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Title: DIFFERENTIAL RESPONSE OF PROXIMAL AND DISTAL CORONARY ARTERIES TO INTRAVENOUS ANESTHETICS

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TITLE: PROPOFOL PRODUCES ENDOTHELIUM-INDEPENDENT VASODILATION AND MAY ACT AS A CALCIUM CHANNEL BLOCKER

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This protocol was undertaken to determine whether the vasodilation produced by propofol (P) is dependent upon endothelium (ED).¹ Isolated rat thoracic aortic rings, with and without ED, were precontracted with KCl or phenylephrine (PE) and exposed to P. Both KCl and PE were used because contractions are produced differently: KCl contractions are due to extra cellular Ca²⁺ influx through voltage gated Ca²⁺ channels (VGCC), while PE contractions involve receptor operated intracellular Ca²⁺ release and Ca²⁺ channels. Thus, the effect of P on two distinct contraction mechanisms with and without ED was evaluated.

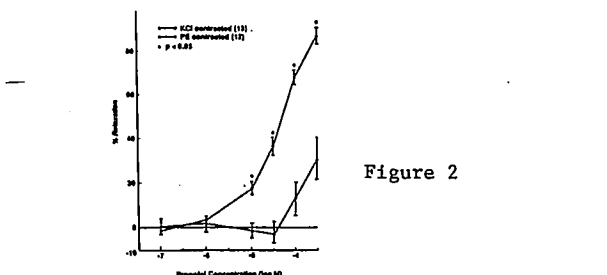
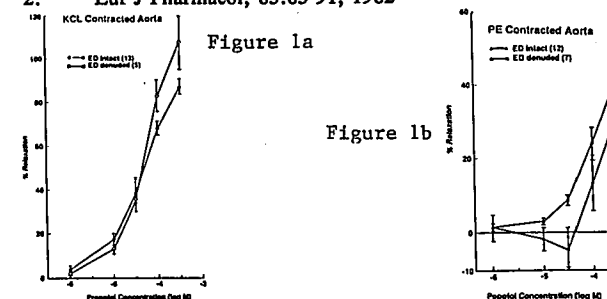
Thoracic aortic rings (3 mm width) were obtained from male Sprague-Dawley rats, suspended in an organ bath in Krebs-Henseleit solution (37° C), and aerated with 95% O₂/5% CO₂. Their isometric responses using a 2 gm resting tension were recorded. The aortic rings were precontracted submaximally with KCl (40 mM) or PE (3 x 10⁻⁷M) prior to and after removal of ED and the relaxation produced by P was observed. Data are expressed as MEAN ± SEM. ANOVA and unpaired Student's t tests were used to determine significance p < 0.05.

P produced a concentration dependent relaxation of aortic rings with no difference in the relaxation comparing rings with and without ED, precontracted with either KCl or PE (Fig 1a & b). But, the response to P was greater in the KCl contracted aortic rings compared to the PE contracted rings (Fig. 2). The P solvent (Intralipid 10%) had no effect.

Thus, P induced vasodilation is not ED dependent, because P produced similar relaxation in the presence and absence of ED. The fact that P relaxation was greater with KCl precontraction (depolarized preparation) than with PE, which is a characteristic property of calcium channel blockers such as nifedipine,² suggests that P relaxation is due to VGCC inhibition.

References

1. Ann Rev Pharmacol Toxicol, 24:175- 197, 1984.
2. Eur J Pharmacol, 85:85-91, 1982



Endothelin, a potent vasoconstrictor hormone released during surgery, is important in the regulation of local blood flow and its effects may predominate in disease states characterized by vasospasm such as unstable angina. The objective of this study was to determine the direct effect of three intravenous anesthetic agents on isolated canine coronary arteries precontracted with endothelin. Following removal of the heart, portions of the left anterior descending coronary artery and its first and second order branches were removed, cut into small segments and separated into groups of proximal (1300-2500 μm) and distal (250-500 μm) vessels. Vascular rings were suspended on tungsten wires in temperature-controlled baths containing a modified Krebs' solution equilibrated with 93.5% O₂ and 6.5% CO₂ and maintained at a physiological pH. After prestretching the vessels to an optimal resting tension and a period of equilibration they were exposed to an EC₅₀ concentration of endothelin. The responses to incremental concentrations of thiopental, ketamine and propofol were recorded. Data were expressed as mean±SEM and analyzed using repeated measures analysis of variance (*p<0.05). Endothelin constricted all coronary vessels. This vasoconstriction was reversed by the three anesthetic agents. Small vessels were significantly more susceptible to the vasodilator effects of the anesthetics (Figure: response to ketamine). At low concentrations propofol produced mild contractions in large vessels. These results demonstrate the antagonism of endothelin effect by intravenous anesthetics. This antagonism may not be seen at anesthetic concentrations seen clinically. The functional differences between proximal and distal coronary arteries include a differential response to intravenous anesthetic agents.

