

## **Coronary vasodilatation following diazepam (Valium)**

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### **Summary**

1. The effects of diazepam (Valium) on coronary and systemic vascular resistance were studied in anaesthetized dogs on cardiopulmonary bypass under conditions of constant heart rate and aortic pressure.
2. Pharmacological doses of diazepam uniformly produced coronary vasodilatation lasting 30 min ; systemic vascular resistance also decreased, but to a lesser degree.
3. When coronary blood flow was maintained constant at physiological levels, diazepam produced no changes in left ventricular contractility, as assessed by peak LV isovolumetric pressure,  $dp/dt$  max, force-velocity, and length-tension relations, whereas previous experiments had demonstrated a positive inotropic effect in a similar preparation in which coronary blood flow was responsive to alterations in coronary vascular resistance.
4. In five dogs, complete separation of the coronary and systemic circulations was accomplished by a double pump-oxygenator system ; direct intracoronary administration of diazepam produced coronary vasodilatation, but coronary pressure and flow were not altered by administration of diazepam to the systemic circulation.
5. It is concluded that diazepam augments myocardial contractility by increasing coronary blood flow. This relationship is independent of extracardiac humoral mechanisms, and appears to require the delivery of diazepam to the coronary circulation.

### **Introduction**

Previous experiments in this laboratory demonstrated that diazepam (Valium) augments myocardial contractility and decreases systemic vascular resistance in dogs during cardiopulmonary bypass with constant aortic pressure and fixed heart rate (Abel, Starosciik & Reis, in preparation). Since Prindle, Gold, Cardon & Epstein (1970) observed that diazepam did not alter the contractile state of isolated cat papillary muscle, reflex effects may be the mechanism by which diazepam improves contractility in the intact, innervated heart, particularly because this drug has been shown to have important effects on the nervous system (Chai & Wang, 1966). The marked and sustained decrease in systemic vascular resistance produced by diazepam, however, suggested the possibility that improved cardiac function might result from decreased coronary vascular resistance and increased coronary blood flow. The present studies were designed to determine the effects of diazepam on coronary vascular resistance, and to explore the relationship of these changes to the positive inotropic effects of the drug.

## Methods

Unselected mongrel dogs of both sexes (weighing 18.2 to 24.6 kg) were anaesthetized with intravenous sodium pentobarbital (35 mg/kg). After endotracheal intubation, respirations were controlled with a positive pressure ventilator supplying 100% oxygen. A bilateral trans-sternal thoracotomy was performed, and sodium heparin (3 mg/kg) was administered intravenously. Extracorporeal circulation and oxygenation was provided by a rotating disc oxygenator supplied with 98% oxygen and 2% carbon dioxide at 6 litres/min, and occlusive roller pumps. The extracorporeal circuits were primed with 4,000–5,000 ml of fresh, heparinized homologous blood in normal saline (3:1 dilution). Blood temperature was monitored by a thermistor in the inferior vena cava, and was maintained at 37° C by a heat exchanger in the extracorporeal circuit. Blood gas tensions and pH of arterial blood were determined periodically. The sino-atrial node was crushed and the heart rate maintained constant by electrical stimulation of the right atrium at 170 beats/min. Aortic and right atrial pressures were measured through indwelling catheters connected to Statham P23Db pressure transducers. The bronchial arteries were ligated to exclude extracoronary myocardial blood flow (Hudson, Moritz & Wearn, 1932). The main pulmonary artery was ligated to ensure collection of all coronary blood returning to the right side of the heart. Twenty-six dogs comprised three groups.

### *Group I: Effects of diazepam on coronary and systemic vascular resistance*

In twelve dogs the various cannulations diagrammatically illustrated in Fig. 1 were performed. The superior and inferior vena cavae were cannulated, draining all systemic venous return to a reservoir, and arterial blood was returned through a cannula in the femoral artery. Arterial inflow was monitored by an electromagnetic flow probe in the line returning blood to the animal. A mean aortic pressure between 75 and 100 mm Hg was selected and maintained constant during each experiment by adjustment of the arterial flow rate. Total coronary venous efflux was collected through large-bore, multifenestrated catheters placed in the ventricles through the atria. Coronary blood flow was measured by timed volume collections of coronary venous efflux, and coronary vascular resistance was calculated as the difference between mean aortic pressure and mean right atrial pressure, divided by coronary blood flow. Systemic vascular resistance (R.U.) was calculated as the quotient of the difference between mean aortic and mean right atrial pressures and systemic blood flow. In seven dogs the sino-atrial node was crushed, and the heart rate maintained constant at 170 beats/min by electrical stimulation of the right atrium. In five dogs ventricular fibrillation was induced by the application of a brief electrical stimulus to the right ventricle.

After a 10–15 min period of control observations, the preservative and vehicle in which diazepam is supplied (0.02 ml/kg) was injected into the oxygenator. After an additional 10 min period of observation, diazepam (0.1 mg/kg in the seven dogs with controlled heart rates, and 0.2 mg/kg in the five dogs with fibrillating ventricles) was administered, and data were recorded from which systemic and coronary vascular resistances could be calculated every minute for 10 min and every 5 min for an additional 20 min.

*Group II: Assessments of ventricular function with coronary blood flow maintained constant*

In nine animals, the various cannulations shown diagrammatically in Fig. 2 were carried out. The femoral artery and right atrium were cannulated, and total cardiopulmonary bypass instituted. Mean aortic pressure was maintained constant during each experiment as described in Group I. A No. 20 F catheter was passed into the ascending aorta through the left subclavian artery, and the aorta just proximal to the origin of the brachiocephalic artery was encircled with a tourniquet. Pressure at the aortic root (coronary artery pressure) was measured through a catheter connected to Statham P23Db pressure transducer. The ascending aorta was occluded around the catheter in it, and arterial inflow through the catheter was instituted at a flow rate sufficient to maintain aortic root pressure identical to systemic arterial pressure. Mean coronary blood flow was measured by an electromagnetic flow probe placed in the line delivering blood to the aortic root, and was maintained constant (average flow = 77.0 ml/100 g ventricle per min) during the remainder of the experiment.

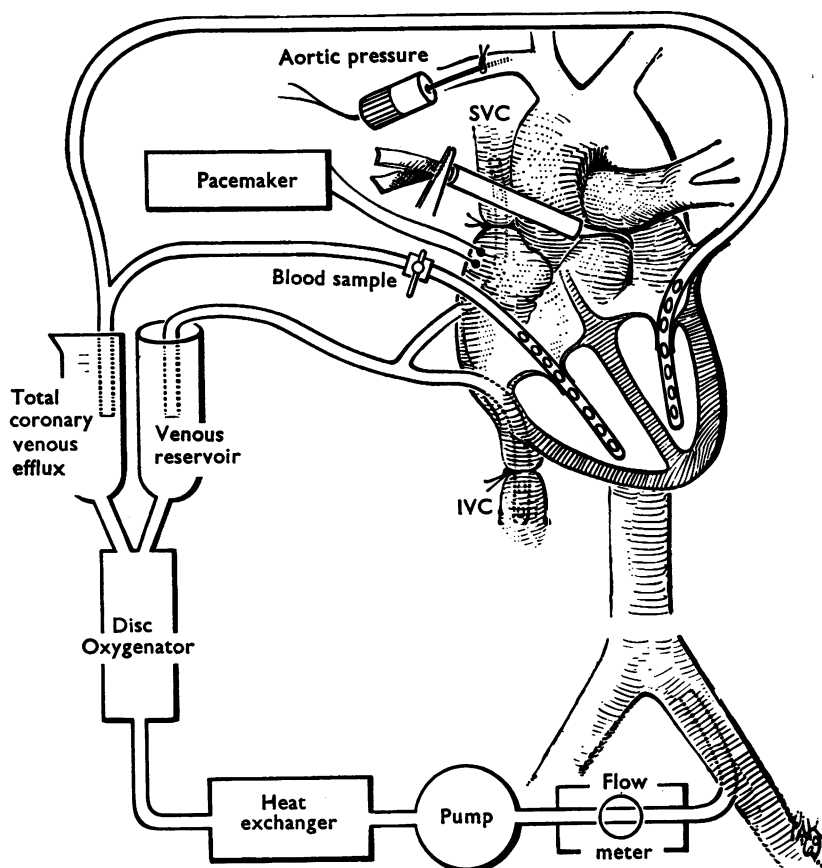


FIG. 1. Schematic representation of the preparation used to determine the effects of diazepam on coronary and systemic vascular resistance and coronary and systemic oxygen consumption. The bronchial arteries were ligated. SVC, Superior vena cava; IVC, inferior vena cava.

Following a 10 min period of control observations, diazepam (0.2 mg/kg) was injected into the oxygenator. Force-velocity curves were constructed before, 2, 5, 10 and 30 min after the administration of diazepam by determining the instantaneous relations between force and contractile element velocity at 10 ms intervals during single isovolumetric beats. Length-tension relations were also determined before, 2, 5, 10 and 30 min after the administration of diazepam by increasing the volume of the intraventricular balloon to 30 ml in a stepwise fashion. Length-tension curves were constructed by plotting the peak systolic force developed versus the increase in internal ventricular radius. The methods used to calculate force and contractile element velocity were identical to those described previously (Reis, Enright, Hannah

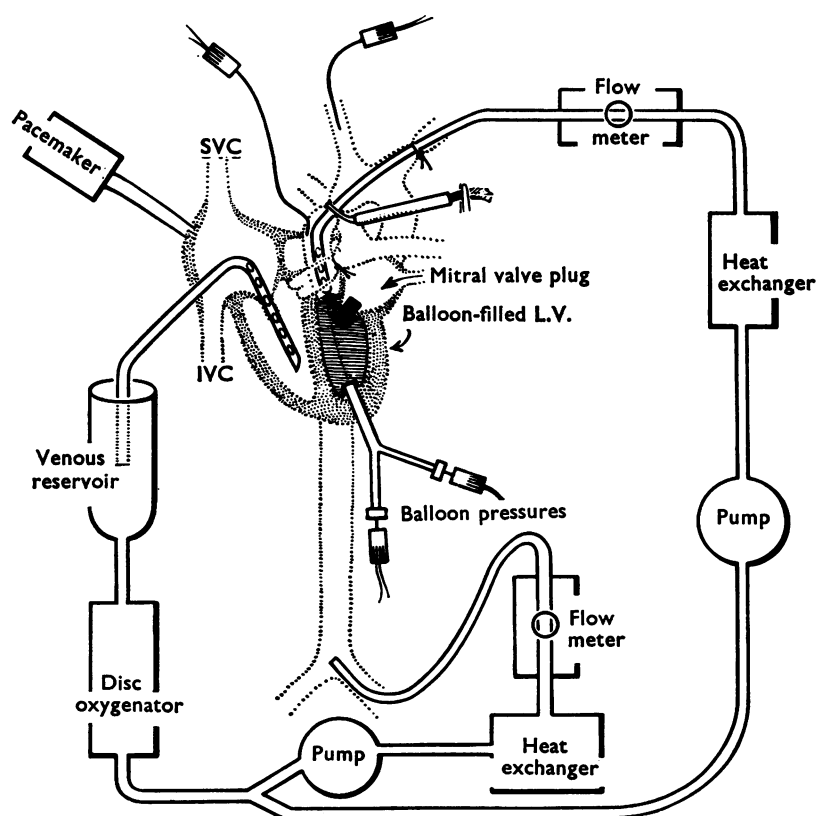


FIG. 2. Schematic representation of the preparation used to assess left ventricular function with coronary blood flow maintained constant.

& Morrow, 1968). Peak systolic isovolumetric left ventricular pressure and the maximum rate of development of left ventricular pressure ( $dp/dt$  max) were also continuously recorded before and for 30 min following the administration of diazepam. The effects of diazepam on systemic vascular resistance and on coronary vascular resistance were also calculated as described in Group I.

*Group III: Complete separation of coronary and systemic circulations*

The cannulations diagrammatically illustrated in Fig. 3 were carried out in five dogs. All branches of the descending thoracic aorta were ligated. The superior and inferior vena cavae were cannulated, and systemic venous return was drained to an oxygenator and then returned to the femoral artery. Coronary venous efflux was drained from both ventricles, through cannulae passed from the atria, to a second oxygenator, and returned to a cannula positioned in the aortic root, as described in Group II. This preparation provided independent and separate coronary and systemic circulations. Arterial inflow through the catheter in the aortic root was measured by an electromagnetic flow probe and adjusted so that the pressure in the ascending aorta was identical to systemic arterial pressure;

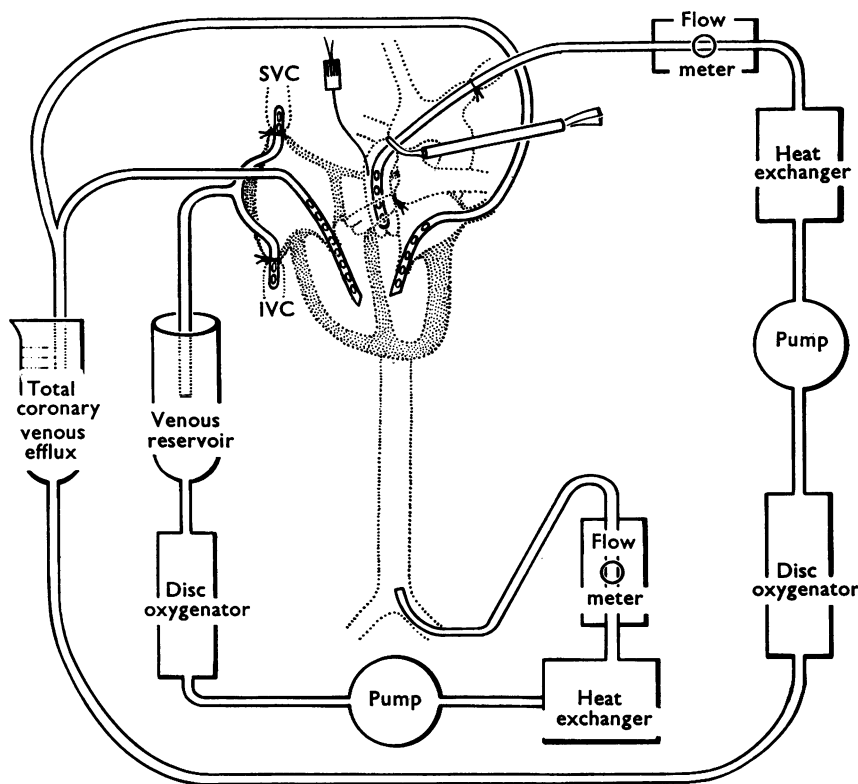


FIG. 3. Diagrammatic representation of the preparation which provided complete separation of the coronary and systemic circulations. Two separate pump-oxygenator systems were used. The bronchial arteries were ligated. Pressure at the aortic root (coronary pressure) and in right subclavian artery (systemic arterial pressure) were continuously recorded. Coronary and systemic blood flows were measured by electromagnetic flow probes placed in the respective perfusion lines returning blood to the animal.

coronary blood flow was then maintained constant at this level for the remainder of the experiment. Systemic blood flow was measured by an electromagnetic flow probe placed in the line returning blood to the femoral artery, and was maintained constant during the experiment. Ventricular fibrillation was induced and, after a 10 min period of control observations, diazepam (0.25 mg/kg) was injected into the oxygenator supplying the coronary circulation, as pressures and flows in both circulations were continuously recorded. Thirty minutes later, diazepam (0.5 mg/kg) was injected into the oxygenator supplying the systemic circulation as pressures and flows were again monitored. In two dogs diazepam was injected into the coronary circulation first, and this was followed by injection into the systemic circulation; in three dogs intracoronary injection followed systemic injection.

Following each experiment the completeness of separation of the coronary and systemic circulations was confirmed by the injection of 0.5 g calcium chloride or 0.5 mg adrenaline into either the systemic or coronary circulation.

## Results

### *Group I: Effects of diazepam on coronary and systemic vascular resistance, and coronary and systemic oxygen consumption*

Coronary blood flow averaged 60.1 ml/100 g ventricle per min (range 43.5 to 82.8) in the seven animals with heart rates fixed at 170 beats/min, and 100 ml/100 g per min (range 83 to 106) in the five animals with fibrillating ventricles. Coronary

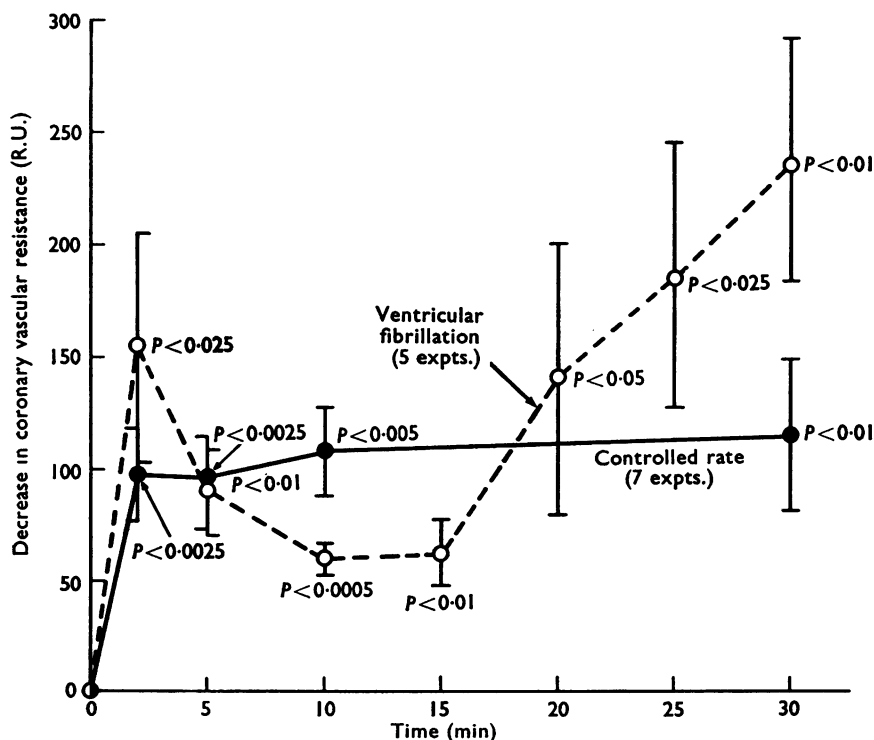


FIG. 4. Mean decreases in coronary vascular resistance observed in twelve dogs following the administration of diazepam. The vertical brackets designate the standard errors of the mean decreases in resistance. The statistical significance for each mean value is indicated. N.S., Not significant.

blood flow increased 35–50 s after diazepam was administered, and an average increase of 14.8% in the dogs with paced hearts ( $P<0.0025$ ), and a 19.6% average increase in the dogs with fibrillating ventricles ( $P<0.025$ ) was evident 2 min after the drug was given. Thirty minutes following diazepam, an average increase in coronary blood flow of 36.8% was present in the dogs with ventricular fibrillation ( $P<0.01$ ) and a 15.1% increase was observed in the group with fixed heart rates ( $P<0.01$ ). The maximum increases in coronary blood flow occurred at variable times following the administration of diazepam, and averaged 29.0% (range 17.8 to 88.0) in the dogs with paced hearts, and 64.7% (range 38 to 87.2%) in those with ventricular fibrillation. Decreases in calculated coronary vascular resistance paralleled the increases in coronary blood flow, and in every instance these changes were

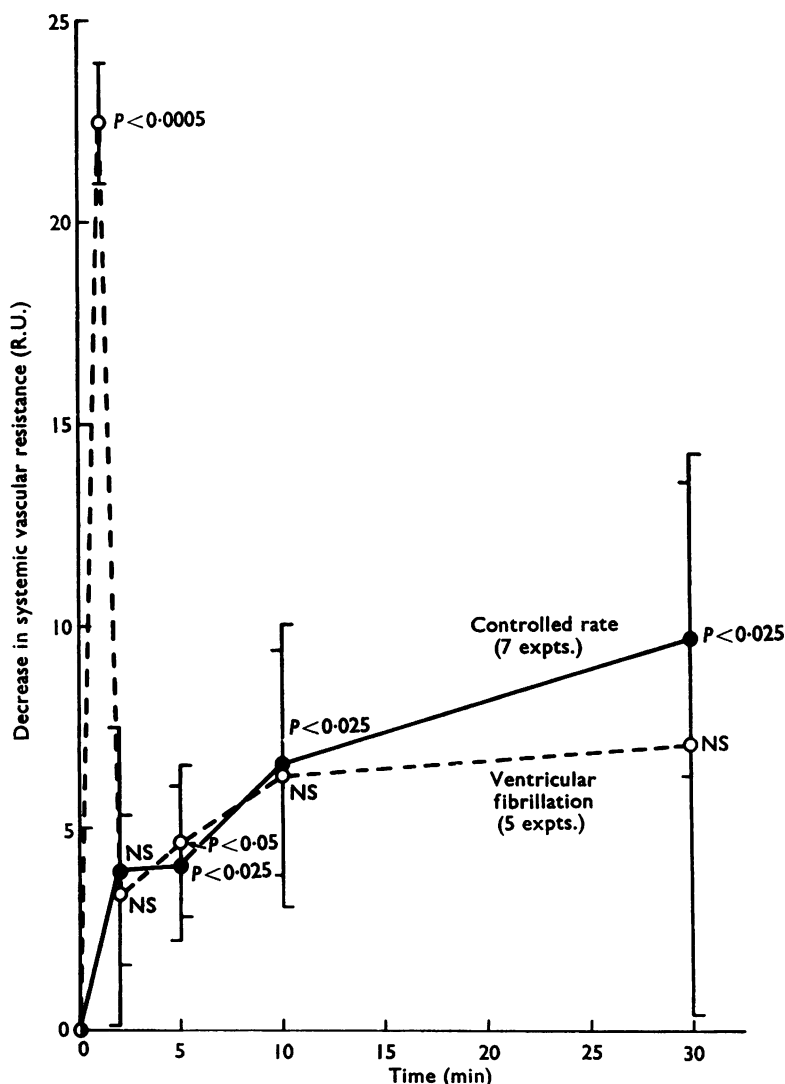


FIG. 5. Mean decreases in systemic vascular resistance observed in twelve dogs following the administration of diazepam.

statistically significant. The mean decreases in coronary vascular resistance observed after the administration of diazepam are summarized in Fig. 4. No significant changes in resistance occurred following administration of the solvent alone, however.

Marked decreases in systemic vascular resistance were observed within one minute after the injection of diazepam; a transient return toward control values then occurred, but significant decreases in resistance recurred within five minutes and persisted for 30 min. These changes are illustrated in Fig. 5.

*Group II: Assessments of ventricular function with coronary blood flow maintained constant*

Peak systolic isometric pressure,  $dp/dt$  max, force-velocity curves, and length tension curves were similar before and after diazepam, indicating that diazepam

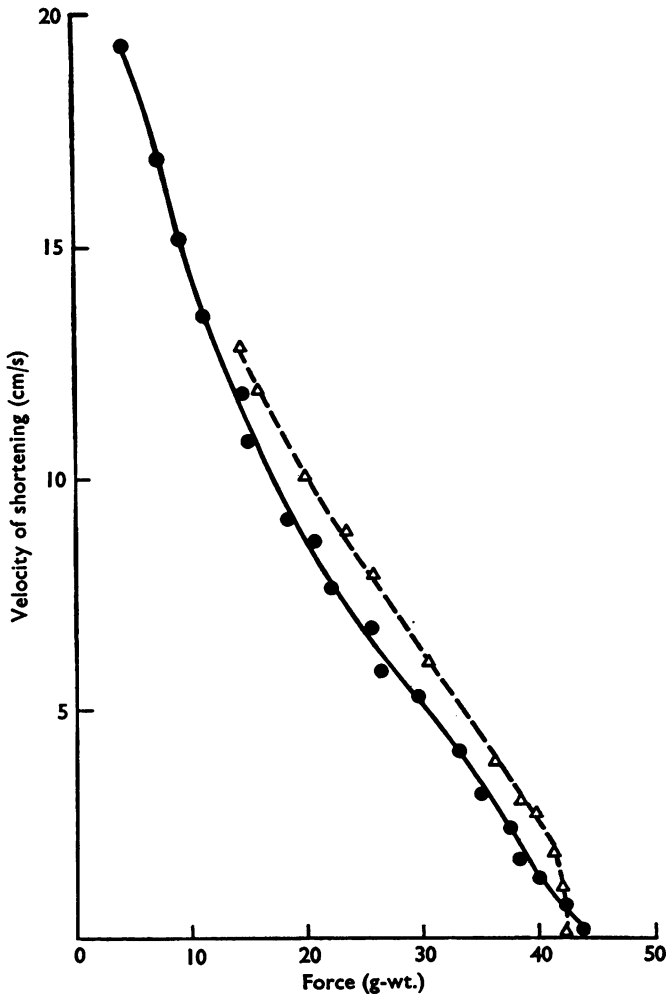


FIG. 6. Force-velocity curves inscribed before (●—●) and 30 min after (△-△) diazepam in an animal in which coronary blood flow was maintained constant. No significant change in myocardial contractility is evident.



had no effect on myocardial contractility when coronary blood flow was maintained constant. Typical force-velocity and length-tension curves inscribed in a dog before and after diazepam are reproduced in Figs. 6 and 7, and the changes in left ventricular peak systolic isometric pressure, and  $dp/dt$  max in all animals are summarized in Table 1.

Coronary vascular resistance averaged  $455.9 \pm 59.5$  R.U. in the control state. Decreases to  $396 \pm 44.6$ ,  $405 \pm 35.5$ ,  $425 \pm 36.7$ , and  $409.8 \pm 55$ , were evident 2, 5, 10 and 30 min after diazepam, respectively. Systemic blood flow averaged 78 ml/kg per min, and systemic vascular resistance averaged  $45.6 \pm 9.5$  R.U. in the control state. A decrease to  $35.5 \pm 6.7$  was evident 2 min following diazepam and systemic vascular resistance averaged  $42.9 \pm 11.5$ ,  $41.9 \pm 9.9$  and  $48.1 \pm 19.6$ , 5, 10, and 30 minutes after diazepam, respectively. The magnitude of these changes are similar to those observed in the Group I animals.

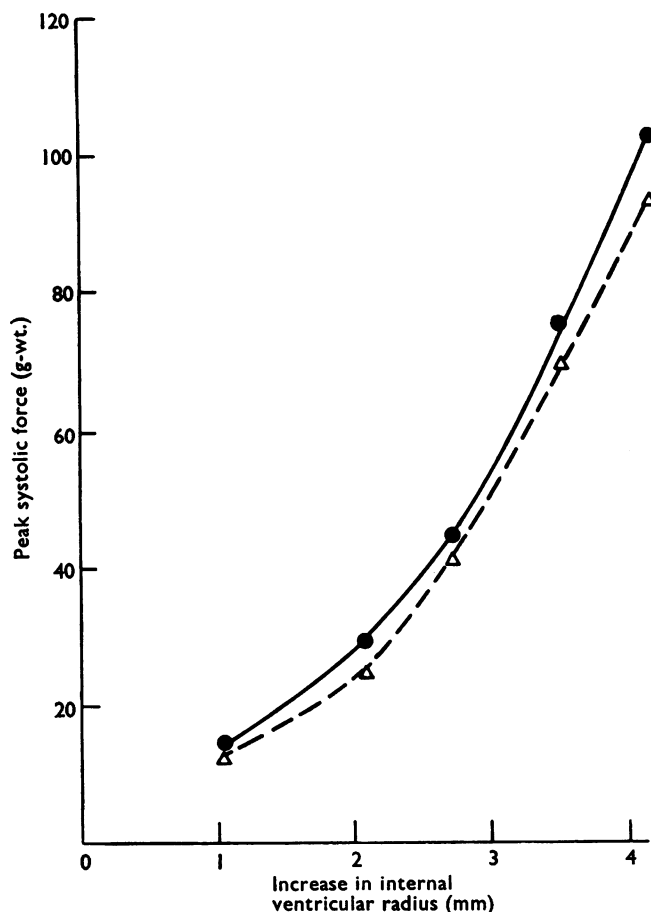


FIG. 7. Length-tension curves inscribed before (●—●) and 5 min after (△--△) diazepam in an animal in which coronary blood flow was maintained constant. No significant change in myocardial contractility is evident.

*Group III: Complete separation of coronary and systemic circulations*

The completeness of separation of the two circulations was confirmed in each animal; adrenaline or calcium chloride injected into one circulation produced changes only in the circulation into which it was injected.

A decrease in coronary vascular resistance occurred in every animal 2–5 min after the administration of diazepam (0.25 mg/kg) into the coronary circulation. A mean decrease of  $11.0 \pm 4.6\%$  ( $P < 0.005$ ) was evident 5 min after injection, and a mean decrease of  $7.0 \pm 3.1\%$  ( $P < 0.05$ ) persisted 30 min after injection. No significant change in systemic vascular resistance was observed after the administration of diazepam to the coronary circulation only. When diazepam (0.5 mg/kg) was given to the systemic circulation only, no significant changes occurred in coronary vascular resistance, but a decrease in systemic vascular resistance similar to that observed in Group I animals occurred. The recordings from a typical experiment in an animal from this group are reproduced in Fig. 8.

TABLE 1. Peak systolic left ventricular isovolumetric pressure and  $dp/dt$  max after diazepam 0.2 mg/kg (coronary blood flow constant)

Time after diazepam (min)	Peak LV pressure (mm Hg) (mean $\pm$ S.E. mean)	$dp/dt$ max (mm Hg/s) (mean $\pm$ S.E. mean)
Control	$66.7 \pm 5.6$	$803 \pm 111$
2	$65.3 \pm 4.7$	$822 \pm 99$
5	$69.4 \pm 5.4$	$840 \pm 93$
10	$67.7 \pm 5.8$	$797 \pm 101$
30	$60.1 \pm 5.2$	$697 \pm 107$

Peak LV pressure and  $dp/dt$  max after diazepam are not significantly different compared with control values ( $P > 0.10$ ).

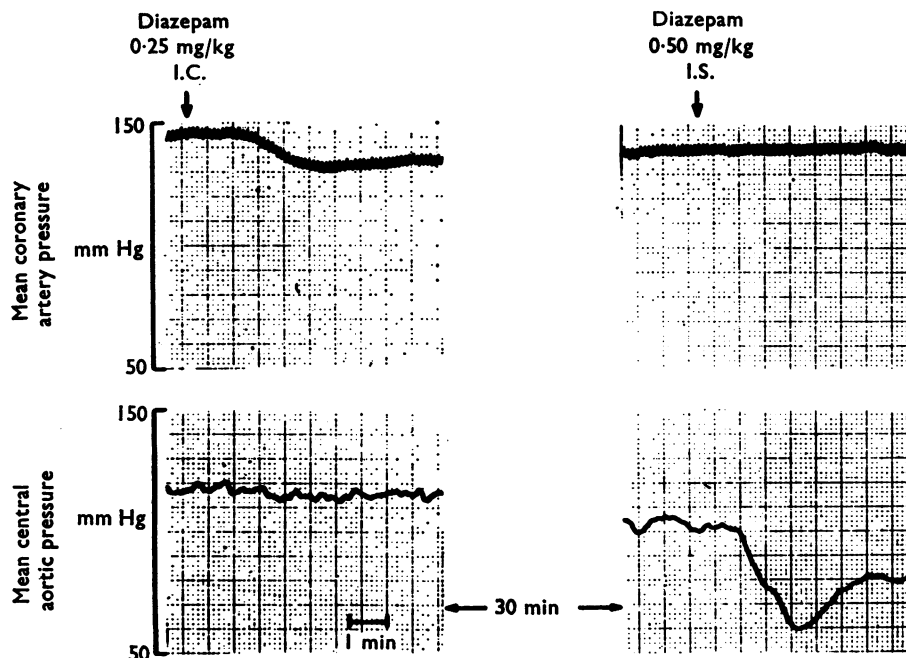


FIG. 8. Effects of diazepam injected into the coronary or systemic circulations in an animal in which the coronary and systemic circulations were isolated and individually perfused by two separate pump-oxygenator systems. Diazepam produced changes only in the circulation into which it was injected. Coronary and systemic blood flows were maintained constant during the experiment. I.C., Intracoronary; I.S., intrasytemic. (1 mm Hg  $\equiv$  1.333 mbar.)

## Discussion

The results of the present experiments indicate that diazepam produces immediate decreases in coronary and systemic vascular resistance. When the coronary circulation was perfused by means of retrograde aortic perfusion from the femoral artery, the onset of vasodilatation in both the coronary and systemic vascular beds occurred within 1 min, approximately the transit time from the injection site to the coronary and systemic circulations. The somewhat longer interval between injection and coronary vascular resistance changes in the animals in which the coronary and systemic circulations were perfused separately, undoubtedly was related to the longer transit time from the oxygenator to coronary circulation, which resulted from the slower extracorporeal flow rate needed in this system.

The changes in systemic vascular resistance were similar to those described previously; the alterations in the vascular resistance of the coronary bed, however, are of considerable interest. Decreased coronary vascular resistance was evidenced both by a decrease in mean pressure in the animals in which coronary flow was maintained constant, and by an increase in coronary flow in the animals in which arterial pressure was maintained constant. Chai & Wang (1966) demonstrated a decrease in arterial resistance in the cat hind limb resulting from a direct effect of diazepam on the arterial bed. The rapidity with which coronary vasodilatation occurred in the present studies suggested a direct or reflex effect of diazepam on the coronary circulation. Because the vasodilatation was sustained for at least 30 min, however, additional mechanisms of action were considered. In this regard, it is of considerable importance that in the animals with complete separation of coronary and systemic circulations, diazepam produced changes only in the circulation into which it was injected. This seems to exclude extracardiac humoral materials or reflex effects due to delivery of the drug to the central nervous system as possible mechanisms by which diazepam produced coronary vasodilatation. Decreases in coronary vascular resistance following diazepam seem to be dependent on the delivery of diazepam to the coronary circulation. In the preparation used in these studies, however, although the coronary and systemic circulations were completely isolated, the innervation of the heart remained intact. The possibility that diazepam produces its effects on the coronary circulation by affecting intracardiac neural pathways influencing coronary vascular resistance is presently being investigated.

In the present experiments, when coronary blood flow was maintained constant, at physiological levels, diazepam produced no change in myocardial contractility, as assessed by peak left ventricular isovolumetric pressure,  $dp/dt$  max, force-velocity, and length-tension relations. Previous experiments, however, demonstrated a positive inotropic effect in a similar preparation in which coronary blood flow was not kept constant, but was allowed to change with alterations in coronary vascular resistance. It would appear, therefore, that diazepam augments myocardial contractility by increasing coronary blood flow.

It has been demonstrated that ventricular contractility and myocardial oxygen uptake are decreased when coronary blood flow is abnormally low, and that both contractility and oxygen uptake increase as coronary blood flow is increased, but there is little evidence that increasing coronary blood flow to a level greater than is needed to supply the metabolic demands of the working heart augments the contractile state. There are recent suggestions (Fisher, Martino, Harris & Kavalier, 1969),

however, that coronary flow may serve as a determinant of ventricular contractility independent of its ability to transport oxygen. Current studies in our laboratory appear to confirm the hypothesis that augmentation of coronary blood flow alone can alter the intrinsic contractile state of the intact ventricle.

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