The Effect of Diltiazem on Coronary Flow Reserve in Humans

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Calcium channel antagonists have been shown to blunt maximal coronary flow after brief coronary occlusion and during pharmacologic coronary dilation in animals. This property, if present in humans, would result in a reduction in coronary flow reserve in the absence of intrinsic abnormalities of the coronary circulation. A reduction of maximal vasodilator capacity by calcium channel antagonists could also constitute an important anti-ischemic mechanism of action of these agents. To evaluate the effect of calcium channel antagonists on coronary flow reserve in awake humans, we measured coronary flow reserve using the coronary Doppler catheter and intracoronary papaverine at baseline and after diltiazem administered by intravenous (125 or 250 μg/kg bolus, 5 μg/kg/min infusion, n=8) or intracoronary (150–600 μg bolus, n=10) routes. Intravenous diltiazem reduced heart rate from 77±18 to 72±17 beats/min (mean±SD, p<0.005) and reduced mean arterial pressure from 96±11 to 86±15 mm Hg (p<0.005). Intravenous diltiazem resulted in a small decrease in coronary flow reserve (peak-to-resting flow velocity ratio) from 3.9±1.2 to 3.6±1.1 (p<0.01). After intracoronary diltiazem, mean arterial pressure was unchanged (control 99±12 mm Hg, diltiazem 97±13 mm Hg), and heart rate was maintained constant by atrial pacing. Coronary flow reserve was unchanged at 3.8±0.9 at baseline and after intracoronary diltiazem. Thus, treatment with diltiazem does not invalidate the measurement of coronary flow reserve for diagnostic purposes. Furthermore, these results suggest that attenuation of maximal coronary dilation by diltiazem is not a mechanism responsible for its antianginal effects. (Circulation 1989;80:1240–1246)

Coronary flow reserve is a useful index of the vasodilator capacity of the coronary circulation. This measurement has been used primarily to assess the physiologic significance of coronary stenoses,1 as well as evaluate the results of coronary angioplasty2 and coronary bypass surgery.3 A limitation to the use of coronary flow reserve is that factors independent of coronary stenosis, such as hemodynamic status, left ventricular hypertrophy, and pharmacologic agents, may also alter measured coronary flow reserve.4 Calcium channel antagonists have been shown to blunt maximal coronary flow after a variety of stimuli in animals. Dymek and Bache5 demonstrated that the acute administration of intravenous nifedipine or diltiazem to conscious dogs blunted reactive hyperemia after brief coronary occlusion by approximately 50%. This effect was noted at a time when resting coronary blood flow and systemic hemodynamics were not altered by the drug. Gross and Warlitier6 noted a reduction in reactive hyperemia after brief coronary occlusion in anesthetized dogs given intravenous diltiazem, nifedipine, and the investigational calcium channel antagonist FR34235. Merrill et al7 reported a decrease in the hyperemic response to intracoronary adenosine and to brief coronary occlusion following intravenous nifedipine in anesthetized dogs. Thus, several canine studies demonstrate that calcium channel antagonists reduce maximal vasodilator capacity. Because there are many interspecies differences in coronary physiology, it would be short sighted to extrapolate these studies to humans.

A reduction in maximal vasodilator capacity by calcium channel antagonists, if present in humans, would have two important clinical implications. First, coronary flow reserve values in patients receiving these agents would be depressed in the absence of intrinsic abnormalities of the coronary circulation. Second, a reduction of maximal vasodilator...
capacity could also constitute an important anti-ischemic mechanism of action of calcium channel antagonists. Subendocardial ischemia due to “coronary steal” during exercise may occur because of dilation of vessels distal to a coronary stenosis with resultant fall in coronary perfusion pressure. Attenuation of this metabolically mediated dilation of resistance vessels in patients could be an important anti-ischemic effect of these agents.

A 3F coronary Doppler catheter developed by Wilson et al9 accurately measures changes in coronary blood flow velocity in conscious patients. Intracoronary injection of papaverine produces maximal coronary vasodilation of short duration, allowing repeated measurements of coronary flow reserve. Using this methodology, the goal of the present study was to evaluate the effect of the calcium channel antagonist, diltiazem, on coronary flow reserve in humans. Diltiazem was administered by the intracoronary and intravenous routes to assess its effect on coronary flow reserve in the absence of systemic hemodynamic changes.

Methods

Patient Population

Patients undergoing elective coronary arteriography for the evaluation of chest pain were considered for study if they met the following criteria: 1) absence of obstructive coronary atherosclerosis or coronary stenosis (≥50% diameter) limited to a single vessel, and 2) left ventricular ejection fraction of more than 50% by contrast or isotope ventriculogram. Ten men and eight women (age, 47.2±8.8 years, mean±SD) were enrolled. One-vessel coronary stenosis was present in three patients, remote myocardial infarction had occurred in one patient, and one patient had undergone previous one-vessel coronary bypass grafting. A coronary artery without obstructive lesions and judged to be most easily cannulated by the coronary Doppler catheter was interrogated; the left anterior descending coronary artery was studied in seven subjects, the left circumflex coronary artery in nine, and the right coronary artery in two. The research protocol was approved by the University of Iowa Institutional Review Board, and written informed consent for the research protocol was obtained from each subject before cardiac catheterization.

Coronary Flow Reserve Measurement

An 8F coronary guiding catheter (USCI Bard, Billerica, Massachusetts or Shiley, Irvine, California) was positioned at the coronary ostium, and a 0.014-inch coronary angioplasty guidewire (USCI Bard) was advanced into the coronary artery to be studied. A 3F 20-mHz coronary Doppler catheter (NuMed, Hopkinton, New York) was advanced over the guidewire into the proximal vessel and positioned to obtain a high-quality phasic signal of blood flow velocity. The pulsed Doppler velocimeter (Bioengineering Department, University of Iowa Hospitals and Clinics, Iowa City, Iowa) was range-gated to maximize the amplitude of the mean coronary blood flow velocity signal. Phasic and mean coronary blood flow velocity (kHz shift), mean arterial pressure obtained from the guiding catheter, heart rate, and electrocardiogram were continuously recorded on a multichannel recorder.

After measurements of resting coronary blood-flow velocity, 6–10 mg papaverine hydrochloride (2 mg/ml 0.9% saline) was injected through the guiding catheter into the coronary ostium and the resultant increase in coronary blood flow velocity was recorded. To confirm that a dose of papaverine produced maximal hyperemia, coronary blood flow velocity was recorded during administration of an additional papaverine dose 2–4 mg larger than the previous dose. The maximal dose of papaverine administered was 12 mg into the left coronary artery and 8 mg into the right coronary artery in all patients. Flow velocity was allowed to return to baseline levels between doses of papaverine. Coronary flow reserve was calculated as the quotient of the peak mean flow velocity (kHz shift) after intracoronary papaverine and the resting mean flow velocity during the 15–30 seconds preceding papaverine administration. Coronary flow reserve measurement was repeated after diltiazem using the largest dose of intracoronary papaverine administered during baseline coronary flow reserve measurement.

Quantitative Coronary Angiography

Coronary arteriography was performed with meglumine diatrizoate 76% in a projection that allowed visualization of the arterial segment that contained the Doppler catheter with minimal vessel foreshortening and overlap. No coronary contrast was injected during the 3 minutes before each angiogram. Angiograms were analyzed by the Pie Data-Reiber method of quantitative coronary angiography. This method has been described in detail elsewhere. Briefly, a 35-mm cinem film frame was digitized to a 1,330×1,770 pixel matrix containing 256 gray levels. After the operator identified the limits of the coronary catheter and arterial segment to be analyzed, the edges of these structures were automatically detected, and the arterial size was corrected for magnification and pincushion distortion. A 1–2-mm long proximal segment of the artery cannulated by the Doppler catheter that was adjacent to a vascular landmark was manually identified and mean segment diameter was determined by computer. Measurements reported represent the average of three separate analyses by one observer of a single angiogram.

Measurement of Diltiazem Plasma Concentration

Venous blood was collected in chilled heparinized glass tubes and immediately centrifuged for 20 minutes at 2,000 rpm. The plasma was separated by glass pipette and stored at −18°. Plasma
Diltiazem levels were determined by high-performance liquid chromatography (Marion Laboratories, Kansas City, Missouri).

Experimental Protocol
Subjects were brought to the cardiac catheterization laboratory in a fasting state. Diazepam (5–10 mg i.v. or p.o.) was given for sedation. No subject received atropine premedication. Any calcium channel antagonist therapy was withheld for at least 24 hours. The study was performed at least 30 minutes after ergonovine administration, and during intravenous infusion of nitroglycerin at 8 µg/min to avoid catheter-induced coronary artery spasm and decrease papaverine-induced dilation of the proximal coronary artery. Diltiazem was administered by the intravenous route in eight patients and by the intracoronary route in 10 patients.

Intravenous Diltiazem Administration
At baseline, mean arterial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, heart rate, and thermodilution cardiac output were measured. Angiography of the coronary artery to receive the Doppler catheter for quantitative analysis was then performed, the coronary Doppler catheter was inserted, and coronary flow reserve was measured. Diltiazem (Marion Laboratories) was then infused in a loading dose of 125 µg/kg (n=4) or 250 µg/kg (n=4) i.v. over 2 minutes, followed by constant infusion 5 µg/kg/min i.v. Hemodynamic measurements were repeated and coronary flow reserve was remeasured 5–10 minutes after the loading dose when coronary flow velocity had returned to the baseline level. The Doppler catheter was removed immediately after flow reserve measurement, and quantitative angiography was repeated approximately 5 minutes after the final dose of intracoronary papaverine. Blood samples were obtained for determination of plasma diltiazem levels in six patients.

Intracoronary Diltiazem Administration
A 6F bipolar pacing catheter was positioned in the right atrium, and atrial pacing at 80 or 90 beats/min (depending on resting heart rate) was performed throughout the study to avoid any change in coronary flow reserve related to sinus bradycardia during intracoronary diltiazem administration. After measurement of mean arterial pressure and quantitative angiography, the coronary Doppler catheter was inserted and coronary flow reserve was measured. Intracoronary diltiazem (20 or 40 µg/ml normal saline, 7.5–15 ml total volume) was then administered in several doses over 2 minutes through the guiding catheter, and coronary flow reserve was remeasured 3–5 minutes after each dose, when coronary flow velocity had returned to the baseline level. The Doppler catheter was removed immediately after the last flow reserve measurement, and quantitative angiography was repeated approximately 5 minutes after the final dose of intracoronary papaverine. In the first two patients, intracoronary diltiazem was administered in doses of 50, 100, and 150 µg. The subsequent eight patients received an initial diltiazem dose of 300 µg, and six of the eight patients were given a second dose of 600 µg. The largest dose administered in the other two patients was 300 µg, due to loss of the flow-velocity signal in one, and development of transient 2:1 atrioventricular block in the other. Because transient 2:1 atrioventricular block developed in an additional patient after receiving 600 µg diltiazem, this dose was not exceeded. Thus, coronary flow reserve was measured after a maximal intracoronary diltiazem dose of 600 µg in six patients, 300 µg in two patients, and 150 µg in two patients.

Data Analysis
All values were expressed as mean±SD. Data were analyzed using the Student’s t test. The response to the largest dose of intracoronary diltiazem was analyzed. Statistical significance was defined as a p value of less than 0.05.

Results
Effect of Intravenous Diltiazem on Systemic Hemodynamics
Intravenous diltiazem infusion resulted in a blood diltiazem level of 263±89.5 ng/ml (n=6) and was similar in the three patients receiving the 250 µg/kg (301±65 ng/ml) and the three receiving 125 µg/kg (224±107 ng/ml) loading doses. During intravenous diltiazem infusion, mean arterial pressure decreased from 96±11 to 86±15 mm Hg (p<0.005) (Figure 1), and heart rate decreased from 77±18 to 72±17 beats/min (p<0.005). Intravenous diltiazem did not significantly alter mean pulmonary artery pressure (baseline, 18±4; diltiazem, 18±7 mm Hg), mean pulmonary capillary-wedge pressure (baseline, 9±2;
diltiazem, 9±3 mm Hg), or cardiac output (baseline, 6.5±1.7; diltiazem, 6.7±1.5 l/min). Systemic vascular resistance decreased from 1,183±414 to 1,034±371 dyne·sec·cm⁻² (p<0.05).

Effect of Intravenous Diltiazem on Coronary Flow Reserve and Coronary Artery Diameter

Baseline coronary flow reserve (peak to resting flow velocity ratio) was 3.9±1.2 (Figure 2). During the intravenous diltiazem-loading dose, coronary flow velocity reached a maximum of 1.24±0.39 times the baseline coronary flow velocity (p<0.1) and returned to baseline (1.01±0.10 times baseline coronary flow velocity, p=NS) within 5 minutes of completing the loading dose. The coronary flow reserve during diltiazem infusion, 3.6±1.1, was slightly decreased (p<0.01) from the baseline flow reserve (Figure 2). Mean diameter of the coronary artery segment that contained the Doppler catheter increased from 3.03±0.64 to 3.31±0.59 mm (n=7, p<0.025).

Effect of Intracoronary Diltiazem on Systemic Hemodynamics

During intracoronary diltiazem administration, heart rate was maintained by atrial pacing at 80 beats/min in four patients and 90 beats/min in six patients. Transient asymptomatic second-degree atrioventricular block developed in two patients during intracoronary infusion. Mean arterial pressure at baseline was 99±12 mm Hg and was unchanged after intracoronary diltiazem at 97±13 mm Hg (p=NS) (Figure 3).

Effect of Intracoronary Diltiazem on Coronary Flow Reserve and Coronary Artery Diameter

A representative recording of coronary flow velocity and flow reserve before and after intracoronary diltiazem is shown in Figure 4, and the results for all patients are summarized in Figure 5. Baseline coronary flow reserve (peak to resting flow velocity ratio) was 3.8±0.9 (Figure 5). During the intracoronary diltiazem infusion of the largest dose of diltiazem, coronary flow velocity increased to a maximum of 2.02±0.74 times the baseline coronary flow velocity (p<0.005) and returned to baseline (0.96±0.12 times baseline coronary flow velocity, p=NS) within 5 minutes of completing the infusion. The coronary flow reserve after the largest dose of intracoronary diltiazem, 3.8±0.9, was unchanged from the baseline flow reserve (Figure 5). Intracoronary diltiazem had no effect on coronary flow reserve at any of the doses administered (600 µg peak dose: control, 4.3±0.8; diltiazem, 4.3±0.8; 300 µg peak dose: control, 3.2±0.6; diltiazem, 3.3±0.8; 150 µg peak dose: control, 2.8±0.1; diltiazem, 2.9±0.2). The diameter of the coronary artery segment that contained the Doppler catheter increased from 3.21±0.42 to 3.40±0.49 mm (n=8, p<0.05).

Discussion

This study demonstrates that systemic administration of the calcium channel antagonist, diltiazem, to patients produces a small reduction in coronary flow reserve. This minimal effect was observed after intravenous administration of diltiazem in doses resulting in plasma levels that equal or exceed those typically occurring after high-dose oral therapy. Decreases in heart rate and arterial pressure were similar to those previously reported after intravenous diltiazem. Coronary flow reserve was unchanged after intracoronary diltiazem administration in doses that produced larger transient increases in coronary flow velocity than intravenous diltiazem produced but no changes in heart rate or arterial pressure. This suggests that the small decrease in coronary flow reserve after intravenous
diltiazem may have been related to concomitant alterations in systemic hemodynamics.

Changes in coronary blood flow velocity were determined using a 3F coronary Doppler catheter. Extensive animal studies validating this catheter have been published.9 Changes in coronary blood flow velocity measured with the Doppler catheter correlated well with changes in measured timed volume collections of coronary sinus blood over a wide range of coronary flows. Identical maximal coronary reactive hyperemia responses were obtained with or without the catheter in the artery under study. When global myocardial flow was altered pharmacologically, changes in coronary blood flow velocity assessed by the catheter were highly correlated with simultaneous measurements of flow velocity measured using an epicardial Doppler probe placed in a separate perfusion field. These findings suggest that changes in blood flow velocity measured in individual coronary arteries by the coronary Doppler catheter accurately reflect changes in coronary blood flow, and that the catheter does not produce physiologically detectable obstruction.

In this study, both intravenous and intracoronary diltiazem resulted in a small increase in proximal coronary artery diameter. Therefore, at a time when resting flow velocity had returned to baseline after diltiazem, volumetric flow was increased. Augmentation of resting coronary flow would favor a decrease in coronary flow reserve after diltiazem. However, the present study demonstrated only a small decrease in coronary flow reserve after intravenous diltiazem and no change after intracoronary diltiazem.

Though coronary vasodilation is generally believed to improve the balance of myocardial oxygen supply and demand, a proischemic effect of vasodilation has been described. The dilation of myocardial resistance vessels distal to a flow-limiting coronary stenosis may increase total coronary flow, leading to a larger pressure drop across the coronary lesion.9 This fall in distal coronary perfusion pressure may produce subendocardial ischemia despite elevated global coronary flow. Supporting this concept is the observation that patients with severe obstructive coronary lesions commonly develop angina and segmental left ventricular dysfunction when given a potent dilator of coronary resistance vessels such as intravenous dipyridamole.15

This “coronary steal” effect may also develop during metabolic, as well as pharmacologic coronary vasodilation.16 Consequently, subendocardial myocardial ischemia during exercise may be worsened by metabolically mediated dilatation of coronary vasculature with resultant reduction in perfusion pressure distal to flow-limiting lesions. Because calcium channel antagonists have been shown to blunt maximal coronary flow after a variety of stimuli in animals, a potential mode of anti-ischemic action of these agents might be to attenuate meta-
bolically mediated dilatation of resistance vessels in nonischemic regions. The present study, which demonstrates minor changes in coronary flow reserve with intravenous diltiazem that may be due to its systemic hemodynamic effects, suggests that reduction in coronary steal by attenuation of coro-

nary hyperemia during exercise is not an important anti-ischemic mechanism of calcium channel antagonists in humans.

Our results are at variance with studies in dogs demonstrating markedly reduced maximal hyper-

emia after calcium channel–antagonist administra-
tion.5–7 In these studies, blunting of maximal coro-

nary flow was observed after treatment with diltiazem, nifedipine, and other calcium channel antagonists in both conscious and anesthetized animals. The effect was observed with reactive hyperemia after transient coronary occlusion and during pharmacologic coronary vasodilation with intracor-

onary adenosine. The present study was conducted with intracoronary papaverine, which is the most commonly used coronary vasodilator for measure-

ment of coronary flow reserve in humans. A poten-
tial explanation of the discrepancy between our results and those in dogs is a selective effect of calcium channel antagonists on coronary dilation occurring with brief coronary occlusion or adeno-

sine administration but not after intracoronary papav-

erine. Another possible explanation is a species difference in the effect of diltiazem on the coronary circulation.

Limited human studies have also revealed moder-
est reduction in coronary vasodilator responses after intravenous diltiazem17 and investigational cal-

cium channel antagonist bepridil18 in patients with coronary atherosclerosis. However, interpretation of theses studies is limited by methodologic defi-
ciencies. Coronary blood flow was measured by coronary sinus thermodilution, a technique with many limitations particularly in patients with coro-

nary disease.19,20 In addition, coronary flow was measured after intracoronary injection of radiographic contrast material, a submaximal coronary vasodilator.10

There are two clinical implications of this study. First, treatment of patients with diltiazem does not invalidate the measurement of coronary flow reserve for diagnostic purposes. This lack of effect on coronary flow reserve may also pertain to other calcium channel antagonists. However, because the relative vasodilator and myocardial depressant activities of these agents vary widely, other calcium channel antagonists may have different effects on coronary flow reserve. Second, our results suggest that reduction in coronary steal by attenuation of coronary hyperemia during exercise is not an important anti-

ischemic mechanism of calcium channel antagonists.

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