QUANTITATIVE IMPORTANCE OF OXYGEN-HEMOGLOBIN BINDING TO OXYGEN TRANSPORT IN CONGESTIVE HEART FAILURE

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To study the quantitative importance of 2,3-diphosphoglyceric acid (2,3-DPG) and oxygen-hemoglobin binding (P50) to oxygen transport in patients with congestive heart failure (CHF), we measured 2,3-DPG levels, hemoglobins, blood gases and circulatory hemodynamics in 30 patients with NYHA Class IV CHF.

Whole blood 2,3-DPG was found to be elevated (mean, arterial=2.58 µmol/ml blood, p=.01, or 20.8 µmol/gm Hb, p<.0001), and significant gradients between arterial, mixed-venous and coronary 2,3-DPG levels were observed (mixed venous=2.40, p=.05 v. arterial; coronary sinus=2.23, p<.04 v. arterial). P50 was correspondingly elevated (mean=29.7, normal=26.6). Since systemic oxygen transport was strictly dependent upon forward cardiac index in CHF (r=.89, p<.0001), the cardiac index would have to be 31% higher (2.94 v. 2.31 L/min/M2, p<.02) at rest if oxygen-hemoglobin binding were normalized in order to maintain systemic oxygen transport and consumption at basal levels (351 and 151 ml O2/min/M2 respectively). Similarly, myocardial oxygen transport was found to be strictly dependent upon coronary blood flow in CHF (r=.99, p<.0001). Coronary blood flow would have to be 48% higher at rest (209 v. 142 ml/min, p=.006) in order to compensate for the fall in myocardial oxygen extraction (from 11.7 to 10.5 vol%) and the rise in cardiac index and left ventricular minute work if oxygen-hemoglobin binding were normalized.

These data confirm that 2,3-DPG is elevated in CHF, and that reduced oxygen-hemoglobin binding plays a critically important role in maintaining systemic and myocardial oxygen transport in this clinical setting.

ADENOSINE ATTENUATES LOSS OF HIGH ENERGY PHOSPHATES IN ISCHEMIC MYOCARDIUM EVALUATED BY PHOSPHORUS NMR SPECTROSCOPY

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Adenosine is an endogenous substance which is produced during the metabolism of ATP. It is known to be a potent arteriolar vasodilator and has also been shown to inhibit neutrophil function and cytotoxicity. There is increasing evidence that adenosine, through these mechanisms, may be cardioprotective. However, the effect of adenosine on high energy phosphates (HEP's) remains unclear. Accordingly, this study was undertaken to determine whether or not adenosine provides a protective effect on ischemic and reperfused myocardium through the preservation of HEP's. Reversible ischemia was produced in anesthetized New Zealand rabbits with a reversible snare placed around the left circumflex artery. Rabbits had a 1.3 cm solenoidal coil placed over the myocardium to be rendered ischemic and data was acquired with a 22 cm bore NMR spectrometer at 2.0 Tesla. HEP's were measured at baseline, after a 10 minute occlusion and after a reperfusion period. Prior to occlusion, 8 rabbits received adenosine (25 mg/kg/IV) and 8 control rabbits received normal saline. All metabolic results are expressed as % of total area under the curve.

During occlusion, Pi increased (p<.001) and PCr decreased (p<.001) as expected. However, in adenosine pretreated rabbits, there was an attenuated loss of PCr (adenosine 25.7 ± 8.6% vs control 12.7 ± 3.4%, p<.002) an attenuated increase in Pi (adenosine 32.7 ± 8.0% vs control 41.1 ± 8.8%, p<.05). There were no significant differences in ATP.

We conclude that adenosine provides a protective effect on HEP metabolism during ischemia and reperfusion in intact rabbit myocardium.

Wednesday, March 21, 1990
4:00PM–5:00PM, Room 26
Cardiovascular Magnetic Resonance Spectroscopy

ENERGETICS AND MECHANICS IN MODERATE AND ADVANCED HEART FAILURE DURING TREATMENT WITH AMRINONE AND AMRINONE PLUS DOBUTAMINE: A ^{31}P MRS STUDY.

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Wether positive inotropic stimulation of the failing myocardium, characterized by a depressed energy state, might be disadvantageous remains unclear. We assessed rate-pressure product (RPP), myocardial oxygen consumption (MVO2), high energy phosphates such as phosphocreatine, ß-adenosine triphosphate (ATP), inorganic phosphate by means of ^{31}phosphorus magnetic resonance spectroscopy and phosphorylation potential (PP) in cardiomyopathic hamster hearts in a moderate and a advanced stage of heart failure during administration of amrinone (AMR) (n=7, respectively) and dobutamine (DOB) (n=7, respectively) alone and during combination of AMR + DOB (n=7, respectively). In normal hamster hearts RPP and MVO2 increased significantly (p<0.001) with DOB while ATP (10.3±0.7 vs 7.8±0.8 mM, p<0.05) and PP (4.95±0.09 vs 3.91±0.13, p< 0.005) decreased compared to control values. During AMR + DOB RPP and MVO2 increased (p<0.01) without a significant change of high energy phosphates. In moderate heart failure RPP and MVO2 increased during administration of AMR (p<0.001), DOB (p<0.001) and AMR + DOB (p<0.001) and PP increased during AMR (4.83±0.06 vs 4.56±0.06, p<0.02) and AMR + DOB (5.02±0.07 vs 4.56±0.06, p<0.001). In advanced heart failure RPP and MVO2 increased during AMR and AMR + DOB (p<0.001). ATP increased during AMR (9.5±0.6 vs 6.5±0.4 mM, p<0.005) and AMR + DOB (8.6±0.6 vs 6.5±0.4 mM, p<0.005), whereas PP increased only during AMR alone (4.17±0.04 vs 3.65±0.09, p<0.05). Though, in this cardiomyopathic hamster model administration of AMR, a phosphodiesterase inhibitor, was advantageous in the treatment of hearts in advanced stage of heart failure compared to DOB, an agent with adrenergic receptor mediated action, and the combination of AMR + DOB. On the other hand, the treatment of hearts in a moderate stage of heart failure with the combination of AMR + DOB was superior compared to either agent alone.

TRANSMURAL DISTRIBUTION OF MYOCARDIAL EDEMA BY PROTON NMR SPECTROSCOPY RESULTING FROM MYOCARDIAL ISCHEMIA AND REPERFUSION

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To determine the distribution and extent of myocardial edema resulting from ischemia and reperfusion, 17 open chest dogs underwent occlusion of the left circumflex coronary artery. Of these, 7 were occluded (occ) for 2 hours (Group I), and 10 were occluded for 2 hours and reperfused (rep) for 2 hours (Group II). Proton nuclear magnetic resonance (NMR) spectroscopy (T1 and T2 relaxation times) and percent water content determined amount of edema. There was a significant increase in the T1 relaxation time within the central ischemic zone in Group II (p<0.01) in both the subendocardium (endo: I=707.8±12.5, II=813.2±36.2) and subepicardium (epi: I=641.7±20.5, II=760.5±34.7). These differences were also seen in the T2 weighted relaxation time in the subendocardium (I=54.7±0.8, II=78.7±6.3, p<0.005) and subepicardium (I=54.0±1.4, II=73.1±4.0, p<0.001). Differences were observed between the myocardial layers with increased values found in the subendocardial T1 relaxation times (p<0.01) for both groups. Comparable increases were noted in the percent water content of the myocardium. Despite similar infarct sizes in the 2 groups, T1 and T2 relaxation times were increased transmurally to a greater extent with reperfusion. Thus, as NMR relaxation times lengthen with an increase in water content, myocardial edema is found following occlusion and is augmented by reperfusion. This edema is greater in the subendocardium than the subepicardium after occlusion and after reperfusion. We conclude that ischemia induced edema is enhanced by reperfusion, both in the subendocardium and subepicardium.