Comparative effects of verapamil, diltiazem, and nifedipine on hemodynamics and left ventricular function during acute myocardial ischemia in dogs

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ABSTRACT The calcium channel-blocking drugs verapamil, diltiazem, and nifedipine are being used with increasing frequency in patients with angina pectoris due to coronary artery disease. Although each of these agents possesses negative inotropic potential, their relative effects on myocardial function in relation to their vasodilator potencies are unknown. We undertook to study this in 20 conscious dogs that had partial occlusions of their circumflex coronary arteries during therapy with placebo, verapamil, nifedipine, or diltiazem. Myocardial blood flow was measured by use of microspheres, and left ventricular function was measured by radionuclide angiography. Drug effects were compared at doses causing equal decreases in mean arterial pressure and coronary vascular resistance of nonischemic myocardium. Global ejection fraction and ejection fraction of the ischemic region were significantly decreased by verapamil (p < .01) and increased by nifedipine (p < .001); diltiazem caused no significant changes. Verapamil significantly increased peak diastolic filling rate (p < .001); nifedipine also increased diastolic filling rate, but only at doses that markedly decreased mean arterial pressure and coronary vascular resistance. The effect of diltiazem on diastolic filling rate was not significantly different than placebo. For doses causing an equal decrease in mean arterial pressure, verapamil decreased heart rate (p < .001), and diltiazem and nifedipine increased heart rate (p < .001).

We conclude that the relative potencies of these three calcium channel-blocking agents on left ventricular systolic and diastolic function during myocardial ischemia are different when compared with their relative vasodilator potencies. These differences may have important clinical implications.


THE ANTIANGINAL POTENTIAL of calcium channel-blocking agents is currently under active investigation. Of the several calcium channel-blocking agents available, the most commonly studied have been verapamil, diltiazem, and nifedipine. These agents have several hemodynamic and electrical effects: they are potent coronary and systemic vasodilators; they possess negative inotropic potential; and verapamil and diltiazem can decrease sinus node automaticity and thereby decrease heart rate. As a result of these effects, angina due to coronary artery disease might be improved. Thus, any negative inotropic actions and slowing actions of the sinus node, as well as any hypotensive effects, may improve angina pectoris by decreasing myocardial oxygen demands. In addition, the capacity of the calcium antagonists to dilate coronary arteries and thereby increase myocardial blood flow may play an important therapeutic role even in patients without frank coronary spasm. On the other hand, if the negative inotropic effects of these drugs were marked, congestive heart failure could be precipitated.

While each of these agents has been shown to possess the capacity for decreasing myocardial contractility, there is considerable controversy concerning the relative magnitude of their myocardial depressant potential. One of the reasons for such controversy is that although each drug has been assessed in intact dogs without ischemia or in isolated muscle preparations, there have been no studies that have used dose-response curves in conscious animals in which reflex mechanisms remain intact and that have investi-
gated the relative effects of all three drugs in the same preparation of myocardial ischemia.

In addition, although each of these drugs exerts beneficial effects in patients with angiina pectoris due to coronary artery disease,12-14 data have emerged suggesting that the potency of these drugs is different regarding their relative inotropic, vasodilator, and electrophysiologic effects. Since it is possible that some patients might be more sensitive to the negative chronotropic action of a calcium channel-blocking agent, some to its vasodilatory effect, and some to any myocardial depressant action, it would be critical to know the relative potencies of the drugs in causing each of these effects. The purpose of the present investigation, therefore, was to compare the effects of verapamil, diltiazem, and nifedipine on heart rate, hemodynamics, and left ventricular function in conscious intact dogs with myocardial ischemia and to evaluate these effects in relation to their vasodilator potencies.

Methods

Twenty foxhounds weighing 22 to 33 kg underwent left thoracotomy through the fourth intercostal space under general anesthesia with 4% thiopental sodium (Pentothal) and halothane. Catheters filled with heparin were inserted through the internal mammary gland into the aorta, through the left atrium into the left ventricle, and into the left atrium. A hydraulic occluder (R. E. Jones Co., Silver Spring, MD) was implanted around the circumflex coronary artery near its origin. A pacemaker was installed onto the right ventricle. The wound was closed and all tubing was passed subcutaneously to the back of the animal and brought through the skin between the scapulae. The dogs were treated with 4 ml of floxacinil intramuscularly.

Protocol. Studies were conducted 7 to 10 days after surgery when the animals appeared healthy. One-half hour before study and approximately 2 hr before drug injection, dogs were sedated with morphine sulfate, 20 mg, intramuscularly. They were studied in the conscious state under control conditions in the absence of myocardial ischemia and during partial coronary occlusion, when four doses of either verapamil, diltiazem, nifedipine, or placebo (normal saline) were infused intravenously. Five dogs were studied in the placebo-treated group, five in the verapamil-treated group, five in the diltiazem-treated group, and five in the nifedipine-treated group. The drugs were given in sequential order. The first dog received verapamil, the second placebo, the third nifedipine, and the fourth diltiazem. This sequence was then repeated until all studies were completed.

Radionuclide angiography was performed to assess left ventricular function. Before imaging, red blood cells were labeled in vivo with 20 mCi of technetium-99m. Imaging was carried out in the left anterior oblique projection by use of an El Scint camera with a high-resolution parallel-hole collimator. A computer-based procedure gated to the electrocardiogram was used to collect and organize the data as previously described.15

During the entire study, left ventricular pressure, aortic pressure, left ventricular dP/dt, left ventricular end-diastolic pressure, left atrial pressure, and heart rate were recorded on a Gould Brush recorder.

Partial coronary occlusion was obtained by filling the hydraulic occluder with saline until there was a decrease in dP/dt and until a wall motion abnormality was seen on radionuclide angiography. The partial coronary occlusion was confirmed during the experiment by noting a wall motion abnormality on radionuclide angiography that became worse during total occlusion and better after reperfusion.

Myocardial blood flow was measured by serial injections of radioactive microspheres, 15 μm in diameter, labeled with 85Sr, 51Cr, 99mTc, 46Sc, 125I, or 141Ce. The microspheres were sonicated for 2 min and were diluted in 3 ml of saline. After a 30 sec collection of arterial blood from the aorta, approximately 2 million microspheres were injected into the left atrium, followed by flushing with 10 ml of saline. Collection of arterial blood continued at 3.8 ml/min for 90 sec after microsphere injection.

Drug doses were as follows: For verapamil and diltiazem, a loading dose of 30 μg/kg/min was infused over 2 min, followed by a constant infusion of 5 μg/kg/min for dose one, 10 μg/kg/min for dose two, 20 μg/kg/min for dose three, and 40 μg/kg/min for dose four. For nifedipine a loading dose of 5 μg/kg/min was infused over 2 min, followed by a constant infusion of 1 μg/kg/min for dose one, 2 μg/kg/min for dose two, 4 μg/kg/min for dose three, and 6 μg/kg/min for dose four. Dogs treated with placebo had normal saline infused at times identical to those used in the drug studies. The total volume infused for animals treated with placebo, verapamil, and diltiazem was 500 ml and the total volume was 400 ml for animals treated with nifedipine.

Each dose was infused over a period of approximately 15 min. Collection of imaging data began 2 min after the start of infusion of each drug dose and lasted 7 to 8 min. Microspheres were injected 3 min after the start of infusion of each dose, and hemodynamic measurements were recorded 3 min later.

At the conclusion of the study the dogs were killed and the hearts were excised. Evans blue dye was injected into the circumflex artery just distal to the site of occlusion. After fixation in formalin, the hearts were cut in six rings from apex to base. Samples were taken from the ischemic zone as defined by the interface between tissue stained by blue dye (ischemic tissue) and that unstained by dye (nonischemic tissue). Samples were divided into subendocardial, midmyocardial, and subepicardial zones. Samples were weighed, and counts were obtained from the tissue samples, blood, and isotope standards.

Data analysis

Radionuclide angiography. After left ventricular and background regions of interest were drawn, left ventricular ejection fraction was calculated by computer analysis of the time-activity curves.16 The diastolic filling rate was computed from the time-activity curve as previously described17 and was expressed in end-diastolic volumes per second.

The regional ejection fraction was derived by a computer program that located the center of gravity of the left ventricle and divided the left ventricle into four quadrants. The left upper quadrant, which demonstrated a wall motion abnormality on cineangiographic display of the gated blood pool scan, was designated as the ischemic region. A time-activity curve for this area was derived and a regional ejection fraction was calculated by computer analysis.

Coronary vascular resistance. Coronary vascular resistance was calculated by dividing the mean aortic pressure by the blood flow to nonischemic myocardium as obtained by the microsphere data.

Statistics. Control vs partial occlusion data were compared by one-way analysis of variance. Dose-response curves and drug effects for doses causing equal decreases in mean arterial pressure and for doses causing equal decreases in coronary vascular resistance were compared by two-way analysis of variance.18
TABLE 1
Hemodynamics and left ventricular function during drug infusions

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MAP = mean arterial pressure (mm Hg); LAP = left atrial pressure (mm Hg); HR = heart rate; EF = ejection fraction; DFR = peak diastolic filling rate in end-diastolic volumes per second; MBF = myocardial blood flow (ml/min/g); IZ = ischemic zone; NZ = normal zone; CVR = coronary vascular resistance (mm Hg/ml/min/g).

*Hemodynamics and left ventricular function during control (C), partial occlusion (PO), and four doses of placebo, verapamil, diltiazem, and nifedipine. Data are expressed as mean ± standard deviation. PO is compared with C and doses 1, 2, 3, and 4 are compared with PO.

Statistical comparisons: \( *p < .05 \); \( \ast p < .01 \); \( \ast\ast p < .002 \); \( \ast\ast\ast p < .005 \).

FIGURE 1. Comparison of dose-response curves for hemodynamics. 1, 2, 3, 4 represent doses 1, 2, 3, and 4 of drug or placebo. The mean and standard deviation of the mean are shown. Nifedipine (N), verapamil (V), and diltiazem (D) all significantly decreased mean arterial pressure (MAP) when compared with placebo (P). V and D significantly increased left atrial pressure (LAP). Change in MAP and LAP are represented as % of partial occlusion (PO).
Results

Hemodynamics. Partial occlusion of the circumflex coronary artery produced a significant decrease in mean arterial pressure (p < .01), an increase in heart rate (p < .05), and no significant change in left atrial pressure.

Dose-response curves were performed to demonstrate drug effect during sustained coronary flow reduction (figure 1). With placebo, mean arterial pressure increased significantly during the experiment (p < .01). When compared with that after placebo, mean arterial pressure was lower after most doses of the three drugs (p < .01).

Left atrial pressure increased slightly but insignificantly during placebo infusion, decreased insignificantly with the first dose of nifedipine, and increased only during high-dose infusion (dose four). Even at that dose, left atrial pressure was still less than that after placebo infusion. Diltiazem and verapamil significantly increased left atrial pressure during higher doses (p < .001).

Myocardial blood flow and coronary vascular resistance. Myocardial blood flow to the ischemic region during partial coronary occlusion was 0.23 ± 0.03 ml/min/g (18% of myocardial blood flow in the normal zone). Myocardial blood flow to the ischemic region remained unchanged throughout the experiment during placebo, verapamil, diltiazem, and nifedipine infusion (figure 2).

Coronary vascular resistance in the normal zone did not change after partial coronary occlusion or during infusion of placebo after occlusion. However, it fell significantly with nifedipine (p < .001), verapamil (p < .01), and diltiazem (p < .001) (figure 2). The ratio of endocardial to epicardial blood flow did not change during placebo, verapamil, diltiazem, or nifedipine infusion. Myocardial blood flow decreased from 0.23 ± 0.03 ml/min/g during partial occlusion to 0.04 ± 0.03 ml/min/g after total coronary occlusion (p < .001), which was 4% of normal zone flow.

Drug effects at matched decreases in mean arterial pressure and coronary vascular resistance. Figures 3 and 4 demonstrate drug effects compared at doses causing equal decreases in mean arterial pressure and coronary vascular resistance. These graphs contain only those points during which mean arterial pressure decreased or did not change in response to the drug. Thus, the graphs differ from figure 1, which contains all data points. Verapamil significantly decreased global ejection fraction and ejection fraction of the ischemic zone (p < .01) even at doses causing no change in mean arterial pressure or coronary vascular resistance. In contrast, nifedipine consistently increased ejection fraction (p < .001). Although this effect was observed before alterations occurred in mean arterial pressure (figure 3), the positive inotropic and vasodilator actions of nifedipine appeared simultaneously, as manifest by the parallel changes in ejection fraction and coronary vascular resistance produced by the drug (figure 4). Diltiazem caused no consistent change in either global or ischemic zone ejection fraction.

Verapamil, even in doses causing little or no decrease in mean arterial pressure or coronary vascular resistance, significantly increased peak diastolic filling rate (p < .001). Nifedipine also increased peak diastolic filling rate (p < .05), but only at doses that caused marked decreases in mean arterial pressure and coronary vascular resistance. Diltiazem did not significantly alter diastolic filling rate.

For equipotent doses causing equal decreases in mean arterial pressure and coronary vascular resistance, verapamil decreased heart rate (p < .001) and diltiazem and nifedipine increased heart rate (p < .001).

Discussion

Each of the drugs studied in this investigation — verapamil, diltiazem, and nifedipine — has been

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shown to inhibit calcium entry into myocardial and smooth muscle cells; each also exerts potent vasodilator actions on coronary and systemic arteries. Despite these similarities, we found that the three drugs differ markedly in their effects on myocardial contractile function, left ventricular diastolic filling, and heart rate. While verapamil reduces global ejection fraction and the ejection fraction of the ischemic zone, nifedipine increases both of these indexes of cardiac function. Diltiazem does not consistently alter global or ischemic zone ejection fraction. Similarly, while verapamil and diltiazem increase left atrial pressure during partial coronary occlusion, administration of nifedipine tends to decrease it. While administration of verapamil is associated with slower heart rates during myocardial ischemia when compared with values observed in placebo-treated dogs, nifedipine and diltiazem consistently increase heart rate.

Previous studies assessing the direct myocardial effects of these drugs have most commonly used preparations in vitro in which the contributing influences of reflex mechanisms are necessarily eliminated. Other studies have used open-chest dogs in which the effects of anesthesia and acute operative trauma profoundly influence hemodynamics and reflex responses. It is therefore uncertain how relevant the data derived from such studies are to the clinical situation.

We used conscious dogs, instrumented over the long-term, to avoid these complicating factors. Equally important, however, was the fact that we constructed dose-response curves, so that we could avoid the limitations inherent in any drug study in which single, arbitrarily chosen, drug doses are compared. Dose-response curves also enabled us to make comparisons of the potencies of each of these drugs on left ventricular inotropic and chronotropic function as related to their vasodilator potency. This was accomplished by assessing drug effects throughout a physiologic dose range and by comparing the effects of physiologically equipotent drug doses, e.g., doses with equivalent vasodilator activity.

Using this technique, we not only found the drugs had different effects on myocardial contractile function, diastolic filling, and heart rate, but that the differences were evident at doses of each drug that exerted identical effects on mean arterial pressure and coronary vascular resistance. Nifedipine increased global ejection fraction and ejection fraction of the ischemic zone.

FIGURE 2. Comparison of dose-response curves for myocardial blood flow (MBF) and coronary vascular resistance (CVR) of the normal zone (NZ) and MBF of the ischemic zone (IZ). The mean and standard deviation of the mean are shown. Verapamil (V), nifedipine (N), and diltiazem (D) all significantly increased MBF and decreased CVR in the NZ, when compared with placebo (P). V, D, N, and P did not change MBF in the IZ. The scale used to represent IZ MBF is expanded for demonstration purposes.
in parallel with its vasodilator actions. Verapamil, in contrast, when assessed at doses producing identical vasodilator effects as nifedipine, decreased both global and ischemic zone ejection fractions.

With this methodology, we also were able to demonstrate that the drugs exhibited different relative potencies when threshold doses causing vasodilatation were compared with threshold doses affecting myocardial contractile function, heart rate, and left ventricular diastolic filling. Thus, verapamil depressed myocardial contractile function even at a dose that was not yet sufficient to alter coronary vascular resistance (figure 4), a finding suggesting that the myocardium may be more sensitive to the calcium-inhibiting actions of this drug than is vascular smooth muscle. It also suggests that a clinically "safe" dose of verapamil, in terms of its myocardial depressant effects, cannot be predicted on the basis of the effects of the drug on arterial pressure.

The improvement in ejection fraction caused by nifedipine and diltiazem at doses causing a 40% decrease in mean arterial pressure is depicted in figure 3.

FIGURE 3. Comparison of drug effect at doses causing an equal decrease in mean arterial pressure (MAP). The mean and standard deviation of the mean for each 10% change in MAP is shown. Ischemic zone (IZ) and global ejection fraction (EF) were increased by nifedipine (N), decreased by verapamil (V), and unchanged by diltiazem (D). Change is presented as % of partial occlusion (PO) before drug administration. Only drug doses that decreased MAP are included, resulting in fewer data points in this figure than in figures 1 and 2.

FIGURE 4. Comparison of drug effects at doses causing an equal decrease in coronary resistance (CVR). The mean and standard deviation of the mean for each 20% change in CVR is shown. Ischemic zone (IZ) and global ejection fraction (EF) were increased by nifedipine (N), decreased by verapamil (V), and unchanged by diltiazem except for a dose causing a 40% decrease in CVR where EF (IZ) was depressed. Change is represented as % of partial occlusion (PO) before drug administration. Only drug doses that decreased MAP are included, resulting in fewer data points in this figure than in figures 1 and 2.
fedipine throughout its dose-response curve suggests that nifedipine, under the conditions of the present study, exerts no physiologically important myocardial depressant actions. Moreover, the threshold dose at which ejection fraction increased was the same as that which caused a decrease in vascular resistance (figure 4), a finding compatible with the concept that improved ejection fraction observed after nifedipine is caused by the afterload-reducing capacity of the drug and reflex stimulation of the heart.

Although diltiazem does decrease global ejection fraction at doses providing large decreases in coronary vascular resistance (figure 4), at doses producing no more than 10 to 15 mm Hg decreases in mean arterial pressure neither global nor ischemic zone ejection fraction was altered. This suggests that diltiazem, when administered in doses producing physiologic changes in arterial pressure and coronary vascular resistance, does not depress normal or ischemic myocardium. However, if the drug were devoid of myocardial depressant activity, ejection fraction would have been expected to increase because of the concomitant decrease in afterload, as was found with nifedipine. Hence, our findings suggest that diltiazem does have negative inotropic effects during moderate myocardial ischemia (a finding also suggested by the increase in left atrial pressure caused by the drug), but that these are milder than the effects of verapamil and are masked by the afterload-reducing actions of the drug and the resulting sympathetic stimulation of the heart caused by baroreceptor reflexes.

Differences in relative potencies of the three drugs on diastolic filling were also observed. Verapamil administration led to large increases in the peak rate of ventricular filling, which had been depressed after partial coronary occlusions. As with systolic cardiac function, verapamil altered diastolic filling at a very low dose, that is, at a dose that was insufficient to alter mean arterial pressure or coronary vascular resistance. Although nifedipine also improved diastolic filling, it did so only at the doses producing large decreases in mean arterial pressure and coronary vascular resistance. Diltiazem exerted no significant effect on diastolic function.

The data demonstrating improvement in early diastolic filling produced by verapamil and nifedipine, although interesting, do not permit conclusions to be drawn as to the mechanism by which this improved filling occurs. The increase in diastolic filling rate produced by verapamil was associated with an increase in left atrial pressure. However, this is not a likely mechanism responsible for the change in diastolic filling that we observed, since filling was altered by the drug at doses lower than those that significantly increased left atrial pressure. Moreover, the increase in diastolic filling rate observed in the nifedipine-treated dogs occurred without an increase in left atrial pressure. The increase in heart rate caused by nifedipine, however, could account in part for the change in diastolic filling rate. Myocardial relaxation, an early diastolic event, is thought to be due in part to the ability of the sarcoplasmic reticulum to take up calcium and to thereby lower sarcoplasmic calcium ion concentration; this in turn results in actin-myosin dissociation.21 Relaxation becomes prolonged with myocardial ischemia22 or an increase in calcium concentration.23

A calcium channel-blocking agent might, by decreasing calcium concentration in the region of the myofibrils, correct defective relaxation. Therefore, an early diastolic phenomenon, such as peak diastolic filling rate, might be particularly sensitive to the effects of calcium channel-blocking drugs in ischemia. Definitive conclusions regarding the precise mechanisms responsible for the observed changes in peak filling rate, however, will require further work.

The experimental preparation of partial coronary artery occlusion used in this investigation was specifically chosen to provide a model of ischemia that did not result in the profound decreases in myocardial flow as seen after total acute coronary occlusion and myocardial infarction. Thus, myocardial blood flow in the ischemic zone after partial occlusion was 18% of normal zone flow. In contrast, total coronary occlusion at the end of each study reduced flow to 4% of normal zone flow. Because of the relatively moderate degree of ischemia, we do not know whether the results of this investigation also apply to situations in which ischemia is more profound, as in acute myocardial infarction, or to situations in which left ventricular failure is present.

This model also provides data for the first time on the effects of three calcium channel-blocking drugs on myocardial blood flow to ischemic myocardium during partial coronary occlusion. Myocardial blood flow to the ischemic region did not show any significant change during the course of the experiment in the placebo-treated dogs. This finding confirms the stability of our preparation of partial coronary occlusion. We found that nifedipine, verapamil, and diltiazem did not alter flow to either the ischemic endocardium or epicardium. This lack of effect was observed despite the fact that nifedipine and verapamil caused large increases in myocardial blood flow and decreases in coronary vascular resistance of nonischemic myocardium.
The lack of effect on flow within partially ischemic myocardium may have been due to the fact that the arterioles of the ischemic zone were already maximally dilated and were therefore not susceptible to further dilatation. A second explanation relates to the fact that we chose to study the actions of these drugs under physiologic conditions, so we made no attempt to control heart rate or arterial pressure (and thereby distending pressure of the coronary artery). It has been shown that alterations in distending pressure of the coronary artery, particularly in preparations in which a coronary artery is partially occluded, can cause passive parallel changes in the resistance of the large epicardial coronary arteries.24 Hence, it is possible that the coronary arterioles were dilated by the calcium channel–blocking agents, but that the resulting effect on coronary vascular resistance was overridden by a concomitant passive increase in resistance caused by the fall in coronary distending pressure. It is also possible that the drugs, by dilating coronary arterioles of the nonischemic myocardium, caused a coronary steal phenomenon. Finally, it should be noted that there usually is marked variability in myocardial flow data when microsphere techniques are used25 and this is particularly true when flow is measured in ischemic tissue.26 It is therefore possible that small changes in flow were induced in these agents, but these could not be detected by this technique.

Other investigators have observed an increase in myocardial blood flow of the ischemic zone with calcium channel–blocking agents.27-30 The difficulty in comparing these studies with our data is that they all used total occlusions, i.e., a model of myocardial infarction. Improvement in flow to the ischemic region in these studies was thought to be secondary to increases in collateral flow. We used partial occlusions (to simulate angina rather than infarction) in which antegrade flow persists. Because the contribution of collateral flow is small under such circumstances,31 direct comparison between our investigation and previous studies is impossible.

Thus, the precise direct effects of verapamil, nifedipine, and diltiazem on the arterioles or collaterals supplying ischemic myocardium cannot be definitively ascertained from the results with this preparation of partial coronary occlusion. However, when partial occlusion occurs due to a fixed stenosis involving a large coronary artery, our data do indicate that any beneficial effect that might be caused by these drugs on myocardial ischemia or function will not be due to any substantial increase in myocardial blood flow.

Although the applicability of the results of this investigation to the clinical situation is unclear, and caution must be taken in extrapolating results from an animal preparation to human subjects, several considerations are relevant. The depression of myocardial contractile function within the ischemic region produced by verapamil may lead, if the ischemic region is sufficiently large, to congestive heart failure. On the other hand, it is also possible that under certain circumstances such depression may be beneficial. As previously proposed, depression of contraction of ischemic myocardium by diminishing myocardial oxygen consumption may actually diminish the degree of ischemic injury.32

In addition, although the results of our study suggest that nifedipine and diltiazem had no important myocardial depressant effects, it does not necessarily follow that these drugs are safe to use in the clinical setting. Diltiazem did substantially increase left atrial pressure despite no or minimal effects on global ejection fraction, and previous studies using nifedipine in an isolated muscle preparation demonstrated that under these conditions, nifedipine has myocardial depressant effects greater than those of verapamil.

Since the preparation of partial ischemia used in this investigation resulted in only mild elevations in left atrial pressure, the results may not be applicable to more severe and extensive myocardial ischemia that lead to frank cardiac decompensation. Nor may they be applicable to situations in which cardiac dysfunction is related to causes other than ischemic heart disease. Hence, while it appears that verapamil is more likely to lead to myocardial decompensation than is nifedipine or diltiazem, it would be premature to conclude that nifedipine and diltiazem are safe to use in all patients who have ischemic or nonischemic forms of cardiac disease.

Despite these uncertainties, it is clear from the results of this investigation that although nifedipine, verapamil, and diltiazem share the common physiologic properties of calcium flux inhibition and vasodilatation, they differ markedly in their effects on cardiac systolic function, diastolic filling, and heart rate. It is therefore likely that clinical situations will arise in which one of these drugs will elicit a more desirable therapeutic effect than the other two, but that another drug would provide optimal effect in a different clinical setting.

We express our appreciation to Mr. William H. Parker who gave valuable assistance in performing surgery and the experiments, to the staff of the Experimental Medicine and Surgery branch of the Division of Research Services who participated in the surgical preparations and in animal care, to Beth Bridau who

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participated in the statistical data analysis, and to June Moon for the preparation of the manuscript.

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_Circulation_. 1984;69:382-390
doi: 10.1161/01.CIR.69.2.382

_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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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