Regional Contractility

Selective Depression of Ischemic Myocardium by Verapamil

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SUMMARY The effects of verapamil (0.02–0.2 mg/kg) on contractility in normal and partially ischemic myocardium were compared with the changes following propranolol (0.01–1.0 mg/kg). Regional contractile function was studied in open-chest dogs with ultrasonic crystals and ischemia was controlled by graded occlusion of a carotid-to-coronary artery shunt. Reduction in shunt perfusion pressure (40–55 mm Hg) resulted in hypokinesia. Verapamil depressed contractility in ischemic myocardium in 5/5 dogs, but did not alter the maximum velocity of shortening (max V) or end-diastolic segment length in normal myocardium. Propranolol in doses sufficient to depress ischemic myocardium also depressed contractile function in normal myocardium. In two dogs without coronary occlusion, verapamil (up to 1.0 mg/kg) increased end-diastolic segment length but did not reduce max V.

We conclude that verapamil selectively depresses ischemic myocardium, a finding that may have clinical implication since ischemic injury can be decreased by reducing contractility (and thereby MVO₂).

VERAPAMIL HAS BEEN USED as an antianginal agent in man and has been shown to prolong survival and reduce ST-segment elevation in dogs following acute coronary artery occlusion. Its salutary effects on ST segments during acute coronary occlusion occur with associated changes in collateral blood flow or the rate of anaerobic metabolism, suggesting that the drug may reduce ischemic injury by a direct myocardial effect.

Since verapamil and ischemia both interfere with the movement of calcium ions at the cell membrane level, it seemed possible that verapamil might be capable of selectively depressing contractile function in ischemic myocardium at concentrations too low to affect normal tissue. To test this hypothesis, several parameters of myocardial contractile function were measured in nonischemic and ischemic segments of the left ventricle using small ultrasonic crystals. The dose-response relation of verapamil on nonischemic and ischemic myocardium was compared to that of propranolol, a potent beta-blocking agent known to decrease contractility.

Methods

Eighteen mongrel dogs of either sex (weight 20–30 kg) were anesthetized with sodium pentobarbital (20–25 mg/kg) and ventilated with room air through a cuffed endotracheal tube. Normal saline was infused at 50 ml/hr for the remainder of the experiment. The experimental preparation is shown diagrammatically in figure 1. A left lateral thoracotomy was performed through the fifth intercostal space and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery (LAD) was dissected free at about 2 cm from its origin, usually above the first major diagonal branch, and prepared for later cannulation. Catheters were placed in the femoral artery and vein, left atrium and left ventricle. Arterial, left ventricular and left atrial pressures were recorded.

Small stab incisions were made with a number 11 scalpel blade; two pairs of ultrasonic crystals (diameter 2 mm) were placed at a depth of 3–4 mm in the anterior left ventricle and secured with purse-string sutures. Each pair of crystals was separated by 1.5–2.0 cm of myocardium and aligned for optimum transmission of sound. One pair was placed outside the ischemic zone (normal segment) and the other within the zone of myocardium perfused by the LAD, but 1–2 cm distal to the level of LAD occlusion; i.e., that segment that would become ischemic after occlusion of the vessel (ischemic segment). The ultrasound crystals were made from 3 MHz piezoelectric crystal (LTZ 5, Transducer Products, Conn) and insulated stainless-steel wire, each crystal being mounted on a short (2 cm) length of plastic tubing (diameter 1.5 mm) to facilitate rotation for optimum alignment. The crystals were dipped in liquid plastic, thereby forming a crude lens that produced divergence of the parallel beam of ultrasound arising from the crystals. The emitter crystal of each pair was stimulated with a 1 kHz pulse-train, so that the resultant ultrasonic pulsed beam induced a response in the receptor crystal. The transmission time of the ultrasound beam was converted electronically to an analog signal output that was recorded. The output was calibrated with two pairs of crystals mounted in a water bath at 1.0 and 2.0 cm apart. Thus, by recording the changes in transmission time, the distance between crystals could be monitored continuously, allowing assessment of myocardial segment length at any point during the cardiac cycle, calculation of the rate of change of segment length (dl/dt or velocity of shortening), and appreciation of the overall pattern of contraction. The segment length changes were displayed from positive to negative so that all the normal systolic events (pressure and segment shortening) were unidirectional. The onset of systole and diastole were determined from the left ventricular pressure waveform, which was displayed alongside the segment length record (fig. 2).

At least 30 minutes was allowed for bleeding to stop after instrumentation. The animal was then given 10,000 units of sodium heparin (USP), and a silastic shunt was created between the left carotid artery and the LAD. A screw clamp

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Dr. Smith is recipient of USPHS International Research Fellowship 1 F05 TWO2176-02.

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Received November 17, 1975; revision accepted May 17, 1976.

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FIGURE 1. Experimental preparation with a carotid-to-left anterior descending (LAD) coronary artery shunt. Two pairs of ultrasonic crystals are shown in normal (N) and ischemic (I; shaded) myocardium. Pressures (P) were recorded from left atrium (LA), aorta (Ao), left ventricle (LV) and the shunt (distal to the screw clamp). PA = pulmonary artery; RV = right ventricle.

was placed on the shunt: the perfusion pressure was measured distal to the screw clamp and recorded. Since the shunt insertion involved ligation of the LAD with temporary ischemia and impairment of contractility prior to full perfusion by the shunt, a period of 1-2 hours was allowed for full recovery of contractile function in the ischemic area.

Baseline recordings of pressure, heart rate and the contractile patterns of the normal and potentially ischemic segments were obtained.

Complete Shunt Occlusion

In three dogs, acute changes in contractile function were studied after sudden complete occlusion of the shunt.

Controlled Shunt Occlusion

In ten dogs, the LAD shunt was occluded gradually until there was mild impairment of contractile function in the ischemic area that was stable for 5-10 minutes. Epicardial electrograms obtained with a cotton-wick electrode in two dogs, showed that this degree of ischemia was insufficient to produce ST-segment elevation. Reduction of shunt perfusion pressure to 40-55 mm Hg produced mild hypokinesia in all normotensive animals (mean arterial pressure 96 ± 14 mm Hg). Preliminary studies showed that over a period of 10-15 minutes, there was no deterioration of hypokinesia in the ischemic segment, provided that the controlled reduction in shunt perfusion pressure was not changed. In two dogs, the collateral supply of the anterior left ventricular wall was so great that the shunt pressure was 40 mm Hg after complete shunt occlusion; in these animals, the experiment was performed with total occlusion of the shunt. After the 5-10 minute period of partial occlusion and mild but stable hypokinesia, in five of ten dogs, verapamil was administered intravenously at two minute intervals to give cumulative doses of 0.02, 0.05, 0.1, 0.15 and 0.2 mg/kg. In the other five dogs, propranolol was administered in a similar manner but with cumulative doses of 0.01, 0.03, 0.1, 0.3 and 1.0 mg/kg.

Controlled Pressure Studies

In three dogs, verapamil was administered after partial shunt occlusion, but the arterial and shunt pressures were kept constant by inflation of an occlusive cuff placed around the descending aorta. The experimental protocol was otherwise identical to that in the previous group of five dogs in which verapamil was given during partial shunt occlusion.

High-Dose Verapamil

The effect of high-dose verapamil on nonischemic myocardium was studied in two dogs without LAD occlusion, in which the arterial pressure was maintained by inflation of an aortic cuff and the heart rate was held constant with atrial pacing. Repeated doses of verapamil (0.1 mg/kg) were administered at two minute intervals to give cumulative doses up to 1.0 mg/kg.

The changes in end-diastolic length and maximum velocity of shortening (max V) in the normal segment and end-diastolic length and mean systolic change in length (shortening or lengthening) in the ischemic segment, which occurred after administration of verapamil, were compared with the changes in these parameters induced by administration of propranolol. The end-diastolic length was taken as the segment length just prior to the onset of systole. Max V was calculated from the slope of the segment length changes and the mean for three consecutive beats was taken. The mean segment length during systole was estimated graphically and subtracted from the end-diastolic length to give the mean systolic change in length. This method of
analysis was found necessary since it was apparent that a gross change in the contractile pattern could occur without any change in either max V or maximal systolic shortening (fig. 3). It should be pointed out that the change in segment length included in this measurement occurred throughout the period of true systole, i.e., measurements were not confined to the ejection period, but also included changes during isovolumetric contraction and relaxation. In this regard, ischemic muscle exhibited a late period of shortening (fig. 2) that began at the end of true systole (as determined by the ventricular pressure pulse) and continued into diastole; the diastolic component of this late systolic shortening was not taken into consideration in the calculation of mean systolic change in length.

All results are expressed as mean ± standard error of mean unless otherwise stated. The significance of results was tested by Student’s t-test.

Results

Sudden Complete LAD Occlusion

Sudden complete occlusion of the LAD shunt produced rapid changes in the contractile pattern of the ischemic segment (fig. 3). Within 4 seconds, paradoxic systolic expansion developed at the end of the systolic plateau of ventricular pressure. After 20–30 seconds of occlusion, the duration of paradoxic expansion increased, occurring earlier in systole and progressively encroaching on the period of initial shortening; however, although difficult to measure after 20 seconds, the maximal velocity of initial shortening did not appear to be altered. At 30 seconds after occlusion, there was practically no initial shortening; some shortening still occurred at the end of systole. Later a dysskinetic pattern developed characterized by paradoxic movement of the ischemic segment that occupied all or nearly all of systole; this was associated with an increase in end-diastolic segment length. The early and progressive changes in the contractile pattern of the ischemic segment were similar in each of the three dogs studied.

Controlled LAD Occlusion

With partial occlusion of the LAD shunt, it was possible to maintain a stable hypokinetic pattern in the ischemic segment. The degree of hypokinesia was generally related to the perfusion pressure; hypokinesia occurred with perfusion pressures of 40–55 mm Hg. The one exception occurred in a dog in which the mean systolic arterial pressure was relatively lower (75 mm Hg); in this dog, a perfusion pressure of 25 mm Hg was necessary to produce hypokinesia. There was a slight but insignificant increase in the diastolic lengths of the ischemic segments but a significant reduction in mean systolic shortening (table 1).

Effects of Verapamil

Verapamil in cumulative doses of 0.02–0.2 mg/kg slowed the heart rate by 13 beats/min, and led to significant decreases in both mean arterial pressure and shunt pressure and a slight increase in left atrial pressure. These changes are listed in table 1 and illustrated in figure 4.

**Table 1. Effects of Shunt and Verapamil or Propranolol.**

<table>
<thead>
<tr>
<th>Table 1. Effects of Shunt and Verapamil or Propranolol</th>
<th>Verapamil-treated group</th>
<th>Propranolol-treated Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Verapamil 0.2 mg/kg</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>163 ± 17</td>
<td>156 ± 13</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>98 ± 10</td>
<td>85 ± 8</td>
</tr>
<tr>
<td>Mean shunt pressure (mm Hg)</td>
<td>99 ± 11</td>
<td>47 ± 6**</td>
</tr>
<tr>
<td>Mean left atrial pressure (mm Hg)</td>
<td>3.6 ± 0.8</td>
<td>4.3 ± 0.6</td>
</tr>
<tr>
<td>Normal segment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic length (cm)</td>
<td>1.79 ± 0.08</td>
<td>1.78 ± 0.08</td>
</tr>
<tr>
<td>Maximal velocity of shortening (mm/sec)</td>
<td>18.3 ± 2.8</td>
<td>17.9 ± 2.7</td>
</tr>
<tr>
<td>Ischemic segment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic length (cm)</td>
<td>2.21 ± 0.17</td>
<td>2.24 ± 0.17</td>
</tr>
<tr>
<td>Mean systolic change in length (cm)</td>
<td>-0.20 ± 0.03</td>
<td>-0.12 ± 0.03</td>
</tr>
</tbody>
</table>

*P < 0.05; ** P < 0.01.
† Segmental shunting is designated as a negative change in segment length; shortening as a positive change in length.
A representative example of the effects of increasing doses of verapamil on regional contractility in normal and ischemic segments is shown in figure 5. The results in each of the five dogs were similar. In the ischemic segment, a stable hypokinetic pattern present after partial shunt occlusion changed to frank dyskinetic movement after administration of verapamil.

The mean changes for the five dogs treated with verapamil are listed in table 1 and displayed in figure 6. In the ischemic segment there was an increase in mean end-diastolic segment length following verapamil and the mean systolic change in segment length (shortening) became positive (lengthening). In the normal segment, there was a slight but significant increase in end-diastolic segment length after the largest dose of verapamil. Maximal velocity of shortening was not reduced by verapamil; if anything, it tended to increase.

Effects of Propranolol

In response to increasing doses of propranolol, heart rate slowed, mean arterial pressure decreased, shunt pressure

![Graphs and Figures]

**Figure 4.** Changes in left atrial pressure (LAP), aortic pressure (AoP), shunt pressure, and heart rate after partial shunt occlusion and administration of verapamil (five dogs) in increasing doses. The points represent mean values and the bar lines standard error of mean.

**Figure 5.** Representative examples of the contractile patterns of normal and ischemic segments of myocardium after partial shunt occlusion (O) and increasing doses of verapamil and propranolol. C = pre-occlusion control. Propranolol depressed velocity of shortening in the normal segment whereas verapamil did not. Dyskinesia in the ischemic segment increased after both drugs. The example of changes after verapamil is taken from a dog in which there was no fall in arterial or shunt pressure after administration of the drug.

**Figure 6.** Mean changes in end-diastolic segment length and maximal velocity of shortening (max V) in the normal segment and end-diastolic segment length and systolic change in length in the ischemic segment, after partial shunt occlusion and after verapamil and propranolol. The points represent mean values and the bar line represents the standard error of the mean.
diminished, left atrial pressure increased. These changes, which are similar to those in the verapamil-treated group, are listed in table 1 and illustrated in figure 4.

A representative example of the effects of propranolol on regional contractility is shown in figure 5; the group data of the propranolol and verapamil-treated dogs are compared in table 1 and figure 6. Propranolol altered the pattern of contraction of the ischemic segment in a manner similar to verapamil. After 1.0 mg/kg of propranolol, there was a slight but insignificant increase in end-diastolic length; as in the verapamil-treated group, the mean systolic change in segment length (shortening) became positive (lengthening). The effects of the two drugs were clearly different, however, in that at no dose level did propranolol cause differential effects in the contractile patterns of the normal and ischemic segments. Thus, there was a slight increase in end-diastolic length in the normal segment after 1.0 mg/kg of propranolol, which was similar to that observed in the verapamil-treated group. However, there was a profound reduction in the velocity of shortening (from 16.4 ± 0.5 to 10.3 ± 2.4 mm/sec; P < 0.01), an effect on normal segment contraction pattern never observed with verapamil over the dose range explored.

Constant Pressure Studies

To exclude the possibility that the increase in dyskinesia which occurred after administration of verapamil might be due to a reduction in shunt perfusion pressure, three additional dogs were studied in which arterial pressure (and hence shunt pressure) was held constant with an inflatable aortic cuff. Thus, the shunt pressure causing hypokinesia was 45, 50, and 52 mm Hg; these pressures were not allowed to change during administration of verapamil. As in the first group of dogs (in which arterial and shunt pressures were allowed to fall following verapamil-induced vasodilatation), there was an increase in end-diastolic segment length in the ischemic segment after verapamil from 2.11 to 2.17 cm and a change from systolic shortening (mean systolic change in length = −0.12 cm) to lengthening (0.05 cm). These results demonstrate that the depressant effect of verapamil on ischemic myocardium is independent of reduction in coronary perfusion pressure.

Effect of High-Dose Verapamil on Normal Myocardium

In two dogs without LAD occlusion, verapamil was administered in cumulative doses up to 1.0 mg/kg. In the first dog, the spontaneous heart rate was 176 beats/minute but atrial pacing at 150 beats/min was required after 0.4 mg/kg of verapamil; higher rates were not possible because of atrioventricular block. In the second dog, the initial heart rate was 194 beats/min; atrial pacing at 180 beats/min was initiated after 0.3 mg/kg of verapamil but third degree atrioventricular block occurred after 0.6 mg/kg so that ventricular pacing was required. In this case, the pacemaker was switched off for 3-4 beats during recordings since the altered contraction pattern made interpretation of drug-induced changes difficult.

Maintenance of arterial pressure was attempted by inflation of the aortic cuff; however, after full doses of verapamil there was a reduction in mean pressure from 150 to 140 mm Hg in one dog and 135 to 110 in the other.

<table>
<thead>
<tr>
<th>Verapamil dose (mg/kg)</th>
<th>End-diastolic segment length (cm)</th>
<th>Maximal velocity of shortening (mm/sec)</th>
<th>Heart rate (beats/min)</th>
<th>Mean arterial pressure (mm Hg)</th>
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<td>Day 1</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>1.82</td>
<td>18.8</td>
<td>205</td>
<td>135†</td>
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<td>0.1</td>
<td>1.90</td>
<td>23.4</td>
<td>194</td>
<td>125</td>
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<tr>
<td>0.2</td>
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<td>31.0</td>
<td>188</td>
<td>125†</td>
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<tr>
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<td>1.91</td>
<td>34.0</td>
<td>182*</td>
<td>125†</td>
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<tr>
<td>0.4</td>
<td>1.90</td>
<td>24.6</td>
<td>150*</td>
<td>110†</td>
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<tr>
<td>0.5</td>
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<td>23.8</td>
<td>180*</td>
<td>105†</td>
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<tr>
<td>0.6</td>
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<td>20.6</td>
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<td>108‡</td>
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<tr>
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<tr>
<td>1.0</td>
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<td>25.0</td>
<td>180*</td>
<td>120‡</td>
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<td>Day 2</td>
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<tr>
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<td>32.7</td>
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<td>38.1</td>
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<td>0.8</td>
<td>2.05</td>
<td>38.9</td>
<td>150*</td>
<td>140†</td>
</tr>
</tbody>
</table>

*Signifies heart rate maintained by electrical pacing. †Signifies arterial pressure maintained by inflation of an aortic cuff.

End-diastolic segment length increased from control values of 1.96 and 1.82 cm to 2.04 and 1.90 cm, respectively, after 0.8 mg/kg of verapamil. In the second dog, the study was extended to a total cumulative dose of 1.0 mg/kg, after which the end-diastolic segment length was 2.05 cm. In contrast to the increase in end-diastolic segment length, which suggested depression of contractility, there was an increase in the velocity of shortening from control values of 21.4 and 18.8 mm/sec to a maximum of 39.9 and 34 mm/sec after 0.3 mg/kg of verapamil. Velocity of shortening after higher doses of the drug was also higher than the control values (36.9 mm/sec after 0.8 mg/kg in the first dog and 25.0 mm/sec after 1.0 mg/kg in the second). These changes are listed in table 2; a representative example of the changes in contractile pattern is illustrated in figure 7.

These results show 1) that in contrast to propranolol, verapamil even in high doses, does not depress velocity of shortening in normal muscle; 2) that velocity of shortening can increase after administration of large doses of
verapamil, although this may result from a shift along the same ventricular function curve; and 3) that depression of normal myocardium after administration of verapamil in doses up to 1.0 mg/kg is primarily related to vasodilator-induced hypotension and depression of heart rate and conduction, both of which were prevented in this study.

Discussion

The present study demonstrates that verapamil in doses of up to 0.2 mg/kg selectively depresses contractile function in ischemic myocardium while sparing that in normal tissue. In contrast, propranolol exerts no such selective effect; whenever the drug is administered in doses sufficient to depress ischemic myocardium, contractile function of normal myocardium is also reduced.

It has been shown that the magnitude of ischemic injury occurring during acute myocardial infarction can be reduced by propranolol or practolol, agents that reduce myocardial contractility and thereby myocardial oxygen consumption. Likewise, verapamil has been shown to be capable of reducing ST-segment elevation in the absence of changes in either collateral blood flow or rate of anaerobic metabolism. These findings, in association with those of the present investigation, suggest 1) that verapamil reduces ischemic injury during coronary occlusion and 2) that this salutary action is produced by the drug selectively reducing the oxygen requirements of ischemic myocardium.

It should be pointed out that administration of verapamil leads to a mild decrease in coronary perfusion pressure, a change that in itself could cause the decrease in contractile function. However, although lowering shunt pressure by mechanically increasing the degree of shunt occlusion from 50-40 mm Hg (changes comparable to those induced by verapamil) does increase hypokinesia, it does not produce the more severe degrees of dyskinesia seen after administration of verapamil. Furthermore, the decrease in contractile function observed after administration of verapamil in the three dogs in which arterial pressure and shunt pressure were held constant, indicates that the drug has a direct depressant action on ischemic myocardium independent of changes in coronary perfusion pressure.

Previous studies have shown that large doses of verapamil (0.5-1.0 mg/kg) induce contractile failure in the open-chest guinea pig. Our studies in two dogs of the effects of high doses of verapamil on normal myocardium suggest that any cardiac toxicity observed at these doses is primarily related to systemic hypotension and to depression of inherent rhythmicity and conduction. Maximal velocity of shortening actually increased after verapamil, reaching a peak after 0.3 mg/kg of the drug. There was, however, a slight increase in end-diastolic segment length so that the increase in velocity of shortening may have resulted, at least in part, from altered length/tension relationships. Maximal velocity of shortening was maintained even after 1.0 mg/kg of verapamil, provided that large changes in heart rate and arterial blood pressure were prevented.

In the experiments in which verapamil was administered in high doses, it is likely that some visceral hyperperfusion occurred following descending aortic occlusion, raising the possibility that reflex release of catecholamines (cardiac neuronal, adrenal, or both) may have aided in the maintenance of the contractile state of the myocardium. This is considered unlikely, however, in view of the fact that no sympathetic-induced increase in heart rate occurred; such a change would have been expected if increased sympathetic stimulation of the heart were present, since verapamil, in contrast to propranolol, does not block sympathetic-induced chronotropic stimulation.

The mechanisms responsible for the different spectrum of actions of verapamil and propranolol on ischemic and nonischemic tissue are unknown. It is of interest to note that while the effects of verapamil on the patterns of myocardial contraction are similar to the early effects of ischemia, those induced by propranolol are not. Thus, during early phases of ischemia, systolic shortening is diminished and frank dyskinesia eventually develops; maximal velocity of shortening remains unaltered. Verapamil produces similar effects on ischemic tissue in that the contractile patterns of ischemic segments are markedly altered without any effect on the maximal velocity of initial shortening. In contrast, depression of maximal velocity of shortening appears to be an intrinsic component of negative inotropic actions of propranolol, whether ischemic or nonischemic myocardium is considered. Thus, the effect of propranolol on maximal velocity of shortening could not be dissociated from other actions of the drug on mechanical performance, i.e., depression of maximal velocity of shortening appeared at whatever dose of propranolol was sufficient to cause a diminution in the extent of systolic shortening, both in ischemic and nonischemic myocardium. These observations suggest that verapamil may preferentially depress ischemic tissue because it has a major effect on one or more of the same cellular mechanisms by which ischemia interferes with contractile function, while propranolol has no such selective action because of different or more complex effects on the contractile mechanism. In this regard, both verapamil and ischemia have been shown to reduce the slow inward current of calcium ions during phase II of the action potential.

The results of this investigation may have clinical implications. Both verapamil and propranolol have been used in the setting of acute myocardial infarction; verapamil has been used to treat supraventricular tachyarrhythmias and propranolol has been used in attempts to diminish ischemic injury (by reducing myocardial oxygen demand). However, propranolol can lead to severe left ventricular failure in patients with borderline left ventricular function, presumably by depressing that portion of nonischemic or partially ischemic myocardium responsible for maintaining cardiac compensation. It is therefore possible that verapamil, by decreasing contractile function in ischemic tissue selectively, may diminish the degree of ischemic injury without significantly interfering with overall pump performance. Selective depression of ischemic myocardium by verapamil also raises the possibility that this drug might protect ischemic myocardium during inotropic interventions. On the other hand, patients with extensive myocardial ischemia could conceivably have catastrophic depression of myocardial contractility following verapamil with a severe hemodynamic deterioration that is not easily reversed.
Acknowledgment

We wish to thank Mr. William Parker and Mr. Richard McGill for their fine technical assistance.

Verapamil used in this study was supplied by the Knoll Pharmaceutical Company, Orange, New Jersey.

References


Correction

Kerber et al.: Circulation 53: 853, 1976. On page 857, table 3, the third column heading should read "Ischemia + counterpulsation + norepinephrine (60 min)." On page 858, table 4, the third column heading should read "Ischemia + counterpulsation + nitroprusside (60 min)."
Regional contractility. Selective depression of ischemic myocardium by verapamil.
H J Smith, R A Goldstein, J M Griffith, K M Kent and S E Epstein

Circulation. 1976;54:629-635
doi: 10.1161/01.CIR.54.4.629
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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