Hematologic and Chemical Changes Observed during and after Cardiac Arrest in a Canine Model—A Pilot Study

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Study Objective. To evaluate the effect of cardiac arrest and cardiopulmonary resuscitation (CPR) on blood chemistry in a canine model.

Design. Evaluative canine animal study.

Setting. Animal laboratory accredited by the Association for Assessment and Accreditation of Laboratory Animals.

Subjects. Twenty-six adult mongrel dogs.

Intervention. The dogs underwent an episode of induced fibrillatory cardiac arrest for 3 minutes followed by 10 minutes of standard CPR. Blood samples were taken at baseline (before cardiac arrest), after 10 minutes of ventricular fibrillation, and 10 minutes after successful resuscitation for determination of blood chemistries and hematologic parameters.

Measurements and Main Results. Glucose, blood urea nitrogen, serum creatinine, sodium, potassium, chloride, calcium, phosphorus, uric acid, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, protein, albumin, cholesterol, triglycerides, iron, white blood cell count, red blood cell count, and hematocrit were measured. Significant changes ($p<0.05$) in values obtained during CPR versus baseline values were noted for all laboratory parameters except blood urea nitrogen, chloride, and alkaline phosphatase. Eighteen dogs achieved return of spontaneous circulation (ROSC); their laboratory values were obtained after CPR. Significant changes ($p<0.05$) after ROSC compared with baseline were noted for all laboratory values except chloride, blood urea nitrogen, uric acid, alkaline phosphatase, glucose, potassium, calcium, triglycerides, iron, red blood cell count, and hematocrit.

Conclusion. Results indicate that significant changes in blood chemistries and hematologic parameters occur during and after CPR. Clinicians should note these normal laboratory parameter changes when interpreting laboratory data in patients who experience cardiac arrest.

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Cardiac arrest results in cessation of circulation, and cardiopulmonary resuscitation (CPR) only partially restores circulation of blood. Hence, compromised blood circulation persists until return of spontaneous circulation (ROSC) is achieved.[1]

Acute alterations to circulation of blood—from no flow (at the time of cardiac arrest) to partial flow (during CPR), and finally to ROSC—can alter acid-base and biochemical parameters.[1–3] However, these effects on overall blood chemistry and hematologic parameters are not well described. Previous studies have either evaluated a limited number of biochemical parameters[4] or examined overall blood chemistry at time points considerably beyond the acute CPR phase.[5]

Without an appreciation of normal chemical and hematologic derangements that occur during and after cardiac arrest, researchers and health care providers cannot adequately evaluate laboratory data in an animal study involving drugs that may alter electrolyte or hematologic parameters, or in an individual patient with cardiac arrest.

Since animal cardiac arrest models are well established and often used to evaluate potential interventions in cardiac arrest, we evaluated the effect of cardiac arrest with CPR after ROSC on laboratory parameters in dogs. To our knowledge, no study has evaluated alterations in overall blood chemistry and hematologic parameters during CPR.

Methods

Laboratory data for 26 adult mongrel dogs (weight 12–16 kg) were collected from two separate studies of cardiac arrest and CPR. Use of these dogs was approved by the Animal Care Institutional Review Committee of Hartford Hospital, Hartford, Connecticut, and the animal laboratory was accredited by the Association for Assessment and Accreditation of Laboratory Animals. In both studies, dogs were anesthetized with thiopental 20 mg/kg followed by α-chloralose 70 mg/kg. They were secured in supine position on a surgical table with a thermoblanket to maintain 37°C body temperature. A cuffed endotracheal tube was placed, and the dogs were ventilated by respirator (Harvard volume respirator model 613) at 10 breaths/minute. At baseline, blood gases were stabilized to an arterial blood pH level of 7.40 ± 0.05 and a partial pressure of carbon dioxide level of 40 ± 5 mm Hg with adjustments of tidal volume and/or administration of sodium bicarbonate as required.

Throughout the study, aortic, left ventricular, and right atrial pressures were measured continuously after proper catheterization, and electrocardiogram readings were taken continuously. All animals received heparin 150 U/kg periodically to maintain catheter patency.

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The study involved induction of ventricular fibrillation, CPR, and then defibrillation using the same methods. Ventricular fibrillation was induced with 80 mA of electrical current through a coronary pacing catheter. After 3 minutes of ventricular fibrillation without ventilation, CPR was performed with a pneumonic chest compression device (Thumper, Michigan Instruments, Grand Rapids, MI) for 10 minutes. The device was set to compress the chest 60 times/minute with a compression duration of 0.5 seconds. Compression force was set to produce an initial coronary perfusion pressure gradient of 20 mm Hg and was maintained throughout the CPR period (perfusion pressure gradient was determined by subtracting left-ventricular mid-diastolic pressure from aortic pressure). After every fifth compression, diastole was prolonged by 0.5 seconds and the lungs were inflated to an inspiratory pressure of approximately 10 cm of water (with 100% oxygen) by a synchronized pressure-limited ventilator.

Aortic blood samples were obtained 58 minutes before ventricular fibrillation, after 8–12 minutes of ventricular fibrillation, and at 10 minutes after ROSC. Glucose, blood urea nitrogen (BUN), serum creatinine (S_{cr}), sodium, potassium, chloride, calcium, phosphorus, uric acid, alkaline phosphatase, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), protein, albumin, cholesterol, triglycerides, and iron (American Monitor Parallel Analyzer, American Monitor, New York, NY) were measured. We also obtained white blood cell count, red blood cell count, and hematocrit (H-6000 Auto Analyzer, Technon Instruments, Austin, TX).

Data Analysis

Laboratory values (expressed as mean ± SD) at baseline, during CPR, and after ROSC were compared using analysis of variance (ANOVA). If ANOVA demonstrated a significant difference, then the t test with Bonferroni correction was used to determine which group(s) were significantly different. A p value less than or equal to 0.05 was considered significant.

Results

Of the 26 dogs undergoing CPR, 18 achieved ROSC. Table 1 shows the laboratory values observed at each stage of our study. Table 2 shows changes during CPR and after ROSC versus baseline values. When ANOVA was used

Table 1. Laboratory Values Observed at Each Stage of Study (baseline, CPR, ROSC)

Laboratory Parameter	Reference Limit	Baseline (n=26)	During CPR (n=26)	After ROSC (n=18)
Glucose (mg/dl)	75–110	108 ± 33.8	232 ± 86.0[a]	219 ± 67.2[a]
Blood urea nitrogen (mg/dl)	7–25	12.6 ± 4.2	12.8 ± 4.8	13.5 ± 5.5
Creatinine (mg/dl)	0.7–1.7	0.84 ± 0.10	0.93 ± 0.12[a]	1.08 ± 0.13[a, b]
Sodium (mEq/L)	135–145	148 ± 3.9	144 ± 4.1[a]	151 ± 4.0[a]
Potassium (mEq/L)	3.2–5.0	3.4 ± 0.4	4.4 ± 0.49[a]	3.8 ± 0.53[a, b]
Chloride (mEq/L)	97–111	115 ± 3.1	115.6 ± 3.2	115.7 ± 3.1
Calcium (mg/dl)	8.8–10.3	9.2 ± 0.4	8.5 ± 0.4[a]	8.4 ± 0.4[a]
Phosphorus (mg/dl)	2.5–4.5	5.1 ± 0.7	5.7 ± 0.79[a]	6.9 ± 1.1[a, b]
Uric acid (mg/dl)	2–9	0.9 ± 0.3	2.5 ± 1.1[a]	0.6 ± 0.4
Alkaline phosphatase (U/L)	25–100	38.7 ± 13.2	47.3 ± 22.6	49.5 ± 23.1
Lactate dehydrogenase (U/L)	100–300	118 ± 53	184 ± 94.3[a]	254 ± 104.3[a, b]
Aspartate aminotransferase (U/L)	5–30	38.3 ± 12.4	115.7 ± 28.1[a]	223.7 ± 69.1[a, b]
Alanine aminotransferase (U/L)	5–30	28.0 ± 15.5	101.1 ± 63.9[a]	221.8 ± 129.1[a, b]
Protein (g/dl)	6.3–8.4	4.5 ± 0.7	3.9 ± 0.8[a]	3.4 ± 0.8[a]
Albumin (g/L)	3.7–5.2	2.2 ± 0.3	1.9 ± 0.4	1.65 ± 0.4[b]
Total cholesterol (mg/dl)	100–245	104 ± 30	82 ± 37.1[a]	80 ± 38.2[a]
Triglycerides (mg/dl)	40–180	26 ± 9.5	45 ± 26.7[a]	26.6 ± 16.0[b]
Iron (µg/dl)	60–150	99.9 ± 30.4	83.0 ± 39.9	85.2 ± 40.1
White blood cell count (x 10^3/mm^3)	4.8–10.0	5.3 ± 3.4	7.3 ± 4.8	6.9 ± 5.3
Red blood cell count (x 10^6/mm^3)	4.6–6.2	5.1 ± 0.7	6.3 ± 1.0[a]	5.5 ± 0.8[b]
Hematocrit (%)	40–54	35.2 ± 4.5	39.6 ± 5.1[a]	37.7 ± 5.4

CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous circulation.
[a]Significant difference from baseline (p<0.05).
[b]Significant difference between CPR and post-CPR periods (p<0.05).

Table 2. Changes in Laboratory Parameters during CPR and after ROSC versus Baseline Values

Laboratory Parameter	% Change during CPR (n=26)	% Change after ROSC (n=18)
Glucose (mg/dl)	↑115 ± 86[a]	↑103 ± 98.7
Blood urea nitrogen (mg/dl)	↑1.4 ± 14.0	↑7.0 ± 30.0
Creatinine (mg/dl)	↑11.3 ± 16.9[a]	↑29.0 ± 35.4[a]
Sodium (mEq/L)	↓2.7 ± 4.4[a]	↑1.8 ± 4.2[a]
Potassium (mEq/L)	↑30.0 ± 22.0[a]	↑12.3 ± 32.3[b]
Chloride (mEq/L)	↑0.5 ± 3.8	↑0.6 ± 4.0
Calcium (mg/dl)	↓7.6 ± 6.4[a]	↓8.2 ± 6.7
Phosphorus (mg/dl)	↑12.5 ± 13.0[a]	↑35.5 ± 60.1[a]
Uric acid (mg/dl)	↑183 ± 279[a]	↓333 ± 418
Alkaline phosphatase (U/L)	↑22.1 ± 71.0	↑28.0 ± 75.0
Lactate dehydrogenase (U/L)	↑56.0 ± 78.0[a]	↑115.0 ± 96.8[a, b]
Aspartate aminotransferase (U/L)	↑202 ± 227[a]	↑484 ± 557[a, b]
Alanine aminotransferase (U/L)	↑261 ± 312[a]	↑692 ± 733[a, b]
Protein (g/dl)	↓14.3 ± 20.0[a]	↓25.2 ± 20.5[a]
Albumin (g/dl)	↓15.9 ± 17.0[a]	↓25.2 ± 20.9[a]
Total cholesterol (mg/dl)	↓16.4 ± 23.6[a]	↓23.2 ± 27.4[a]
Triglycerides (mg/dl)	↑72.7 ± 181[a]	↑2.3 ± 68.6
Iron (µg/dl)	↓16.9 ± 31.3[a]	↓14.7 ± 32.0
White blood cell count (x 10^3/mm^3)	↑37.4 ± 42.0[a]	↑29.3 ± 55.7[a]
Red blood cell count (x 10^6/mm^3)	↑24.3 ± 48.3[a]	↑6.9 ± 19.7
Hematocrit (%)	↑12.6 ± 14.1[a]	↑7.0 ± 20.5

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[b]Significant difference between CPR and post-CPR periods (p<0.05).

to compare each laboratory parameter for the three stages (baseline, during CPR, and after ROSC), significant differences were found for all except BUN, chloride, alkaline phosphatase, iron, and white blood cell count concentrations. Values for the CPR period differed significantly

from those at baseline for all laboratory parameters except BUN, chloride, alkaline phosphatase, albumin, total cholesterol, iron, and white blood cell counts. When post-CPR data for the 18 animals that achieved ROSC were compared with baseline values, BUN, chloride, uric acid, alkaline phosphatase, triglyceride, iron, white blood cell count, red blood cell count, and hematocrit levels were not significantly different. Hence uric acid, triglyceride, red blood cell count, and hematocrit levels changed significantly during CPR from baseline values, but changes that occurred in the post-CPR period lost significance compared with baseline values. Conversely, albumin and total cholesterol levels did not change significantly during CPR but changed significantly after ROSC. Compared with laboratory parameters obtained during CPR, potassium, triglycerides, red blood cell count, and hematocrit levels were significantly lower after ROSC, whereas liver transaminases (LDH, AST, ALT), creatinine, and phosphorus were significantly higher after ROSC.

Discussion

Significant changes for most chemical and hematologic parameters occur during cardiac arrest with CPR compared with baseline values. Similarly, changes induced during CPR are generally maintained 10 minutes after ROSC for most parameters.

Potassium levels after ROSC were significantly lower than during CPR. The potassium increase during cardiac arrest and CPR may be due to an extracellular shift of potassium by ventricular fibrillation-induced acidosis. Similarly, after ROSC, acidosis theoretically would be abolished and potassium would again shift intracellularly. This initial increase in potassium during CPR followed by a decrease toward normal after successful ROSC has been described.[6] In addition, serum potassium increased from 3.7 ± 0.3 mEq/L at baseline to 3.9 ± 0.6 mEq/L 5 minutes after resuscitation in a study of cardiac arrest in 30 adult mongrels.[4] After the transient increase in serum potassium concentration occurred, concentrations decreased below baseline value, achieving a nadir 45–60 minutes after resuscitation. These researchers suggested that endogenous catecholamines could have induced potassium release from the liver or that tissue ischemia and trauma associated with chest massage increased serum potassium concentrations.

Our study showed serum calcium concentrations 0.7 and 0.8 mg/dl lower than baseline values during CPR and 10 minutes after ROSC, respectively. Likewise, the earlier study[4] demonstrated serum calcium concentrations 0.7 mg/dl lower than baseline values both 5 and 15 minutes after resuscitation. The researchers hypothesized that since endogenous epinephrine activates cellular calcium channels, the decrement in serum calcium may have occurred secondary to increased entry of calcium into cells. However, we also found a reduction in circulating albumin concentrations. Since approximately 80% of circulating calcium is bound to albumin, and the free calcium level is important in physiologic processes, a correction factor (corrected calcium = measured calcium + 0.8 [normal albumin – actual albumin]) was used.[7] Using baseline albumin as normal for dogs, we calculated the corrected calcium concentrations during CPR as 8.7 mg/dl and 10 minutes after ROSC as 8.8 mg/dl, which were still less than the baseline value of 9.2 mg/dl.

In general, reductions in circulating albumin concentrations are due to the combination of three separate effects: extravasation of albumin into the extravascular compartment due to increased capillary permeability to a new equilibrium, downregulation of hepatic albumin synthesis by actions of cytokines (tumor necrosis factor, interleukin-1, and interleukin-6), and increased albumin catabolism.[8] In this very short time from baseline to cardiac arrest and then ROSC, the only factor that could account for this effect would be a shift of more albumin out of the vasculature and into the extracellular space. This mechanism has been the most rapid means of albumin reduction in patients with other conditions.[8] Whether it explains the cholesterol reductions observed in our study is not known.

Conversely, results of liver transaminase function tests (LDH, AST, ALT) were significantly higher after than during CPR, although values for both were significantly higher than baseline values. The increase in transaminases after ROSC versus during CPR may represent a washout phenomenon (e.g., liver damage may be occurring primarily during cardiac arrest, but blood flow is insufficient to carry markers for liver injury into general circulation for detection until ROSC is achieved). Impairment of liver blood flow during cardiac arrest and CPR has been demonstrated by our research group and others.[9, 10] This phenomenon would be similar to that seen after thrombolytic or primary angioplasty therapy during acute

myocardial infarction for creatine kinase MB.[11]

Since the liver stores red blood cells, it may lose some capacity to hold onto this blood component during CPR, which could explain the increase in both red blood cell count and hematocrit. However, the actual reason is not known.

Study Limitations

Some limitations of data collected in this study must be noted. First, animal models have been used as a surrogate for humans in advanced cardiac life support research and provide information on qualitative rather than quantitative changes that could be expected. Second, our model used a short duration of cardiac arrest and CPR and therefore may not apply to prolonged arrest situations. Third, pH was not continuously evaluated during the study; if it had been, it may have further elucidated why changes in other substances occurred.

Clinical Implications

In light of our findings, clinicians should be aware that blood chemistries and hematologic parameters may change in animals and humans during CPR. Alterations of a specific parameter could be due to cardiac arrest, rather than being a cause or precipitant of arrhythmia. For example, if the serum potassium level during CPR is low-normal (3.5–3.7 mEq/L) during cardiac arrest, presence of hypokalemia (a potential contributor) before the arrest cannot be ruled out. Similarly, appreciating that liver transaminases rise after ROSC could be important. Increased AST and ALT levels observed in our study were 3–8 times the upper limit of normal. Administration of intravenous amiodarone during and after cardiac arrest could be valuable but should be stopped if it causes liver toxicity.[12] However, if increased AST and ALT levels mistakenly are attributed to amiodarone rather than considered a consequence of cardiac arrest with CPR, premature termination of amiodarone could put patients at risk. Furthermore, patients who need other beneficial agents, such as 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors or fibric acid derivatives, may not be given these agents because of perceived (but actually nonexistent) hepatic impairment.

Conclusion

Several chemical and hematologic parameters change during cardiac arrest with CPR; others change after ROSC. Clinicians need to know which parameters change during and after cardiac arrest when they explore causative factors regarding an arrhythmic event or a potential subsequent problem.

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