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Effects of Calcium Channel Blockers on Coronary Vasoconstriction Induced by Endothelin-1 in Closed Chest Pigs

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The purpose of this study was to determine the effects of endothelin-1 on the coronary vascular bed of closed chest pigs. Endothelin-1 (3 to 30 pmol/kg body weight) was selectively administered into the left anterior descending coronary artery. Coronary blood flow and epicardial vessel diameter were measured by quantitative arteriography. Arterial pressure increased after a 30 pmol/kg dose and heart rate was not changed.

Coronary blood flow and vessel diameter of the left anterior descending artery significantly decreased by 74% and 32%, respectively ($p < 0.01$ versus control) after the 30 pmol/kg dose, whereas these variables modestly decreased in the left circumflex artery. Endothelin-1 in doses of 10 to 30 pmol/kg produced electrocardiographic ST segment elevation associated with decreased oxygen saturation of coronary sinus venous blood. Endothelin-induced coronary vasoconstriction was significantly inhibited after treatment with intravenous diltiazem (0.2 mg/kg, n = 6) or nifedipine (0.1 mg/kg, n = 5), but not after vehicle administration (n = 4).

This study demonstrates that intracoronary administration of endothelin-1 causes significant myocardial ischemia through coronary vasoconstriction, which is inhibited by a calcium channel blocker. The data suggest that calcium influx into the smooth muscle cells appears to be involved at least in part in the mechanism of endothelin-induced coronary vasoconstriction in vivo.

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The vascular endothelium contributes to the regulation of vascular tone by releasing endothelium-derived relaxation factor or factors or vasoconstricting agent or agents (1–3). Endothelin-1, a newly discovered endothelium-derived peptide, is known to elicit marked constrictor activity in isolated mammalian vessels (4–6). Recently, endothelin has been shown (7–10) to produce coronary vasoconstriction after intravenous or intracoronary administration in open chest animals. Despite the potent vasoconstrictor activity in vitro, epicardial coronary diameter decreased by <10% in studies in vivo (8,9). The mechanism of action of endothelin in the coronary vascular bed has not been examined in closed chest animals in detail.

The goal of this study was to determine the direct effects of endothelin-1 on the coronary vascular bed of anesthetized closed chest pigs in which loss of coronary vasoreactivity due to surgical manipulation appears to be modest or negligible. Because most reported studies in vitro have shown the vasoconstrictor activity of endothelin on large conduit vessels, the diameter of epicardial coronary arteries was measured before and after the administration of endothelin-1 by means of arteriography. The specific aims were as follows: 1) We tested the hypothesis that endothelin-1 causes coronary vasoconstriction and myocardial ischemia. For this purpose, the electrocardiogram (ECG) and oxygen saturation of arterial and coronary sinus venous blood were measured. 2) We examined whether endothelin-1 acts on epicardial coronary arteries or small coronary vessels, or both. 3) We explored the mechanism of action of endothelin-1 by evaluating the effects of two calcium channel blockers. We selected miniature pigs as an experimental model because their cardiovascular anatomy and physiology are known to be similar to those of humans (11).

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Methods

Experimental preparation. This study conformed to the Position of the American Heart Association on Research Animal Use adopted in 1984. Fifteen male Yucatan miniature pigs (15 to 25 weeks old and 15 to 20 kg in weight) were sedated with intramuscular ketamine hydrochloride (10 mg/kg) and then anesthetized with 1.0% to 1.5% isoflurane. Arterial pH, partial pressure of oxygen (pO_2) and partial pressure of carbon dioxide (pCO_2) were kept within normal limits. Physiologic saline solution (50 ml/h) and heparin (5 000 U bolus injection followed by 1,000 U/h) were continuously infused through a cannula inserted into an ear vein during the experiment. After the carotid artery was exposed, an 8F preshaped Kifa catheter was inserted through the artery into the orifice of the left coronary artery. Arterial pressure measured with a Statham transducer and ECG leads I, II, aVF, V_1 and V_6 were monitored by use of a Gould polygraph system and recorded on a multichannel recorder. Rectal temperature was maintained at 37.0° to 37.5°C by an external heating pad. In some pigs, a 7F catheter was introduced into the coronary sinus vein through a jugular vein for blood sampling.

Coronary arteriography and quantitative analysis. The X-ray image intensifier was positioned to obtain a right anterior oblique projection of the left coronary artery; this position was maintained constant throughout the experiment. Cineangiograms were monitored with a Phillips angiographic unit and recorded on 35 mm cinefilm at a speed of 50 frames/s. Nonionic contrast medium (iopamidol 76%, Squibb Diagnostic) was used as the angiographic dye.

The measurement of coronary artery diameter was performed as previously described (12,13). Briefly, a coronary artery segment was selected from an end-diastolic frame and diameter was measured with digital calipers. The size of the angiographic catheter was used as a reference standard, which allowed diameters to be calibrated in absolute values (mm). Transit time required for the contrast medium to pass two regions of interest along the proximal left anterior descending or circumflex artery was obtained. The value of mean blood flow velocity (V) was then calculated (V = distances in two regions of interest/transit time). Estimation of coronary blood flow (CBF) was made from a value of the velocity and a mean arterial cross-sectional area (CSA) at regions of interest (CBF = V × CSA). Previous studies (14) have reported that paired measurements of mean coronary blood flow with the method we used versus an epicardial electromagnetic flow probe have correlated closely. Percent reduction in coronary blood flow and coronary diameter (CD) was estimated as follows: [(CBF or CD after nitroglycerin − CBF or CD after endothelin) ÷ (CBF or CD after nitroglycerin)] × 100.

Experimental protocols. Preliminary experiments showed that >100 pmol/kg doses of intracoronary administration of endothelin-1 caused irreversible hemodynamic changes or lethal events. Thus, we arbitrarily utilized 3, 10 and 30 pmol/kg doses to determine the effects of endothelin-1 in this study.

Coronary arteriography was performed in the control condition and a few minutes after intravenous nitroglycerin (0.4 mg) in all 15 pigs. Values of vessel diameter and blood flow obtained after administration of nitroglycerin were used as a standard to calculate percent changes of these variables, which may minimize the possible influence of coronary artery tone at rest on the results. Thirty minutes after the nitroglycerin study, endothelin-1 in doses of 3, 10 and 30 pmol/kg was administered into the left anterior descending artery. Intracoronary administration was performed by means of a 2F radiopaque catheter that was introduced through the Kifa catheter and positioned in the proximal vessel with the aid of fluoroscopy. Coronary arteriography was performed routinely 1 to 3 min after each dose when endothelin-induced ST segment changes were at the maximal level. Bolus injection was completed in 30 s and the volume of each injection was <1 ml. Each bolus dose was followed by a 10 min observation period. Measurements of left anterior descending artery diameter and flow were performed on a coronary segment distal to the infusion catheter. Oxygen saturation of systemic arterial and coronary sinus venous blood samples was measured before and after the 30 pmol/kg dose of endothelin-1. To assess the time course of the effects of endothelin-1, coronary angiograms were then performed at 10 min intervals after the control study.

After a 60 min period was allowed for washout, endothelin-1 challenge was repeated 10 min after pretreatment with saline solution (n = 4), intravenous diltiazem (0.2 mg/kg, n = 6) or nicardipine (0.1 mg/kg, n = 5).

Definition of ischemic changes on ECG. At the end of the study, the infusion catheter was removed and replaced by a 2F balloon catheter, which was positioned at the proximal left anterior descending artery. The balloon was then inflated for 3 min while the ECG was recorded. We defined significant ischemic changes as ST segment elevation or depression >0.2 mV lasting for 30 s in lead I or V_1, or both. All animals developed significant changes after balloon occlusion of the left anterior descending artery by this criterion.

Drugs. Pure synthetic endothelin-1 (Peptide International) was dissolved in sterile distilled water in a concentration of 100 μmol/ml and stored at 0°C until used. Nifedipine and diltiazem were purchased from Sigma Chemicals.

Statistical analysis. Data were expressed as mean values ± SEM. Analysis of variance for repeated measures or Student's *t* test was used to test equivalence of hemodynamic variables, coronary blood flow and coronary diameters. When a significant difference was detected, multiple comparison *t* tests were applied. The incidence of ischemic

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Table 1. Incidence of Ischemic ST Segment Change After Endothelin-1 Administration

	Baseline (saline solution)	Endothelin-1 (pmol/kg)		
		3	10	30
Control study (n = 4)				
1st injection	0/4	0/4	3/4	4/4
2nd injection	0/4	0/4	3/4	4/4
Diltiazem study (n = 6)				
Before	0/6	1/6	4/6	6/6
After diltiazem	0/6	0/6	1/6*	5/6
Nifedipine study (n = 5)				
Before	0/5	1/5	3/5	4/5
After nifedipine	0/5	0/5	1/5†	4/5

*$p < 0.05$ versus before diltiazem. †$p < 0.07$ versus before nifedipine. Total incidence of ischemic ST segment changes (elevation or depression) after intracoronary administration of saline solution or endothelin are shown. For definition of ischemic changes, see Methods section.

ST changes was analyzed by Fisher's exact test. A probability <0.05 was considered to be significant.

Results

Effects of endothelin-1 on the coronary vascular bed. Administration of vehicle into the left anterior descending artery had no effect. Arterial pressure did not change after 1 and 10 pmol/kg doses, but it increased after 30 pmol/kg. Heart rate did not change until significant ischemia developed. Intracoronary administration of endothelin-1 produced dose-related increases in the incidence of ischemic ST segment change in lead I or V_1, or both; 2, 10 and 14 of the 15 pigs showed significant ST changes after 3, 10 and 30 pmol/kg doses, respectively (Table 1). These ischemic ST changes began at 20 to 30 s after initiation of administration and continued for 2.5 ± 0.5 min after the 10 pmol/kg dose and 3.8 ± 0.4 min after the 30 pmol/kg dose. Oxygen saturation of the coronary sinus venous blood was significantly ($p < 0.01$) decreased from 56 ± 4% in the control condition to 25 ± 3% during ischemic ST elevation induced by 30 pmol/kg of endothelin-1; arterial oxygen saturation remained unchanged (n = 5).

Coronary angiograms obtained after administration of endothelin-1 showed delayed filling of contrast medium into the peripheral left anterior descending artery (Fig. 1). Coronary blood flow along this artery decreased in a dose-dependent manner after 3, 10 and 30 pmol/kg of endothelin-1, whereas that along the left circumflex artery modestly but significantly decreased after 10 and 30 pmol/kg doses (Tables 2 to 4). Endothelin-1 also produced dose-related reductions in left anterior descending artery diameter; however, the level of diameter reduction after the 30 pmol/kg dose was as much as 32 ± 4%. The left circumflex artery diameter slightly but significantly decreased only after

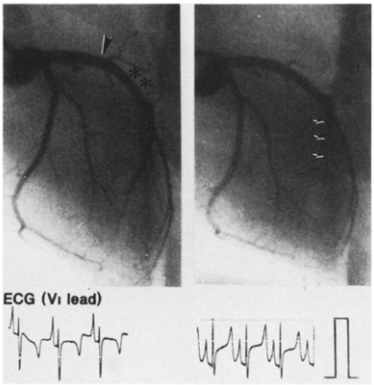

Figure 1. Serial angiograms (end-diastolic frames) and electrocardiograms (ECG) before (**left**) and after (**right**) intracoronary administration of endothelin-1. After endothelin-1, the filling of the contrast agent into the peripheral left anterior descending coronary artery was markedly delayed compared with that into the left circumflex coronary artery. This finding was associated with myocardial ischemia as demonstrated by significant regional changes in the ST segment on the ECG. The **large arrowhead** indicates the site of endothelin administration. The **small arrows** indicate the site of filling delay on the contrast agent. **Asterisks** show the left anterior descending coronary artery.

30 pmol/kg of endothelin-1. The endothelin-induced diameter reduction recovered to the baseline level by 10 min after either the 3 or the 10 pmol/kg dose and by 40 min after the 30 pmol/kg dose.

Effects of diltiazem or nifedipine on endothelin-induced vasoconstriction and ischemia (Fig. 2 and 3). Control experiments with repeated administration of endothelin-1 (Table 2) showed that hemodynamic variables, coronary artery diameter and coronary blood flow in response to endothelin-1 in the doses we used were similar after the first and the second administration of the peptide. In experiments where the effects of 0.2 mg/kg of diltiazem (Table 3, Fig. 2) and 0.1 mg/kg of nifedipine (Table 4, Fig. 3) were studied, mean arterial pressure significantly decreased to a similar extent after either diltiazem or nifedipine. Heart rate was not significantly changed by diltiazem, but it increased after nifedipine. A slight but significant increase in coronary diameter and blood flow was observed after diltiazem and nifedipine administration. Percent reduction in epicardial vessel diameter of the left anterior descending artery, induced by 10 and 30 pmol/kg doses of endothelin-1, was

Table 2. Effects of Repeated Administration of Endothelin-1 on Hemodynamic Values, Coronary Artery Diameter and Coronary Blood Flow (n = 4)

	First Endothelin-1 Study (pmol/kg)				Second Endothelin-1 Study (pmol/kg)			
	Control	1	10	30	Control	1	10	30
MAP (mm Hg)	85 ± 3	84 ± 2	89 ± 3	95 ± 4§	88 ± 2	89 ± 3	92 ± 3	98 ± 3§
HR (beats/min)	90 ± 5	92 ± 4	96 ± 5	89 ± 6	94 ± 3	91 ± 4	90 ± 4	85 ± 4
Coronary artery diameter (% reduction)								
LAD	6 ± 1	10 ± 4	19 ± 4§	30 ± 4§	4 ± 1	12 ± 4*	24 ± 4§	33 ± 4§
LCx	5 ± 1	4 ± 2*	7 ± 4*	12 ± 4*†	5 ± 1	6 ± 2*	9 ± 4*	9 ± 2*‡
Coronary blood flow (% reduction)								
LAD	2 ± 1	15 ± 5†	40 ± 8§	79 ± 12§	5 ± 2	19 ± 5‡	46 ± 10§	70 ± 12§
LCx	1 ± 1	5 ± 3*	9 ± 5*‡	10 ± 9*‡	2 ± 1	9 ± 4*	13 ± 5*‡	15 ± 6*‡

*$p < 0.05$, †$p < 0.01$ versus left anterior descending (LAD) coronary artery, ‡$p < 0.05$, §$p < 0.01$ versus control. Data are mean values ± SEM. Mean arterial pressure (MAP) and heart rate (HR) are absolute values. Values of coronary artery diameter and coronary blood flow are percent change from those obtained after intravenous nitroglycerin. LCx = left circumflex coronary artery.

inhibited after pretreatment with diltiazem or nifedipine (Fig. 2 and 3). Inhibition of coronary blood flow in the left anterior descending artery by diltiazem or nifedipine was noted at 3 and 10 pmol/kg doses, but was not seen at the 30 pmol/kg dose. These inhibitory effects produced by diltiazem and nifedipine appeared similar. Endothelin-induced reductions in coronary vessel diameter and blood flow in the left circumflex artery were not statistically affected by diltiazem or nifedipine. Arterial pressure and heart rate responses to endothelin-1 were stable after diltiazem or nifedipine.

The incidence of ischemic ST changes induced by 10 pmol/kg of endothelin-1 was decreased after pretreatment with diltiazem or nifedipine, whereas that produced by the 30 pmol/kg dose was not statistically reduced (Table 1). Neither duration of the ischemic ST changes nor time to the onset of ischemia was affected after treatment with these two calcium channel blockers.

Discussion

Endothelin and myocardial ischemia. One result of the present study, showing that decreased coronary blood flow induced by intracoronary administration of endothelin-1 with stable or increased arterial pressure, indicates that coronary vascular resistance significantly increased in response to endothelin-1. The ECG ischemic changes and oxygen desaturation in coronary sinus venous blood suggest

Table 3. Effects of Diltiazem on Endothelin-Induced Coronary Vasoconstriction (n = 6)

	Endothelin-1 Before Diltiazem (pmol/kg)				Endothelin-1 After Diltiazem (D) (pmol/kg)				
	Control	3	10	30	Control	D	3	10	30
MAP (mm Hg)	86 ± 3	84 ± 4	89 ± 5	96 ± 7‡	84 ± 3‡	76 ± 4§	80 ± 5	82 ± 4	86 ± 8
HR (beats/min)	95 ± 4	93 ± 8	96 ± 6	99 ± 6	100 ± 5	98 ± 4	99 ± 5	101 ± 5	105 ± 4
Coronary artery diameter (% reduction)									
LAD	4 ± 3	12 ± 5	22 ± 4§	32 ± 4§	6 ± 1	2 ± 3‡	8 ± 3	14 ± 3‡‖	19 ± 3§¶
LCx	1 ± 1	4 ± 2*	8 ± 4*‡	10 ± 4*‡	4 ± 1	0 ± 1‡	3 ± 2	2 ± 2‡	5 ± 2†
Coronary blood flow (% reduction)									
LAD	1 ± 0	20 ± 5§	48 ± 8§	76 ± 10§	5 ± 2	2 ± 1‡	4 ± 2¶	22 ± 4§¶	66 ± 9§
LCx	1 ± 0	8 ± 4*	10 ± 5†§	11 ± 8*§	4 ± 2	0 ± 1‡	3 ± 2	6 ± 4*	10 ± 5*‡

*$p < 0.05$, †$p < 0.01$ versus left anterior descending coronary artery. ‡$p < 0.05$, §$p < 0.01$ versus control. ‖$p < 0.05$, ¶$p < 0.01$ versus before diltiazem. Abbreviations and format as in Table 2.

Table 4. Effects of Nifedipine on Endothelin-Induced Coronary Vasoconstriction (n = 5)

	Endothelin Before Nifedipine (pmol/kg)				Endothelin After Nifedipine (N) (pmol/kg)				
	Control	3	10	30	Control	N	3	10	30
MAP (mm Hg)	83 ± 5	86 ± 4	90 ± 6	98 ± 6§	84 ± 5	74 ± 4§	75 ± 5‡	78 ± 3	80 ± 6
HR (beats/min)	100 ± 6	96 ± 5	104 ± 6	109 ± 6	106 ± 5	114 ± 5§	110 ± 6	108 ± 6	110 ± 7
Coronary artery diameter (% reduction)									
LAD	5 ± 2	10 ± 3	20 ± 5§	30 ± 5	6 ± 1	2 ± 1‡	6 ± 3	16 ± 4‡	20 ± 4§¶
LCx	2 ± 1	4 ± 3*	8 ± 5*‡	11 ± 5*‡	5 ± 1	3 ± 1‡	3 ± 3	5 ± 3*	6 ± 4†
Coronary blood flow (% reduction)									
LCD	3 ± 1	22 ± 5§	44 ± 5§	73 ± 11§	6 ± 2	2 ± 0‡	10 ± 3¶	33 ± 6§¶	68 ± 10§
LCx	1 ± 1	6 ± 5*	9 ± 5*‡	12 ± 9*‡	5 ± 2	1 ± 0‡	4 ± 3	6 ± 5†	12 ± 5*‡

*$p < 0.05$, †$p < 0.01$ versus left anterior descending coronary artery. ‡$p < 0.05$. §$p < 0.01$ versus control. ‖$p < 0.05$, ¶$p < 0.01$ versus before nifedipine. Abbreviations and format as in Table 2.

that decreased coronary flow was due to an active constriction of coronary vessels rather than to a reduction in myocardial oxygen requirements. Available published data (6) have not shown a negative inotropic effect on the heart. These results suggest that picomolar doses of endothelin-1 produced a significant decrease in coronary blood flow associated with myocardial ischemia by constricting coronary vessels. These data confirm previous studies (7–9) in anesthetized open chest animals. However, the unique actions of endothelin-1 on the coronary vascular bed were obtained with bolus administration of exogenous compound, and the selected doses were determined empirically on the basis of the irreversible responses to doses >100 pmol/kg. These doses may be higher than those occurring naturally in vivo, raising the possibility that the coronary vascular response to the peptide that occurs in physiologic or pathophysiologic conditions might not be equivalent to that observed in the present study.

Vasoconstriction of large versus small coronary vessels. It has been demonstrated that endothelin produces potent constriction not only in isolated conduit vessels (4–6), but also in small vessels (15,16). Thus, we attempted to differentiate the level of coronary artery that is responsible for producing myocardial ischemia. For this purpose, coronary arteriography was utilized because the technique provides a means to evaluate vasoreactivity on the entire epicardial coronary vessel tree in closed chest animals without the need of surgical dissection around coronary vessels. In the present study, when decreased coronary blood flow with significant ischemic changes was observed, the degree of epicardial diameter reduction was as much as 32%. On a theoretic basis (17), the degree of endothelin-induced narrowing of the epicardial coronary artery observed in our study was not great enough to significantly decrease coronary blood flow and render the perfused myocardium ischemic. Therefore, it appears reasonable to conclude that the preferential site of endothelin-induced constriction with the doses we used is at the level of the small coronary arteries rather than epicardial arteries. It is plausible to assume that higher doses of the peptide would cause intense vasoconstriction at levels from epicardial to small coronary vessels because the degree of vasoconstriction would depend on the doses administered.

These findings are compatible in part with studies in open chest dogs (8,9); however, our results differ from those studies (8,9) with regard to the greater degree of constriction of the epicardial vessels into which endothelin was administered (32% versus 9.6% and 0% diameter reduction, respectively, in the previous studies). These differences may be ascribed not only to differences in species, but also to variations in experimental conditions (closed versus open chest).

Comparison with other vasoconstrictor agents. Among vasoconstrictor agents that have been reported to produce coronary vasoconstriction in vivo, the effects of endothelin-1 appear to be similar to those of vasopressin (18), angiotensin II (19) and leukotriene (13); especially in large doses (that is, μmol/kg doses), they produce similar effects on the coronary vasculature as have been shown with endothelin-1 in this study. However, in terms of effective doses, endothelin-1 appears to be a more potent coronary constrictor than those agents. Indeed, in vitro studies (4–6) of mammalian vascular tissues have shown that endothelin-1 is the most potent vasoconstrictor described to date.

Effects of calcium channel blockers. Unlike sustained vasoconstrictor activities of endothelin-1 shown in isolated pig coronary arteries and prolonged pressor effects in the rat in vivo (4,6), the present study showed that coronary vaso-

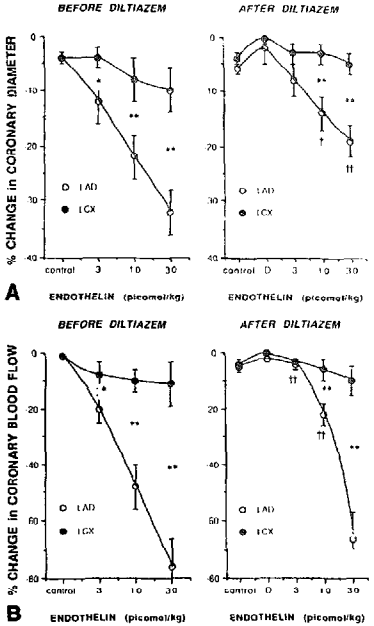

Figure 2. Effects of diltiazem on endothelin-induced changes in epicardial coronary artery diameter (A) and coronary blood flow (B). *p < 0.05, **p < 0.01 between the left anterior descending (LAD) and left circumflex (LCX) coronary arteries. †p < 0.05, ††p < 0.01 before diltiazem.

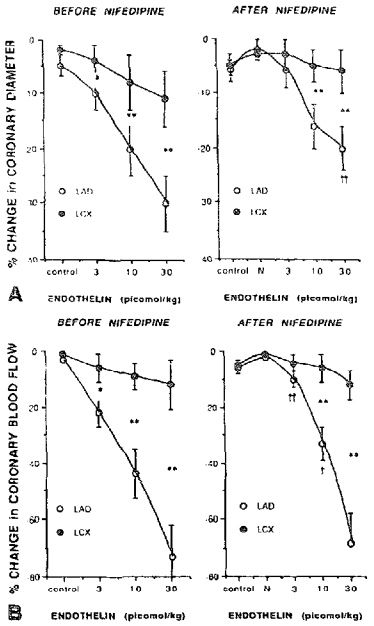

Figure 3. Effects of nifedipine on endothelin-induced changes in the epicardial coronary artery diameter (A) and coronary blood flow (B). *p < 0.05, **p < 0.01 between the left anterior descending (LAD) and left circumflex (LCX) coronary arteries. †p < 0.05, ††p < 0.01 before nifedipine.

constrictor responses to pmol/kg doses of intracoronary endothelin-1 were transient and reversible. In this regard, Ezra et al. (7) reported that the decrease in coronary blood flow was transient after intracoronary administration of endothelin-1 in doses up to 30 pmol/kg. Moreover, our control study, with repeated administration of the peptide in the absence of any antagonists, suggests that tachyphylaxis of coronary constrictor responses to endothelin-1 did not occur in our experimental protocol.

A role for calcium channels in mediating vascular contraction induced by endothelin-1 remains controversial. Endothelin-induced enhancement of calcium influx through the voltage-dependent ion channel has been postulated as a mechanism (4); however, it was found more recently that endothelin-1 may have a specific receptor on the sarcolemma (20) and may evoke vasoconstriction by activating intracellular calcium mobilization (21–23). The present study demonstrates that endothelin-induced epicardial vessel narrowing and diminution in coronary blood flow were significantly inhibited by pretreatment with the calcium channel blockers diltiazem and nifedipine. Inhibition by these calcium channel blockers of epicardial vessel constriction was predominantly noted at a 30 pmol/kg dose, whereas the inhibition of reduction in coronary blood flow was observed at 3 and

10 pmol/kg doses of endothelin-1. The inhibitory effects produced by diltiazem and nifedipine appeared similar with the doses used. Although further analysis with regard to the vascular mechanism of action of endothelin-1 is required, it is reasonable to propose from our data that calcium influx through calcium channels (the voltage-dependent or receptor-operated calcium channels, or both) appears to be involved at least in part in the mechanism of endothelin-induced coronary vasoconstriction in vivo.

Limitations of the study. The present study has limitations. 1) Estimation of coronary blood flow by calculating the transit time of the contrast agent is subject to error (16,17). However, by standardizing the volume as well as the period of injection, the relative changes in transit time in each animal can be assessed with acceptable accuracy. A published experiment (13) has shown that this measurement is applicable to evaluation of changes in blood flow in response to vasoconstrictor agents. 2) Because the contrast material is known to cause modest vasodilation by itself, estimation of coronary blood flow by the technique we used might lead to underestimation of actual changes in coronary blood flow. However, the percent changes in coronary blood flow after endothelin-1 that we observed are comparable with those reported in a study in open chest pigs (7). 3) Whether endothelin is produced in enough quantity in situ to produce effects similar to our results in unknown. Thus, although picomolar doses of exogenous compound were actually effective enough to produce vasoconstriction and ischemia, specific physiologic meaning of the present study awaits confirmation.

Clinical implications. The effects of endothelin-1 on the coronary vascular bed in pigs were unique in that picomolar doses of exogenous endothelin-1 caused myocardial ischemia through coronary vasoconstriction. The clinical implications of the present study are equivocal at the present time, but would be greatly enhanced when the precise nature of the production and release of endothelin-1 in situ is clarified. Indeed, more recent studies (24) demonstrated that endothelin-1 release or gene expression in endothelial cells is stimulated by thrombin, epinephrine, A23187, phorbol esters and shear stress, implying that various stimuli on endothelial cells might be associated with enhanced endothelin-1 release (25). We speculate, therefore, that endothelin-1 may have a role in physiologic and pathophysiologic control of vascular tone and coronary blood flow. Coronary vasospasm is known to occur primarily in diseased vessels with atherosclerotic plaque (12,25,26), where defective endothelial function and hyperreactive contraction of smooth muscles are present (12,13,25–27). In these pathologic circumstances, endothelin-1 could be a contributory factor in causing coronary vasospasm. Moreover, our results provide data of potential therapeutic usefulness by showing the preventive effects of calcium channel blockers on endothelin-induced coronary vasoconstriction.

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