >70 mm Hg. Trimethaphan, dopamine, neosynephrine, furosemide, sodium bicarbonate, and fluids (normal saline) were used as needed. Cephazolin 1 g i.v. was given 5 h after the insult and continued every 8 h for 2 days.

At the end of 9 h of postinsult monitoring, the animal was removed from the magnet. The arterial cannula, aortic catheter, Swan-Ganz catheter, and double-lumen catheters were removed, vessels were ligated, and cutdowns were irrigated and sutured. The scalp flap was irrigated and sutured. Paralysis and sedation were reversed with neostigmine 1 mg, atropine 0.5 mg, and naloxone 2 mg i.v. The animal was then assessed as to its ability to adequately ventilate spontaneously. When ventilation was determined to be adequate as indicated by rate, depth, and end-tidal CO, monitoring, the endotracheal tube was removed. Extubation was delayed up to 18 h post insult in those cases with inadequate spontaneous ventilations and pharyngeal swelling.

After reversal of paralysis and sedation, neurologic deficit scoring was done using the system developed at the Resuscitation Research Center (Safar et al., 1982; Gisvold et al., 1984). It was repeated at 24 h post insult and then daily for a week if the animal survived. ³¹P NMR spectroscopy was repeated at 30 and 144 h post ischemia in surviving animals.

Analysis of variance and profile analysis were used to assess statistical significance. Adjustment of α was performed to correct for multiple comparisons and in doing so maintained an overall α of p < 0.05 for statistical significance. All values represent means ± 1 SD.

RESULTS

Baseline variables did not differ significantly between the groups (Table 1) with the exception of $P_a co_2$. This difference, although statistically significant (p < 0.03), was not felt to be clinically important (8-min VF = 35 ± 5 mm Hg, 12-min VF = 34 \pm 4 mm Hg, 16-min VF = 41 \pm 2 mm Hg).

The time courses for changes in pH_a and brain pH (pH_b) are depicted in Fig. 1. There was a significant decrease in pH_a at 5 min of CPB. With further reperfusion and sodium bicarbonate administration, pH_a returned to baseline by 30 min with a small but statistically significant overshoot at 60 min. There was a significant lag in the correction of $pH_{\rm b}$, which required 60 min of CPB to return to control levels. The increase in pH_{b} from its nadir was linear with no secondary deterioration once baseline levels were reached. Sodium bicarbonate was given in divided doses over the course of the experiment to each animal according to its pH_a. The 8-, 12-, and 16-min groups received totals of 213 \pm 69, 230 \pm 119, and 233 \pm 47 mEq of bicarbonate, respectively. There was no significant difference between the groups with respect to bicarbonate dose (p > p)0.05).

The time courses of NMR spectra are depicted in

TABLE 1. Baseline variables (mean \pm SD) among the three ischemic groups

	Groups			
Variables	8-min VF	12-min VF	16-min VF	
Physiologic				
$P_{0}O_{2}$ (mm Hg)	92 ± 7	88 ± 9	81 ± 4	
$P_{a}co_{2}$ (mm Hg)	35 ± 5	34 ± 4	41 ± 2	
pH	7.34 ± 0.03	7.35 ± 0.03	7.32 ± 0.02	
Temp. (°C)	37.5 ± 0.4	37.7 ± 0.6	37.1 ± 0.3	
Hematocrit (%)	41 ± 7	42 ± 7	38 ± 7	
ACT (s)	126 ± 23	114 ± 18	123 ± 18	
Lactate (mmol/L)	0.60 ± 0.20	1.02 ± 0.47	0.78 ± 0.47	
Glucose (mg/dl)	143 ± 11	125 ± 25	123 ± 10	
Hemodynamic				
MABP (mm Har)	155 ± 13	151 ± 18	157 + 33	
MPAP (mm Hg)	26 ± 6	20 ± 6	28 ± 2	
PCWP (mm Hg)	9 ± 3	8 f 5	11 ± 3	
Central venous pressure	,	010		
(mm Hg)	7 L 3	9 f 3	6 + 1	
Cardiac output (ml/kg/min)	180 ± 65	170 ± 30	157 ± 29	
Heart rate (beats/min)	152 ± 8	148 ± 38	138 ± 13	

All p > 0.05, except $P_a co_2$ (p < 0.03) by analysis of variance. Temp, temperature. ACT, activated clotting time. MAP, mean arterial pressure. MPAP, mean pulmonary artery pressure. PCWP, pulmonary capillary wedge pressure. VF, ventricular fibrillation.

Table 2. Profile analysis was utilized to assess differences between the groups with respect to NMR parameters over time. Because of the limited number of animals in each group, five time points (baseline, end of ischemia, 1-h CPB, 2-h CPB, and 7 h off CPB) were used in this analysis. The groups followed the same trend over time for every variable. Analysis of later spectra (i.e., 30 and 144 h) was limited by the numbers of surviving animals but also showed no differences between groups. The differences between groups for all variables were not statistically significant (p > 0.05). With a power of -0.80, the minimum differences from the 8-min group that could have been detected are 0.06, 0.35 and 0.18 for phosphocreatine $(PCr)/P_i$ + PCr, PCr/ β -ATP, and pH_b, respectively. For all variables there were, however, overall differences among the time points.

Pairwise comparisons of the time points were done to determine where the differences occurred for each variable. For pH_b and $PCr/P_i + PCr$, pairwise comparisons showed that the end-ischemia value was different from that at all other time points (p < 0.05). For PCr/ β -ATP, the baseline value differed from the end-ischemia and 1- and 2- h CPB values. The end-ischemia value also differed significantly from values at all other time points.

To determine if the three groups had the same time course of recovery after ischemia, the slopes of the regression lines for each animal were used and tested to see if they were equal across the groups. The time points used in this analysis were end ischemia and 12, 24, 36, 48, and 60 min after starting CPB. No differences were detected among the three groups for the variables pH_{b} and PCr/P_{i} +



FIG. 1. Time course of changes in arterial (A) and brain (B) pH during ischemia and reperfusion. **EI**, end ischemia; CPB, cardiopulmonary bypass. *p < 0.05 compared with baseline.

PCr. An overall difference was detected for PCr/ β -ATP and pairwise comparisons showed that 12-min ischemic animals differed from the 8- and 16-min ischemic animals.

Results of neurologic deficit scoring are depicted in Table 3. Contrary to the NMR parameters, the VF groups did not follow the same trend over time (p < 0.0001). The 8-min VF group differed from the 12- and 16-min VF groups at 24, 48, and 144 h (p < 0.006, p < 0.0006, p < 0.0002, respectively). At 12 h the groups did not differ (p > 0.05). All ³¹P spectra done at **30** and 144 h post insult were similar to baseline (Fig. 2).

DISCUSSION

The chemical shift of the P_i signal varies relative to intracellular pH and is the basis for measurement of pH with ³¹P NMR. PCr is insensitive to pH changes in the physiologic range and thus provides a reference by which to measure P_i shifts. Comparison of a calibration curve obtained in an appropriate in vitro solution gives a chemical shift difference between PCr and P_i that can be applied to in vivo data to measure pH (Moon and Richards, **1973).** It is generally accepted that the measured pH is that of the cytoplasm. Intracellular pH measurements

Spectra time	Ischemia time (min)	PCr/P _i + PCr	PCr/β-ATP	Brain pH
Baseline	8	0.74 ± 0.07	1.63 ± 0.28	7.04 ± 0.01
	12	0.73 ± 0.00	1.75 ± 0.28	7.02 ± 0.04
	16	0.75 ± 0.04	1.93 ± 0.29	7.03 ± 0.02
End ischemia	8	а	a	6.30 ± 0.09
	12	а	a	6.19 ± 0.08
	16		а	6.18 ± 0.10
1-h CPB	8	0.73 ± 0.05	1.94 ± 0.09	6.97 ± 0.05
	12	0.74 ± 0.05	2.48 ± 0.53	6.98 ± 0.07
	16	0.75 ± 0.04	2.31 ± 0.54	7.01 ± 0.04
2-h CPB	8	0.67 ± 0.07	2.06 ± 0.29	7.03 ± 0.04
	12	0.71 If: 0.09	2.03 ± 0.38	7.10 ± 0.15
	16	0.70 ± 0.02	2.22 ± 0.34	6.99 ± 0.03
7-h CPB	8	0.67 ± 0.08	2.14 ± 0.63	7.18 ± 0.22
	12	0.70 ± 0.06	2.07 ± 0.57	7.08 ± 0.11
	16	0.72 ± 0.04	2.27 ± 0.50	7.05 ± 0.02
30 h after VF	8	0.75 ± 0.04 (n = 4)	1.71 ± 0.36	7.11 ± 0.08
	12	0.78 ± 0.05 (n = 2)	1.90 ± 0.32	7.03 ± 0.05
	16	0.78 ± 0.01 (n = 3)	1.81 ± 0.11	7.04 ± 0.10
144 h after VF	8	0.78 ± 0.03 (n = 4)	1.90 ± 0.10	7.13 ± 0.03
	12	0.76 ± 0.00 (n = 2)	2.07 ± 0.38	7.12 ± 0.08
	16	h	b	b

TABLE 2. Time course of NMR spectral data (mean \pm SD)

Profile analysis was used to compare spectral data over time between groups and showed **no** significant differences (p > 0.05). ^{*a*} Values for ATP and phosphocreatine (PCr) have fallen below nuclear magnetic resonance (NMR)–detectable limits. Only inorganic

phosphate and monophosphoesters remain in these spectra.

^b No animals survived to 144 h in the 16-min group.

Pi, inorganic phosphate. β -ATP, beta ATP.

CPB, cardiopulmonary bypass; VF, ventricular fibrillation.

Time (h post VF)	8-min VF	12-min VF	16-min VF
12	336 ± 30	364 ± 33	357 ± 51
24	210 ± 76	425 ± 113	416 ± 93
48	139 ± 95	406 ± 130	469 ± 68
144	71 ± 77	413 ± 123	$500 \pm 0''$

TABLE 3. Neurologic deficit scores (mean \pm SD) overtime in the ischemic groups

A score of 500 indicates brain death and a score of 0 indicates a neurologically intact animal. If an animal died before grading, its score was set to 500.

^{*a*} All 16-min ventricular fibrillation (VF) animals died prior to 144 h.

made with ³¹P NMR are consistent with those obtained using other techniques (Petroff et al., 1985). The accuracy of intracellular pH measurements is accepted to be within 0.1 pH unit in absolute terms and to be within 0.05 pH unit or better for relative changes in pH (Moon and Richards, 1973).

The importance of correlating clinical outcome with the experimentally used endpoints of cerebral injury has been emphasized by Hossmann et al. (1987). In this report they describe the complete metabolic and functional recovery of a cat after 1 h of normothermic complete cerebral ischemia. Despite neuropathologic examination 1 year after ischemia that revealed almost complete atrophy of the dorsal hippocampus and striatum, the cat had recovery of integrative neurologic function. Previous studies have documented the restitution of cerebral energy state that can occur after cerebral ischemia but could not address the clinical outcome of the animals (Nordstrom et al., 1978; Welsh et al., 1978).



FIG. 2. ³¹P nuclear magnetic resonance spectra obtained at baseline and 30 h post ischemia. The spectra are similar despite a marked difference in neurologic status. A, phosphornonoesters; **B**, inorganic phosphate; C, phosphodiesters; D, phosphocreatine; E, γ-ATP; F, a-ATP; G, β-ATP.

The NMR methodology employed in this study enables correlation between intracellular pH and energy metabolites that was previously unobtainable.

This study indicates that energy metabolites rapidly return to baseline regardless of the length of cardiac arrest from 8 to 16 min. Secondary energy failure did not occur in this model. Other insults have been associated with a secondary energy failure after initial recovery (Hinzen et al., 1972). This failure occurs at -3-8 h post reperfusion.

The small sample size in this study makes it potentially subject to **P** error, which is the failure to find a true difference between groups when such a difference exists (Brown et al., 1987). Despite this limitation, it appears that ³¹P NMR spectroscopy is not sensitive enough to predict neurologic outcome in animals after cardiac arrest and resuscitation. Spectra of dogs appeared quite similar despite grossly different neurologic status. Perhaps the recoveries of high-energy phosphates and intracellular pH are necessary, but not sufficient, conditions for good neurologic outcome. Return of high-energy phosphate metabolism in the 16-min ischemic animals may indicate that the neurons and supportive cells have survived but that the intricate intercellular communications critical to higher brain function have been severely disrupted. The return of energy metabolism after 16 min of cardiac arrest indicates a potential for recovery of neurologic function but does not ensure it.

CONCLUSION

Although the pattern of return of pH_b and brain energy status did not differ between the VF groups, there were significant differences in neurologic outcome between them. Recovery of pH_b and brain energy metabolism as detected by ³¹P NMR spectroscopy is not a sensitive indicator of neurologic outcome in canine global ischemia.

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REFERENCES

- Ames A II, Guarian BS (1963) Effects of glucose deprivation on function of the isolated mammalian retina. J Neurophysiol 26:617–624
- Brown CG, Kelen GD, Ashton JJ, Werman HA (1987) The beta error and sample size determination in clinical trials in emergency medicine. Ann Emerg Med 16:183–187
- Crockard HA, Gadian DG, Frackowiak **RSJ**, Proctor E, Allen K, Williams SR, Russell RWR (1987) Acute cerebral ischemia: concurrent changes in cerebral blood flow, energy metabolites, pH, and lactate measured with hydrogen clearance and ³¹P and 'H nuclear magnetic resonance spectroscopy. II. Changes during ischemia. *J Cereb Blood Flow Metab* 7:394– 402

- Gadian DG (1983) Whole organ metabolism studied by NMR. Annu Rev Biophys Biochem 12:69–89
- Gadian DB, Radda GK, Richards RE, Seeley PJ (1979) 31-P NMR in living tissue: the road from a promising to an important tool in biology. In: Biological Applications of Magnetic Resonance (Shulman RF, ed), New York, Academic Press, pp 463-533
- Gisvold SE, Safar P, Roa G, Moossy J, Bron K, Alexander H (1984) Prolonged immobilization and controlled ventilation do not improve outcome after global brain ischemia in monkeys. Crit Care Med 12:171–179
- Gordon RE, Hanley PE, Shaw D (1982) Topical magnetic resonance. Prog NMR Spectros 15:1–47
- Grenell RG (1946) Central nervous system resistance: the effects of temporary arrest of cerebral circulation for periods of two to ten minutes. J Neuropathol Exp Neurol 5:131–154
- Hinzen DH, Muller U, Sobotka P, Gebert E, Lang R, Hirsch H (1972)Metabolism and function of dog brain recovering from longtime tissue ischemia. Am J Physiol 233:1158–1164
- Hossmann KA, Schmidt-Kastner R, Ophoff BG (1987) Recovery of integrative central nervous function after one hour global cerebro-circulatory arrest in normothermic cat. J Neurol Sci 77:305-320
- Kabat H, Dennis C, Baker AB (1941) Recovery of function following arrest of the brain circulation. Am J Physiol 132:737– 747
- Ljunggren B, Ratcheson RA, Siesjo BK (1974) Cerebral metabolic state following complete compression ischemia. Brain Res 73:291–307
- Martin GB, Nowak RM, Carden DL, Eisiminger R, Tomlanovich MC (1987)Cardiopulmonarybypass vs CPR as treatment

for prolonged canine cardiopulmonary arrest. Ann Emerg Med 16:628–636

- Moon RB, Richards JH (1973) Determination of intracellular pH by ³¹P magnetic resonance. J *Biol Chem* 148:7276–7278
- Nordstrom CH, Rehncrona S, Siesjö BK (1978) Effects of phenobarbital in cerebral ischemia. Part II. Restitution of cerebral energy state, as well as of glycolytic metabolites, citric acid cycle intermediates and associated aminoacids after pronounced incomplete ischemia. Stroke 9:335–343
- Paschen W, Sato M, Pawlik G, Umbach C, Heiss WD (1985) Neurology deficit, blood flow and biochemical sequence of reversible focal ischemia in cats. J Neurol Sci 68:119–134
- Petroff OAC, Prichard JW, Behar KL, Alger JR, den Hollander JA, Shulman RG (1985) Cerebral intracellular pH by ³¹P nuclear magnetic resonance spectroscopy. *Neurology* 35: 781-788
- Pretto E, Safar P, Saito R, Stezoski W, Kelsey S (1987) Cardiopulmonary bypass after prolonged cardiac arrest in dogs. Ann Emerg Med 16:611–619
- Safar P, Gisvold SE, Vaagenes P (1982) Long-term animal models for the study of global brain ischemia (GBI). In: Protection of Tissues Against Hypoxia (Waciquier A, Borger M, Amery WK, eds), Amsterdam, Elsevier Biomedical Press, pp 147-170
- Thulborn KR, du Boulaya GH, Duchen L, Radda G (1982) A³¹P nuclear magnetic resonance in vivo study of cerebral ischemia in the gerbil. J Cereb Blood Flow Metab 2:299–306
- Weinberger LM, Gibbon MH, Gibbon JH (1940) Temporary arrest of the circulation to the central nervous system: I. Physiologic effects. Arch Neurol Psychiatry 43:615–643
- Welsh FA, Ginsberg MD, Rieder W, Budd WW (1978) Diffuse cerebral ischemia in the cat. II. Regional metabolites during severe ischemia and recirculation. Ann Neurol 3:493–501