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Title: DICHOROACETATE ENHANCES MYOCARDIAL RECOVERY FOLLOWING GLOBAL ISCHEMIA
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Introduction: During cold cardioplegic arrest utilized to perform cardiac surgery, myocardial metabolic requirements are not eliminated and functional and metabolic recovery following global ischemia can be impaired.¹ Dichloroacetate (DCA), a carboxylic acid, increases the activity of pyruvate dehydrogenase (PDH), which converts pyruvate to acetyl CoA, and has been noted to limit ST-T wave changes during coronary occlusion and improve myocardial efficiency in heart failure and following warm ischemia.² We tested the hypothesis that DCA could improve myocardial recovery in a surgical, globally ischemic, isolated heart model.

Methods: 16 rabbits (5-6 kg), anesthetized with pentobarbital, had a median sternotomy and cardiectomy performed. The beating hearts were suspended from a perfusion column by aortic cannulation. Retrograde coronary perfusion with oxygenated Krebs-Ringers bicarbonate solution (KRB) was established at 80 mmHg. Indices of contractility: developed pressure (DP, mmHg) and dP/dt (mmHg/sec), and metabolic status: coronary flow (CF, ml/min), myocardial oxygen consumption (MVO₂, mlO₂/mg), and normalized mechanical utilization efficiency (DP/MVO₂, %mmHg/ %mlO₂/mg) were obtained at preischemic baseline. Modified St. Thomas cardioplegia was used to induce arrest, followed by 120 minutes of ischemia at 34°C. Following ischemia, hearts were reperfused with either KRB (CON) or KRB containing 1 μM DCA. Functional and metabolic indices were obtained at 15, 30, and 45 minutes after reperfusion; results are shown as percent recovery from preischemic baseline at 45 minutes of reperfusion (mean ± SD, * = p < 0.05 by ANOVA vs CON).

	N	DP	dP/dt	CF	MVO ₂	DP/MVO ₂
CON	10	37±8	43±10	92±23	51±19	73
DCA	6	62±4*	67±5*	76±13	71±9*	87

Results: As shown, functional recovery was significantly better in hearts reperfused with DCA. Developed pressure recovered to 62% of baseline in DCA hearts compared to 37% recovery in CON hearts. Recovery of dP/dt was also improved in DCA versus CON hearts (67% versus 43%). CF was not different between groups after reperfusion, but MVO₂ was increased in the DCA vs CON hearts (71% of baseline versus 51%), and mechanical utilization efficiency was also enhanced over time with DCA.

Discussion: These data indicate that DCA improves contractility and metabolic recovery following global ischemia as compared to CON. Despite the protective effect of cold cardioplegia and restoration of substrates necessary for energy regeneration upon reperfusion, oxidative phosphorylation is impaired and myocardial function deteriorates. The enhanced myocardial function and improved metabolic status noted with DCA may result from increased oxidative phosphorylation due to altered PDH activity. DCA is a promising new agent for enhancing myocardial recovery as DCA can improve functional recovery, even when given following ischemia. Further investigations are required to delineate the mechanism of DCA's beneficial effect.

1. Bolling SF, Bies LE, Gallagher KP, et al. Augmenting intracellular adenosine improves myocardial recovery. *J of Thor Cardiovasc Surg* 4:229-236, 1990.
2. Stacpoole PW. The pharmacology of dichloroacetate, *Metabolism* 38:1124-44, 1989.

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TITLE: THE EFFECT OF NUCLEOSIDE TRANSPORT INHIBITOR ON THE NORMOTHERMIC ISCHEMIC HEART.

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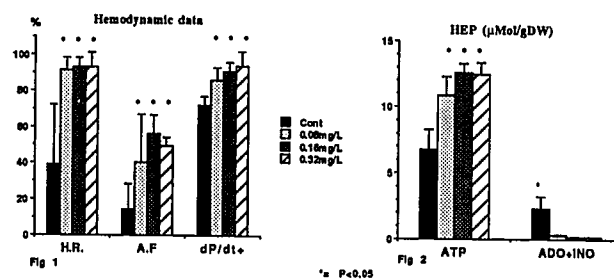
Exogenous adenosine has been shown to have a beneficial effect on the ischemic myocardium in terms of its antiarrhythmic properties and enhancing postischemic myocardial function. In this study we evaluated the effect of R75231, a nucleoside transport inhibitor (NTI) on normothermic ischemia in an isolated rabbit heart model in terms of recovery of function and preservation of high-energy phosphate (HEP).

Twenty-four isolated working rabbit hearts were perfused at 37°C with heated and oxygenated Krebs Henseleit Buffer. The hearts underwent 20 min of Langendorff perfusion (LD), followed by 15 min of working heart (WH). During the experiments, hemodynamic parameters, including heart rate (HR) aortic pressure (AP), aortic flow (AF), coronary flow (CF), and left ventricular pressure (LVP), and its first derivative (dP/dt+ and -) were monitored. For the next 30 min period the hearts were randomly allocated to 4 groups: Group one (n=6) received solvent. Groups two through four (n=6 each) received 0.08, 0.16, 0.32mg/L of NTI respectively. A 20 min period of normothermic global ischemia was induced. Reperfusion was then initiated: 5 min LD mode, followed by 20 min in the WH mode. During the reperfusion period drugs were present in the perfusate. At the end of the exp. left ventricular biopsies were taken to assess HEP.

Results: NTI produced a decrease in both cardiac output and heart rate but not significantly (p>0.05). There was also a decrease in left ventricular filling pressure and dP/dt + and - in all doses used, but not statistically significant. Coronary flow was increased in all doses (p>0.05).

Twenty min of global normothermic ischemia in solvent treated hearts resulted in severe myocardial damage, in which 50% of the hearts developed ventricular fibrillation. 20% had partial recovery of AF, and HR (see fig.1). NTI at all doses significantly improved recovery parameters: AF recovered 80% of control. NTI prevented ventricular fibrillation after reperfusion and all hearts kept on beating (p<0.02). Furthermore, all hearts in all groups did develop a high LVP resulting in the production of aortic flow.

After 20 min reperfusion, the HEP contents were as follows: in the solvent group the ATP was 7.6±3.5 μMol/g and the 0.08 mg/l group had a mean ATP of 10±3.3μMol/g (p<0.05). In group 3 and 4, the HEP were significantly better preserved: 11.7±1.9 and 12.1±2.1 μMol/g respectively (p<0.01),



- Ref. 1. *Circulation* 80:1536-1543,1989
 2. *Anesthesiology* 73(3A):A628,1990