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TITLE: USE OF A PUTATIVE EXCITATION-CONTRACTION UNCOUPLER TO IMPROVE FUNCTION OF ISOLATED HEARTS AFTER 22 HOURS OF COLD HYPOPERFUSION

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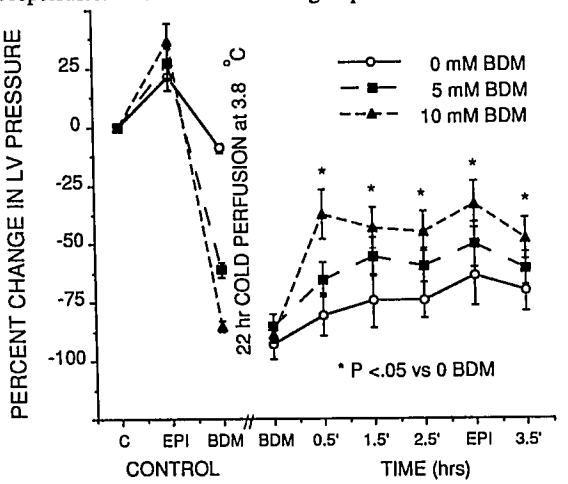
Donor hearts are typically arrested in cold cardioplegic solution, stored in a cold salt solution, and transplanted into the recipient within 3-4 hrs. Dysrhythmias and depressed cardiac function are common with reperfusion in the recipient due to ischemia during storage and to reperfusion injury. Long-term protection of explanted hearts would allow improved utilization of heart donations. We tested whether cardiac function could be improved upon normothermic reperfusion by depressing function before, during and shortly after prolonged hypothermic arrest with 2,3 butanedione monoxime (BDM), a drug which reversibly depresses contractile function while having little effect on excitatory function.

Guinea pig hearts (n=21) were isolated and perfused at 55 mmHg with a modified Krebs' solution to which were added (in mM): 2.5 Ca^{2+}, 4.5 K^+, 2 pyruvate, 11.5 glucose, and 16 mannitol. Heart rate (HR), isovolumetric left ventricular pressure (LVP), coronary flow (CF), and O_2 extraction (%O_2E) were measured at 36.7 ± 0.1 °C. Epinephrine (EPI), 0.5 μM, was infused to test inotropic responsiveness. Hearts were divided into 3 groups, 0 BDM (n=7), 5 mM BDM (n=7), and 10 mM BDM (n=7) and perfused at low constant flow (2.5 ml/min) during 22 hrs of hypothermic arrest at 3.8 ± 0.1 °C. BDM was infused 20 min before and during hypothermic arrest, and for 30 min after normothermic reperfusion. Hearts were monitored continously for 4 hours with normothermic reperfusion. Data are means ± SEM.

BDM depressed, by dose, LVP (fig) and O_2E before cold perfusion. All 0 BDM hearts exhibited ventricular fibrillation (VF) with re-warming at constant perfusion pressure; 2 hearts could not be converted with lidocaine. Two hearts in the 5 mM BDM group, but none in the 10 mM group, exhibited VF which converted with lidocaine. For each group 3.5 hrs after reperfusion, HR had returned to within 2-6 ± 2% of pre-hypothermic control values, CF remained reduced by 44-46 ± 7%, and the increase in O_2E was higher (P <.05) in both the 5 and 10 BDM groups (74 ± 16%) than in the 0 BDM group (31 ± 13%). LVP improved significantly with reperfusion in the 10 mM BDM group:



Our results indicate that BDM affords improved mechanical function and protection against dysrhythmias when given before, during, and after prolonged hypothermic perfusion. Although return of overall function is suboptimal, this approach may prove useful to reduce cardiac work and metabolism in the transplant period.

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Title: **CHRONICALLY INFARCTED RAT HEARTS DEMONSTRATE ENHANCED HALOTHANE MYOCARDIAL DEPRESSION**

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Little is known about how the halogenated anesthetics interact with chronic compensatory hypertrophy following myocardial infarction (MI). Hypertrophic myocardium displays both decreased heterometric and homeometric autoregulation (**HETERO**, length-dependent alterations; **HOMEO**, inotropic changes caused by sudden increases in wall tension).[1] These changes result, in part, from alterations in the calcium transient in hypertrophied myocytes.[2]

We studied the effects of halothane (H) in the chronically infarcted rat heart. Left coronary artery ligation was accomplished in five animals (+MI); four animals underwent sham operation without coronary ligation (-MI). Six to eight weeks after operation hearts were removed from the animals and studied as an isolated working heart preparation. A 3 Fr micromanometer was placed into the left ventricle (LV) and left atrial (LA) flow was quantified with an electromagnetic flow probe. LV pressure (**LVP**), cardiac output (**CO**), and LA pressure (**LAP**) were measured. Derived variables were LV dP/dt, stroke volume (**SV**=CO/HR) and k_{ha}, the rate of rise in LVP after aortic outflow occlusion (k_{ha}=the slope of ln [1-(P_t-P_i)/(P_{max}-P_i)] *vs* time, where P_i, P_{max}, and P_t equal peak LVP initial, maximum, and at time t, respectively). LAP (preload) was incremented at constant peak left ventricular pressure (100 mmHg) and heart rate (300·min^{-1}) to generate a Starling curve. At maximal LAP, aortic outflow was occluded for 15 sec to generate k_{ha}. Each heart was then exposed to 1.0% H for 15 minutes. A second Starling curve and k_{ha} were obtained. Data were analyzed using paired and unpaired t-test with α=0.05.

In these hearts the relationship between SV and LAP typified the Frank-Starling phenomenon of length-dependent control of inotropic state (HETERO). Occluding aortic outflow permitted estimation of k_{ha} (HOMEO) . Maximal SV and the corresponding LAP and LV dP/dt, and k_{ha} after aortic occlusion, are shown in Table 1 for both ±MI groups. In the absence of H, +MI displayed a noticeable but non-significant decrease in SV (p=0.38), which occurs at a higher LAP, when compared to -MI. SV was depressed by H in +MI (p=0.02) but less so in -MI groups (p=0.06). H also increased LAP at maximal SV in both +MI (p=0.05) and -MI (p=0.03) groups. H depressed dP/dt significantly in +MI, but not in -MI hearts. Likewise H decreased k_{ha} in the +MI(p=0.04) but not in the -MI hearts (p=0.11).

These data show that both heterometric and homeometric autoregulation is impaired in the chronically infarcted rat heart, and that these hearts show a greater sensitivity to the negative inotropic effects of halothane. In the chronically infarcted heart, it is postulated that in the presence of H, calcium handling is disturbed to a greater degree than in the normal myocardium.

1. Pawlusch DG, *et al*: **Am J Physiol** 256:H1139-H1147, 1989
2. Moore RL, *et al*: **Am J Physiol** 260:C327-C337, 1991

-MI (n=4)

	dP/dt	SV	LAP	K_{ha}
-H	3544±200	0.23±.01	12.4±1.8	0.32±.01
+H	3223±187	0.17±.02	17.2±1.1*	0.20±.06
Δ(%)	9.0	26.1	38.7	37.5

+MI (n=5)

	dP/dt	SV	LAP	K_{ha}
-H	3329±170	0.20±.02	16.3±2.7	0.40±.06
+H	2715±203*	0.13±.02*	23.2±1.2*	0.17±.06*
Δ(%)	18.4	35.0	42.3	57.5

Table 1. Maximal SV (ml), +dP/dt (mmHg·sec^{-1}), optimal LAP (mmHg) and K_{ha} (sec^{-1}), with or without chronic MI, and (+) or (-) 1.0% H. All values are mean ± SEM. * signifies p<0.05, compared to -H condition in same group.