which tissue entrapment of two different-sized microspheres was compared. This criticism is without merit. The method of direct venous collection might be considered superior on two grounds: (1) It avoids the necessity to assume that the larger microspheres are completely trapped; and (2) It permits a determination of the size distribution of the microspheres that are shunted (and therefore of the arteriovenous pathways traversed). Second, Park *et al.* are not correct when they infer that shunted microspheres necessarily indicate flow that has passed through "nonnutritive" vessels. When a microsphere is shunted, it means only that the microsphere has passed through an arteriovenous vessel with a larger diameter than it. In the absence of more information, it is not possible to distinguish whether the shunted microsphere passed through a direct arteriovenous "nonnutritive" anastamosis or through a distended capillary.

In conclusion, when hemodynamic conditions are controlled *in vivo,* isoflurane consistently causes an increase in CBF, accompanied by a reduction in oxygen extraction.[2–4] These are classic signs of pharmacologic dilation of coronary resistance vessels. It remains to be determined whether the isoflurane-induced constriction of small coronary arteries demonstrated by Park *et al. in vitro* is a phenomenon unique to their preparation or whether it has more wide-ranging application.

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In Reply:—Although Crystal questions whether isoflurane-induced vasoconstriction of resistance coronary arteries is a preparation-dependent phenomenon without wide-ranging application, we have gathered multiples pieces of evidence to the contrary. First, this phenomenon has been observed in four different species—namely, rabbits,[1] rats,[2] pigs,[3] and human right atrial appendage arteries* (fig. 1). However, the effect of isoflurane depends on vessel size, and isoflurane dilates large epicardial arteries.[1,2] Second, isoflurane has been observed to attenuate β-adrenergic, cAMP-mediated vasodilation[4] in resistance coronary arteries. Third, in the same preparation, another anesthetic, halothane,[2] does not elicit constriction, but dilation, of resistance coronary arteries. We submit that the weight of evidence favors that the direct effect of isoflurane on small resistance coronary arteries (~100 μm) is constriction but depends on preexposure tone.[2]

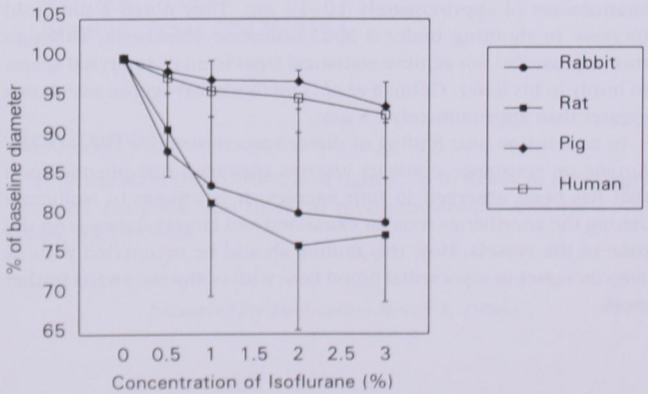

Fig. 1. Percent change from baseline diameter *versus* concentration of isoflurane for resistance coronary arteries from four species. Data are presented as mean ± SD. Isoflurane caused concentration-dependent constriction of resistance coronary arteries in all four species ($P < 0.05$ for each).

* Unpublished observation.

CORRESPONDENCE

The apparent discrepancy between our *in vitro* findings of isoflurane-induced constriction of resistance coronary arteries and multiple *in vivo* studies suggestive of isoflurane-mediated dilation of resistance coronary arteries[5,6] has been discussed extensively in our papers.[1,2] We will not reiterate this here. *In vivo* studies such as by Crystal *et al.*[5] measure changes in myocardial blood flow (MBF) as a surrogate for small resistance artery vasomotion. Merely measuring changes in MBF does not indicate the vascular site of isoflurane-mediated effect. An increase in MBF may represent dilation of small resistance coronary arteries, dilation of larger arteries, and/or increase in nonnutritive shunting. A mild to modest increase in MBF that is reported in most *in vivo* studies (The studies by Crystal's group are an exception in this regard in that they report a nearly maximal increase in MBF with isoflurane.) can be explained easily without invoking primary dilation of resistance coronary arteries. Dilation of large arteries, which is reported to occur in both our preparation[1,2] and that of others,[7] will have a magnified effect on flow because of flow-mediated release of nitric oxide,[8] and the vascular resistance will decrease more than would be predicted just based on diameter changes of the large vessels. Alternatively, an increase in coronary shunting will yield an increase in MBF even without dilation of resistance coronary arteries.

Two representative microsphere studies that addressed coronary shunting with isoflurane anesthesia are those of Crystal *et al.*[5] and Gelman *et al.*[9] Unlike the impression Crystal received, our intention[2] was not to compare the relative merits of the two studies and declare one superior to the other. Our intention was to point out the uncertainty of ascertaining the degree of shunting with microsphere methods. Various sources of error in measuring regional blood flows with radioactive microspheres reduce precision of estimate (*i.e.,* large SDs and *P* value) but do not lead to a systematic over- or underestimation of mean flow.[10,11] In addition, venous sampling of microspheres, as was done by Crystal *et al.,*[5] has been demonstrated to underestimate the amount of shunting, compared with direct tissue sampling.[12]

In the canine circulation, studied by Crystal *et al.*[5] and Gelman *et al.,*[9] the diameter of the capillaries is 3–8 μm.[11] Gelman *et al.*[9] implied that entrapment of 9-μm microspheres represents nutritive flow through the capillaries, and entrapment of 15-μm microspheres represents nutritive and nonnutritive flow, and therefore, the difference in flows measured represents shunted flow through arteriovenous anastomoses of approximately 10–15 μm. They noted a threefold increase in shunting under 2 MAC isoflurane anesthesia, although this increase did not achieve statistical significance. As Crystal seems to imply in his letter, Gelman *et al.'s* methods may ignore any shunts greater than approximately 15 μm.

In conclusion, our finding of direct vasoconstrictive effect of isoflurane on resistance coronary arteries appears a real phenomenon that has been observed in four species. It is unique to isoflurane among the anesthetics thus far examined and largely depends on the tone of the vessels. How this finding should be reconciled with *in vivo* increases in myocardial blood flow with isoflurane awaits further work.

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