Diltiazem-induced blockade of sympathetically mediated constriction of normal and diseased coronary arteries: lack of epicardial coronary dilatory effect in humans

KENNETH F. HOSSACK, M.D., B. GREG BROWN, M.D., PH.D., DOUGLAS K. STEWART, M.D., AND HAROLD T. DODGE, M.D.

ABSTRACT
To determine mechanisms of benefit from diltiazem, 13 patients with coronary disease performed sustained isometric handgrip exercise and repeated the procedure during intravenous infusion of diltiazem (0.25 mg/kg bolus followed by 0.003 mg/kg/min). Cardiovascular responses to handgrip, diltiazem, their combination, and nitroglycerin were assessed by hemodynamic and electrocardiographic measurements and by computer-assisted measurements of normal and diseased segments of epicardial coronary arteries. Handgrip produced increases in heart rate (12%; p < .001), pulmonary arterial pressure (19%; p < .005), and pulmonary wedge pressure (33%; p < .005). Diltiazem produced significant reductions in heart rate (7%; p < .05) and aortic pressure (14%; p < .001). Pulmonary arterial pressure and pulmonary wedge pressure were unchanged by diltiazem. Diltiazem did not prevent the increase in heart rate or in aortic or wedge pressure associated with handgrip. Diltiazem prolonged atrioventricular conduction from 0.18 ± 0.03 to 0.20 ± 0.03 sec (p < .001). Compared with control values, nitroglycerin reduced aortic pressure (14%; p < .005), pulmonary arterial pressure (38%; p < .001), and pulmonary wedge pressure (42%; p < .005). Heart rate was unchanged. The constriction (20%) in lumen area of normal coronary arterial segments during handgrip was effectively prevented by infusion of diltiazem (1%; p < .001). Nitroglycerin produced a significantly greater increase (20%) in diameter of normal coronary arterial segments than diltiazem (3%; p < .001) and tended to have a more favorable effect than diltiazem on stenosis minimum area and flow resistance. The handgrip-induced constriction of minimum area and increase in stenosis flow resistance was prevented during diltiazem infusion. Diltiazem is a minimal epicardial coronary dilator compared with nitroglycerin, but it effectively blocks sympathetically mediated constriction of normal and diseased epicardial coronary arteries in human beings.


DILTIAZEM, a slow channel-blocking drug, is an effective agent for improving duration of exercise and reducing the signs and symptoms of myocardial ischemia in patients with exertional angina.1 The mechanism of action is related in part to a reduction in submaximal myocardial oxygen demand,1,2 but other studies have suggested that oral diltiazem may improve myocardial blood flow during exertion in patients with exertional angina.3,4 This evidence was based on observations in noninvasive studies made during exercise testing. The calcium slow channel-blocking drugs are frequently called "potent coronary vasodilators," although this perception is not well documented in humans. Diltiazem improves coronary sinus blood flow by 20% in animals,5 and one report indicated an increase in blood flow in humans during short-term intervention;6 however, the change was not statistically significant.

To further define the mechanisms of diltiazem’s apparent benefit to myocardial perfusion, the effects of intravenous diltiazem on systemic and pulmonary hemodynamics and on epicardial coronary arteries and stenoses in the resting state and during isometric handgrip exercise were measured. These effects were compared with those of sublingual nitroglycerin, a potent

From the Department of Medicine, Division of Cardiology, University of Washington, Seattle.
Supported in part by a grant-in-aid from Marion Laboratories, Kansas City.
Address for correspondence: Kenneth F. Hossack, M.D., Department of Medicine, Division of Cardiology, 777 Bannock St., Denver, CO 80204-4507.
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dilator of epicardial coronary vessels. A previously validated computer-assisted method for measurement of coronary arterial dimensions was used.7

Methods

Patient selection. Eleven men and two women (mean age 57 ± 6 years) participated in the study after signing an approved document of informed consent. Coronary arteriographic studies were performed for the evaluation of exertional angina in 11 patients and the other two patients were asymptomatic after bypass surgery. None of the patients had symptoms or histories consistent with coronary arterial spasm. Six patients had three-vessel disease, two had two-vessel disease, four had one-vessel disease, and one had a mild (30% stenosis) right coronary lesion.

Study protocol. Twenty-four hours before study all cardiac medications were discontinued. Patients were studied in the fasting state and premedication with oral diazepam was used. A Swan-Ganz catheter was placed in the pulmonary artery and coronary arteriographic examination was performed with the Judkins technique. The diagnostic portion of the catheterization was completed and the video tape was reviewed. In each patient a vessel was selected for study on the basis of clear visualization of the area of stenosis without distortion by overlapping vessels. Cineangiograms of this vessel were made in two perpendicular views that showed the anatomy and disease most clearly. Baseline hemodynamic measurements, including aortic pressure, pulmonary arterial pressure and pulmonary capillary wedge pressure, were made. Heart rate and PR interval were measured from the electrocardiogram recorded at 100 mm/sec paper speed.

Patients then performed sustained handgrip (4 min) at 25% of their predetermined maximal grip strength, using a hand ergometer. During the fourth minute hemodynamic variables and heart rate were recorded and a single injection of contrast medium into the coronary artery was made. Patients then rested until blood pressure and heart rate returned to control values. Diltiazem was then given as an intravenous bolus (0.25 mg/kg) followed by continuous infusion (0.003 mg/kg/min). This dose regimen was chosen to achieve steady-state plasma levels similar to those obtained with an oral dose of 360 mg/day; it was believed from clinical experience that patients tolerated this dose well and that it provided significant symptomatic benefit, whereas smaller oral doses of diltiazem were often ineffective. Seven to 10 min after commencement of the diltiazem infusion, a new hemodynamic steady state was achieved, and hemodynamic and cineangiographic determinations were repeated. Patients then repeated the handgrip effort during continued diltiazem infusion. During the fourth minute hemodynamic and cineangiographic determinations were repeated. Blood samples were taken for measurement of plasma diltiazem levels during the control state and after 10 min of diltiazem infusion.

The diltiazem infusion was terminated and hemodynamic variables were allowed to return to baseline values. Sublingual nitroglycerin (0.4 mg) was then given and 3 to 5 min later hemodynamic and cineangiographic determinations were repeated. Nitroglycerin was chosen because this was previously shown to dilate epicardial coronary arteries.9 The study indicated that the effects of sublingual nitroglycerin on coronary arteries, measured 4 min after the doses, were similar to the effects of 0.05 mg of intracoronary nitroglycerin. Thus the use of nitroglycerin provided a comparison for the effect of diltiazem alone. The sequence of drug administration was not randomized because of the possibility of a carry-over effect of nitroglycerin obscuring the effects of diltiazem or handgrip. Nitroglycerin was used as a means of assessing the vasomobility of the coronary arteries, and this study was not designed to evaluate the effect of nitroglycerin on handgrip responses.

Analysis of angiograms. The methodology for computerized analysis of coronary arteriograms was described in detail previously.7 The technique involved digitizing the borders of selected coronary arterial segments from a magnified projection of the cineangiogram. Corrections for pincushion distortion and magnification were made. Lumen diameter and area in normal and diseased segments were measured, with a dimensional accuracy of ± 100 μm (SD). Percent diameter and area reduction in the stenosis and its flow resistance were estimated, assuming 1 ml/sec flow. An earlier study demonstrated the reproducibility of control measurements. Although absolute measurements were not validated in vivo, individual measurements are very reproducible, and in this study each patient served as his own control. Changes seen with intervention can therefore be attributed to the intervention. The previous study addressed the issue of the effect of contrast on coronary dimensions. When repeat angiograms were made 4 min after the prior injection no significant changes were detected.

In this study, both normal segments and stenosed segments were chosen for analysis. The normal segments were defined as vessels without lumen irregularities and were grouped according to cross-section area: large vessels >8 mm², moderate vessels 4 to 8 mm², and small vessels <4 mm². (Typically, the left main artery is 16 mm² and the proximal anterior descending is 7.5 mm².) Stenoses of 20% to 49% and 50% to 90% diameter reduction were analyzed separately.

Statistical analysis. Paired t testing was used to test the significance of hemodynamic differences between resting control values and values during diltiazem infusion and between values during handgrip with and without diltiazem. The hemodynamic effects of nitroglycerin were compared with resting control values.

The coronary vasoconstriction responses to handgrip, expressed as a percent change in lumen area, were measured in the presence and absence of the diltiazem infusion and compared by means of paired t testing. Similarly, the change from the control lumen area during diltiazem infusion was compared with the change from the area during infusion of diltiazem to that after sublingual nitroglycerin. This comparison avoided the potential contribution of residual diltiazem to the nitroglycerin effect. Effects on stenosis flow resistance were evaluated in a similar fashion.

Results

Hemodynamics. In table 1 changes in hemodynamic values and heart rate are shown. Handgrip resulted in a significant increase in heart rate (+9 beats/min; p < 0.05) and mean arterial pressure (+17 mm Hg; p < 0.001) and in small but significant elevations in mean pulmonary arterial pressure (+4 mm Hg; p < 0.005) and pulmonary capillary pressure (+4 mm Hg; p < 0.005).

Compared with the resting control values, diltiazem significantly reduced heart rate (−5 beats/min; p < 0.05) and mean arterial pressure (−13 mm Hg; p < 0.001). Pulmonary arterial and pulmonary capillary pressures were unchanged. During diltiazem infusion, handgrip produced a rise in heart rate (+8 beats/min; p < 0.001), mean arterial pressure (+19 mm Hg; p < 0.001), mean pulmonary arterial pressure (+2 mm Hg;
TABLE 1
Heart rate and hemodynamic effects in 13 patients (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Diltiazem</th>
<th>Nitroglycerin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>72 ± 11</td>
<td>67 ± 11A</td>
<td>68 ± 15 NS</td>
</tr>
<tr>
<td>Rest</td>
<td>81 ± 14</td>
<td>73 ± 15A</td>
<td></td>
</tr>
<tr>
<td>Handgrip</td>
<td>&lt; .01</td>
<td>&lt; .01</td>
<td></td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>93 ± 17</td>
<td>80 ± 15C</td>
<td>80 ± 13b</td>
</tr>
<tr>
<td>Rest</td>
<td>110 ± 18</td>
<td>99 ± 22A</td>
<td></td>
</tr>
<tr>
<td>Handgrip</td>
<td>&lt; .005</td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary pressure (mm Hg)</td>
<td>21 ± 6</td>
<td>21 ± 6 NS</td>
<td>13 ± 3c</td>
</tr>
<tr>
<td>Rest</td>
<td>25 ± 8</td>
<td>23 ± 8A</td>
<td></td>
</tr>
<tr>
<td>Handgrip</td>
<td>&lt; .005</td>
<td>&lt; .05</td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary capillary pressure (mm Hg)</td>
<td>12 ± 6</td>
<td>11 ± 4 NS</td>
<td>7 ± 2b</td>
</tr>
<tr>
<td>Rest</td>
<td>16 ± 7</td>
<td>16 ± 7NS</td>
<td></td>
</tr>
<tr>
<td>Handgrip</td>
<td>&lt; .005</td>
<td>&lt; .005</td>
<td></td>
</tr>
</tbody>
</table>

Paired t testing vs control values: ^p < .05; ^p < .005; ^p < .001.

p < .05), and pulmonary capillary pressure (+5 mm Hg; p < .005). These increases were not significantly different from those observed with handgrip alone.

Administration of nitroglycerin did not change heart rate significantly, but mean arterial pressure (−13 mm Hg; p < .005), mean pulmonary arterial pressure (−8 mm Hg; p < .001), and mean pulmonary capillary pressure (−5 mm Hg; p < .005) were all reduced significantly.

Electrocardiographic studies. The control mean PR interval was 0.18 ± 0.03 sec and increased to 0.20 ± 0.03 sec (p < .001) during diltiazem infusion. None of the patients had PR intervals greater than 0.20 sec before diltiazem while six had first-degree heart block during the infusion; in no patient did a higher degree of block develop.

Angiographic studies. In figure 1 a series of computer-generated measurements of a coronary arterial segment is shown, illustrating the changes seen in one patient with the various interventions. In table 2 and figure 2 the effects of the various interventions on coronary lumen cross-sectional area are shown according to the vessel size. Handgrip resulted in a significant reduction in lumen area; the percentage reduction was greatest in the smaller vessels.

Diltiazem infusion produced no significant change in cross-sectional area compared with that during the resting state. The coronary constriction observed during handgrip alone was prevented with handgrip during diltiazem infusion.

Nitroglycerin produced an increase in the mean cross-sectional lumen area. The increase was significant for the largest vessels. Nitroglycerin had a significantly greater vasodilating effect on normal vessels than diltiazem (figure 2).

In figure 3 the relative changes in minimum area of mild stenoses (20% to 49%) and hemodynamically significant stenoses (50% to 90%) with handgrip, diltiazem, handgrip plus diltiazem, and sublingual nitroglycerin are shown. Handgrip produced a significant constriction of mild and hemodynamically significant lesions. The constriction with handgrip was significantly greater than that with handgrip plus diltiazem (p < .01). Nitroglycerin appeared to be a more potent dilator of the diseased arterial segments than diltiazem, but the difference was not statistically significant.

Stenosis resistance was estimated with an assumed blood flow of 1 ml/sec. Compared with control, there was a significant increase in resistance during handgrip; this constriction was almost completely prevented by diltiazem (p < .05 for mild stenoses; p < .02 for severe stenoses) as seen in figure 4. Figure 4 also shows the changes with diltiazem and with nitroglycerin. Although nitroglycerin appeared to reduce stenosis resistance more effectively than diltiazem, the difference was not statistically significant.

The mean plasma level during diltiazem infusions was 154 ± 68 ng/ml. Apart from the prolongation of the PR interval with diltiazem, no significant side ef-
TABLE 2

Effects on cross-sectional area of normal vessel segments (mean ± SD)

<table>
<thead>
<tr>
<th>Vessel size</th>
<th>Control</th>
<th>Diltiazem</th>
<th>Nitroglycerin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4 mm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 39)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>2.3 ± 0.9</td>
<td>2.3 ± 0.9 NS</td>
<td>2.8 ± 1.0 NS</td>
</tr>
<tr>
<td>Handgrip</td>
<td>1.8 ± 1.3</td>
<td>2.2 ± 0.3 NS</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>&lt;.001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>4–8 mm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>5.4 ± 0.9</td>
<td>5.4 ± 1.4 NS</td>
<td>6.1 ± 2.0 NS</td>
</tr>
<tr>
<td>Handgrip</td>
<td>4.2 ± 1.2</td>
<td>5.4 ± 1.3 NS</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>&lt;.001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>&gt;8 mm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>11.0 ± 2.6</td>
<td>10.6 ± 2.2 NS</td>
<td>12.3 ± 2.7 NS</td>
</tr>
<tr>
<td>Handgrip</td>
<td>9.8 ± 3.2</td>
<td>10.9 ± 2.4 NS</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>&lt;.005</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Paired t testing vs control values: *p < .05; **p < .001.

Effects occurred as result of drug, handgrip exercise, or catheterization and angiographic examination.

Discussion

The response to isometric exercise in normal subjects is different from that in patients with coronary artery disease. In both groups there is an increase in systemic pressure and heart rate; however, in the normal subjects there is a greater increase in cardiac output. This is a sympathetically mediated response; the increase in cardiac output is mediated via α-receptor stimulation, which is responsible for the increase in peripheral tone. In cardiac patients cardiac output does not increase to the same extent, primarily because of a fall in stroke volume, and there is a greater increase in peripheral resistance.

It is postulated that α- and β-stimulation are centrally mediated neurogenic reflexes. Significant increases in plasma catecholamines occur with handgrip. In animals, coronary vessels constrict as a result of α-stimulation. In humans this stimulation is responsible for mediating the response to the cold-pressor test and to isometric exercise. The importance of calcium influx as an integral part of the α-mediated constriction of coronary arteries has been demonstrated in animal studies, while calcium influx is less important in the constriction of peripheral arteries.

The changes with handgrip during infusion of diltiazem demonstrate the differential effect of calcium slow-channel blockade on α-adrenergic stimulation of peripheral and coronary vessels. There was a significant rise in mean arterial pressure, indicating that diltiazem did not prevent the α-mediated peripheral vasoconstriction while the reduction in coronary cross-sectional area seen with handgrip alone was effectively prevented by diltiazem. Similar findings have been shown for nifedipine with the cold-pressor test and for verapamil with handgrip exercise.

The effects of handgrip in this study showed the predicted rise in heart rate and arterial pressure; the rise in filling pressure was less marked than that in a previously reported study but probably reflects differences in severity of coronary disease. In this study there was an 11% to 25% reduction in cross-sectional area of vessels with handgrip and a marked increase (103%) in flow resistance in significant (>50%) lesions.

FIGURE 2. Effects of the study interventions on normal segments of three coronary vessels of different sizes (<4 mm², 4 to 8 mm², and >8 mm²). Data expressed as mean percentage change from control. The effect of handgrip is compared with the effect of handgrip during intravenous infusion of diltiazem and the effect of diltiazem is compared with that of nitroglycerin. Paired t testing is used to test significance of difference. HGP = handgrip; DIL = diltiazem; NTG = nitroglycerin.
FIGURE 3. Effect of diltiazem on handgrip-induced constriction of normal and diseased coronary arteries. Percentage change from control cross-sectional area with the various interventions is shown for normal segments and for diseased segments grouped according to mild (20% to 49%) and severe (50% to 90%) lesions. The results of paired t testing are shown (see figure 2 for definitions of symbols). n = p < .01; nn = NS; HGP = handgrip; DIL = diltiazem; NTG = nitroglycerin.

With patients at rest, intravenous diltiazem had both direct cardiac and peripheral effects. Prolongation of atrioventricular conduction and slowing of heart rate occurred with a mean plasma diltiazem level of 154 ± 68 ng/ml. Similar effects on atrioventricular conduction and heart rate were reported previously with short- and long-term oral diltiazem.2, 26, 27 Diltiazem produced a 12% reduction in mean arterial pressure, but there was no evidence of left ventricular dysfunction. Despite the direct cardiac and peripheral effects, diltiazem had no effect on the cross-sectional area of normal coronary arteries or stenoses in patients at rest. These findings may appear to be at variance with those of other studies in animals9 and in human experiments6 in which diltiazem improved myocardial blood flow. However, an increase in blood flow is caused by dilation of coronary resistance vessels rather than of the larger arteries that were measured in this study. A recent study with nifedipine failed to show a significant change in epicardial coronary diameter,28 and verapamil is only a mild coronary arterial dilator.21

The results of this study indicating that diltiazem prevented the coronary vasoconstriction associated with handgrip are interpreted as indicating that diltiazem blocks α-mediated coronary vasoconstriction, probably by blockade of receptor-activated calcium slow channels. Coronary tone is modulated by local factors as well as sympathetic and parasympathetic influences. There is some evidence from animal studies to suggest that diltiazem may alter neurotransmission.29 The potential therefore exists that the inhibitory effect of diltiazem on the sympathetically mediated vasoconstriction caused by handgrip observed in this study may be the result of partial blockade of sympathetic neurotransmission by diltiazem. Given the design of the study, it is not possible to definitively answer this question; however, this mechanism would not explain the differential effects on the peripheral and coronary circulation. After infusion of diltiazem, handgrip produced the same rise in systemic pressure presumably caused by peripheral constriction while the constriction in coronary arteries was prevented. Furthermore, studies in vitro21 that did not involve neurotransmission indicate that diltiazem blocks the norepinephrine-induced contraction of coronary arteries but has little effect on other blood vessels, suggesting that the effect is mediated via receptor-activated slow channels rather than by blockade of neurotransmission. It is well accepted that the reduction in caliber of epicardial coronary arteries with isometric exercise is an α-mediated response.13, 21, 30 and the effects with diltiazem appear to be best explained on the basis of

FIGURE 4. The percentage change from control values of flow resistance (assuming 1 ml/sec flow) are shown for the various interventions. Mean values are shown for mild (20% to 49%) and severe (50% to 90%) stenoses. Results of paired t testing are shown (see figure 2 for definitions of symbols). HGP = handgrip; DIL = diltiazem; NTG = nitroglycerin.
blockade of the response. However, other mechanisms of action have not been disproved.

Sublingual nitroglycerin was administered to patients after infusion of diltiazem had been discontinued to evaluate the vasomobility of the patient’s coronary arteries with standard therapy. Both agents produced a similar fall in mean arterial blood pressure, but nitroglycerin produced a marked reduction in preload. Nitroglycerin had a significantly greater effect than diltiazem on the cross-sectional area of normal vessels. The effect on minimum areas and flow resistance tended to be greater with nitroglycerin.

In patients with coronary artery disease optimal medical therapy should decrease myocardial oxygen consumption while increasing flow through the stenosis under conditions that usually provoke ischemia. Results of noninvasive exercise studies indicated that for the same myocardial oxygen demand, myocardial ischemia was reduced after diltiazem, suggesting that this drug improved blood flow to areas that developed ischemia during exercise. Exercise studies have clearly demonstrated that diltiazem reduces myocardial oxygen demand at submaximal exercise levels. Additional studies have shown that increasing the daily dosage of diltiazem from 240 to 360 mg/day provides additional improvement in exercise capacity. This improvement in exercise capacity was not accompanied by an additional fall in submaximal pressure rate product, suggesting that other mechanisms were responsible for the improvement in performance.

During handgrip, intravenous diltiazem reduced myocardial oxygen demand by reducing both heart rate and blood pressure. The marked increase in flow resistance across lesions of >50% stenosis was prevented during diltiazem infusion. Thus diltiazem during the stress of handgrip reduced myocardial oxygen demand and improved myocardial blood flow.

It is conceivable that inappropriate sympathetically mediated constriction of epicardial coronary arteries may occur with dynamic exercise. It is well documented that this form of exercise is accompanied by large increases in circulating catecholamines to account for increased sympathetic stimulation. This study demonstrates that diltiazem has several potentially beneficial effects for treating patients with angina. In addition to reducing myocardial oxygen demand by lowering heart rate and blood pressure, the drug virtually prevents ß-mediated vasoconstriction of normal and diseased segments of epicardial coronary arteries. It is speculated that vasoconstriction of epicardial coronary arteries occurs in some patients with exertional angina. Prevention of vasoconstriction during dynamic exercise is postulated as a mechanism that explains the previously reported evidence from noninvasive studies of improved myocardial blood flow after infusion of diltiazem during exercise.

References

25. Lee AB, Brown BG, Bolson E, Dodge HT: Coronary stenosis constriction as a major factor in ischemic left ventricular dysfunction induced by isometric handgrip. Circulation 66(suppl II): II-249, 1982
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K F Hossack, B G Brown, D K Stewart and H T Dodge

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