Patients With Evidence of Coronary Endothelial Dysfunction as Assessed by Acetylcholine Infusion Demonstrate Marked Increase in Sensitivity to Constrictor Effects of Catecholamines

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Background. Studies in patients undergoing cardiac catheterization have demonstrated that normal coronary arteries dilate and atherosclerotic arteries constrict in response to exercise and the cold pressor test, but the mechanisms are unknown. These vasomotor responses are mirrored by the vasomotor response to the endothelium-dependent agent acetylcholine. Exercise and the cold pressor test are associated with adrenergic stimulation and increased circulating catecholamines. The present study tested the hypothesis that coronary arteries with intact endothelial function are relatively resistant to the constrictor effects of catecholamines, whereas arteries with loss of endothelial function have increased sensitivity to catecholamine-induced constriction.

Methods and Results. The vasomotor function of the coronary endothelium was assessed by serial acetylcholine infusions (final concentration, $10^{-4}$ to $10^{-6}$ M) in 30 segments in 15 patients with minimal or no evidence of coronary atherosclerosis. The acetylcholine responses were related to the vasomotor response to intracoronary phenylephrine infusion (final concentration, $10^{-4}$ to $10^{-6}$ M) in the same segments. In the group of 18 segments that constricted to acetylcholine, there was a constrictor response to phenylephrine at an approximately 100-fold lower concentration than the group of 12 segments that did not constrict to acetylcholine.

Conclusions. These results suggest that the endothelial dysfunction that characterizes early and late atherosclerosis is associated with a marked increase in sensitivity to the constrictor effects of catecholamines. This finding may explain the constrictor responses of atherosclerotic coronary arteries to exercise and the cold pressor test. In stenotic coronary arteries this mechanism may play a role in the production of myocardial ischemia. (Circulation 1992;85:1390–1397)

Key Words • acetylcholine • catecholamines • endothelium • coronary artery disease

Stimuli for myocardial ischemia, such as exercise and exposure to cold, are associated with adrenergic stimulation and increased circulating catecholamines. In addition to producing an increase in myocardial oxygen demand, such stimuli have been associated with absolute decreases in myocardial perfusion and epicardial constriction in patients with early and advanced coronary atherosclerosis. In the presence of stenoses it is possible that abnormal coronary artery constriction plays a role in the pathophysiology of clinical ischemic syndromes, but the mechanisms of this constriction are unknown.

Recently the importance of the vascular endothelium in the control of arterial tone has been recognized. The endothelium elaborates vasodilators in response to acetylcholine, $\alpha_2$-adrenergic receptor agonists, increased blood flow, and a number of other clinically relevant factors. In animals and isolated human coronary segments, pathological conditions such as atherosclerosis lead to the loss of this vasodilator function, which results in unopposed and increased vasoconstrictor effects in response to these and other stimuli. In patients with either coronary risk factors or angiographic evidence of atherosclerosis, the normal vasodilator response to intracoronary acetylcholine infusion is replaced by coronary constriction. In addition, loss of endothelium-dependent vasodilation has been demonstrated in coronary arteries that constrict during exercise and the cold pressor test. Adrenergic nerve stimulation and circulating catecholamines produce constriction of epicardial coronary...
arteries through the stimulation of α1- and α2-adrenergic receptors on vascular smooth muscle. In experiments, normal endothelium limits the constrictor effects of catecholamines. Removal of the endothelium from vascular rings produces a significant increase in the sensitivity of arteries to these constrictor effects.

We hypothesize that the abnormal constrictor responses of atherosclerotic coronary arteries in patients may in part reflect a loss of endothelial vasodilator function and an inability to limit the constrictor effects of circulating catecholamines. The purpose of the present study was to test this hypothesis by examining the vasomotor response to intracoronary phenylephrine infusion of coronary arteries with and without evidence of endothelial dysfunction as assessed by intracoronary acetylcholine (ACH).

Methods

Patients

Patients referred for cardiac catheterization to evaluate coronary artery disease were considered for enrollment in the study. Patients with unstable angina, previous myocardial infarction, valvular heart disease, history of congestive heart failure, or peripheral vascular disease were excluded. Informed consent was obtained in accordance with the requirements of the Brigham and Women's Hospital Committee for the Protection of Human Subjects from Research Risks and the West Roxbury Veterans Administration Medical Center Research Committee. Therapy with vasoactive agents, including calcium channel blockers, β-adrenergic blockers, angiotensin converting enzyme inhibitors, and long-acting nitrates, were discontinued 18 to 24 hours before catheterization. Unrestricted use of sublingual nitroglycerin was permitted up to 1 hour before study, but no patient had an episode of chest pain while off medications. Patients taking α-adrenergic antagonists were excluded.

Diagnostic right- and left-heart catheterization was performed using a standard percutaneous femoral approach. Patients were excluded from the study if any of the following was present: any left main coronary artery narrowing, left anterior descending coronary artery stenosis greater than 30%, occlusion of the right coronary artery or the circumflex artery with collateral filling of the posterior descending coronary artery and atrioventricular nodal artery, elevated left-heart filling pressures, or abnormal left ventricular systolic function.

Study Design

After completion of the diagnostic catheterization, an additional 5,000 units heparin was injected intravenously, and an 8F guiding catheter was positioned in the ostium of the left coronary artery. A 2.5F (tip diameter) Doppler infusion catheter (Millar Instruments, Inc., Houston, Tex.) was positioned in the middle portion of the left anterior descending coronary artery (distal to the first diagonal and first septal branches). The use of this device to assess intracoronary blood flow velocity has been described in detail elsewhere.26,27 The Doppler catheter was connected to a velocimeter (Millar Instruments, Inc.), and mean and phasic velocity waveforms were displayed on a multichannel oscillographic recorder (Electronics for Medicine, Pleasantville, N.Y.). Throughout the protocol coronary blood flow velocity, ECG (standard lead I), and femoral arterial and guiding catheter pressures were monitored continuously.

Experimental Protocol

Intracoronary ACH infusion was used to test endothelium-dependent vasodilator function, and phenylephrine was chosen to test the response of the coronary artery to the constrictor effects of catecholamines. Serial drug infusions at 0.8 ml/min were made selectively into the left anterior descending coronary artery in the following sequence through the lumen of the Doppler catheter using an infusion pump (Harvard Apparatus, Inc., South Natick, Mass.): 1) 2-minute control infusion of 5% dextrose in sterile water, 2) three 2-minute ACH infusions (0.14, 1.4, and 14.0 μg/min) yielding final estimated intracoronary blood concentrations of 10⁻⁸ to 10⁻⁶ M, 3) 5-minute repeat control infusion, 4) five 2-minute phenylephrine infusions (0.016, 0.16, 1.6, 5.3, and 16.0 μg/min) yielding estimated final blood concentrations of 10⁻⁹ to 10⁻⁶ M, 5) 5-minute repeat control infusion, and 6) nitroglycerin 40 μg over 2.5 minutes. The final estimated blood concentrations of ACH and phenylephrine were calculated using the infusion rate of 0.8 ml/min, the known concentration of infused drug, and an assumed left anterior descending coronary artery blood flow of 80 ml/min.

At the end of each infusion, coronary blood flow velocity, ECG, and blood pressure tracings were recorded; then, quantitative angiography was performed. Nonionic contrast medium (Omnipaque, Winthrop-Breon Laboratories, New York, N.Y.) was injected into the left coronary artery at a rate of 7 ml/sec for a total of 9 ml with a power injector (Medrad, Pittsburgh, Pa.) to standardize vessel opacity. A biplane cineangiographic system (Polydiagnost-C, Philips Medical Systems, Shelton, Conn.) was set to position the left anterior descending coronary artery in the center of each field of view and at a single position in space (isocenter).7,8,17,18,27

Analysis of Arterial Dimensions

Atherosclerosis is a segmental disease, and our previous studies have demonstrated that vasomotor responses vary between segments.7,8,17,19 Therefore, two technically suitable coronary segments distal to the Doppler catheter were selected in each patient by an operator unaware of the response to phenylephrine. All segments were free of side-branches and were at least 7 mm in length. When there was visible constriction to ACH, one segment was selected to include the region of constriction. Using an automated, previously validated system of quantitative angiography,7,8,17,18,29 the diameter of each segment was measured during control infusion and during each infusion of ACH or nitroglycerin. A second operator, who was unaware of the response to ACH, then determined the diameter of the same segments during repeat control infusion and each dose of phenylephrine. For diameter analysis, each segment was centered and the single-frame cine image was digitized (20–40 μm/pixel) with the use of a video camera (Cohu, San Diego, Calif.) connected to a video interface (Recognition...
tion Concepts, Incline Village, Nev.) and a Micro-Vax II computer (Digital Equipment Corp., Maynard, Mass.). Two-line profile averaging was used to minimize anatomic noise, and 16 video images were summed to minimize video noise. Four adjacent cine frames in end diastole were scanned and averaged with two anatomic features used to ensure accurate alignment. Calibrated grids filmed at isocenter were used to scale the data from pixels to millimeters. The two anatomic features were used to identify the segment in each cine run. The result was a mean diameter for the segment at control and at the end of each drug infusion. The phenylephrine diameters were determined by an operator blinded to the responses to ACH.

**Estimation of Change in Coronary Blood Flow**

Changes in coronary blood flow were estimated by correcting changes in mean blood flow velocity, as measured by the Doppler catheter, for changes from control in estimated cross-sectional area of the vessel. Given the limitations of the Doppler catheter, no attempt was made to determine absolute coronary blood flow.26,27

**Statistical Analysis**

For all patients, the change in blood pressure, heart rate, and coronary blood flow from control in response to the peak doses of ACH, phenylephrine, and nitroglycerin received by the patient were compared using the Wilcoxon signed rank test. All segments (two per patient) were then grouped according to their response to ACH as measured by quantitative angiography as ACH constrictors (group 1) and ACH nonconstrictors (group 2). A constrictor response was defined as more than 5% decrease in mean diameter from control at the highest ACH dose received by the patient. Dose–response curves of the percent change in segment diameter in response to phenylephrine were constructed for each group. Group differences in the vasoconstriction of the vessel to phenylephrine were examined at each dose using the Wilcoxon rank sum test and the Bonferroni correction.40 Diameter determinations were made for five doses of phenylephrine in this analysis and by the Bonferroni method; a p value five times lower than 0.05 (p<0.01) was required to achieve significance. The assumption that the two segments act independently was tested by examining the correlation between the responses for the two segments from each individual. A nonparametric analysis was chosen to avoid making assumptions about the normality of the data that could not be verified because of the relatively small sample size.

The relation between the diameter responses to ACH 10^{-7} M and to phenylephrine 10^{-7} M were compared using regression analysis. The effects of baseline diameter, nitroglycerin response, distance of the segment from point of drug infusion, change in heart rate, change in blood pressure, change in coronary blood flow, previous treatment with β-blockers or antiplatelet drugs, the total serum cholesterol and presence or absence of hypertension, a positive family history for coronary artery disease, or a history of cigarette smoking on the phenylephrine response were also examined using a separate linear regression for each variable. Binary variables were dummy coded so that they would fit into the regression framework. Assuming that the segments acted independently, patient specific variables were duplicated for each segment for this analysis. The criterion of significance (two tailed) for this analysis and for the paired comparison of diameter and hemodynamic responses and control was p<0.05. The data are presented as mean±SD.

**Results**

**Patients**

Sixteen patients were enrolled in the study. One patient was excluded from further analysis after study because the Doppler catheter was recognized to be in a small diagonal branch instead of the left anterior descending coronary artery. The mean age of the 15 remaining patients was 48±8 years. Thirteen were men and two were women. Thirteen patients presented with atypical chest pain and a negative or nondiagnostic exercise test. Eight patients were found to have angiographically smooth coronary arteries, and five had only luminal irregularities of the left anterior descending coronary artery and no stenosis greater than 30%. Two patients presented with typical angina, and each was found to have a circumflex stenosis greater than 70% and luminal irregularities in the left anterior descending coronary artery. All had normal hemodynamics and normal left ventricular function by ventriculography or echocardiography. The mean serum cholesterol for the group was 221±45 mg/dl. The ACH responses but not the phenylephrine responses of five of these patients were previously reported.16

To minimize the risk to the patient, higher doses of ACH and phenylephrine were omitted when visible constriction was observed. In addition, the 10^{-9} M phenylephrine dose was omitted after no significant vasoconstriction response from baseline was observed in six patients, and the 10^{-6} M dose was eliminated in three patients to limit the contrast load. Thus, all patients received ACH 10^{-8} M, 13 patients received ACH 10^{-7} M, eight received ACH 10^{-6} M, six received phenylephrine 10^{-8} M, 12 received phenylephrine 10^{-7} M, 14 received phenylephrine 10^{-6} M, 13 received phenylephrine 10^{-5} M, and eight received phenylephrine 10^{-6} M. Representative angiograms from one patient are shown in Figure 1.

**Hemodynamic Responses**

ACH infusion produced no change in heart rate (control, 67.7±9.5 bpm; peak ACH, 67.3±8.2 bpm) or systolic blood pressure (control, 131±14 mm Hg; peak ACH, 129±17 mm Hg). Mean estimated coronary blood flow did not change significantly from control (43±78% increase) for the group of patients as a whole (range, 44% decrease to 260% increase in flow). There were no symptoms or ECG changes.

Phenylephrine infusion produced no significant change in heart rate (control, 64.7±6.3 bpm; peak phenylephrine, 64.7±9.8 bpm) or systolic blood pressure (control, 129±16 mm Hg; peak phenylephrine, 136±17 mm Hg; p=NS). Mean estimated coronary blood flow did not change significantly from control (9±34% decrease) at peak phenylephrine dose (range, 36% decrease to 30% increase); an 8±19% decrease occurred at phenylephrine 10^{-7} M. There was no
FIGURE 1. Five coronary angiograms of left anterior descending coronary artery (LAD) in right anterior oblique view from a single patient are displayed. In control (C1), LAD is smooth and free of stenoses. During peak acetylcholine (Ach) infusion, a proximal segment (upper arrow) is markedly constricted, whereas a distal segment (lower arrow) remains unconstricted. After recontrol infusion (C2), LAD diameter returns to baseline in both segments. During peak phenylephrine infusion (Pe) the same proximal segment (upper arrow) constricts, whereas the same distal segment (lower arrow) remains unconstricted. During nitroglycerin infusion (NTG), both segments dilate markedly. The segment with evidence of endothelial dysfunction as assessed by acetylcholine infusion is more sensitive to constrictor effect of phenylephrine than the segment with intact endothelial function.

Vasomotor Responses to Acetylcholine

A total of 30 left anterior descending coronary artery segments were examined (two per patient) using quantitative angiography. On the basis of the response to Ach, all of the segments were grouped as Ach nonconstrictors (group 1, n=12) or Ach constrictors (group 2, n=18) (Figure 2). Group 1 demonstrated no significant change from control: 2±4% for Ach 10⁻⁸ M, 1±5% for Ach 10⁻⁷ M, and 7±8% for Ach 10⁻⁶ M. Group 2 demonstrated a significant dose-dependent decrease in diameter (constriction) to Ach: -10±10% for Ach 10⁻⁸ M (p<0.01), -17±11% for Ach 10⁻⁷ M (p<0.0001), and -27±7% for Ach 10⁻⁶ M (p<0.01). After the 5-minute repeat control infusion the vessel diameter was unchanged from baseline and there was no significant difference between groups.

There were no significant group differences in segment length (group 1, 9.4±2.1 mm; group 2, 10.4±1.7 mm) or in segment diameter (group 1, 1.40±0.29 mm; group 2, 1.50±0.26 mm). Segments in each group dilated equally in response to nitroglycerin (group 1, 31.2±15.7%; group 2, 36.3±16.3%; p=NS) (Figure 2), and for all segments, the response to Ach was independent from the response to nitroglycerin (r=0.03, p=NS), indicating that there were no differences in baseline tone between the two groups. There was no correlation between the vasomotor response to Ach and the distance of the segment from the origin of the left anterior descending artery (r=0.04, p=NS).

Vasomotor Responses to Phenylephrine

The dose–response to phenylephrine in group 1 differed markedly from group 2 (Figure 3). In group 1 (Ach nonconstrictors) there was no significant constriction in response to phenylephrine 10⁻⁸ M (0.3±3.2%), 10⁻⁷ M
indicate that pressure, the hypertension, relate to treatment (RC).

FIGURE 2. The percent change in coronary segment diameter in response to acetylcholine infusions with final estimated blood concentrations of 10^{-8} M to 10^{-6} M (ACH-8, ACH-7, and ACH-6), repeat control infusion (RC), and nitroglycerin infusion (NTG) are displayed. Group 1 (n=12 segments) was defined as those segments without constrictor response to acetylcholine (reflecting intact endothelial function), and group 2 (n=18 segments) was defined as those segments with constrictor response to acetylcholine (reflecting endothelial dysfunction). Coronary diameter returned to control during recontrol infusion. There was no significant difference between groups in response to NTG. Error bars, mean±SD.

(2.3±7.2%), and 10^{-6.5} M (-4.7±11.7%). Only the highest dose of phenylephrine (10^{-6} M) produced significant constriction (-10.9±8.8%, p<0.01). In contrast, the dose--response to phenylephrine in group 2 segments (ACH constrictors) was shifted to the left by approximately 100-fold. There was no significant constriction to phenylephrine 10^{-9} M (-2.8±4.7%, p=NS). However, there was significant constriction from baseline in response to 10^{-8} M (-4.8±5.6%, p<0.01), phenylephrine 10^{-7} M (-12.8±7.3%, p<0.0001), phenylephrine 10^{-6.5} M (-15.2±6.2%, p<0.0001), and phenylephrine 10^{-6} M (-17.7±6.9%, p<0.02). By the Wilcoxon rank sum test, the differences between groups were significant at 10^{-7} M (p=0.0001) and phenylephrine 10^{-6.5} M (p=0.004), and closely approached significance at phenylephrine 10^{-6} M (p=0.014), where a value of p<0.01 was required for significance using the Bonferroni correction.

In 26 segments from the 13 patients who received both ACH 10^{-7} M and phenylephrine 10^{-7} M, univariate regression analysis demonstrated that the response to ACH 10^{-7} M was a significant predictor of the phenylephrine response (r=0.61, p<0.001) (Figure 4). Univariate analysis demonstrated that the baseline diameter, the baseline coronary blood flow, the response to nitroglycerin, the distance of the segment from point of drug infusion, the change in heart rate, the change in blood pressure, the change in coronary blood flow, previous treatment with β-blockers or antiplatelet agents, the total serum cholesterol and presence or absence of hypertension, a positive family history for coronary artery disease, or a history of cigarette smoking did not relate to the response to phenylephrine 10^{-7} M. These findings indicate that differences in baseline coronary tone, a systematic difference in location and size of the studied segment, hemodynamic responses, an extended effect of longer acting β-blockers and antiplatelet agents, and coronary risk factors did not influence the response to phenylephrine in the studied patients. Finally, the relation between the phenylephrine responses for the two segments from each patient was examined using univariate regression analysis. There was no significant relation between the two responses (r=0.34, p=NS), further supporting the assumption that they behaved independently.

In nine patients both analyzed segments had the same directional response to ACH (dilation or constriction). However, six patients demonstrated significant constriction in a localized region of the left anterior descending coronary artery and no constriction in another region. In these patients, the response to phenylephrine demonstrated a similar pattern with more marked constriction in the region that constricted to ACH (Figure 1). Thus, even within single vessels, the response to phenylephrine paralleled the response to ACH.

Two patients demonstrated visible constriction in at least one segment at the lowest dose of ACH (10^{-8} M), and for reasons of patient safety they did not receive any higher doses. It is possible, but highly improbable, that these patients might have been misclassified as having possible endothelial dysfunction on the basis of this single dose of ACH. To exclude this possibility, the analysis of the dose--responses to phenylephrine was repeated excluding these two patients. As in the original
larly increased serum cholesterol, probably reflecting early atherosclerosis not detectable by angiography or an abnormality of endothelial function that precedes atherosclerosis. In contrast, angiographically smooth arteries in younger patients with fewer coronary risk factors will dilate in response to ACH, presumably reflecting preserved endothelial function. Therefore, in the present study it is likely that the smooth coronary segments that constricted to ACH had early atherosclerosis not detectable by angiography.

The effect of the sympathetic nervous system on epicardial coronary tone is complex. Experimental studies have demonstrated that α₁-adrenergic receptors and α₂-adrenergic receptors on vascular smooth muscle mediate vasoconstriction and β-adrenergic receptors mediate vasodilation. Intact endothelium modulates the constrictor effects of catecholamines by a number of mechanisms. Stimulation of α₂-adrenergic receptors on endothelial cells leads to the release of EDRF and limitation of the constrictor effects of norepinephrine. Intact endothelium also takes up and metabolizes norepinephrine, provides a barrier to diffusion into the vessel lumen, and may inhibit release of norepinephrine from sympathetic nerves. Martin et al observed that removal of endothelium from isolated arterial rings increased the sensitivity to constriction by norepinephrine and phenylephrine from four- to sixfold without altering the maximal effect.

In patients, exercise and the cold pressor test activate the sympathetic nervous system and increase circulating catecholamines. These complex stimuli also increase myocardial oxygen demand by increasing heart rate and blood pressure. In patients with angiographically normal arteries, such stimuli also produce dilation of epicardial coronary arteries, a response only partially blocked by propranolol. It is probable that the release of EDRF in response to increased blood flow also contributes to this response. In contrast, patients with angiographic evidence of atherosclerosis demonstrate epicardial coronary artery constriction in response to these stimuli, despite equal changes in catecholamines and hemodynamics. Loss of endothelium-dependent vasodilation has been demonstrated in coronary arteries that constrict during exercise and the cold pressor test. The present study suggests that enhanced responsiveness to catecholamines in the presence of endothelial dysfunction may in part explain the augmented constriction that occurs in atherosclerotic coronary arteries during exercise.

Intracoronary phenylephrine infusions were made in this study to examine the effects of α-adrenergic stimulation in isolation from other effects of exercise such as increased heart rate, blood pressure, and coronary blood flow. Phenylephrine was used because it is a more selective α-receptor agonist than norepinephrine and has a relatively short duration of action in comparison with other α-agonists such as methoxamine. Norepinephrine was avoided because of its more potent vasoconstrictor effects and concerns about its multiplicity of actions including its β-adrenergic effects on coronary tone, heart rate, and myocardial contractility, which make interpretation of results difficult. The possibility of performing the study with concurrent β-blockade was considered to exclude the reported minimal β-adrenergic effects of phenylephrine, but was discarded be-
cause of the concern of causing more severe coronary constriction and prolonging the protocol.

It is difficult to assess local concentrations of catecholamines in the vessel wall during exercise or other clinical stimuli for ischemia because of the combined effects of neurally released and circulating norepinephrine. However, the dose range of phenylephrine used in this study (10⁻⁹ to 10⁻⁶ M) probably corresponds to physiological levels of catecholamines because phenylephrine is approximately 10 times less potent than norepinephrine in simulating coronary artery constriction⁶⁰ and that exercise produces plasma norepinephrine concentrations in the range of 10⁻⁹ to 10⁻⁸ M.²⁻⁴

The use of human subjects imposed several limitations on this study. To avoid precipitating severe, prolonged coronary constriction, the higher doses of phenylephrine were eliminated in the patients with visible constriction at the lower doses. If these higher doses were given, more marked constriction probably would have occurred and the differences between the two groups would have been even greater. The clinical relevance of these observations must be viewed with caution because arteries with hemodynamically significant coronary stenoses were excluded from this study. In the studied population, 18% constriction of epicardial coronary arteries would be unlikely to produce ischemia. However, if the observed increase in sensitivity to catecholamines and the apparent endothelial dysfunction were operative in a vessel with a significant stenosis, constriction to this extent could significantly limit coronary blood flow. Previous experiments and patient studies do indicate that arteries with early atherosclerosis respond similarly to vessels with more advanced disease.⁶⁻⁸,¹³,¹⁴,¹⁸

The order of ACH and phenylephrine infusion would ideally have been randomized in this study. However, phenylephrine may have a prolonged effect (20 minutes), and the time to reestablish the control state after phenylephrine would have lengthened the protocol excessively. The half-life of ACH in vivo is extremely short,¹⁷,¹⁸ and in this study the coronary artery diameter and blood flow returned to baseline in both groups before phenylephrine infusion. Another potential limitation of the study was the assumption that the responses of the two segments from each individual patient behaved independently. The lack of significant correlation between the two responses suggests that there is no significant departure from this assumption.

Finally, the possibility that the results of this study represent hypersensitivity of vascular smooth muscle to ACH and phenylephrine cannot be excluded. However, the dose range of ACH employed, the response to nitroglycerin, and the extensive supporting animal studies all suggest that, at least in part, a defect in endothelial vasomotor function in the group of segments that constricted to ACH and demonstrated increased sensitivity to phenylephrine.

Conclusions

In the present study coronary segments demonstrating constriction to ACH had a constrictor response to phenylephrine at an approximately 100-fold lower concentration than the group of segments that did not constrict to ACH. Prior animal and human experiments suggest that a constrictor response to ACH reflects dysfunction of the arterial endothelium produced by early and late atherosclerosis. Therefore, the findings of this study raise the possibility that endothelial dysfunction in atherosclerosis results in an increased sensitivity to the constrictor effects of catecholamines in patients. These results could explain the observation that epicardial coronary arteries constrict during exercise and other stimuli associated with increased circulating catecholamines in patients with early and advanced atherosclerosis. This mechanism may play a role in the production of clinical ischemia in patients with atherosclerotic coronary artery stenoses.

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