Title : PROTECTION FROM MYOCARDIAL ISCHEMIA: ROLE OF ANESTHETICS

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Barbiturate-induced protection against experimental partial cerebral ischemia has been documented in many species. The most likely mechanism is reduction of functional workload. Reduction of myocardial workload and oxygen consumption ($M\dot{V}_{O_2}$) during acute regional myocardial ischemia is currently widely practiced. Indeed, β adrenergic blockade is reported to result in reduced myocardial infarct size in many species including man. Anesthetics, by direct myocardial depression and peripheral vasodilation, can decrease $M\dot{V}_{O_2}$, in a dose-related, i.e. controllable way. The question whether reduction of overall $M\dot{V}_{O_2}$ by anesthetics during acute regional myocardial ischemia can result in protection of ischemic myocardium is the subject of this study. A corollary question, namely whether there are qualitative differences between anesthetics with respect to protection against myocardial ischemia, was also investigated.

Methods: Because the various models of estimating infarct size are controversial, we chose to examine ischemic left ventricular (LV) myocardial tissue quality, by measuring regional blood flow, high energy phosphate content, and mitochondrial function, comparing each to normal LV muscle from the same animal biopsied at the same time. Dogs (N=17) were surgically prepared during 0.8% halothane anesthesia, using a standard right heart bypass to enable direct Fick determinations of overall $M\dot{V}_{O_2}$. "Control" anesthetic circumstances, namely halothane 0.2% V/V end-expired, nitrous oxide 70% were then established at a steady state. $M\dot{V}_{O_2}$'s in triplicate, all relevant pressure and flows, blood gases, arterial and coronary lactates and pyruvates, and arterial catecholamines were determined. Next, the anesthetic regimen under study (see below) was established, and the above values remeasured. Following demonstration of steady $M\dot{V}_{O_2}$, the left anterior descending (LAD coronary artery was ligated. $M\dot{V}_{O_2}$'s and all hemodynamic parameters were measured q 5 min during LAD occlusion. Radioactive microspheres were injected into the left atrium at 18 min post-ligation for regional blood flow determinations. At 20 min post-ligation, two large left ventricular biopsies were taken simultaneously, one from the area of flow distribution of the LAD ("ischemic" biopsy), the other from the posterior ventricular wall ("normal" biopsy). These were analyzed for ATP, phosphocreatine, lactate, pyruvate, ADP, AMP, after freezing (within 1 sec) in liquid N_2. Another portion of each biopsy was analyzed for mitochondrial function using standard methodology. Biopsies were also counted for regional flow determinations. Three anesthetic regimens were studied: "control" - 70% N_2O + 0.2% halothane (N=5); "halothane" - 0.90 ± .02% end-tidal (N=7); < 0.2% halothane plus pentobarbital 40 mg/kg (N=5).

Results: Regional flow determinations indicated that all "ischemic" biopsies had less than 10% of the flow delivered to the "normal" biopsies. Table 1 ranks the three anesthetic techniques with respect to arterial pressure, heart rate, $M\dot{V}_{O_2}$, and ATP "depletion" (normal minus ischemic biopsy values). ATP "depletion" was approximately 30% in both the "control" and the halothane groups, and was significantly ($P < .05$) greater (44%) in the barbiturate group. This was not a function of overall $M\dot{V}_{O_2}$ because the halothane group had the lowest, and the control group the highest $M\dot{V}_{O_2}$'s. Mitochondrial functional deterioration (measured by state 3, state 3/state 4, ADP:O ratios), was not significantly different at 20 min of ischemia among the three groups. Myocardial lactate extraction decreased significantly during occlusion in both the halothane and the barbiturate groups, but not in the "control" group, despite the fact that this group had the highest arterial pressures and highest overall $M\dot{V}_{O_2}$'s. Heart rates were very nearly equal in all groups (Table 1).

Conclusions: We conclude that barbiturate anesthesia resulted in significantly greater reductions in ATP content in ischemic ventricular tissue than either halothane (with lower $M\dot{V}_{O_2}$'s) or 70 percent N_2O + 0.2% halothane (with higher $M\dot{V}_{O_2}$'s). We consider that this is therefore likely due to the barbiturate itself. We further conclude that reduction of overall $M\dot{V}_{O_2}$ per se does not necessarily protect ischemic myocardium. Finally, it appears that there are qualitative differences between anesthetics with respect to myocardial protection which may not solely depend upon hemodynamic alterations, and that barbiturates do not exert specific protection against myocardial ischemia as they do in brain.

Table 1[a]

Anesthetic Technique	N	ATP Depletion[c] μM/gm	$M\dot{V}_{O_2}$ ml O_2/min· 100 gm	Mean Art. Pressure mmHg	Heart Rate
1. "Control"[b]	5	1.34±.35 (26.9%)	10.3±1.3	116±11	157±16
2. Halothane 0.90% V/V end-exp	7	1.62±.22 (31.0%)	6.7±.3	69±5	153±5
3. Pentobarbital 40 mg/kg	5	2.37±.14 (43.5%)	8.9±.8	95±8	157±11
Statistical Significance		1V2-NS 1V3-P<.05 2V3-P<.05	1V2-P<.01 1V3-NS 2V3-P<.02	1V2-P<.01 1V3-NS 2V3-P<.02	NS

a. ± SEM
b. "Control" - 0.2% halothane + 70% N_2O
c. "depletion" = normal minus ischemic biopsy values