Hemodynamics and Coronary Flow Following Diltiazem Administration in Anesthetized Dogs and in Humans*

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In this study, the systemic and coronary hemodynamic changes associated with the administration of diltiazem, a recent calcium antagonist, were evaluated in three different situations as follows: following a 200 μg/kg intravenous bolus of the drug in 12 open-chest anesthetized dogs; following two successive intravenous infusions of diltiazem (15 μg/kg/min and 30 μg/kg/min), each for a period of ten minutes, in eight patients with angina pectoris investigated by coronary arteriography; and following a single oral dose of 120 mg of diltiazem in 17 patients undergoing hemodynamic monitoring in the coronary care unit after a recent myocardial infarction. Diltiazem was found to be a coronary vasodilator acting on the large coronary arteries and on collaterals. Its effects on myocardial oxygen requirements were variable; as a rule, the predominant effect was a drop in systemic vascular resistance or in heart rate. When systemic vascular resistance changed little, heart rate tended to decrease significantly; however, when systemic vascular resistance decreased notably, heart rate remained unchanged because of a reflex attempt to increase systemic blood pressure. Cardiac performance and left ventricular end-diastolic pressure were not affected and this lack of change in cardiac inotropism may confer an advantage to diltiazem over other calcium antagonistic drugs in patients with coronary heart disease.

Calcium antagonists represent an important new class of antianginal,1-5 antiarrhythmic,6-8 and possibly, antihypertensive9,10 drugs. The three most widely studied compounds are verapamil, nifedipine, and diltiazem. Although more recent and less extensively investigated, diltiazem has been found highly effective, in noncontrolled clinical trials, in the medical treatment of effort angina,4,5 unstable angina,11 and particularly, Prinzmetal's angina.12-14

The systemic and coronary hemodynamic effects of diltiazem have been evaluated in open-chest anesthetized dogs15-20 and rarely in man.21,22 Particularly, coronary hemodynamics and myocardial metabolism have not been previously described in humans following the oral or intravenous administration of this pharmacologic agent.

The present review summarizes three clinical and experimental investigations recently carried out at our institution. First, the effects of a bolus of 200 μg/kg of diltiazem administered intravenously to open-chest anesthetized dogs were examined and will illustrate the relatively complex mechanisms of action of the drug. Secondly, the systemic and coronary hemodynamic changes occurring after intravenous infusions of 15 μg/kg/min and 30 μg/kg/min of diltiazem were evaluated in a small group of patients with angina pectoris prior to coronary arteriography. Finally, the effects of a single oral dose of diltiazem (120 mg) and nifedipine (20 mg) were compared in patients undergoing hemodynamic monitoring in the coronary care unit after a recent myocardial infarction.

**Materials and Methods**

**Experimental Study**

The purpose of this experimental study was to examine whether intravenous administration of a bolus of diltiazem, 200 μg/kg, improved the hemodynamics and coronary flow of open-chest anesthetized dogs following an isolated critical left circumflex artery stenosis. A second purpose of the study was to examine the influence on heart rate, left ventricular end-diastolic pressure, cardiac contractility, and coronary flow of the reduced afterload induced by diltiazem. To evaluate this effect, the aorta was constricted, and systemic blood pressure was maintained at a constant pretreatment level during the intravenous administration of a second 200 μg/kg bolus of diltiazem.

Twelve mongrel dogs weighing 25 to 35 kg were anesthetized with pentobarbital sodium, and respiration was controlled by a Harvard respirator. Electrocardiographic leads were attached to the limbs. Catheters were placed in the right femoral artery and vein. A left thoracotomy was performed through the fourth intercostal space. A Konigsberg P 22 high fidelity catheter was introduced into the left ventricle through the apex. Electromagnetic flow probes (Carolina Medical Electronics) were placed around the left circumflex and anterior descending coronary for plastic coronary flow measurement. A micrometric constrictor was positioned in the proximal portion of the left circumflex artery and was...

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used to produce a critical stenosis of the artery defined as the degree of narrowing which completely abolished reactive hyperemia.

Diltiazem, 200μg/kg, diluted in 20 ml of saline solution, was injected over a period of two to three minutes through the femoral vein catheter. Measurements were obtained after approximately 10 minutes. The same procedure was repeated after constriction of the ascending aorta using a No. 0 silk thread placed around the vessel and intermittently tightened to maintain a constant aortic pressure at a predrug level.

Radioactive microspheres were injected intravenously during the presence of critical coronary stenosis and during diltiazem treatment before and after aortic constriction.

Hemodynamic Studies in Humans

Intravenous Administration of Diltiazem. Coronary hemodynamics and myocardial metabolic changes induced by diltiazem infusion (15 and 30μg/kg/min) have not been previously described. Consequently, this study was undertaken to evaluate these factors in patients with angina pectoris submitted to coronary arteriography.

All patients were men. Mean age was 46 (range 32 to 57) years. Four patients had a previous myocardial infarction, but none had clinical signs or required active treatment for congestive heart failure. Akinesis or dyskinesis in one or more segments on the left ventriculogram was present in four patients. Seventy percent or greater coronary artery stenoses were present in three major vessels in three patients, in two vessels in two patients, and in one vessel in three patients.

The protocol included the following measurements: heart rate, aortic and left ventricular pressures, dye dilution cardiac output, thermodilution coronary sinus blood flow, and blood sampling for oxygen, glucose, and lactate contents obtained simultaneously from the aorta and coronary sinus in the following three conditions: (a) in a control state ten minutes after catheter instrumentation; (b) during the first and last five minutes of a ten-minute diltiazem infusion at a rate of 15μg/kg/min; and (c) during the first and last five minutes of a ten-minute infusion at a rate of 30μg/kg/min.

A 12-lead ECG was displayed automatically every minute throughout the procedure to examine possible ST-T changes or arrhythmias.

Finally, the study was completed by left ventriculography and coronary arteriography.

Oral Administration of Diltiazem. This study was undertaken to establish the safety of diltiazem in patients with a recent myocardial infarction and to demonstrate potential hemodynamic benefits of calcium antagonist drugs in these patients.

The patients were studied 48 to 72 hours after the onset of an acute myocardial infarction. All patients were in a stable condition, were less than 70 years old, had a well-documented myocardial infarction, and were monitored in the coronary care unit with Swan-Ganz and intraarterial catheters.

Following basal monitoring for approximately one hour, the patients received, in a double blind fashion, a single oral dose of placebo, 120 mg of diltiazem, 20 mg of nifedipine. The hemodynamic measurements, including heart rate, systemic arterial pressures, thermodilution cardiac output, and pulmonary arterial pressures, were measured at 15, 30, 60, 90, 120, 180, and 260 min.

Results

Experimental Study

Coronary Flow. Coronary flow in the normal left anterior descending artery increased by 52 percent (p<.01) (Table 1). Flow did not increase in the stenotic circumflex artery because of the fixed resistance to flow created by the critical stenosis.

When the aortic pressure was raised and maintained at the pretreatment level, coronary flow increased to 100 percent above control level (p<.01) in the normal left anterior descending artery, probably because of a higher coronary perfusion pressure combined with the potent vasodilating action of the drug.

As shown in Figure 1, flow in the border zone between the normal and ischemic areas also increased significantly (p<.01). This increased flow probably originates from the normal conductance vessels through collaterals.

Hemodynamic Measurements. Mean aortic pressure decreased by 30 percent (p<.01) following diltiazem administration. Thus, the drug is equally a systemic vasodilator.

Heart rate remained unchanged. However, when aortic pressure was raised to pretreatment level, heart rate decreased by 15 percent (p<.05), illus-

| Table 1—Systemic and Coronary Hemodynamics in Open Chest Anesthetised Dogs (N = 12) |
|---------------------------------|-----------------|-----------------|
| Critical Stenosis               | Diltiazem, 200μg/kg (Δ%) | Constant Aortic Pressure (Δ%) |
| Heart rate, beats/min           | 164 ± 29        | 155 ± 22 (-4%)  | 140 ± 10 (-15)* |
| Mean aortic pressure, mm Hg    | 129 ± 18        | 90 ± 10 (-30)† | 128 ± 15 . . . |
| Left ventricular end diastolic pressure, mm Hg | 11 ± 3         | 10 ± 2 (-9)    | 13 ± 4 (+18)   |
| dp/dt max, mm Hg/sec            | 2185 ± 641      | 1921 ± 438 (-12)| 2353 ± 497 (+7) |
| LCA flow (stenotic artery), ml/min | 21 ± 12       | 17 ± 11 (-19) | 21 ± 11 . . . |
| LAD flow (control artery), ml/min | 34 ± 15        | 52 ± 25 (+52)† | 68 ± 34 (+100)† |

* p<.05.
† p<.01.
trating the fact that the negative chronotropic action of the drug may be masked by a reflex increase in heart rate when systemic blood pressure falls significantly.

Left ventricular end-diastolic pressure and left ventricular dp/dt maximum were unchanged before and after aortic constriction.

**Hemodynamic Studies in Humans**

**Intravenous Administration of Diltiazem** (coronary hemodynamics). Coronary sinus blood flow increased slightly (Table 2) but not significantly during diltiazem infusion at a rate of 15 μg/kg/min: 11 percent at five minutes (NS), and 12 percent at ten minutes (NS) and at a rate of 30 μg/kg/min: 28 percent at five minutes (NS) and 50 percent at 10 minutes (NS). The coronary vasodilating effect of diltiazem appeared to be dose-related.

There was a reciprocal fall in coronary vascular resistance which was comparable in importance (24 percent) to the rise in coronary sinus blood flow. An interesting phenomenon was a significant rise in coronary venous oxygen saturation and a fall in

**Table 2—Effects of Intravenous Administration of Diltiazem on Coronary Hemodynamics and Myocardial Metabolism in Patients with Angina Pectoris (N = 8)**

<table>
<thead>
<tr>
<th></th>
<th>Control, 0 min</th>
<th>Diltiazem, 15 μg/kg/min × 10 min</th>
<th>Control, 25 min (Δ%)</th>
<th>Diltiazem, 30 μg/kg/min × 10 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary sinus blood flow, ml/min</td>
<td>125 ± 25 (0)</td>
<td>139 ± 14 (+11)</td>
<td>140 ± 24 (+12)</td>
<td>133 ± 32 (+6)</td>
</tr>
<tr>
<td>Coronary vascular resistance, mm Hg/ml/min</td>
<td>0.98 ± 14</td>
<td>0.87 ± 13 (−11)</td>
<td>0.74 ± 11 (−24)</td>
<td></td>
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<tr>
<td>LV oxygen extraction, percent</td>
<td>57 ± 5</td>
<td>52 ± 5 (−9)</td>
<td>45 ± 5 (−21)†</td>
<td></td>
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<tr>
<td>LV oxygen consumption, ml/min</td>
<td>295 ± 94</td>
<td>305 ± 109 (+3)</td>
<td>273 ± 94 (−7)</td>
<td></td>
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<tr>
<td>LV glucose extraction, percent</td>
<td>9 ± 2</td>
<td>5 ± 2 (−44)</td>
<td>4 ± 1 (−56)</td>
<td></td>
</tr>
<tr>
<td>LV lactate extraction, percent</td>
<td>24</td>
<td>21 (−13)</td>
<td>14 (−42)</td>
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</tbody>
</table>

*Mean ± standard error of the mean.
†p < 0.05.
left ventricular oxygen extraction from 57±5 to
45±5 (a reduction of 21 percent, p<.05) during
infusion of 30µg/kg/min of diltiazem. This reduced
oxygen uptake also appears to be dose-related in
humans.

Left ventricular oxygen consumption, which rep-resents the product of coronary flow and left ven-
tricular oxygen extraction, was not significantly altered, since both factors moved in opposite di-
rections during diltiazem administration.

Left ventricular glucose extraction decreased from
9 percent before drug treatment to 5 percent (NS)
and 4 percent (NS) during the infusion of 15µg/kg/
min and 30µg/kg/min of diltiazem, respectively.

Left ventricular lactate extraction decreased from
24 percent before drug treatment to 21 percent
(NS) and 14 percent (NS) during infusion of 15µg/
kg/min and 30µg/kg/min of diltiazem, respectively.

In individual cases, left ventricular lactate produc-
tion did not appear to be aggravated nor improved
following diltiazem administration.

Systemic hemodynamics. No significant hemody-
namic changes were observed following the intra-
venous infusion of 15µg/kg/min of diltiazem for ten
minutes (Table 3).

Following the infusion of 30µg/kg/min intra-
venously for ten minutes, systolic, diastolic, and
mean aortic pressures decreased between 10 percent
and 15 percent (NS), and systemic vascular resis-
tance decreased by 20 percent (p<.05).

Fifteen minutes after cessation of drug admin-
istration, the fall in blood pressure persisted, and
heart rate, which had remained unchanged during

<table>
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<th>Table 3—Systemic Hemodynamic Effects of Intravenous Administration of Diltiazem in Patients with Angina Pectoris (N = 8)</th>
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<tr>
<td><strong>Diltiazem, 15µg/kg/min×10 min</strong></td>
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<td>----------------------------------</td>
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<tr>
<td><strong>Control, 0 min</strong></td>
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<tr>
<td>Heart rate, beats/min</td>
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<tr>
<td>Arterial pressures, mm Hg</td>
</tr>
<tr>
<td>Systolic</td>
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<tr>
<td>Diastolic</td>
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<tr>
<td>Mean</td>
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<tr>
<td>Left ventricular end-diastolic pressure, mm Hg</td>
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<tr>
<td>Cardiac index, L/min/m²</td>
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<tr>
<td>Systemic vascular resistance, dyne/sec/cm²</td>
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<td>*Mean ± standard error of the mean. tP &lt; .05.</td>
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</table>

the drug infusion, began to show a reduction (7 percent, NS). The protocol has been modified to
extend the period of observation in future studies.

Left ventricular end-diastolic pressure and cardiac
index were unchanged during diltiazem administra-
tion.

Oral Administration of Diltiazem. Heart rate de-
creased by 11 percent in patients receiving diltiazem
and increased by 5 percent in those receiving nife-
dipine (p<.001) (Table 4). On the other hand, sys-
temic vascular resistance decreased by 16 percent
(p<.01) and cardiac index increased by 12 percent
(p<.01) with nifedipine and remained practically
unchanged with diltiazem (a reduction of 2 percent
and 4 percent, respectively). Finally, the pressure
rate product, an indirect index of myocardial oxygen
consumption, decreased by 15 percent with dilti-
azem and only 6 percent with nifedipine (p<.05).

No significant hemodynamic changes were ob-
served following placebo administration.

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<th>Table 4—Hemodynamic Effects of a Single Oral Dose of Diltiazem (120 mg) and Nifedipine (20 mg) in Patients with a Recent Myocardial Infarction</th>
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</thead>
<tbody>
<tr>
<td><strong>Diltiazem, %</strong></td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Heart rate</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
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<tr>
<td>Cardiac index</td>
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<tr>
<td>Pressure rate product</td>
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**DISCUSSION**

The systemic hemodynamic effects of oral and intravenous administration of diltiazem are not well known in man, and to our knowledge, the coronary hemodynamic and myocardial metabolic changes induced by this drug have not been previously described.

In many respects, our data in humans indicate trends or show changes which are in good agreement with observations previously made in anesthetized dogs.

As occurs with nitrates and beta-blocking agents, the action of calcium antagonist drugs on myocardial ischemia is complex and represents the sum of modifications in various factors which affect the balance between myocardial oxygen requirements and oxygen supply.

At least three mechanisms appear to be involved in the pharmacologic action of diltiazem. First, the drug is a potent dilator of the large conductance coronary arteries and of coronary collaterals. This is due to selective and specific inhibition of calcium influx into the smooth muscle cells of the coronary arteries. Second, diltiazem is, to a lesser extent, a peripheral vasodilator leading to a reduction in systemic blood pressure and in afterload. Third, diltiazem has a direct effect on the myocardium exerting a noncompetitive beta-blocking action, i.e., a weak negative chronotropic and inotropic action. Reduction in myocardial oxygen requirements is due to a combination of these effects.

In our experimental study in anesthetized dogs, coronary flow increased 50 percent when the blood pressure was allowed to fall and 100 percent when the blood pressure was maintained constant in the normal left anterior descending artery, i.e., when perfusion pressure was returned to pretreatment level. Coronary flow did not increase beyond the fixed stenosis in the circumflex artery. However, in the border zone, flow increased significantly. This increased perfusion must originate from the normal conductance vessels through coronary collaterals. Abundant collaterals are present in normal dogs, and previous studies have demonstrated that diltiazem exerts a significant effect on coronary collaterals, being responsible for redistribution of blood flow to ischemic areas.

Mean aortic pressure decreased by 30 percent in anesthetized dogs, demonstrating that diltiazem is equally a systemic vasodilator. Previous studies have shown that, at a dose which increases coronary flow by 100 percent in anesthetized dogs (0.1 mg/kg), diltiazem produces 25 percent, 37 percent, and 10 percent increases in the femoral, carotid, and renal blood flow, respectively. Thus, diltiazem dilates the coronary arteries much more than the other vessels.

Heart rate remained unchanged when the systemic blood pressure was allowed to fall but decreased by 15 percent following diltiazem administration when the blood pressure was maintained constant. Thus, the negative inotropic effect of the drug can be masked by a reflex increase in heart rate when systemic blood pressure decreases in humans.

Left ventricular end-diastolic pressure was unchanged when diltiazem was administered intravenously in this study and in studies using human subjects. It has been suggested that in contrast to nitroglycerin, calcium antagonist drugs, including diltiazem, do not decrease the venous return to the heart and may increase it. Left ventricular dP/dt max was unchanged, and previous studies have also demonstrated that diltiazem has relatively little influence on the contractile force of the heart. In the present study, a significant negative inotropic effect was not unmasked by the rise in aortic pressure to pretreatment levels.

The increase in coronary sinus flow in humans after injection of two progressive doses of diltiazem suggests that in man, as has been shown in anesthetized dogs, the increase in coronary flow is dose related.

A very interesting phenomenon has also been observed in anesthetized dogs and appears to be shared by other calcium antagonist drugs, such as verapamil and nifedipine. This is a significant rise (p<.05) in coronary venous oxygen saturation and a concomitant fall in left ventricular oxygen extraction during intravenous administration of diltiazem in man. This effect also appears to be dose-related. We have no entirely satisfactory explanation for this phenomenon except that it is well known that calcium antagonistic drugs directly induce a calcium deficiency in the heart muscle with a reduction of adenosine triphosphate consumption which leads to a decrease in isometric tension and oxygen uptake.

Left ventricular glucose extraction decreased from 9 percent to 5 percent and 4 percent during diltiazem administration. Again, the explanation may be a reduced myocardial energy expenditure because of less availability of calcium ions.

Left ventricular lactate extraction decreased from 24 percent to 14 percent during diltiazem administration, but did not tend to induce lactate production. Again, this lower extraction may be related to a decreased uptake produced as a direct effect of the drug.

Our study has shown that an infusion rate of 15µg/kg/min of diltiazem for ten minutes did not induce any systemic hemodynamic effects. With 30µg/kg/
min for ten minutes, however, moderate changes in blood pressure and a significant reduction in systemic vascular resistance were observed. Heart rate began to decrease approximately 15 minutes after the end of the drug infusion. Left ventricular end-diastolic pressure was unchanged suggesting that diltiazem causes little venodilatation.

Cardiac index was unchanged because of a lack of a strong negative inotropic influence or because of a reflex increase in cardiac contractility following afterload reduction.

Finally, our results following the oral administration of diltiazem and nifedipine suggest that in patients with a recent myocardial infarction, the most important hemodynamic change associated with diltiazem is a reduction in heart rate which is maximum approximately three hours after a single oral dose of 120 mg and which is primarily responsible for a significant reduction in myocardial oxygen consumption; on the other hand, the most significant hemodynamic change associated with a single oral dose of 20 mg of nifedipine is an afterload reduction which is most likely responsible for a significant rise in cardiac index. These data suggest that both drugs may have somewhat different clinical indications in patients with recent myocardial infarction.

In summary, the action of diltiazem on myocardial ischemia is complex, and in many instances, probably represents the summation of various hemodynamic changes which tend to favorably influence the myocardial oxygen needs vs supply ratio.

Diltiazem produces a selective inhibition of calcium influx into the smooth muscle cells of the coronary arteries and dilates both the large coronary arteries and presumably also collaterals. In man, this effect on the conductance vessels is probably responsible for the drug’s clinical efficacy in patients with rest angina and with Prinzmetal’s angina in whom coronary spasm is an important mechanism of myocardial ischemia. In addition, increased flow through collaterals may effect a redistribution of blood flow from the normal to the ischemic myocardial segments and may be beneficial to patients with severe coronary artery disease.

Through peripheral vasodilatation, diltiazem decreases systemic blood pressure and vascular resistance. It also exerts a direct action on the myocardium which results in a negative chronotropic and inotropic effect. In man, these effects appear to be dose-related. They are also variable, a reduction in blood pressure and systemic vascular resistance inducing a reflex rise in heart rate and cardiac contractility. In general, left ventricular end-diastolic pressure and cardiac performance are not altered by diltiazem administration. The reduction in myocardial oxygen requirements produced by diltiazem administration depends on the interaction of these different factors.

It should be noted that since left ventricular oxygen extraction decreases as coronary blood flow increases, left ventricular oxygen consumption may not decrease following the administration of the drug. However, myocardial oxygen requirements may nevertheless be decreased following a reduction in calcium availability and energy expenditure by the heart muscle.

Finally, because it does not seem to affect cardiac performance or increase cardiac contractility, diltiazem may possess some hemodynamic advantages over other calcium antagonists in the treatment of patients with severe coronary artery disease.

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