

EDITORIAL VIEWS

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Does Isoflurane Produce Coronary Vasoconstriction?

Although the early studies on the effect of volatile anesthetics on the coronary circulation from our laboratory suggested that halothane, enflurane, and isoflurane had minimal direct effects,¹⁻³ in a study in humans, Reiz *et al.* first suggested that isoflurane might be a coronary vasodilator.⁴ Others previously showed that vasodilators, such as adenosine and sodium nitropruside, which preferentially dilated the smaller resistance coronary vessels, were capable of maldistributing blood from ischemic to nonischemic areas, producing the phenomenon known as "coronary steal."^{5,6} Buffington *et al.* demonstrated that, under the proper circumstances, isoflurane could produce this maldistribution of coronary blood flow in an ischemic model.⁷ However, a variety of studies in intact animals and humans over the next decade suggested that coronary vasodilation produced by isoflurane was considerably less profound than that produced by adenosine and that "coronary steal" was probably not a clinical problem.⁸⁻¹⁹ Studies in isolated coronary arteries also universally demonstrated vasodilation.²⁰⁻²⁵ The most recent controversy has centered around the experiments of Crystal *et al.* in an *in situ* perfused dog heart, where isoflurane appeared to be practically as potent a vasodilator as adenosine, in contrast to all previous studies.²⁶

In this issue of the Journal, Park *et al.* studied the effects of isoflurane on the diameter of isolated segments of rabbit coronary artery during varying conditions.²⁷ They found that the effects differed according to the initial diameter of the vessels. Arteries smaller than 180 μ in diameter, which they defined as "resistance vessels," responded to increasing concentrations of isoflurane with a decrease in diameter (vasoconstriction), whereas the vessels whose diameter exceeded 290 μ (conductance vessels) showed a slight increase in diameter (vasodilation) to increasing con-

centrations of isoflurane. The diameters of the intermediate-size vessels did not change in response to isoflurane. Both the vasoconstriction and the vasodilation produced by isoflurane were endothelium-dependent. Also, the vasoconstriction was abolished by indomethacin, suggesting that a cyclooxygenase product was involved, but neither nitro-L-arginine methyl ester nor methylene blue, inhibitors of nitric oxide synthase and guanylyl cyclase, respectively, changed the effect, suggesting that release of nitric oxide was not a factor. On the other hand, all three treatments reduced the vasodilation produced by isoflurane in the large vessels.

As noted above, if isoflurane produced coronary steal, it should preferentially dilate the small resistance coronary arterioles.^{5,6} Two groups have attempted to measure coronary artery diameters in intact animals. Using quantitative radiographic techniques, Sill *et al.* studied the effect of halothane and isoflurane on large coronary vessel diameter in dogs, measured total coronary blood flow by Xenon washout, and calculated coronary vascular resistance.⁹ They saw no effect of isoflurane on the diameter of the large conductance coronary vessels and, in as much as there was a significant decrease in calculated coronary vascular resistance, deduced that isoflurane must have produced vasodilation in the small coronary resistance arterioles. In a particularly pertinent experiment for this editorial, Conzen *et al.* measured the effects of volatile anesthetics (including isoflurane) and adenosine on coronary vessel diameter in intact dogs.²⁸ Using a video measurement technique similar to that reported by the Marcus laboratory at Iowa,^{29,30} they examined the effect of halothane, enflurane, and isoflurane on vessels whose diameters ranged from 20 to 500 μ . They confirmed Sill *et al.*'s deduction that isoflurane preferentially dilated the small coronary resistance vessels to a greater extent than the larger conductive vessels and considerably more than halothane and enflurane but not nearly as much as adenosine (fig. 1).

Furthermore, Hatano *et al.* and Nakamura *et al.* confirmed the observations of Sill *et al.*⁹ and Conzen *et al.*²⁸ in isolated coronary artery rings or strips from dogs.^{31,32} In their experiments, isoflurane preferentially

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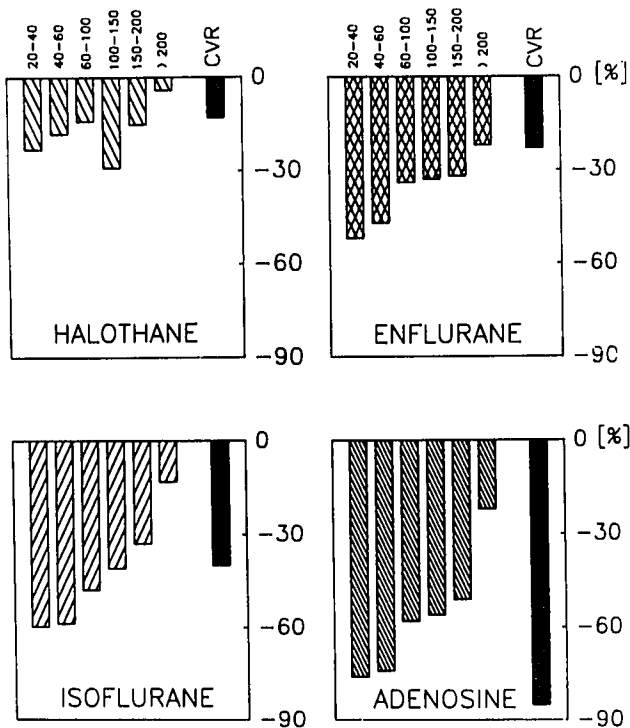


Fig. 1. Effect of volatile anesthetics and adenosine on segmental resistance of small coronary arteries and total coronary vascular resistance. Reprinted with permission.²⁸

dilated small coronary arteries (smaller than 0.9 mm), whereas halothane preferentially dilated large coronary arteries (greater than 2.5 mm). The investigators admitted that their small coronary arteries probably were not the major resistance vessels but demonstrated differential effects of nitroglycerin and adenosine similar to previous demonstrations of these vasodilators in coronary conductance and resistance arteries.^{5,6} Thus, not only have all previous studies in intact animals and humans and in isolated animal and human coronary artery rings or strips shown coronary vasodilation by isoflurane, but the coronary vasodilation has been preferentially present in the very resistance arterioles in which Park *et al.* have seen coronary vasoconstriction!

Conzen *et al.* also measured myocardial blood flow (by radiolabeled microspheres) and left ventricular oxygen dynamics and showed that only isoflurane and, to a much greater degree, adenosine decreased coronary vascular resistance and coronary arteriovenous oxygen extraction.²⁸ In as much as coronary blood flow is controlled mainly by oxygen supply-demand relationships, the latter is probably a more physiologic definition of

coronary vasodilation in that decreased coronary arteriovenous oxygen extraction suggests that coronary blood flow is in excess of myocardial oxygen needs.³³ All previous investigators confirmed the coronary vasodilating properties of isoflurane by showing this decreased coronary arteriovenous oxygen extraction.^{4,7,10,11,17-20} These observations make it difficult to understand how isoflurane-induced coronary vasoconstriction in isolated resistance arterioles could be physiologically and pharmacologically relevant. Park *et al.* suggested that both the decrease in total coronary vascular resistance and decreased myocardial oxygen extraction could result from constriction of the resistance vessels if there were significant arteriovenous shunting proximal to these vessels. Gelman *et al.* showed increased shunting of microspheres in dogs, especially at high concentrations of isoflurane, but the effect was not consistent and hence not statistically significant.⁸ On the other hand, with the profound coronary vasodilation produced in their coronary perfusion model, Crystal *et al.* reported no effect of isoflurane on coronary arteriovenous shunting of similar microspheres.²⁶

In the last 5 yr, the importance of the vascular endothelium in control of smooth muscle has become apparent, and a number of studies on the effect of anesthetics on isolated coronary vascular smooth muscle have been published both with and without the influence of the endothelium.^{21-26,31,32} However, all of these studies have examined the effect of isoflurane on vascular smooth muscle rings or strips that were precontracted with a variety of agents including potassium, phenylephrine, serotonin, and prostaglandins. Although Stone and Johns reported that isoflurane produced further vasoconstriction in a phenylephrine-precontracted segment of rat thoracic aorta and that this vasoconstriction was endothelium-dependent, as Park *et al.* have demonstrated for coronary arterioles in the current publication,³⁴ it is important to note that these results were from a different vessel (probably a conducting vessel) and in a different species. Furthermore, the experimental approach of Park *et al.* is unique. As mentioned above, previous *in vitro* experiments measured changes in tension from coronary strips or rings that were precontracted. Park *et al.* measured coronary vascular diameters in untreated vessels, which undoubtedly are a better estimate of the actual resistance effects. However, their experiment was conducted in a "no-flow" preparation, which is, as they point out, nonphysiologic. The effect of nitro-

glycerin in this preparation was identical to that reported in the other types of experiments³⁵; that is, nitroglycerin preferentially dilated the large conductance vessels defined as greater than 190 μ and had little effect on the small resistance vessels defined as 80–100 μ . It is of some interest that these studies were conducted in porcine vessels, a much larger species than the rabbit, and that the diameters of both conductance and resistance vessels in this larger heart were smaller than those in the current experiment in rabbits. Consequently, not only must these investigators confirm that their preparation is physiologically relevant, but the question of species variation must be investigated.

Certainly there is considerable difference between species and vascular beds, especially as far as endothelial function is concerned.^{36–40} Unlike virtually all other vessels studied, porcine coronary artery does not respond to acetylcholine with endothelium-dependent, nitric oxide-mediated vasodilation because of a lack of the appropriate muscarinic receptors on the endothelium.^{38,40} Instead, acetylcholine acts directly on muscarinic receptors on the porcine coronary vascular smooth muscle to elicit vasoconstriction. Endothelium-dependent effects also may vary from one vascular bed to another within the same species. For example, nitric oxide synthase is not expressed in the endothelium of rat pulmonary arterioles smaller than 80 μ but is prominent in the vascular endothelium of bronchial arterioles of the same size.³⁹

The apparent stimulation of endothelium-dependent, nitric oxide-mediated vasodilation by isoflurane is a controversial aspect of the current work by Park *et al.* While the mechanism of inhalational anesthetic interaction with the vascular nitric oxide-guanylyl cyclase signaling pathway remains uncertain, many published studies have demonstrated clear inhibition of nitric oxide-dependent vasodilation of isolated vessels by isoflurane.^{41–48} The data of Park *et al.* are consistent, however, with an *in vivo* study by Greenblatt *et al.*⁴⁹ that indirectly suggested, using the radioactive microsphere technique, that isoflurane may stimulate nitric oxide-dependent relaxation in some vascular beds of the rat.

In summary, the current study by Park *et al.* presents a diametrically opposed effect of isoflurane in the coronary circulation to that of all previous investigations. Although they have demonstrated that isoflurane can produce coronary vasoconstriction in their model, the questions that must be answered before these differences are explored further relate to the unique model and the species of animal these investigators used. Only

then will the meaning of these interesting experiments be apparent.

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