Title : ANESTHETICS VS. GLOBAL MYOCARDIAL ISCHEMIC DETERIORATION

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During cardiac surgery, usual practice is to crossclamp the aorta and infuse cold hyperkalemic "cardioplegic" solutions intermittently, while the heart remains globally ischemic. There is little argument that the resultant hypothermia is protective. Considerably less evidence exists that the hyperkalemic solution delays myocardial deterioration. No evidence exists regarding anesthetics as possible protectants in this situation. Barbiturates have been shown to protect against brain ischemic injury, at least from partial ischemia, whereas halothane has resulted in larger infarcts and worsened deficits. Currently, barbiturates are often administered in large doses in an effort to "protect" brain in patients who have suffered cardiac arrest. We studied the effects of two anesthetics, namely halothane and pentobarbital, on left ventricular myocardial tissue deterioration in dogs during aortic crossclamping. Our purposes were a) to discover whether anesthetics are qualitatively different with respect to myocardial deterioration during global ischemia and b) to learn whether "cerebrally protective" doses of pentobarbital might also "protect" ischemic myocardium.

Methods: Dogs (n=11) were placed on cardiopulmonary bypass, cannulating femoral artery and right atrium, using a bubble oxygenator. Flows were adjusted to keep mean arterial (aortic) pressure at 73 ± 2.7 mmHg. Bypass was continued for 15 minutes, to establish steady-state nasopharyngeal temperatures of 28°C. Arterial blood gases were adjusted to PaO_2 145 ± 15 torr, $PaCO_2$ 40 ± 1.3 torr, pHa 7.33 ± .02, prior to bypass and again during the pre-crossclamp period on bypass. Group I (n=5) received halothane in sufficient O_2 to keep PaO_2 as noted, balance N_2. End-expired halothane concentration was held at 0.86 ± .01 percent V/V, for at least 15 min prior to bypass. The same inspired concentration was then added to the oxygenator. Group II (n=6) received pentobarbital, 40 mg/kg for anesthesia. Bypass was without hemodilution (donor dog blood prime). EEG's indicated no significant change in anesthetic level upon institution of bypass in the barbiturate group. The aorta was then crossclamped, and standard "cardioplegia" solution* at 28°C was infused (200 ml over 2 min). One minute after this, the first left ventricular biopsy was taken. Biopsies of LV wall were then taken at 3, 5, 10, 20, 30, 60, 90 and 120 minutes of aortic crossclamp, frozen in liquid N_2, for ATP, phosphocreatine, ADP, AMP, lactate, pyruvate. Standard mitochondrial function analyses were performed on biopsies obtained at 1, 60, and 120 min. Ventricular muscle temperature was carefully maintained at 28°C throughout the experiment. Fifty cc cardioplegia was infused every 15 min thereafter.

* Cardioplegia solution contained per liter: 20 mM K^+, 0.5 mM Ca^{++}, 247 mM glucose, 8 mM Mg^{++}, 200 mM Mannitol; pH 7.4 adjusted with $NaHCO_3$, milliosmolality -530.

Results: (See Table 1) Myocardial ATP averaged 6.16 ± .16 μM/gm in the halothane group (I), 6.18 ± .24 μM/gm in the pentobarbital group, at the first biopsy (3 min after crossclamp). At and beyond 60 minutes, ATP values were significantly lower in the pentobarbital group. By 120 minutes, ATP was 2.38 ± .25 μM/gm (decrease of 61%) in Group I, whereas ATP was 1.37 ± .19 μM/gm (decrease of 78%) in the pentobarbital group II ($p < .01$). Mitochondrial function, measured in standard fashion by state 3, state 3/state 4, ADP: O ratios, with glutamate and succinate/rotenone, had deteriorated approximately 30 percent by 120 minutes, with no significant difference in degree of deterioration between groups, although state 3 respiration was significantly lower in the halothane group throughout the experiment.

Conclusions: 1) Myocardial ATP depletion and mitochondrial functional deterioration during aortic crossclamp at 28°C are appreciable (35-50 percent - ATP; 15-20 percent - mitochondria) at 60 minutes, and severe (60-75 percent - ATP; 25-35 percent - mitochondria) at 120 minutes. 2) Pentobarbital clearly did not ameliorate the deterioration in ATP stores relative to halothane anesthesia. 3) The capability of ventricular myocardial mitochondria to convert ADP to ATP was, however, better maintained during pentobarbital anesthesia.

Table 1

	"Control" (3 min crossclamp)		120 min Crossclamp	
	ATP μM/gm	Mitochond. Function State 3 naO_2/min/mg	ATP μM/gm	Mitochond. Function State 3 naO_2/min/mg
Halothane 0.88% n=5	6.16 ±.16	90.7 ±9.7	2.38† ±.25	61.4 ±5.6
Pentobarbital 40 mg/kg n=6	6.18 ±.24	146.6 ±8.7	1.37† ±.19	104.6 ±9.2

† $P < .01$ (Student's unpaired "t" test)