TITLE: Alteration of Vascular Responsiveness to Isoflurane and Halothane by the Endothelium

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INTRODUCTION: Investigations of the interaction of the vascular endothelium and volatile anesthetics has provided evidence that some vascular effects of volatile anesthetics may be mediated by the endothelium (1-3). We assessed the effect of isoflurane and halothane on norepinephrine (NE) induced contractions in endothelium intact and denuded rat aorta and carotid artery.

MATERIALS AND METHODS: Ring segments of rat aorta and carotid artery were prepared for in vitro recording of isometric tension as described elsewhere (2). Endothelial function was assessed by response to acetylcholine (10^{-4} M) following contraction with NE. Equilibration was allowed for 120 minutes followed by a baseline dose-response curve to cumulative doses of NE (10^{-9} M to 10^{-5} M). One or two rat MAC halothane (1.2% and 2.4%) or isoflurane (1.3% and 2.6%) was administered in random order and a dose-response curve determined, followed by a recovery curve. Dose-response curves were then determined during the alternate concentration of the same anesthetic agent and during recovery. Dose-response curves were performed at one hour intervals. Responses were adjusted to % of maximal contraction (T_{max}) of the baseline curve. T_{max} and ED_{50} values were calculated for each curve, and data analyzed by ANOVA with Duncan's post-hoc test where appropriate.

RESULTS: In rat aortic specimens with intact endothelium, halothane produced significant enhancement of the T_{max} during recovery from 1 MAC. In the absence of endothelium, there was significant enhancement of T_{max} during 1 MAC halothane and during recovery from both 1 and 2 MAC halothane. ED_{50} was not changed under any conditions. Isoflurane produced significant increases in T_{max} during 1 MAC levels and during recovery from 1 and 2 MAC in preparation with intact endothelium. The ED_{50} was significantly shifted to the right with 2 MAC isoflurane in preparations with endothelium. In preparation without endothelium, T_{max} was increased following 2 MAC isoflurane and ED_{50} was shifted to the right during 1 and 2 MAC.

In carotid artery preparations with intact endothelium, halothane produced a significant decrease in T_{max} during 2 MAC and an increase in T_{max} during recovery from 1 and 2 MAC. In the absence of endothelium, there was significant enhancement in T_{max} during recovery from 1 and 2 MAC halothane but there was no depression evident at 2 MAC. There was no alteration in ED_{50} under any conditions. Isoflurane produced a significant increase in T_{max} during 1 MAC and during recovery from 1 and 2 MAC in endothelial intact specimens. The ED_{50} was not altered in endothelial intact preparation. In preparations without endothelium, T_{max} was increased during recovery from 1 MAC isoflurane. The ED_{50} was significantly shifted to the right during 2 MAC isoflurane.

DISCUSSION: Removal of the endothelium altered the interaction between NE and halothane or isoflurane in rat aorta and carotid artery. This alteration was dependent on both the volatile anesthetic in use and the vascular bed. There was no evidence of direct depression in smooth muscle contractility by either anesthetic. Both agents produced potentiation of contractions during recovery in the presence and absence of endothelium. Isoflurane produced enhancement of norepinephrine contractions in both the aorta and carotid artery appear to be partially endothelially mediated. The presence of the endothelium also helped prevent isoflurane induced shifts in the ED_{50} to the right. Changes in the ED_{50} suggest competitive antagonism of NE by isoflurane. Halothane appears to act in part by different mechanisms than isoflurane. Halothane decreased T_{max} in carotid preparations with endothelium, and this depression was reversed by removal of the endothelium.

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TITLE: EFFECTS OF MIDAZOLAM AND FLUMAZENIL ON CORONARY CIRCULATION AND CONTRACTILITY OF AN ISOLATED RABBIT HEART

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When compared to diazepam and flunitrazepam, midazolam (MID) seems to induce, in humans, limited effects on the coronary vasculature related to changes in myocardial oxygen consumption. However, direct effects of midazolam on the coronary circulation and on myocardial performance remain controversial.

A blood perfused isolated rabbit heart preparation (modified Langendorff technique) was used to determine the potential direct effects of MID on coronary circulation and myocardial performance and their eventual reversibility by flumazenil (FLU). Human stored RBC's were whashed and resuspended in a modified Krebs-Henseleit buffer. Blood was oxygenated and equilibrated to achieve a normal acid-base balance. After quick preparation, the aorta was cannulated and retrograde aortic perfusion was performed. The speed of coronary pump which reflects coronary blood flow (CBF) may vary to maintain a constant perfusion pressure at 80 mm Hg. A cannulated fluid-filled balloon was placed in the left ventricle (LV) in order to monitor LV pressures. The balloon was inflated to maintain constant LV volume and to produce a LV end diastolic pressure (LVEDP) of 10 mmHg. The atria were paced at a constant rate of 130 b/min. After baseline measurements, MID concentration in the perfusate was increased from 10^{-6} to 10^{-4} M. The same dose-response curve was obtained under infusion of 10^{-5} M FLU. Eight experiments were obtained.

	MIDAZOLAM CONCENTRATION					
	Basal	10^{-6} M	3 10^{-6} M	10^{-5} M	3 10^{-5} M	10^{-4} M
CBF ml/min/g						
MID	1.76±0.32	1.77±0.32	1.75±0.32	1.91±0.32	2.44±0.39**4.42±0.59**	
MID + FLU	1.62±0.31	1.70±0.30	1.78±0.31	1.99±0.30	2.68±0.48**3.83±0.35**	
dP/dt max mm Hg/s						
MID	1994±214	2000±209	2012±198	2037±203	2075±193	2037±152
MID + FLU	2100±195	2106±199	2106±194	2075±190	2143±194	2037±191

** p<0.01 vs Basal

Relevant data are presented in the table. No significant effect of MID on myocardial contractility was observed even at the highest concentrations. A potent direct vasodilator effect is observed at supratherapeutic concentrations. A high concentration of FLU does not modify the dose-response curve.

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