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## DETECTION OF ACUTE MYOCARDIAL INFARCTION USING A REAL-TIME CARDIAC ELECTRICAL BIOMARKER

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**Introduction:** The cardiac electric field is known to be dipolar such that 3 lead-vectors should describe the field. Eigenvalue modeling (EVA) of the 12-lead electrocardiogram (ECG) can quantify dipolar vs. multipolar forces yielding a cardiac "electrical" biomarker (CEB) for detection of acute myocardial infarction (AMI). **Hypothesis:** The objective was to test a CEB model that quantifies the multipolar activity of the derived 12-lead ECG to detect AMI. **Methods:** This is a blinded, case-controlled study in which voltage-time ECG data arrays were analyzed from 102 patients with AMI and 248 patients with non-AMI. ECGs with missing leads, wandering baseline, and excessive noise were excluded. Simplex optimization was used to derive the 12-lead ECG from just 3 basis lead-vectors (I, II, V2) stored in the cardiac monitor. The CEB was computed from the derived ECG by EVA to detect AMI and then compared to both an ECG interpretive algorithm (ECGI), and to ST voltage changes (ST) consistent with AMI, tested against the interpretations of the blinded physician reference standard. Sensitivities, specificities, and negative and positive predictive values were calculated. The 95% confidence intervals were computed for analysis of statistical significance. The measured vs. derived ECGs morphologies were compared using the Pearson correlation. **Results:** The CEB had a sensitivity of 88.0%, specificity of 91.3%, negative predictive value (NPV) of 95.0% and positive predictive value (PPV) of 80.2%. The ECGI had a sensitivity of 54.3%, specificity 77.4%, NPV 80.9%, PPV 49.0%. The ST had a sensitivity of 59.5%, specificity 68.6%, NPV 80.7%, PPV 43.5%. The CEB showed superiority to the ECGI and ST at $p < 0.0001$. The derived 12-lead ECG morphologies showed high correlation with the measured 12-lead ECG. **Conclusions:** The multipolar forces of the cardiac electrical field can be quantified from the derived 12-lead ECG to compute a CEB that reliably detects the presence of AMI. This cardiac "electrical" biomarker is readily computed directly from the patient cardiac monitor and displayed in real-time. This will allow an immediate, cost-effective, and efficient means of detecting AMI in patients who are being monitored in acute care settings.

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## MP4OX IMPROVES OXYGEN CONSUMPTION AND SURVIVAL IN A RAT MODEL OF EXTREME HEMODILUTION

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**Introduction:** Cell-free hemoglobin solutions employed as blood replacement fluids have failed to improve oxygen consumption (VO2) due to inappropriate oxygen release characteristics and vasoconstriction, properties that limit oxygen delivery. MP4OX (pegylated human Hb) is an oxygen therapeutic agent formulated at low Hb concentration (4.3 g/dL), with high oxygen affinity (P50 = 5 mmHg) and high colloid osmotic pressure (COP = 70 mmHg). **Hypothesis:** The present study was conducted to demonstrate that MP4OX maintains VO2 in a model of extreme hemodilution despite its high oxygen affinity. **Methods:** Studies were conducted in a rat model of continuous exchange transfusion (ET) and extreme anemia. Conscious male SD rats (290 - 327 g) received ET (0.5 ml/min × 100 min) with one of the following solutions 1) Hextend; 2) PEG-albumin; 3) MP4OX. PEG-albumin served as a pegylated non-O2 carrying protein with matched COP. Whole body VO2 was measured from O2 content in inlet and outlet air of known flow rate with the rat in a sealed chamber. **Results:** Baseline VO2 was similar in all groups (20-25 ml/kg/min). Hemodilution was similar in all groups as reflected by the trajectory of hematocrit decline with time, falling to <5% after 70 min of ET. Hemodilution with either Hextend or PEG-albumin resulted in a rapid decline of VO2 (<4 mL/kg/min) at Hb below 4.2 g/dL, and mortality was 100% in both groups by 80 minutes, with terminal arterial lactate >21 mmol/L. Hemodilution with MP4OX improved survival (87%), VO2 (11 ± 4 ml/min/kg), and arterial lactate (8 ± 2 mmol/L) at 160 minutes (1 hour after completion of ET).In follow up studies, rats that were initially hemodiluted with PEG-albumin for 40 minutes to a total Hb of 4.0 g/dL, followed by 'rescue' exchange transfusion with MP4OX, exhibited intermediate survival times, VO2, and lactate concentrations. **Conclusions:** These data demonstrate that MP4OX improves oxygen consumption compared to non-oxygen carrying plasma expanders and limits oxygen debt during extreme hemodilution. The data support the concept that MP4OX, a high-affinity hemoglobin molecule, imparts significant benefit as an oxygen therapeutic agent.

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## A POLYMORPHISM WITHIN THE GLUTATHIONE BIOSYNTHESIS PATHWAY IS ASSOCIATED WITH INCREASED OXIDANT STRESS IN INFANTS AFTER UNDERGOING CARDIOPULMONARY BYPASS

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**Introduction:** Glutamate cysteine ligase (GCL) is the rate-limiting enzyme for de novo glutathione synthesis. Polymorphisms within the genes encoding GCL can lead to decreased glutathione synthesis and increased host susceptibility to oxidant injury. **Hypothesis:** We hypothesize that an insertion/deletion polymorphism, located within the gene that encodes the catalytic subunit of the GCL enzyme, predisposes infants undergoing cardiopulmonary bypass (CPB) to oxidant injury. **Methods:** Infants undergoing CPB were genotyped using the Taqman Allelic Discrimination assay. Urine isoprostane concentrations, an indicator of oxidant stress, were measured using gas chromatography-mass spectroscopy and compared between genotypes. To determine whether oxidants can directly affect pulmonary artery smooth muscle cells (PA SMC) tone, cytosolic calcium ([Ca2+]i), the major determinant of SMC tone, was measured in PA SMC from a 2.5 month old infant treated with H2O2. **Results:** Infants homozygous for the deletion allele (Del/Del genotype) had significantly higher median urine isoprostane levels (10.6 ng/mg creatinine) as compared to infants heterozygous (3.0 ng/mg creatinine) or homozygous (4.7 ng/mg creatinine) for the insertion allele ($p < 0.05$). Addition of H2O2 to PA SMC caused a significant increase in human PA SMC [Ca2+]i. **Conclusions:** Infants with the Del/Del genotype have increased urine isoprostane concentrations after undergoing CPB, suggesting an increased susceptibility to oxidant injury. Moreover, oxidant stress directly increases human infant PA SMC [Ca2+]i in vitro. Taken together, these findings suggest that patients with the Del/Del genotype may be uniquely vulnerable to oxidant injury and, therefore, at increased risk for pulmonary hypertension after CPB.

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## CHANGES IN SUBSTRATE UTILIZATION IN RAT HEARTS FOLLOWING HEMORRHAGE AND RESUSCITATION WITH KETONE SOLUTION

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**Introduction:** To determine if ketone bodies are an effective metabolic substrate for the support of cardiac metabolism after resuscitation from severe hemorrhage shock. **Hypothesis:** A resuscitative fluid containing ketone bodies improves cardiac function in hemorrhagic shock. **Methods:** 48 hours prior to the hemorrhagic shock exposure, two groups (n = 7/group) of male Sprague Dawley rats were maintained on a high protein diet. Then the animals were anesthetized and cardiac metabolism was assessed by Positron Emission Tomography after injection of 18-Fluorodeoxyglucose. (18-FDG; volume <0.5 ml) in the tail vein. Scans were obtained at 60 and 120 minutes post-injection. The following day, the rats were again anesthetized and the femoral artery and vein were cannulated for measurement of hemodynamics, and sampling for blood gases, pH, base deficit, HCO3, glucose, Hgb, and oxygen saturation. After baseline measurements, arterial exsanguination was performed so that arterial pressure fell to 30-35 mmHg, and the shed volume was recorded. Data were recorded every 30' after induction of shock for 180'. Following 55' of hypotension, the animals were resuscitated over the course of 5' with normal saline or a Ketone Ringer solution, with twice the volume of the blood shed. Then the PET scan was repeated to assess uptake of 18-FDG after 60 and 120 minutes post-injection. At 120', surviving animals were euthanized and kidney and intestinal tissue samples were collected for subsequent histological analyses. **Results:** Hemodynamics and acid-base responses, including blood pressure, heart rate, base excess and pH were improved following resuscitation with ketone ringers solution. Intestinal ischemia/reperfusion injury was less in the group resuscitated with ketone ringers. Initial qualitative image analysis indicates that uptake of 18-FDG was greater in the animals resuscitated with ketone ringer's solution as opposed to normal saline. **Conclusions:** In a model of severe hemorrhagic shock, cardiac function is improved sooner with rats resuscitated with ketone bodies as evidenced by improved hemodynamics, acid-base balance, and glucose uptake as seen in MicroPET imaging.