The Effect of Verapamil on Mechanical Performance of Acutely Ischemic and Reperfused Myocardium in the Conscious Dog

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SUMMARY The effect of verapamil, an inhibitor of transmembrane calcium flux, was studied in intact conscious dogs with myocardial ischemia produced by inflating a balloon cuff implanted on the left anterior descending coronary artery. Six dogs received a continuous infusion of verapamil (10 μg/kg per min) beginning prior to coronary occlusion, and six received normal saline infusions. Systolic ejection shortening (SES) was measured from subendocardial ultrasonic crystals implanted in the central ischemic zone (IZ) and border zone (BZ), and in a nonischemic control zone (CZ). Hearts were paced at a constant heart rate with periodic introduction of closely coupled extrasystoles. SES was measured both for normally paced beats and during postextrasystolic potentiation (PESP). Regional myocardial blood flow was measured by injecting radioactive microspheres before, during, and after coronary occlusion. There were no significant differences between verapamil-treated dogs and saline control dogs in mean aortic pressure, heart rate, left ventricular end-diastolic pressure or dP/dt, cardiac output, or regional myocardial blood flow in IZ, BZ, or CZ. Differences in mechanical performance between two groups were noted, however. In the IZ, SES was abolished completely for normally paced beats in both groups but was significantly preserved for PESP beats in the verapamil-treated animals. In the BZ, SES was significantly reduced for normally paced beats only in the saline controls, and PESP responses were preserved to a significantly greater degree in the verapamil-treated animals. These results indicate that verapamil pretreatment exerts beneficial effects upon mechanical performance of ischemic myocardium. Since no changes in systemic hemodynamics or regional myocardial blood flow were observed, the effect may be due to the calcium-antagonistic properties of the agent.


VERAPAMIL (Haas and Härtfelder, 1962), a member of the group of drugs termed calcium antagonists, is a potent inhibitor of calcium influx through the sarcolemma with antiarrhythmic properties (Andersson, 1978; Johansson, 1978). Verapamil has been shown to protect myocardial tissue from acute ischemic and hypoxic injury by several techniques, including reduction of epicardial ST segment elevation (Smith et al., 1975; Wende et al., 1975; Berdeaux et al., 1976; Smith et al., 1977), and reduction of histological necrosis (Reimer et al., 1977) and ultrastructural damage (Nayler et al., 1976). Loss of myocardial tissue mass and the resultant impairment of left ventricular performance is an important feature of both experimental and clinical acute myocardial infarction. Thus far, no studies have been performed to assess the role that verapamil may have in affecting regional contractile performance of severely ischemic myocardium. The one study to date that investigated the effect of verapamil on regional performance employed a model of partial ischemia in open-chest dogs. That study suggested that the drug might selectively depress myocardial performance in the partially ischemic region (Smith et al., 1976).

Reperfusion of ischemic myocardium may be associated with increased cellular injury (Bresnahan et al., 1974; Lang et al., 1974, Jennings et al., 1975), although the extent of necrosis is dependent on the duration of transient ischemia (Ginks et al., 1972; Maroko et al., 1972). Reperfusion injury, which is believed to be related in part to calcium overloading of intracellular organelles, has been shown to be minimized by reperfusing with calcium-free blood (Ashraf et al., 1978). By interfering with calcium influx into the myocardial cell, calcium antagonists such as verapamil may alter favorably the reperfusion response following severe ischemia.

The purpose of the present study was to investigate the effect of verapamil upon the intrinsic and latent contractile response (after postextrasystolic potentiation) in severely ischemic myocardium. In addition, the potential for verapamil to modify reperfusion injury after acute myocardial ischemia was assessed. Our studies show that verapamil exerts a salutary effect upon contractile performance of ischemic myocardium.
Methods

Male mongrel dogs weighing 14–26 kg were anesthetized with pentobarbital (25 mg/kg, iv), intubated, and ventilated with room air using a Harvard respiratory pump (Harvard Apparatus Co., Inc.). Electrocardiograms were monitored throughout surgery. A thoracotomy was performed through the left 5th intercostal space, the pericardium opened, and the heart exposed. Bipolar pacemaker electrodes were attached to the right ventricular free wall. After a portion of the left anterior descending coronary artery had been dissected free, a 3.5-mm balloon occluder (R.E. Jones, Silver Springs, Md.) was secured at a level just distal to the first diagonal branch. The quantity of saline needed to fully inflate the balloon and produce cyanosis of the myocardium distal to the balloon was recorded. Tygon catheters (i.d. 1.02 mm) were inserted into the aorta and left atrium. Pairs of ultrasonic crystals (5 MHz) 2 mm in diameter were inserted into the left ventricular subendocardium through stab wounds made approximately 1 cm apart and were secured in place. One set of crystals was placed in the center of the region of potentially ischemic myocardium, termed the ischemic zone. Another set of crystals was placed in a region of myocardium, termed the control zone, which was outside the region of potential ischemia. A third set of crystals was placed at the margin of the area of cyanosis produced by transient coronary occlusion, termed the border zone. All catheters and wires were tunneled through the interscapular space and exteriorized, the chest was closed, and dogs were allowed to recover for a period of 1 week.

On the day of study, dogs were given morphone sulfate (1 mg/kg, im), then placed in the right lateral decubitus position. A micromanometer tipped catheter (Millar Instruments, Inc.) was inserted into the left carotid artery under local anesthesia with 2% lidocaine and advanced into the left ventricular cavity. Aortic pressure was measured with a Statham P23Db pressure transducer. Ventricular pacing was initiated at 140–150 beats/min with a Grass model S44B stimulator (Grass Instruments, Inc.). Coupled extrasystoles were produced using an electronic circuit which resulted in a complete compensatory pause. From previous studies in this laboratory, a coupling interval known to cause significant postextrasystolic potentiation was fixed at the onset of the experiment (Boden et al., 1978). All hemodynamic measurements including left ventricular pressure, aortic pressure, the electronically generated first derivative of left ventricular pressure (left ventricular dP/dt), as well as the electrocardiogram and intercrystal segment lengths for the three zones, were recorded throughout the study on a Brush 480 multichannel recorder (Gould, Inc., Instrument Systems Division). The technique for performing dynamic segment length measurements with these implanted crystals was similar to that described previously (Theroux et al., 1976; Vatner et al., 1976). An electrical impulse stimulated one crystal, and the resultant sound wave travelled through the myocardium at 1.5 × 10^3 mm/sec. A voltage was generated in the juxtaposed crystal which was proportional to the transit time. Calibration of intercrystal distances was performed in situ by generating signals of known time duration from a calibrated pulse generator. Cardiac output was determined by the indicator dilution technique (Liang and Huckabee, 1973), using indocyanine green (Cardio-green, Hynson, Westcott and Dunning, Inc.). Indocyanine green was injected into the left atrium, and aortic blood was sampled and cardiac output obtained with a Gilford model 140 cardiac output system (Gilford Instrument Laboratories, Inc.).

After instrumentation and recording of baseline measurements, the dogs were divided randomly into two treatment groups, one to receive normal saline, and the other verapamil (Isoptin, Knoll Pharmaceutical Co.). Solutions for infusion were prepared by one of us (CL) without the knowledge of the other investigators, who were responsible for performing the experiments and analyzing the data, after which the treatment code was broken. Thus the study was performed in a blinded fashion. An infusion of either normal saline or verapamil (10 μg/kg per min) dissolved in normal saline was administered by a Harvard infusion pump (Harvard Apparatus Co., Inc.) at a rate of 0.229 ml/min, and continued for the duration of the experiment. After 30 minutes of infusion, all measurements were repeated. In addition, myocardial blood flow was measured at this point by injecting radioactive microspheres, 15 ± 3 (sd) μm in diameter, labeled with ^14^Ce, ^11^Sn, or ^46^Sc. The method used was a modification of that described by Domenech et al. (1969). Microspheres were suspended in 10% dextran with 0.01% Tween 80 by vigorous agitation, then injected through the left atrial catheter followed by flushing with an additional 10 ml of normal saline over a 60-second period. Beginning 15 seconds before microsphere injection and continuing for 90 seconds thereafter, blood was collected through the aortic catheter at a rate of 7.75 ml/min, by use of a Harvard withdrawal pump. A total of 600,000 to 1,200,000 microspheres were administered with each injection.

Following these measurements, the coronary artery balloon occluder was inflated with the same volume of saline recorded at surgery. Absence of leakage from the balloon was confirmed by transiently withdrawing the same amount of infusate, then sealing the balloon tubing after reinsertion. The balloon occluder remained inflated for 2 hours (ischemic period), after which the occlusion was released (reperfusion period). Upon release of the occlusion, the volume of infusate withdrawn was quantified to exclude leakage during the occlusive period. Serial measurements of all recorded data including cardiac output were taken after 10, 30, 60, and 120 minutes of ischemia and after 10, 30, and
60 minutes of reperfusion. Injections of radioactive microspheres for myocardial blood flow determinations were made after 120 minutes of ischemia, and again after 45 minutes of reperfusion.

After 1 hour of reperfusion the animals were returned to their cages. Twenty-four hours later, each dog was killed with an overdose of pentobarbital. After the heart had been removed, 1.0 ml of methylene blue dye (4 mg/100 ml) was injected directly into the left anterior descending coronary artery at the site of the balloon occluder. The weight of the left ventricle, including the interventricular septum, was obtained after these tissues had been separated from the right ventricle and atria. A transmural section of myocardium corresponding to the stained area of the left ventricular surface, designated the ischemic risk region, was excised and weighed. The ratio of weight of the ischemic risk region to total left ventricular weight \( \times 100 \) was termed the percent of left ventricle at ischemic risk. In three dogs, an alternative method was employed: prior to death these animals were anesthetized, a thoracotomy was performed, the balloon occluder was reinfated, and 10 ml of methylene blue dye (9 mg/100 ml) were injected rapidly into the left atrium. After 10 seconds, the heart was removed. In these studies, the section of unstained myocardium was excised and considered to represent the ischemic risk region. A single transmural tissue block was removed from the zone in which each set of crystals was implanted, divided into epicardial and endocardial portions, and weighed. Each portion was analyzed separately to assess regional myocardial blood flow by \( \gamma \) emission counting, using a Packard Auto-Gamma Spectrometer with a model 9012 multichannel analyzer (Packard Instrument Company, Inc.). Regional myocardial blood flow was calculated using a PDP-11/10 minicomputer (Digital Equipment Corp.). Regional myocardial blood flow was calculated by the reference sample method by means of the following equation: myocardial blood flow (ml/g per min) = aortic blood reference flow (ml/min) \( \times \) tissue nuclide activity/aortic blood reference nuclide activity \( \times \) tissue weight (g). Flow values in the border zone (BZ) and ischemic zone (IZ) were corrected for microsphere loss (Capurro et al., 1979) by referencing the measurements obtained from these zones prior to coronary occlusion to flow values obtained in the control zone (CZ), according to the formula: % microsphere loss = \( \frac{\text{Flow}_{\text{CZ}} - \text{Flow}_{\text{BZ,IZ}}}{\text{Flow}_{\text{CZ}}} \) \times 100.

All data were analyzed and all decisions regarding whether to include or exclude animals that developed ventricular fibrillation were made prior to breaking the treatment code. A decision was made to include in the analysis all dogs that survived to the end of the occlusive period after the second microsphere injection. For the three segment length measurements, single representative normally paced beats (also referred to as "intrinsic" beats) and postextrasystolic beats were selected for analysis at each experimental time point. Systolic ejection shortening, defined as segmental excursion during the ejection phase of systole, was obtained by transposing aortic valvular opening and closing pressures from the aortic to the left ventricular pressure tracing, then measuring the concurrent segmental shortening in each of the three segments. The amount of shortening was normalized for intercrystal distance and converted to a percentage using the formula: % systolic shortening = \( \frac{\text{shortening in mm}}{100} \) / \( \text{end-diastolic segment length in mm} \).

Data for the saline controls and verapamil-treated animals were analyzed by two-way analysis of variance for independent groups with repeated measures (Winer, 1962), and the significances of differences between preocclusion values at 30 minutes of infusion and experimental values were determined by Dunnnett's test (Dunnett, 1964). Values of % systolic shortening in normally paced and potentiated beats were compared using Student's \( t \)-test for paired data. Values for all data were considered significant if \( P < 0.05 \). Data are presented in the tables, figures, and text as mean ± SEM, except as noted.

**Results**

Fifteen dogs were studied. Nine dogs were given normal saline, and six received verapamil. Of the nine animals receiving saline infusions, three developed ventricular fibrillation during coronary occlusion and were excluded from further data analyses. Two additional saline-treated animals developed ventricular fibrillation during coronary reperfusion; their data were included, though the number of points for analysis during reperfusion was reduced accordingly. None of the verapamil-treated dogs developed ventricular fibrillation during coronary occlusion or reperfusion. The difference between overall incidence of ventricular fibrillation in saline-treated dogs (5 of 9 experiments) and verapamil-treated dogs (0 of 6 experiments) was significant (\( \chi^2 = 18.0, df = 1, P < 0.001 \)). In these experiments, the extrasystolic coupling interval for the saline control group was 193 ± 4 msec, and for the verapamil-treated animals 192 ± 4 msec.

**Hemodynamic Responses**

There were no significant differences in any measured hemodynamic variable between the saline controls and the verapamil-treated animals, although significant changes occurred within each group during ischemia and reperfusion (Table 1). During ischemia, the only significant changes observed were a decline in cardiac output and an increase in systemic vascular resistance in the controls. During reperfusion, a significant increase in intrinsic heart rate due to supraventricular tachy-
cardia, in excess of the paced rate, was noted in the controls. This increase in rate was not observed in dogs receiving verapamil. Also, a small but significant increase in left ventricular end-diastolic pressure occurred during reperfusion in verapamil-treated dogs, and a decrease in left ventricular dP/dt was noted in both groups. The apparent trend toward a decrease in mean aortic pressure during ischemia and reperfusion in the verapamil-treated group did not achieve statistical significance (Table 1).

**Segmental Performance in Normally Paced and Potentiated Beats**

These data are presented in Figures 1 and 2. Figure 1 displays percent systolic shortening for normally paced and potentiated beats throughout the experiment, and shows the significant changes that occurred in these measurements during occlusion and reperfusion in each group. Also identified in Figure 1 are significant differences between normally paced and potentiated beats at each experimental point. In addition, a comparison was made of percent systolic shortening in controls vs. verapamil-treated dogs. No significant differences were noted for normally paced beats throughout the experiment, but significant differences were observed for potentiated beats, and these are shown in Figure 2.

In the control zone, neither group of animals showed a significant change in systolic shortening during either normally paced or potentiated beats throughout the experiment, and postextrasystolic potentiation was also uniformly present, except during reperfusion in the control group (Fig. 1). In this group, potentiation was lost during reperfusion, probably due to the spontaneous increase in intrinsic heart rate, which may have limited the potentiated response (Table 1). There were no significant differences between controls and verapamil-treated dogs for either normally paced or potentiated beats (Fig. 2).

In the border zone, a significant reduction of systolic shortening during both normally paced and potentiated beats was observed in controls during both ischemia and reperfusion; this did not occur in verapamil-treated dogs, except that systolic shortening was reduced for potentiated beats during reperfusion (Fig. 1). In both groups, significant potentiation was noted throughout, except for apparent failure to potentiate during reperfusion in the controls; however, these measurements are difficult to interpret because of the increase in intrinsic heart rate and the limited number of data points (see legend to Fig. 1). When saline control and verapamil-treated dogs were compared, the verapamil-treated dogs showed significantly greater values of systolic shortening for potentiated beats during both ischemia and reperfusion (Fig. 2).

In the ischemic zone, systolic shortening during coronary occlusion was reduced virtually to zero for normally paced beats in both controls and verapamil-treated animals, and potentiation also was lost in controls (Fig. 1). In the verapamil-treated group, significant potentiation was maintained during ischemia and reperfusion though at a reduced level (Figs. 1 and 2).

**Myocardial Blood Flow**

There were no significant differences between myocardial blood flow measurements in controls vs. verapamil-treated animals in the endocardium or epicardium, either before or after onset of ischemia (Table 2). After coronary occlusion, myocardial blood flow was significantly reduced in both groups in the ischemic zone, with reversal of the normal endocardial to epicardial flow ratio. Flow also was reduced significantly during ischemia in the border zone of the verapamil-treated dogs, although the
HOURS

**FIGURE 1** Systolic ejection shortening (SES) as a percent of end-diastolic segment length during control, at 30 minutes of infusion (0 hrs), during ischemia (0 to 2 hours) and during reperfusion (2-3 hours). Upper panel shows the control zone, middle panel the border zone, and lower panel the ischemic zone. Left side shows normal saline controls and right side shows verapamil-treated dogs. Infusion was started after initial measurements made at —0.5 hour. Percent SES for normally paced beats represented by dashed lines, and for potentiated (PESP) beats by solid lines. For each data point, n = 6, except during reperfusion in saline controls, where n = 4 at 30 and 60 minutes (due to ventricular fibrillation in two dogs); in addition, n = 5 at 10 minutes, 1 at 30 minutes, and 3 at 60 minutes of reperfusion for border zone PESP beats in saline controls (due to technical difficulties). An asterisk (*) indicates a significant difference (P < 0.05) in percent SES comparing normally paced to PESP beats at each respective time interval. A dagger (†) indicates a significant difference (P < 0.05) in percent SES comparing experimental points to values at 30 minutes of infusion (0 hour).

Values remained in the normal range, and did not differ from the controls (Table 2).

During reperfusion a limited number of myocardial blood flow measurements were made (n = 3 in each experimental group). Flow values in the ischemic zone showed a directional increase in both controls (epicardium, 1.51 ± 0.18; endocardium, 1.70 ± 0.23 ml/g per min) and verapamil-treated dogs (epicardium, 0.95 ± 0.11; endocardium, 1.19 ± 0.21 ml/g per min.). Flow values in the border zone and control zone remained in the normal range in both groups.

**Ischemic Risk Region**

The percent of the left ventricle at ischemic risk was 26.7 ± 2.4% in the control group and 22.4 ± 2.1% in the verapamil-treated animals (P < 0.2, unpaired t-test). The values for percent of the left ventricle at ischemic risk obtained from the three animals in which methylene blue dye was injected in vivo prior to death were 29.6, 24.5, and 27.4. Because these values were similar to the mean values for the other animals, they were included in the analysis.

**Discussion**

The findings in the present study indicate that the infusion of verapamil prior to and during acute coronary occlusion has a salutary effect upon mechanical function of ischemic canine myocardium. This effect was independent of significant alterations in heart rate, since the hearts were paced, of regional myocardial blood flows or arterial pressure, which did not differ significantly between control and treated animals, and of the size of the ischemic risk region, which was similar in the two groups. In addition, the incidence of ventricular fibrillation was significantly reduced by verapamil infusion.

In this study, segmental performance was assessed by implanting ultrasonic length transducers in the subendocardium, a method which has been used by several investigators (Theroux et al., 1976; Vatner et al., 1976). It is well recognized that segmental systolic shortening is impaired promptly and markedly in ischemic zones of myocardium following coronary occlusion. Postextrasystolic potentiation of systolic shortening still may be elicited for a short time (Dyke et al., 1975; Crozatier et al., 1977; Boden et al., 1978) but, within 10 minutes, this is also abolished in the subendocardium (Crozatier et al., 1977). Studies using length gauges attached to the epicardium indicate that stable postextrasystolic potentiation may persist in this location for up to two hours (Boden et al., 1980), perhaps due to better perfusion known to exist in the epicardial myocardium. At the subendocardial level, however, shortening of both intrinsic and postextrasystolic beats is abolished at a time when the myocardium is still viable, as evidenced by rapid reappearance of systolic shortening when the occlusion is released (Crozatier et al., 1977). We reasoned that the effect of verapamil might be manifested by improved systolic shortening of either intrinsic or postextrasystolic beats. Therefore we routinely produce premature beats in these experiments, and examined postextrasystolic shortening, as a measure of latent contractile behavior.
After coronary occlusion, there was a rapid reduction in systolic shortening in the central zone of ischemia in both control and verapamil-treated animals. Similar changes, but of lesser magnitude, occurred in the border zone of ischemia in the control animals only (Fig. 1). Systolic shortening of postextrasystolic beats was abolished in the central zone of ischemia in control dogs, but was preserved to some degree in the verapamil-treated animals. In the border zone, postextrasystolic systolic shortening still was present following coronary occlusion in both groups of dogs, but to a greater degree in the verapamil-treated group (Fig. 2). These changes indicate that verapamil significantly preserved mechanical performance of both ischemic zone and border zone myocardium during coronary occlusion. This was manifested by differences in systolic shortening for postextrasystolic beats (Fig. 2). Systolic shortening for normally paced beats in the border zone was maintained only in verapamil-treated dogs (Fig. 1).

Following reperfusion, systolic shortening in the verapamil-treated dogs showed no consistent changes, suggesting that performance neither deteriorated nor improved (Fig. 1). The same was true for intrinsic beats in the control animals. In this group, the postextrasystolic response could not be readily assessed due to the increase in intrinsic heart rate (Table 1).

Several possibilities have been raised to explain the mechanism by which verapamil may reduce ischemic myocardial injury. These include: (1) improvement of myocardial blood flow in the area of ischemia; (2) reduction of afterload; (3) reduction of transmembrane calcium flux into ischemic myocardium. Verapamil is known to relax coronary vascular smooth muscle and to increase coronary blood flow to nonischemic myocardium (Haas and Härterfelder, 1962; Berdeaux et al., 1976; Smith et al., 1977). However, the effects of verapamil upon ischemic zone myocardial blood flow have varied in the hands of different investigators, either showing no change (Smith et al., 1977) or an increase (Berdault, 1976). In the latter experiments, the increase in flow in the ischemic zone was abolished when the verapamil-induced decrease in heart rate was controlled by pacing the heart at a constant rate, suggesting that the increase in flow during bradycardia was due to prolongation of diastole rather than to a direct coronary vasodilator effect. The present experiments, in which heart rate also was held constant by pacing, are in agreement with these findings. Neither border zone nor ischemic zone blood flow was significantly different in verapamil-treated animals compared to controls. In fact, at the doses of verapamil employed, there were also no significant increases in regional myocardial blood flow in the normal nonischemic myocardium in the verapamil-treated animals. This may be a dose-related effect, as earlier experiments which

**Table 2** Regional Myocardial Blood Flow in ml/g per min before and during Coronary Occlusion for Saline Control and Verapamil-Treated Animals

<table>
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<tr>
<th></th>
<th>Control zone</th>
<th>Border zone</th>
<th>Ischemic zone</th>
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<tbody>
<tr>
<td></td>
<td>Epi</td>
<td>Endo</td>
<td>Epi</td>
</tr>
<tr>
<td>Saline controls (n = 6)</td>
<td></td>
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<tr>
<td>Preocclusion</td>
<td>1.29 ± 0.20</td>
<td>1.76 ± 0.07</td>
<td>1.10 ± 0.14</td>
</tr>
<tr>
<td>Ischemia</td>
<td>1.62 ± 0.30</td>
<td>2.19 ± 0.22</td>
<td>1.60 ± 0.35</td>
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<tr>
<td>Verapamil (n = 6)</td>
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<tr>
<td>Preocclusion</td>
<td>2.04 ± 0.30</td>
<td>2.74 ± 0.44</td>
<td>1.21 ± 0.34*</td>
</tr>
<tr>
<td>Ischemia</td>
<td>1.63 ± 0.27</td>
<td>2.24 ± 0.50</td>
<td>1.40 ± 0.66*</td>
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*P < 0.05 comparing ischemia to preocclusion, by analysis of variance. Epi = epicardium; Endo = endocardium.
demonstrated coronary vasodilation in normal non-ischemic myocardium employed larger dosages of verapamil (Berdeaux et al., 1976; Smith et al., 1977). It is also noteworthy that mechanical dysfunction was apparent in the border zone in the control group, despite the fact that regional blood flow decreased insignificantly compared to the preocclusion control, and remained in the normal range (Table 2). Vatner et al. (1979) have noted also that minor decrements in coronary flow may be associated with significant impairment of subendocardial systolic shortening.

In addition to acting as a coronary vasodilator, verapamil also dilates the peripheral arterioles. A decline in peripheral vascular resistance and systemic arterial blood pressure usually is noted following administration of the drug in anesthetized dogs (Smith et al., 1975; Wende et al., 1975; Berdeaux et al., 1976; Reimer et al., 1977, Smith et al., 1977). The consequent reduction in afterload may have independent effects upon ischemic myocardial injury and upon myocardial performance. A fall in arterial pressure may be associated with increased ischemic damage to the myocardium, due to reduction of coronary perfusion (Maroko et al., 1971). On the other hand, a fall in arterial pressure may also facilitate an increase in segmental systolic shortening due to a passive mechanical effect (Theroux et al., 1976). Certainly a marked decline in arterial pressure would be expected to exert deleterious effects. Selwyn et al. (1979) have shown that nifedipine, another calcium antagonist, will produce salutary effects when infused into animals with coronary occlusion in small doses that produce only mild hypotension. When larger doses that cause marked hypotension are employed, further damage to ischemic myocardium results.

In the present experiments in conscious animals, no significant changes in systemic vascular resistance or mean aortic pressure were noted in the verapamil-treated dogs (Table 1). However, peripheral vascular resistance did increase following coronary occlusion in the control group, accompanied by a decline in cardiac output. These differences in the response of peripheral vascular resistance in the two groups may reflect blunting of reflex vasoconstriction following coronary occlusion in the verapamil-treated animals. Furthermore, the failure of peripheral resistance and arterial pressure to decline in the verapamil-treated animals, unlike the findings in anesthetized animals, may be due to relative intactness of autonomic reflexes known to be characteristic of conscious animal preparations (Vatner and Braunwald, 1975). In any case, it seems unlikely that the improved mechanical performance noted in verapamil-treated animals in these experiments can be related to a reduction in arterial pressure and afterload, since significant changes did not occur. Whether the trend toward a reduction in mean aortic pressure in verapamil-treated animals would emerge as significant if larger numbers of animals were studied remains conjectural (Table 1). Since it appears unlikely that verapamil exerted a salutary effect on mechanical performance of ischemic myocardium in these experiments by affecting heart rate, systemic hemodynamics, or regional myocardial blood flow, this leaves open the possibility that the effects were mediated through the calcium-blocking properties of the agent (Fleckenstein, 1971). Presumably, inhibition of transmembrane calcium flux is responsible for the myocardial depressant effects which are seen when verapamil is given in higher dosages (Fleckenstein, 1971; Naylor and Szeto, 1972), and also might be responsible for the antiarrhythmic effects of the drug (Anderson, 1978). Indeed, Smith et al. (1976) have suggested that verapamil may reduce myocardial injury through a selective depression of contractility and oxygen requirement in ischemic myocardium when given in doses too low to affect contractility of normal myocardium. These experiments, which were carried out in anesthetized open-chest dogs with partial coronary occlusion, are at variance with the present studies, which showed not only improved postextrasystolic potentiation responses in all areas of ischemia, but also less depression of intrinsic performance in border zones of ischemia in verapamil-treated animals. The discrepancies between these findings cannot be explained readily, but may relate to differences in the experimental preparations.

One further mechanism that might influence the results of the present study is related to effects of ischemia and verapamil administration upon conduction of impulses into and depolarization of ischemic myocardium. Elharrar et al. (1977) have shown that pretreatment of anesthetized dogs with verapamil prior to experimental coronary occlusion leads to some return towards normal of the conduction delay that is observed in ischemic myocardium. In one example presented, the bipolar electrogram spike was lost completely in the ischemic myocardium during a temporary coronary occlusion but reappeared during a subsequent coronary occlusion when verapamil pretreatment was given. These results may imply that verapamil improves ischemic myocardial performance to some degree by facilitating more rapid or complete depolarization of ischemic tissue. Furthermore, opposite effects on conduction delay were noted by other investigators when verapamil was given subsequent to coronary occlusion (Kupersmith et al., 1976), suggesting that local drug concentrations may exert important effects. These findings also could explain in part the difference between our findings and those of Smith et al. (1976), who also administered verapamil after the production of ischemia.

The results of coronary reperfusion in these experiments must be regarded as inconclusive. Thus, there was no consistent change in intrinsic performance of either the central or border zone of ischemic myocardium in either group, or in the postextrasystolic potentiation response of the verapamil-treated animals. The postextrasystolic potentiation re-
sponse was uninterpretable in the control group due to the increase in the intrinsic heart rate. Theoretically, verapamil might protect against reperfusion injury associated with calcium overload (Ashraf et al., 1978). Such an effect has been demonstrated during low-flow ischemia in buffer-perfused rabbit hearts using nifedipine, another calcium antagonist, by Henry et al. (1977). Nifedipine also prevented accumulation of calcium bound to mitochondria in these experiments. Thus far such results have not been obtained with verapamil. Reimer et al. (1977) were unable to demonstrate reduction of necrosis in dogs when verapamil was given just prior to coronary reperfusion. In other experiments, verapamil failed to prevent hypoxia-induced accumulation of calcium in buffer-perfused rabbit hearts (Nayler et al., 1976). Verapamil has, however, been demonstrated to reduce tissue calcium accumulation in other types of tissue injury, such as isoproterenol-induced myocardial necrosis (Fleckenstein, 1971).

Early studies with verapamil showed that the drug reduced the incidence of ventricular fibrillation during acute myocardial ischemia in dogs (Kaumann and Aramendia, 1968), and this finding is confirmed by the present study. Although it was postulated originally that verapamil might act by suppressing calcium-dependent slow conduction in reentrant pathways of ischemic myocardium, recent studies have shown that verapamil improves conduction in ischemic canine myocardium in both acute (Elharrar et al., 1977) and chronic (El-Sherif and Lazzara, 1979) experiments. This finding is consistent with a reduction in the degree of myocardial ischemia resulting from verapamil treatment, rather than an electrophysiological effect mediated by the calcium-antagonistic actions of the drug.

Studies of other calcium antagonists have yielded results that are similar in some respects to the present study, but differences are also noted. Nifedipine has been shown to improve impaired subendocardial systolic shortening of the ischemic zone in dogs with coronary occlusion (Henry et al., 1979) and also to reduce ischemic necrosis (Henry et al., 1978). Unlike verapamil, nifedipine appears to increase ischemic zone myocardial blood flow in the absence of bradycardia (Henry et al., 1978; Henry et al., 1979; Selwyn et al., 1979). Nifedipine lacks the antiarrhythmic properties of verapamil (Andersson, 1978; Johansson, 1978) but, unlike verapamil, does not produce atrioventricular block (Henry et al., 1978). The relative merits of these and other calcium antagonists such as diltiazem, which also has been shown to reduce ischemic injury (Weishaar et al., 1979), will require further investigation.

Acknowledgments

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