Effects of Verapamil and Propranolol on Changes in Extracellular K⁺, pH, and Local Activation During Graded Coronary Flow in the Pig

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The β-adrenergic and calcium channel blocking agents are known to reduce heart rate and alter myocardial contractility. More recent evidence suggests that both agents affect the metabolic consequences of ischemia, independent of their effects on heart rate and contractility. We used a low-flow model of ischemia in swine with heart rate held constant by atrial pacing. Blood was shunted from the carotid artery to the left anterior descending coronary artery through a controlled-flow roller pump to assess the threshold flow for the rise in extracellular potassium ([K⁺]e) and fall in extracellular pH (pHe) associated with ischemia during control situations and after the administration of either propranolol or verapamil. We also measured the changes in activation delay and contractility associated with graded flow reductions in the presence and absence of these drugs. We found that when heart rate is held constant, 1) verapamil shifts the threshold flow for [K⁺]e and pHe to lower levels, but propranolol does not; 2) verapamil lessens activation delay, while propranolol aggravates the delay; and 3) verapamil reduces afterload and selectively depresses contractility in the reperfused ischemic zone. We conclude that the calcium channel blockers and the β-adrenergic–blocking agents have different effects and possibly different modes of action and should not be considered interchangeable when evaluating therapeutic options for patients with ischemic heart disease. (Circulation 1989;79: 939–947)

The β-adrenergic–blocking agents and the calcium channel blocking agents are both used in the treatment of patients with effort-induced ischemia1–2 due to coronary artery disease. The beneficial effects of these agents are attributed to their ability to reduce heart rate and contractility, thereby lessening the myocardial oxygen requirement. In addition, there is evidence to suggest that both the β-adrenergic– and the calcium channel blocking agents may alter the metabolic consequences of reduced coronary blood flow independently of changes in heart rate or contractility.3,4

The ability of both groups of agents to decrease the rate of accumulation of extracellular K⁺ and H⁺ after the complete interruption of coronary blood flow5–8 has been attributed to this mechanism. These effects would be expected to allow the myocardium to tolerate lower levels of coronary blood flow without becoming ischemic.

Our recent studies9 have shown that the changes in extracellular potassium concentration ([K⁺]e) and extracellular pH (pHe) are the most sensitive markers of ischemia when coronary blood flow is progressively reduced. As such, they provide a means for assessing the effects of physiologic and pharmacologic interventions on the coronary blood flow associated with the onset of ischemia. The present experiments were conducted to determine if propranolol or verapamil or both were capable of altering the coronary flow associated with the first change in [K⁺]e and pHe when heart rate was held constant. We also studied the effects of these drugs on myocardial activation during the progressive reduction of coronary blood flow because it is known that the drugs exert opposite effects in the setting of no-flow ischemia. Specifically, verapamil lessens8,10,11 whereas propranolol exaggerates the activation delay.3,12
Our results indicate that when heart rate is held constant, propranolol and verapamil exert different effects on the coronary flow associated with the first changes in \([K^+]_o\) and \(pH\), and on the changes in activation that accompany a progressive decrease in coronary flow.

Methods

Twenty-seven domestic pigs weighing 22–38 kg were immobilized with ketamine and anesthetized with thiaymal sodium (25 mg/kg). Anesthesia was maintained with \(\alpha\)-chloralose (30–50 mg/kg) as needed. The animals were ventilated through an endotracheal tube with a Harvard respirator with a mixture of air and oxygen to maintain arterial oxygen saturation (>95%), \(PaO_2\) (35–45 mm Hg), and \(pH\) (7.35–7.45). Catheters were placed in the descending aorta for arterial blood pressure monitoring and blood gas sampling and in the femoral vein for infusion of saline, anesthetics, and drugs. Left ventricular pressure and its first derivative (dP/dt) were measured with a Millar pressure transducer inserted into the left ventricle through the apex. The hemodynamic data were continuously displayed on a 12-channel Graphtec Linearcoer.

After a midsternal thoracotomy, the heart was suspended in the pericardium, and the right atrium was paced to maintain a constant heart rate, which ranged from 110 to 160 beats/min. A carotid artery to left anterior descending (LAD) coronary artery shunt was produced as previously described.9 In brief, a polyethylene catheter was placed in the right carotid artery; 7,000 units heparin were administered intravenously; the catheter was routed through a roller pump (Cole-Palmer); and the distal end was inserted into the LAD below the first diagonal branch (Figure 1). The control LAD flow was set at 1.2–1.5 ml/kg body wt/min and ranged from 30 to 50 ml/min. Heparin (3,000 units) was given intravenously at 60-minute intervals to ensure cannula patency. Epicardial and core temperatures were continuously monitored with Yellow-Springs temperature probes and maintained at 35–38°C.

Miniature \(K^+\) and \(H^+\)-sensitive electrodes were constructed and calibrated as previously described.13 On average, 3 \(K^+\) (range, 2–6) and 2 \(H^+\) (range, 2–5) ion-sensitive electrodes were placed in the midmyocardium at various locations within the central ischemic area. The precise positions of all electrodes were determined after each experiment by careful dissection. All electrodes included in this study were located in the midmyocardium (>3 mm from endocardium and epicardium) within the center of the ischemic zone (>10 mm from the visible cyanotic border). The amplified signals from all ion-sensitive electrodes were sampled at 30-second intervals by a Digital Equipment Corporation PDP-11/03 minicomputer during the TQ segment of the cardiac cycle. The millivolt readings were converted to \([K^+]_o\) and \(pH\) with the Nernst equation and the calibration curve for each electrode as previously described.13 In addition, the signals from two randomly selected \(K^+\) electrodes and two randomly selected \(pH\) electrodes were continuously recorded along with the hemodynamic data on a Graphtec Linearcoer. The in vivo integrity of the electrodes was determined before and after each LAD flow reduction sequence by the rapid intravenous injection of 3 meq KCl and by 60-second periods of respiratory acidosis. Data were accepted only from electrodes that demonstrated reproducible responses to each KCl bolus or period of acidosis and that maintained a stable baseline throughout the study. In all, 66 of 101 \(K^+\) electrodes (65%) and 40 of 75 \(pH\) electrodes (53%) met these calibration criteria.

Local bipolar electrograms were recorded by five Teflon-coated stainless-steel bipolar electrode pairs placed in the subepicardial. One electrode pair was placed in the nonischemic zone, and four pairs were placed in the ischemic zone within 5 mm of the \(K^+\)-sensitive electrodes. The bipolar electrograms were filtered between 50 and 500 Hz and continuously monitored along with a lead II electrocardiogram. This filtering permitted identification of the high-frequency deflection of the electrogram until it became fractionated. The signals were recorded 15 seconds before each flow reduction step on a Honeywell 1858 visicorder at a paper speed of 400 mm/sec. Local activation time was measured from the onset of the QRS complex in the electrocardiogram to the peak of the intrinsic, high-frequency deflection in each local electrogram. In some experi-
ments, ultrasonic crystals were inserted into the ischemic and nonischemic regions to determine segment length shortening as previously described. The preparation was allowed to stabilize for at least 60 minutes after placement of the ion-sensitive electrodes. Blood flow into the LAD was reduced sequentially at 5-minute intervals as follows: 50, 40, 30, 20, 15, 10, 5, 2.5, and 0 ml/min; blood flow then returned to control flow. The first sequential flow reduction served as a control (C1). The animals were then divided into three groups: control (C2, n = 8), verapamil (V, n = 10), and propranolol (P, n = 9).

In the verapamil group, an intravenous loading dose of 0.2 mg/kg verapamil was initiated 20 minutes after C1 and administered over a 20-minute period. This was followed by a constant infusion of 6.5 μg/kg/min. In the propranolol group, an intravenous loading dose of 0.4 mg/kg propranolol was initiated 40 minutes after C1 and administered over a 5-minute period. This was followed by a constant infusion of 3 μg/kg/min. In all groups, the second flow reduction was performed 50 minutes after C1. These drug concentrations were similar to those previously used by us and others to achieve serum levels comparable to those achieved in humans.

\([\text{K}^+]_e\), pHc, and local activation changes were monitored to determine the flow at which the measured parameter first changed during the graded LAD flow reduction. This was labeled the threshold flow for that parameter and was identified as follows: \([\text{K}^+]_e\) increase >0.3 mM, pHc fall >0.03, and activation delay >2 msec. Hemodynamic data were statistically compared for the three experimental groups with analysis of variance. The magnitudes of the ionic and activation changes within a particular group were analyzed with the single \(\text{K}^+\) electrode, pH electrode, and bipolar electrode from each animal showing the earliest change during C1 in conjunction with a Student’s t test for paired data. These same electrodes were used to compare threshold flows across groups with analysis of variance statistical techniques. While not illustrated, we confirmed these single electrode threshold analyses using all of the available electrode data from each animal and found no substantial differences in the results.

**Results**

Table 1 shows the mean values of serum potassium, arterial pH, heart rate, mean arterial pressure, and maximum left ventricular dP/dt in each group before the first and second flow reductions. These variables were similar in the three groups before the first flow reduction and returned to their control values after reperfusion. The values of serum potassium, arterial pH, and heart rate before the second flow reduction were the same as those before the first in all groups. Mean arterial pressure and maximum dP/dt were also unchanged before the second flow reduction in the control group. In contrast, verapamil caused a decrease in mean arterial pressure of 31 mm Hg and a decrease in maximum dP/dt of 32% \((p < 0.001)\). Propranolol decreased maximum dP/dt by 23% \((p < 0.01)\) but did not change mean arterial pressure significantly.

The mean changes in \([\text{K}^+]_e\) and pHc associated with the progressive reduction in LAD flow in the control group are shown in Figure 2. The threshold flow for \([\text{K}^+]_e\) was 18.1 ± 2.1 ml/min in C1 and 15.6 ± 3.6 ml/min in C2. These values, which are analogous to those reported previously, did not differ statistically between C1 and C2. The subsequent increase in \([\text{K}^+]_e\) associated with the progressive reduction in LAD flow was comparable in the two flow reductions. The maximum \([\text{K}^+]_e\) achieved was 11.3 ± 0.57 mM in the first flow reduction and 11.2 ± 0.57 mM in the second. The LAD flow associated with the initial fall in pHc was similar to the threshold flow of the \([\text{K}^+]_e\) change as previously reported. The pHc changes in the two LAD flow reduction sequences were alike, except at flows of 5 and 2.5 ml/min. At these flows, the fall in pHc was significantly less \((p < 0.05)\) and, respectively, in the second flow reduction than in the first. Comparable pHc differences have been reported for sequential episodes of no-flow ischemia and are known to be predictable. For statistical purposes, we compared the changes in pHc after the administration of propranolol and verapamil to the changes in pHc anticipated on the basis of the data obtained from the second control flow reduction as previously described.

Figure 3 shows changes in \([\text{K}^+]_e\) and pHc in the verapamil group. The threshold flow for the increase in \([\text{K}^+]_e\), during the first flow reduction was 15.5 ± 1.2 ml/min. This is the same as the C1 values in the control group. After verapamil, the threshold \([\text{K}^+]_e\) was 8.3 ± 1.4 ml/min. This change in threshold was statistically significant \((p = 0.006)\). An equivalently significant threshold change was observed for pHc \((p = 0.006)\). At all LAD flows less than 15 ml/min,
CONTROL

Figure 2. Bar charts of the effect of two successive coronary flow reductions on midmyocardial \([K^+]_e\) and \(pH_e\). Values are reported as mean ± SEM for the first (C1) and second (C2) controlled flow reductions. Note the statistically significant differences in the \(pH_e\) in C2 at flows of 5.0 and 2.5 ml/min (*p<0.05; †p<0.01). The numbers at the base of the bars in this and subsequent figures indicate the number of animals subjected to the associated level of coronary flow.

VERAPAMIL

Figure 3. Bar charts of effects on \([K^+]_e\) and \(pH_e\) during an initial controlled flow reduction (C1) and in a second reduction (V) after the administration of verapamil (0.2 mg/kg). Values are reported as the mean ± SEM. For statistical purposes, the \(pH_e\) in C2 was compared with the anticipated \(pH_e\) based on the results of the control studies. *p<0.05; **p<0.02; †p<0.01.

Figure 4 shows the changes in \([K^+]_e\) and \(pH_e\) in the propranolol group. Propranolol did not significantly alter the threshold flow for the rise in \([K^+]_e\) and fall in \(pH_e\) (16.1±1.1 compared with 14.4±2.1

the absolute change in \([K^+]_e\) and in \(pH_e\) were significantly less after verapamil administration than during the preverapamil flow reduction (\(p<0.05\–0.01\).
ml/min for [K⁺]e in the prepropranolol and postpropranolol flow reductions, respectively). Furthermore, propranolol did not significantly influence the changes in [K⁺]e, even though [K⁺]e was less at flows of 15, 10, and 5 ml/min or significantly exaggerate pHe fall, even though pHe was consistently lower than anticipated at flows less than 15 ml/min.

Figure 5 shows the activation delay associated with the progressive reduction of coronary flow in each group. In the control group, activation delay first occurred at a flow of 14.8±1.7 ml/min and was equivalent in the C₁ and C₂ reductions. The flow associated with the onset of the activation delay in the preverapamil and prepropranolol flow reductions were comparable to the control group. After verapamil, activation delay first occurred at 9.2±1.3 ml/min and was less at lower levels of flow than in the preverapamil sequence. These differences were statistically significant (p<0.005). Propranolol did not alter the flow at which activation delay first occurred but increased the magnitude of the activation delay at coronary flows less than 10 ml/min.

To determine if the effects of propranolol and verapamil on activation could be explained by their effects on [K⁺]e, we compared, where possible, the activation delay associated with a common level of [K⁺]e. There were four matched [K⁺]e points in the control group, three in the verapamil group, and three in the propranolol group. Table 2 illustrates this comparison. In the control group, activation delay was similar at equivalent [K⁺]e and pHe values. Verapamil lessened the activation delay despite equivalent [K⁺]e. It should be noted that acidosis was less marked during the postverapamil flow reduction at equivalent [K⁺]e levels, making a direct comparison at equal [K⁺]e and pHe levels impossible. Propranolol, however, aggravated the activation delay at equivalent [K⁺]e values even though less acidosis was present.

We then performed five additional experiments to correlate the effects of verapamil on the changes in [K⁺]e, to its effect on contractility as determined by the changes in segmental length shortening measured by ultrasonic crystals implanted into the ischemic and nonischemic zone. Figure 6 illustrates the results before and after verapamil in these experiments. During the preverapamil flow reduction, [K⁺]e began to rise when coronary flow was reduced to 20 ml/min. Fractional shortening in the ischemic area began to decrease at flows below 20 ml/min, falling by 45% at a flow of 10 ml/min and 76% at a flow rate of 5 ml/min. Although not shown, reperfusion resulted in a 91% recovery of fractional shortening. The administration of verapamil decreased regional contractility of the reperfused myocardium within the distribution served by the carotid-LAD shunt by 55% but caused only a 23% decrease in contractility in the nonischemic myocardium outside of the distribution of the shunt (not shown). During the postverapamil flow reduction, the rise in [K⁺]e did not occur until coronary flow was reduced to 10 ml/min, but the curve relating the changes in fractional shortening to the decrease in coronary flow was not significantly altered. This is
most clearly seen in the normalized plot of the changes in fractional shortening.

Discussion

Our experiments had two purposes: 1) to determine if verapamil and propranolol were capable of altering the threshold coronary flow associated with the changes in extracellular $K^+$ and pH that we have recently shown to be the most sensitive markers of ischemia and 2) to compare the effects of these agents on the changes in activation associated with low-flow ischemia. Our results indicate that verapamil shifts the threshold flow for the ionic markers of ischemia to lower levels and lessens the activation delay associated with low-flow ischemia. In contrast, propranolol shows neither of these effects. Further, verapamil, not propranolol, decreases afterload and selectively depresses contractility within the ischemic area.

Previous work has shown that the calcium channel blocking agents verapamil and diltiazem attenuate the rise in extracellular $K^+$ and fall in extracellular pH that occurs in the setting of no-flow ischemia. Our results show that verapamil also reduces the coronary flow at which the first changes in $[K^+]_e$ and pH occur. The possible mechanisms by which verapamil induces this effect include improving nutrient flow to the ischemic zone; reducing myocardial work by decreasing afterload, contractility and rate; or providing metabolic protection independent of changes in myocardial work. In our pig model with controlled coronary blood flow and low collateral circulation, an effect of verapamil on nutrient flow is unlikely. Indeed, others have shown that verapamil does not alter regional myocardial blood flow in association with low-flow ischemia even in dogs where collateral flow is more abundant. In each of our experiments, heart rate was constant, thus eliminating this parameter. However, mean arterial blood pressure was significantly reduced after verapamil. In addition, verapamil significantly depressed contractility in the nonischemic zone, had an even greater effect in the reperfused myocardium, and caused a further decrease in contractility as coronary flow was progressively reduced. This selective depression of contractility in the ischemic area is similar to that reported by Smith et al. and by Urquhart et al. Romson et al. used a flow reduction protocol and doses of verapamil similar to those of our study, but reported a nonselective depression of contractility.

Table 2. Comparison of Activation Delay at Similar Levels of $[K^+]_e$ Rise

<table>
<thead>
<tr>
<th>$[K^+]_e$ (mM)</th>
<th>pH</th>
<th>Activation delay (msec)</th>
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<td></td>
<td></td>
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<tr>
<td>C1</td>
<td>C2</td>
<td></td>
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<tr>
<td>11.78</td>
<td>11.00</td>
<td>7.10</td>
</tr>
<tr>
<td>9.07</td>
<td>9.29</td>
<td>7.23</td>
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<tr>
<td>Control</td>
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</tr>
<tr>
<td>12.24</td>
<td>11.99</td>
<td>7.04</td>
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<tr>
<td>8.88</td>
<td>8.95</td>
<td>6.97</td>
</tr>
<tr>
<td>C1</td>
<td>V</td>
<td>C1</td>
</tr>
<tr>
<td>8.48</td>
<td>8.17</td>
<td>7.19</td>
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<tr>
<td>Verapamil</td>
<td></td>
<td></td>
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<tr>
<td>7.45</td>
<td>7.31</td>
<td>6.85</td>
</tr>
<tr>
<td>9.34</td>
<td>9.34</td>
<td>6.50</td>
</tr>
<tr>
<td>C1</td>
<td>P</td>
<td>C1</td>
</tr>
<tr>
<td>8.87</td>
<td>8.87</td>
<td>7.19</td>
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<tr>
<td>Propranolol</td>
<td></td>
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<tr>
<td>9.61</td>
<td>9.68</td>
<td>6.72</td>
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<tr>
<td>7.65</td>
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<td>7.12</td>
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C1, first control reduction; C2, second control reduction; V, verapamil reduction; P, propranolol reduction.
in the ischemic and nonischemic myocardium. Sherman et al\textsuperscript{27} reported that in the setting of no-flow ischemia, verapamil enhanced postextrasystolic potentiation in the center of the ischemic zone. The apparent differences between their results and our observations are probably due to differences in experimental design.

In our present experiments, as in our previous studies of low-flow ischemia,\textsuperscript{8} the decreases in fractional shortening during the predrug flow reduction never occurred at LAD flows that did not cause a change in [K\textsuperscript{+}]\textsubscript{e}. After verapamil, the decrease in fractional shortening induced by the reduction in LAD flow occurred at flows that were not associated with an increase in [K\textsuperscript{+}]\textsubscript{e}. This observation suggests that the decrease in contractility may have protected the myocardium from the metabolic consequences of the decrease in coronary flow, resulting in a dissociation of the contractile and ionic markers of ischemia. In our experiments, contractility in the reperfused ischemia zone returned to 91\% of its control value after the initial control flow reduction. The administration of verapamil before the second flow reduction resulted in a greater reduction in contractility in the reperfused zone than in the normal myocardium. Thus, we cannot exclude the possibility that the preceding ischemic episode contributed to this effect of verapamil and to the further reduction in contractility observed during the postverapamil reduction in LAD flow. Further experiments are required to address this possibility as well as to clarify the influence of the verapamil-induced decrease in afterload on the observed changes in the threshold flow for the rise in [K\textsuperscript{+}]\textsubscript{e} and pH\textsubscript{e}.

There is convincing evidence to support the concept that verapamil provides metabolic protection to the ischemic myocardium even in the absence of a primary effect on contractility. Lange et al\textsuperscript{3} observed that verapamil lessened the decrease in ATP associated with 15 minutes of total coronary occlusion. Watson et al\textsuperscript{20} administered verapamil after an 80\% reduction in coronary flow had caused extracellular pH to fall to the range of 6.1–6.8 and observed a return of pH towards control values. Although they did not record contractility, it is reasonable to assume that it had decreased in association with the fall in pH\textsubscript{e}.

The changes that we have observed after the administration of verapamil do not necessarily imply that verapamil delayed the occurrence of ischemic cell injury in our preparation. However, Reimer et al\textsuperscript{21} reported that in dogs the administration of verapamil before a 40-minute occlusion of the circumflex coronary artery was associated with significantly less necrosis than was present in the untreated animals.

Verapamil is known to decrease the frequency of ventricular arrhythmias, to prevent ventricular fibrillation,\textsuperscript{22–25} and to lessen the degree of conduction slowing during no-flow ischemia.\textsuperscript{8,10,11,26,27} Our results indicate that verapamil also reduces the magnitude of the activation delay that occurs as coronary flow is reduced. The protective effect of verapamil on the rise in [K\textsuperscript{+}]\textsubscript{e} and fall in pH\textsubscript{e} undoubtedly contributes to the lessening of the ischemia-induced local activation delay. However, these effects persisted when matched for equivalent values of [K\textsuperscript{+}]\textsubscript{e}. While we could not match simultaneously for equivalent values of [K\textsuperscript{+}]\textsubscript{e} and pH\textsubscript{e}, our previous study of no-flow ischemia\textsuperscript{8} showed that at comparable pH levels, activation delay was less after verapamil than during the control occlusion despite higher [K\textsuperscript{+}]\textsubscript{e} levels. These results, of course, must be interpreted in light of the transmural gradients for the potassium and activation changes noted by Mori et al\textsuperscript{28} and the fact that we measured [K\textsuperscript{+}]\textsubscript{e} and activation at disparate sites in the myocardium. Nevertheless, these results suggest additional effects of verapamil beyond its effects on [K\textsuperscript{+}]\textsubscript{e} and pH\textsubscript{e}, such as a lessening of cellular uncoupling\textsuperscript{29} or a decrease in the inhomogeneity of the change in [K\textsuperscript{+}]\textsubscript{e} and pH\textsubscript{e} or both.\textsuperscript{8}

The \textbeta-\textadrenergic–blocking agents, like the calcium channel blocking agents, have been reported to reduce the rate of rise of [K\textsuperscript{+}]\textsubscript{e}\textsuperscript{5,6} induced by no-flow ischemia and to lessen the rate and magnitude of the decrease in pH\textsubscript{e} during no-flow\textsuperscript{30} and low-flow\textsuperscript{31} ischemia. We were unable to document a significant effect of propranolol on the threshold flow for the change in [K\textsuperscript{+}]\textsubscript{e} and pH\textsubscript{e} or on the magnitude of the subsequent changes in [K\textsuperscript{+}]\textsubscript{e} and
pH, accompanying the sequential reduction in flow. Our study indicates that even in the absence of a significant effect on $[K^+]_o$, and pH, propranolol exaggerates the conduction delay at each level of low-flow ischemia. This result, when combined with the 23% fall in dP/dt, indicates that β-blocking doses of propranolol were used. It is consistent with other studies showing that propranolol administration2 and sympathetic denervation32 aggravate local activation delay induced by no-flow ischemia when heart rate is fixed, whereas isoproterenol administration6 and sympathetic stimulation33 lessen the activation delay.

In summary, our results indicate that when heart rate is held constant, verapamil provides metabolic protection to the myocardium that permits coronary flow to be reduced to lower levels before the ionic markers of ischemia appear. In addition, verapamil lessens the activation slowing associated with ischemia. Propranolol does not permit a greater reduction in coronary flow before the appearance of the ionic markers of ischemia and aggravates the activation slowing associated with ischemia. Verapamil decreases afterload, selectively depresses contraction within the reperfused ischemic zone, and may dissociate the contractile, ionic, and electrical changes that occur as coronary flow is reduced. In contrast, propranolol does not reduce afterload and is reported to improve contractility within the ischemic zone.34,35 Although further studies are needed to determine if the effects of verapamil on ionic and electrical markers of low-flow ischemia are secondary to its effects on contractility and afterload, our results suggest that the calcium channel blocking agents and the β-adrenergic–blocking agents should not be considered to be equivalent or interchangeable when evaluating therapeutic options for patients with ischemic heart disease.

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References


**KEY WORDS** * low-flow ischemia * extracellular K⁺ and pH

* calcium channel blockers * β-adrenergic-blocking agents

* regional contractility
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