

# Halothane Relaxes Previously Constricted Isolated Porcine Coronary Artery Segments More Than Isoflurane

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Coronary vasodilation by halothane and isoflurane were compared using *in vitro* tension recording. Porcine left anterior descending coronary arterial segments (1.5–2.0 mm o.d.) were constricted with either K<sup>+</sup> (30 mM) or prostanoid U44069 ( $6 \times 10^{-7}$  M) in the absence of other drugs or anesthetics. Following stabilization of constriction, arteries were exposed to halothane or isoflurane at 0.5, 1.0, 1.5, 2.0, and 3.0% concentrations. K<sup>+</sup> (30 mM) induced constriction was reduced by halothane at 1.5, 2.0, and 3.0% and U44069 ( $6 \times 10^{-7}$  M) induced constriction was reduced at 0.5, 1.0, 1.5, 2.0, and 3.0%. K<sup>+</sup> (30 mM) induced constriction was reduced by isoflurane only at 3.0% and U44069 ( $6 \times 10^{-7}$  M) induced constriction was reduced by isoflurane only at 2.0 and 3.0%. U44069 induced constriction was more susceptible than K<sup>+</sup> induced constriction to relaxation by halothane or isoflurane. Halothane was more potent than isoflurane as a direct relaxant of porcine epicardial left anterior descending arterial segments previously constricted with K<sup>+</sup> (30 mM) or U44069 ( $6 \times 10^{-7}$  M). (Key words: Anesthesia: cardiovascular. Anesthetics, volatile: halothane; isoflurane. Arteries: coronary; vascular muscle. Heart: coronary vasodilation. Potency: anesthetics; MAC.)

THE EFFECTS OF HALOTHANE and isoflurane on the coronary circulation remain controversial. It has been frequently contended that, *in vivo*, isoflurane is a coronary vasodilator.<sup>1-4</sup> Halothane, in general, has not been considered a potent coronary dilator.<sup>3,4</sup>

The confusion surrounding the effects of these agents on the coronary circulation arises because contradictory results from different preparations under different conditions have been reported. Using *in vivo* techniques, it is difficult to precisely control the effects of isoflurane and halothane on systemic hemodynamics, myocardial metabolism, and contractile mechanisms, all of which indirectly influence the coronary circulation. Defining the direct or "pharmacological" action of these agents on the coronary circulation thus becomes complex.

This study compares the *in vitro* effects of halothane and isoflurane on pre-constricted, functionally denervated arterial segments from porcine epicardial left anterior

descending (LAD) coronary arteries in a carefully controlled setting. K<sup>+</sup> and U44069, a stable analogue of prostaglandin PGH<sub>2</sub>, were used to induce active constriction of the LAD segments. These agonists were chosen because of their different mechanisms mediating smooth muscle contraction. K<sup>+</sup> primarily mediates constriction by depolarization and stimulation of external Ca<sup>2+</sup> entry, and U44069 through both external Ca<sup>2+</sup> entry and internal Ca<sup>2+</sup> release.<sup>5-7</sup> Our aim was to obtain anesthetic dose-response relationships without the influence of *in vivo* effects of anesthetics on systemic hemodynamics, myocardial metabolism, and contractile mechanisms, which might indirectly influence the coronary circulation.

## Methods

Pig hearts from male and female pigs (weight 90–130 kg) were obtained from a local abattoir. The heart was removed within 5 min of slaughter and placed in cooled (4° C) Ionic Solution for Mammals (ISM) (composition, mM: 130 NaCl, 16 NaHCO<sub>3</sub>, 0.5 NaH<sub>2</sub>PO<sub>4</sub>, 4.7 KCl, 1.8 CaCl<sub>2</sub>, 0.4 MgCl<sub>2</sub>, 0.4 MgSO<sub>4</sub>, 13 HEPES and 5.5 dextrose; pH 7.4). The LAD coronary artery was dissected free, connective tissue removed using a dissecting microscope, and 1 mm wide circular ring segments cut between the second and third ventricular branches (1.5–2.0 mm o.d.). Arterial segments were threaded with stainless steel hooks and suspended in temperature-controlled, constant-flow muscle chambers. High fidelity force transducers (Akers, Norway) were used for tension recording (sensitivity 1-9000 dynes).

Muscle chambers were perfused with oxygenated (95% O<sub>2</sub>-5% CO<sub>2</sub>) ISM at 37° C. Arterial segments were stretched to obtain 1750 dynes passive force. Segments were then functionally denervated using 6-hydroxydopamine<sup>8</sup> and restretched as needed to maintain 1750 dynes passive force. Adrenergic denervation was done to eliminate the release of catecholamines which might influence the direct effect of agents studied. Following a 1-h stabilization and washout with ISM, the segments were constricted with either K<sup>+</sup> (30 mM) or U44069 ( $6 \times 10^{-7}$  M), a stable epoxymethano-derivative of PGH<sub>2</sub><sup>9</sup> [Upjohn: 9-11-dideoxy 9 $\alpha$ ,11 $\alpha$ -epoxymethano prostaglandin F<sub>2</sub> $\alpha$ ]. K<sup>+</sup> (30 mM) solution was prepared by replacing Na<sup>+</sup> ion in the ISM on an equimolar basis. After stabilization of constriction, halothane or isoflurane was added in incremental steps to achieve steady-state concentrations, and the effect on tension was measured.

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Each anesthetic concentration was maintained for 15–20 min or until a stable tension was obtained.

Four coronary segments were studied at any given time: two as parallel controls constricted with the agonist but not exposed to isoflurane or halothane, and two constricted with the same agonist followed by addition of isoflurane or halothane. Only one agonist and anesthetic agent were studied per coronary artery segment. Parallel controls showed no preparation fatigue with time.

Isoflurane or halothane was added to ISM using special glass bubbling columns. Ninety-five per cent O<sub>2</sub>-5% CO<sub>2</sub> flowing through calibrated anesthetic vaporizers bubbled through these columns saturating ISM with the appropriate per cent of volatile agent. Saturated ISM was then pumped to the muscle chamber through special glass tubing using a peristaltic pump.

The apparatus was sealed to maintain appropriate anesthetic concentration. For every experiment at each anesthetic concentration, electron capture gas chromatographic measurement using heptane extraction documented actual anesthetic concentrations in ISM bathing the arterial segment.<sup>10</sup> Each perfusate sample was taken immediately adjacent to the arterial segment under study. Expected concentrations to be studied, in μg/cc ISM, were as follows: halothane 32, 64, 96, 128, 192; and isoflurane 21, 43, 64, 86, 128. Based on anesthetic solubility coefficients, these concentrations correspond to predicted concentrations for ISM at 37° C saturated with 0.5, 1.0, 1.5, 2.0, and 3.0% of the volatile agent, respectively.<sup>11</sup> Anesthetic concentrations were always increased incrementally in the above order. Randomization of the order that anesthetic concentration was given was not done, because of the concern that prolonged effect from higher concentrations might influence the results seen with lower concentrations.<sup>12</sup>

A total of 80 arterial segments from 24 pigs were studied. Data for each group (those constricted with K<sup>+</sup> or U44069) are presented as per cent maximal tension generated during initial constriction. Adjustments for tonic increase in tension with time were made using the parallel control for each arterial segment. A repeated measure ANOVA was applied, followed by a multiple comparison of means to obtain *P* values. The Bonferroni Multiple Comparison Procedure was used to maintain an overall significance level of *P* < 0.05.

### Results

Results of gas chromatographic measurement of solution anesthetic concentrations are listed in table 1. Expected anesthetic concentrations in ISM were calculated using solubility coefficients for 37° C and osmolarity 308 mOsm/l (halothane 0.825; isoflurane 0.590).<sup>11</sup> Concentrations were accurately reproduced between experi-

TABLE 1. Concentration of Anesthetics in ISM

	Desired Gas Concentration Equilibrated with ISM %	Calculated Concentration μg/cc	Measured Concentration μg/cc	Calculated Gas Concentration Equilibrated with ISM %
Halothane	0.5	32	22 ± 0.5	0.34
	1.0	64	58 ± 0.8	0.9
	1.5	96	90 ± 1.0	1.4
	2.0	128	125 ± 1.4	1.95
	3.0	192	189 ± 1.7	2.95
Isoflurane	0.5	21	20 ± 0.3	0.47
	1.0	43	45 ± 0.8	1.01
	1.5	64	66 ± 0.9	1.54
	2.0	86	90 ± 1.4	2.09
	3.0	128	127 ± 2.3	2.97

Measured concentrations represent means ± standard errors of the mean for 20 measurements.

ments, as shown by the small SEM. Measured anesthetic concentrations showed minimal deviation from those expected corresponding to ISM at 37° C saturated with: isoflurane 0.47, 1.01, 1.54, 2.09, 2.97%; and halothane 0.34, 0.90, 1.40, 1.95, 2.95. Halothane 0.34% showed the greatest deviation from that expected. The expected concentrations of 0.5, 1.0, 1.5, 2.0, and 3.0% will be referred to below.

Sample tension recordings are shown in figure 1. Anesthetic induced relaxation was gradual, reaching a relaxation plateau in about 10–20 min. Relaxation was as rapid at low as at higher concentrations. Active force for K<sup>+</sup> induced constriction averaged 4680 ± 236 (SEM) dynes and for U44069 induced constriction averaged 3073 ± 244 (SEM) dynes.

Halothane significantly reduced K<sup>+</sup> (30 mM) induced constriction of the LAD coronary artery segments at 1.5, 2.0, and 3.0% (table 2), and U44069 (6 × 10<sup>-7</sup> M) induced constriction at 0.5, 1.0, 1.5, 2.0, and 3.0%. Halothane at the highest concentration virtually eliminated all U44069 induced constriction. In contrast, isoflurane significantly reduced K<sup>+</sup> (30 mM) induced constriction only at 3.0% and U44069 (6 × 10<sup>-7</sup> M) induced constriction only at 2.0 and 3.0%. Isoflurane actually appeared to enhance U44069 induced constriction at 0.5%, although the trend was not statistically significant.

In comparing the ability of halothane *versus* isoflurane to relax K<sup>+</sup> induced constriction, halothane induced relaxation was significantly greater than that seen with isoflurane at 1.5, 2.0, and 3.0%. For U44069-induced constriction, halothane induced relaxation was significantly greater than isoflurane at 0.5, 1.0, 1.5, 2.0, and 3.0%.

Halothane and isoflurane were both more efficacious in relaxing U44069 *versus* K<sup>+</sup> induced constriction of LAD coronary artery segments.

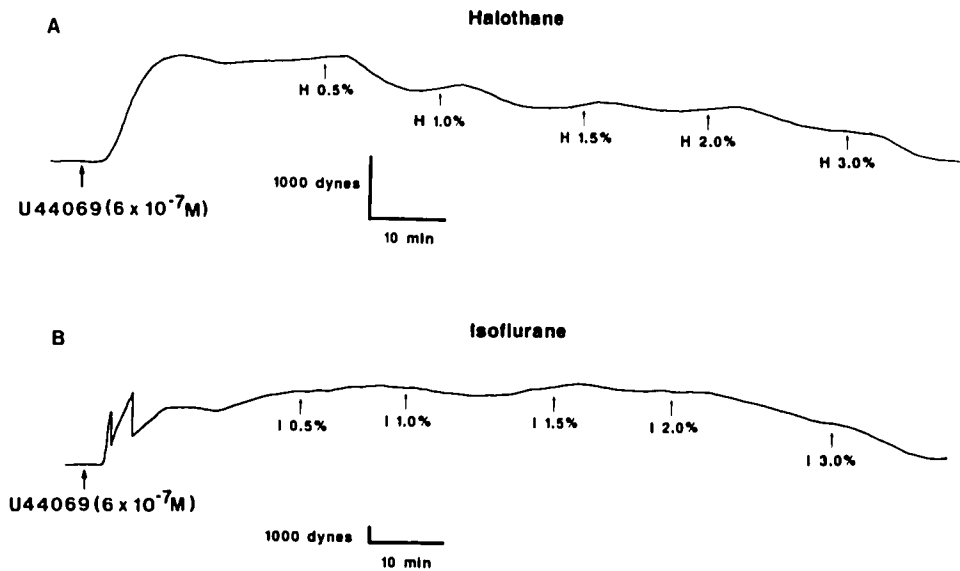


FIG. 1. A. U44069 induced sustained constriction which was relaxed by halothane (H) in a dose-dependent manner. B. U44069 induced constriction was relaxed only at higher isoflurane (I) concentration. Relaxation of prostanoid U44069 ( $6 \times 10^{-7}$  M) induced sustained constriction was greater and occurred at lower concentration with halothane (A) than with isoflurane (B).

### Discussion

These experiments point to definite differences between the abilities of halothane and isoflurane to relax U44069 and K<sup>+</sup> induced constriction in functionally denervated isolated pig epicardial LAD coronary artery segments in the absence of any other drugs and anesthetics. Halothane was clearly the more potent and efficacious vascular relaxant.

Isoflurane has often been regarded as a potent coronary vasodilator, although its site of action remains unclear.<sup>3</sup> Recently, Sill *et al.*, studying intact dogs, found no epicardial coronary dilation with isoflurane.<sup>13</sup> They concluded that isoflurane dilated intramyocardial vessels. Whether this vasodilation is a direct pharmacological action or secondary to the actions of isoflurane on systemic hemodynamics, myocardial metabolism, and/or contractile mechanisms is not clear. Gilbert *et al.* recently reported that isoflurane preserved coronary reserve in pigs, again questioning whether isoflurane really has a potent vaso-

dilator effect.<sup>14</sup> In contrast, halothane substantially reduced coronary reactive hyperemic responses, implying a coronary dilatory action, or an inhibitory effect on coronary autoregulation.<sup>14</sup>

If isoflurane can directly (pharmacologically) reduce coronary vascular resistance at clinically relevant concentrations, our study suggests that its vasodilatory site of action, at least in the pig, is unlikely to be in large LAD segments. *In vitro* experiments by Blaise *et al.*, showing that isoflurane attenuated dog epicardial coronary constrictive responses to phenylephrine, and prostaglandin F<sub>2α</sub>, but not to K<sup>+</sup>, were performed using an anesthetic concentration (2.3%) above the clinical range and cannot necessarily be extrapolated to lower, clinically relevant concentrations.<sup>15</sup> Their phenylephrine, PGF<sub>2α</sub>, and K<sup>+</sup> results correlate well with those seen in our dose-response experiments at 2% and 3%. Blaise *et al.* did not study isoflurane concentrations below 2%, concentrations at which we saw no significant vasodilator response.

The greater relaxant effect of halothane *versus* isoflu-

TABLE 2. Anesthetic Effect on K<sup>+</sup> and U44069 Contractile Tension in Porcine LAD Coronary Artery Segment

	Percent Maximal Tension at Given Percent Anesthetic (Mean ± SEM)					
	0	0.5	1.0	1.5	2.0	3.0
<b>Halothane</b>						
Expected gas concentration (%)	0	0.5	1.0	1.5	2.0	3.0
Calculated gas concentration (%)	0	0.34	0.9	1.4	1.95	2.95
K <sup>+</sup> (30 mM) constriction	100	100 ± 3	89 ± 4	72 ± 7*†	52 ± 10*†	24 ± 7*†
U44069 ( $6 \times 10^{-7}$ M) constriction	100	67 ± 11*†‡	31 ± 11*†‡	23 ± 9*†‡	12 ± 6*†‡	2 ± 2*†‡
<b>Isoflurane</b>						
Expected gas concentration (%)	0	0.5	1.0	1.5	2.0	3.0
Calculated gas concentration (%)	0	0.47	1.01	1.54	2.09	2.97
K <sup>+</sup> (30 mM) constriction	100	108 ± 4	108 ± 5	103 ± 5	98 ± 5	83 ± 6*
U44069 ( $6 \times 10^{-7}$ M) constriction	100	118 ± 6	98 ± 8	79 ± 18	70 ± 13*	44 ± 10*†

\* Significantly different ( $P < 0.01$ ) compared to 0%.

† Significantly different ( $P < 0.01$ ) compared to isoflurane at same concentration.

‡ Significantly different ( $P < 0.01$ ) compared to relaxations of K<sup>+</sup> induced constriction.

rane is of interest because halothane has been previously thought to be much less of a direct coronary vasodilator than isoflurane.<sup>3</sup> Despite this, there are numerous *in vitro* studies which have shown halothane to inhibit drug-induced contractions of rat aorta, rabbit aorta, and rabbit mesenteric vein.<sup>12,16,17,18</sup> One study in rat aorta found that 1 and 2% halothane caused approximately the same degree of relaxation as 4 and 6% isoflurane, respectively.<sup>18</sup> In another study, using an *in vivo* dog preparation, halothane decreased coronary vascular resistance 12% in the working heart and 25% in the non-working heart.<sup>19</sup> No comparison to isoflurane was made.

For pigs, 1 MAC halothane has been variously reported between 0.91–1.25%, and isoflurane between 1.45–1.55%.<sup>20–23</sup> In our study, isoflurane's relaxation of both K<sup>+</sup> and U44069 induced constrictions did not occur at clinically relevant concentrations, whereas halothane's relaxation of K<sup>+</sup> induced constriction occurred at concentrations only slightly greater than 1 MAC. Halothane's ability to relax U44069 induced constriction occurred at clinically relevant concentrations, even at levels below 1 MAC.

U44069 induced constriction was significantly more susceptible than K<sup>+</sup> induced constriction to relaxation by both halothane and isoflurane. This observation is of interest, because it is opposite that found for calcium channel blockers to which halothane and isoflurane are often compared.<sup>24</sup> Calcium channel blockers have been found to be more potent and efficacious in relaxing K<sup>+</sup> induced constriction *versus* prostanoid or norepinephrine induced constriction of vascular smooth muscle.<sup>25–27</sup> K<sup>+</sup> is thought to mediate contraction through depolarization and stimulation of external Ca<sup>++</sup> entry.<sup>7</sup> Prostanoids and norepinephrine are thought to mediate constriction through both external Ca<sup>2+</sup> entry and internal Ca<sup>2+</sup> release.<sup>5–7,26</sup> The greater efficacy of calcium channel blockers in relaxing K<sup>+</sup> *versus* prostanoid induced constriction has been attributed to their ability to block external Ca<sup>++</sup> entry. The greater efficacy of halothane and isoflurane in relaxing U44069 *versus* K<sup>+</sup> induced constriction implies a mechanism of action different from that of calcium channel blockers.

The mechanism by which isoflurane and halothane act on vascular smooth muscle is not known. Studies using myocardial tissue suggest that these agents may affect Ca<sup>++</sup> movement or availability at the cell membrane, sarcoplasmic reticulum, and contractile proteins.<sup>24,28,29</sup> Comparable studies on vascular smooth muscles have not been done. Blaise *et al.* have recently presented evidence suggesting that the coronary vasodilatory effect of isoflurane is mediated in part by a mechanism requiring intact coronary vascular endothelium.<sup>30</sup> Larach *et al.* have shown halothane to preferentially interfere with  $\alpha_2$  *versus*  $\alpha_1$  adrenoceptor-mediated vasoconstriction.<sup>31</sup> Sprague *et al.*

reported that the actions of isoflurane and halothane on rat aorta did not appear to be mediated through beta-adrenergic receptors.<sup>18</sup>

Although our experiments show less relaxation of large porcine coronary vessels by isoflurane compared to halothane, it is possible that isoflurane and halothane have different effects on smaller coronary vessels and/or whatever coronary collateral circulation might be present. If this were true, it would imply that halothane and isoflurane mediate vascular smooth muscle relaxation through different mechanisms. Such is the case with dipyridamole and nitroglycerin. Dipyridamole dilates smaller coronaries to a greater extent than larger ones, whereas nitroglycerin dilates larger vessels more than small.<sup>32</sup> Further work in this area is needed to clarify the mechanisms of action of these agents on vascular smooth muscle.

Although our experiments do not directly address the question of whether isoflurane *per se* can cause coronary steal, they do clearly point to the importance of separating direct pharmacological actions of these agents on the coronary vasculature from powerful indirect coronary actions mediated by anesthetic-induced changes in systemic hemodynamics, myocardial metabolism, or contractility.

We conclude that isoflurane in clinically relevant concentrations did not relax denervated porcine epicardial LAD segments previously constricted with K<sup>+</sup> or U44069. In contrast, halothane in clinically used concentrations did relax K<sup>+</sup> and U44069 induced constriction. Both isoflurane and halothane preferentially relaxed U44069 *versus* K<sup>+</sup> induced constriction, implying a mechanism of action different from that of calcium channel blockers.

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