Title: **COMPARATIVE DOSE RESPONSE CARDIAC EFFECTS OF THIOPENTAL, ETOMIDATE, KETAMINE AND PROPOFOL IN PERFUSED, ISOLATED GUINEA PIG HEARTS**

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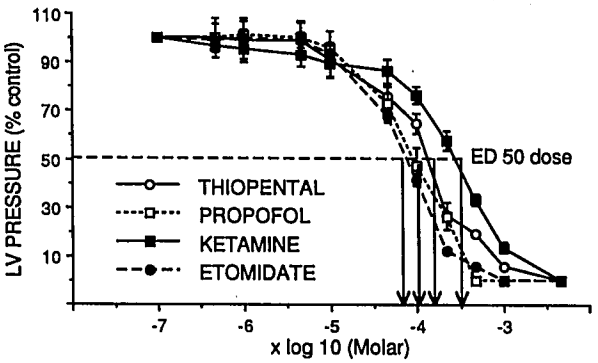
Anesthetic induction agents variably cause cardiovascular depression *in vivo*, but their direct cardiac effects have not been compared. We examined the direct dose related effects of four anesthetic induction agents on cardiac mechanical and metabolic function in hearts isolated from guinea pigs. After i.p. ketamine (20 mg) and heparin 32 guinea pigs were decapitated and their hearts were isolated and perfused retrogradely through the aorta at 55 torr with Krebs solution gased with 96% O_2-4% CO_2 (pH 7.4; 37°C). Heart rate (HR, beats/min) and AV conduction time (AVCT, ms) were recorded with bipolar electrodes placed in the superior right atrium and in the right ventricle. Also measured were: isovolumetric left ventricular pressure (LVP, control 98±7 torr) via a saline-filled balloon; coronary flow (CF, ml/min/g) via a flow probe at the aorta; and aortic and right atrial (coronary sinus) PO_2 (mmHg) via in-line O_2 electrodes. % O_2 Extraction (%O_2 E) was calculated. After control readings, increasing equimolar concentrations (10^{-7} to 10^{-3} M) of thiopental, etomidate, ketamine or propofol were perfused intracoronarily to a given heart for 10 min periods with intermediate control periods. Each heart received only one drug. Data are means ± SEM and were analyzed by ANOVA with LSD tests; * = P <.05 vs controls.

The ED_{50} values (figure) show propofol and etomidate are 5 to 7 times more potent than ketamine in depressing isovolumetric LVP. % O_2E decreases along with LVP while CF increases mildly, indicating that O_2 supply exceeds O_2 demand (table).



	MOLAR	HR	AVCT	CF	%O2 E
PROPOFOL	1x10-6	197±6	59±3	4.6±3	65.2±3.2
	1x10-5	185±9	59±4	4.8±.3	61.1±3.4
	1x10-4	149±15*	77±6*	6.8±.3*	37.5±3.4*
	5x10-4	SA arrest	AV dissoc	7.8±.5*	30.1±7.5*
KETAMINE	1x10-6	196±7	64±2	5.3±.7	69.2±4.1
	1x10-5	186±6	67±3	5.0±.6	64.6±4.3
	1x10-4	166±8*	68±4	5.0±.4	61.1±7.4
	5x10-4	119±10*	137±15*	5.8±.3	38.2±9.8*

This *in vitro* study shows that each of these induction agents is a direct cardiac depressant with only moderate dose dependent differences. *In vivo*, reduction of peripheral resistance and capacitance by these agents are also important in causing a fall in blood pressure.

Title: **ENDOTHELIUM DEPENDENT RELAXATION IN CANINE CORONARY COLLATERAL VESSELS**

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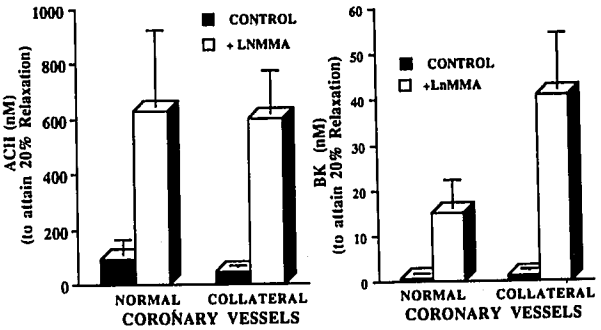
Several species including dogs and humans can develop collateral vessels in response to narrowing of a major coronary artery. Although endothelial dysfunction in the microvasculature fed by these collaterals has been documented,[1] the direct measurement of endothelial function in isolated coronary collateral vessel segments has not been investigated. The purpose of this study was to examine endothelium-mediated responses in isolated segments of coronary collateral vessels.

Following chronic left circumflex coronary occlusion *via* an Ameroid constrictor, collateral vessels (150-200 μm) were visually identified, removed and cut into small segments (2 mm) and suspended on tungsten wires in temperature controlled baths (37°C) containing a modified Krebs solution equilibrated with 93.5% O_2 and 6.5% CO_2 and pH of 7.38-7.42. The vessels were gradually prestretched to an optimal resting tension and were then allowed to equilibrate. Normal coronary arteries of a similar size were used as a control. All vessels were preconstricted with PGF_{2a} ($3x10^{-6}$M) and exposed to cumulative doses of either bradykinin (BK) or acetylcholine (ACH) to obtain endothelium mediated relaxation[2] (i.e. relaxation equal to or greater than 20% of constriction). After repeated washouts, and following recovery at basal resting tension, the same procedure was carried out in the presence of 300 μM N^G-monomethyl-L-arginine (LnMMA) in order to inhibit endothelium-mediated relaxations.[3] Data were analyzed by paired t-test and expressed as mean±SEM. A p value of 0.05 or less was considered statistically significant.

The results demonstrated no significant difference between normal- and collateral vessel-endothelium mediated relaxations. This suggests that endothelium is present and functional in coronary collateral vessels. In a recent study,[4] it was postulated that isoflurane may inhibit coronary constriction *via* endothelium-mediated relaxation. This action of isoflurane may also occur in the collateral circulation and could be of importance in patients with coronary artery disease requiring general anesthesia.



References:

1) *Clin Res* 37:886A, 1989 (Abstract).
2) *Proc Natl Acad Sci USA* 79:2106, 1982.
3) *Br J Pharmacol* 96:418, 1989.
4) *Anesthesiology* 67:513, 1987.