To the Editor:—Midazolam is a new water-soluble 1–4 benzodiazepine used for induction of anesthesia. Laboratory investigations in the dog demonstrate a dose-related decrease in left ventricular dP/dt after the administration of midazolam. Indirect evidence (increase in pulmonary artery diastolic pressure with decreased cardiac index) from the dog also suggests a transient negative inotropic effect when midazolam (10 mg/kg) is given. As there are no studies comparing the relative negative inotropic effect of midazolam with that of diazepam on the isolated heart, we have completed a series of experiments examining the effects of these two benzodiazepines on left ventricular (LV) myocardial contractility.

The inotropic effect of midazolam and diazepam was determined in a modified Langendorff retrograde perfusion system recently described in detail. Incremental increases were made in the concentration of benzodiazepines in the perfusate. These concentrations were 14, 16, 18, and 20 μg/ml of midazolam and 15, 20, 25, and 30 μg/ml diazepam. Duration of perfusion at each drug concentration was 14 min, and the LV dP/dtmax measurements were made at peak effect (usually within 5 min). The ED₅₀ myocardial depression was 15.1 ± 2.6 μg/ml with midazolam and 22.7 ± 3.2 μg/ml for diazepam. Midazolam is a ½-fold more potent negative inotropic drug than diazepam in this preparation. The slopes of the dose effect curve are significantly (P < 0.01) different (fig. 1); relatively small changes in midazolam concentration exert greater decrements in contractility than seen with diazepam, since the midazolam curve is steeper than that of diazepam. Of note is that at small degrees (20%) of myocardial depression differences between midazolam and diazepam were less pronounced than at high (80%) degrees of depression.

The clinical relevance of these relative negative inotropic data are not clear, since we found that when a small group (n = 5) of patients who had abnormally elevated pulmonary artery occluded pressure (PAO > 18 mmHg) and low CI (≤2.0 l/min/m²), were anesthetized with midazolam (0.2 mg/kg iv), their PAO and CI returned to normal. The presumed reason for the improvement in these variables was the vasodilating effect of midazolam: any negative inotropic effects were more than adequately counterbalanced by the decrease in afterload. Midazolam tends to decrease SVR more than diazepam and produces greater venodilation. We believe that there are subtle but important differences in cardiovascular effects of midazolam and diazepam. In view of the relatively greater negative inotropic effects and potential for vasodilation, midazolam probably should be given with caution to hypovolemic patients and those with significant left ventricular impairment.

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Some Questions Concerning the Effects of Hydralazine on Cardiopulmonary Function in Canine Low-Pressure Pulmonary Edema

To the Editor:—The report by Ghignone et al., suggests that hydralazine has a potential role in the management of noncardiac pulmonary edema. If confirmed in subsequent human studies, these data will be a useful adjunct to current management. However, before applying these results to clinical investigation, it may be worthwhile to discuss some methodologic questions that limit the applicability of the data to clinical practice.

First, the dose of oleic acid (0.8 ml/kg) reported in this study is greatly in excess of that usually employed to produce canine lung injury. If the reported dose is correct, it makes comparison of these data with those of other studies of oleic acid-induced pulmonary edema very difficult.

Second, the cardiovascular status of the animals is different from that which is usually observed in canine oleic acid-induced pulmonary edema. Cardiac output, as reported in this study, increased 90 min after the administration of oleic acid. Review of several other studies in which oleic acid was used to induce canine pulmonary edema suggests that oleic acid infusion reduces cardiac output. Apparently the increase in cardiac output in this study is associated with volume expansion before the administration of oleic acid and administration of fluid during the study to maintain a wedge pressure in excess of the baseline wedge pressure. It is possible that augmentation of cardiac output with volume administration increased Qs/Qt% before the administration of hydralazine, and therefore attenuated any increase in Qs/Qt produced by the drug. The effects of hydralazine in animals that have not been volume expanded would be of considerable interest. If hydralazine supports cardiovascular function and reduces pulmonary microvascular pressure in ARDS without the need for preliminary fluid loading, it should be clinically invaluable.

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