Constrictor and Dilator Responses to Intracoronary Acetylcholine in Adjacent Segments of the Same Coronary Artery in Patients with Coronary Artery Disease

Endothelial Function Revisited

Hassan El-Tamimi, MD; Michael Mansour, MD; Thomas J. Wargovich, MD; James A. Hill, MD; Richard A. Kerensky, MD; C. Richard Conti, MD; Carl J. Pepine, MD

Background In patients with angiographically detectable atherosclerosis or in those with risk factors for coronary artery disease, intracoronary acetylcholine causes coronary constriction instead of endothelium-derived relaxing factor–mediated dilation. Therefore, it has been hypothesized that diffuse endothelial dysfunction precedes development of coronary atherosclerosis. We tested this hypothesis in a systematic investigation of the effects of ascending doses of acetylcholine on the diameters of nonstenotic segments of the left coronary artery in patients with advanced atherosclerosis and coronary risk factors.

Methods and Results Effects of intracoronary infusion of acetylcholine (10^-6 to 10^-4 mol/L) on diameters of proximal, middle, and distal nonstenotic segments of the left coronary artery were studied in 28 consecutive patients with chronic stable angina, positive exercise tests, and angiographic evidence of obstructive atherosclerosis (≥50% reduction in lumen diameter in at least one vessel). Two patterns of response to the maximal acetylcholine dose (10^-4 mol/L) were observed. In 21 patients (group 1), only constriction was observed in all left anterior descending and circumflex artery segments studied (16±3%, 19±4%, and 23±4%, respectively; P<.01 compared with control). In 7 other patients (group 2), both constriction and dilation were observed in adjacent segments of the same vessel; maximal acetylcholine dose caused constriction in 14 left anterior descending artery segments from a control diameter of 1.94±0.19 to 1.33±0.26 mm (37% reduction, P<.01) and dilation in 16 other segments from 1.63±0.22 to 1.93±0.21 mm (25% increase, P<.01). In the circumflex artery, this dose caused constriction in 16 segments from a control diameter of 1.88±0.14 to 1.33±0.17 mm (31% reduction, P<.01) and dilation in 12 segments from 1.37±0.12 to 1.71±0.09 mm (34% increase, P<.01).

Conclusions In 25% of patients studied with advanced angiographic coronary atherosclerosis and coronary risk factors, coronary segments with acetylcholine-inducible dilatation are present. In these patients, the endothelium is not diffusely dysfunctional as currently believed but rather shows marked segmental heterogeneity in the response to acetylcholine reflecting degrees of endothelial dysfunction. (Circulation. 1994;89:45–51.)

Key Words • acetylcholine • arteries • atherosclerosis

The endothelium plays a critical role in modulating vasomotor tone. The vascular effects of acetylcholine on human coronary arteries are complex. Acetylcholine has been shown to cause vasoconstriction in the presence of an intact endothelium mediated by release of endothelium-derived relaxing factor and to cause vasodilation in the absence of functional endothelium by direct stimulation of vascular smooth muscle.1,2 Previous studies have shown that intracoronary acetylcholine infusion causes constriction in patients with obstructive coronary atherosclerosis, even in arteries that appear only minimally irregular angiographically, and dilation in subjects with normal coronary arteries.3–7 On the basis of these findings, it has been proposed that diffuse endothelial dysfunction is present in atherosclerotic coronary arteries. However, pathological studies and, more recently, studies carried out using intravascular ultrasound have shown a lack of correlation between angiographic findings and the extent of atherosclerosis.3–10

To further investigate the distribution of coronary endothelial dysfunction in patients with coronary atherosclerosis, we undertook a systematic study in a highly homogeneous group of patients characterized by (1) stable angina pectoris, (2) a positive exercise test, (3) multiple coronary risk factors, and (4) obstructive coronary atherosclerosis. In these patients, we analyzed the response to ascending doses of intracoronary infusion of acetylcholine in segments of the left coronary artery using quantitative angiography.

Methods

Patients Twenty-eight consecutive patients with chronic stable angina and a positive exercise test for myocardial ischemia (>1.0 mm horizontal or downsloping ST-segment depression) were studied during clinically indicated cardiac catheterization. There were 27 men and 1 woman aged 46 to 75 years. Six of these patients had a previously documented myocardial infarction (>6 months). Eight patients had one-vessel disease (>50% diameter stenosis), 17 had two-vessel disease, and 3
TABLE 1. Patient Demographic and Coronary Risk Factors

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+ indicates present; –, absent.

had three-vessel disease. No patient had a history suggestive of coronary artery spasm. The cardiac risk factor profile of the patients was as follows: 15 patients were hypertensive (systolic blood pressure ≥150 mm Hg, diastolic blood pressure ≥90), 20 had hypercholesterolemia (total serum cholesterol ≥210 mg/dL), 6 had maturity-onset diabetes, 18 were current tobacco smokers, and 18 had family history of coronary artery disease (Table 1).

The study protocol was approved by the institutional review boards at the University of Florida Health Center and the VA Medical Center, and all patients gave informed consent.

Acetylcholine Preparation

A stock solution of acetylcholine (Miochol, Cooper Vision) was prepared by dissolving the sterile powder in 20% mannitol to reach X mol/L concentration. The stock solution was then diluted in saline at the beginning of the study.

Study Protocol

Antianginal therapy was discontinued at least 24 hours before planned elective catheterization (5 patients were taking 100 mg metoprolol and 40 mg nifedipine daily, 15 patients were taking 240 mg verapamil daily, and 8 patients were taking 180 mg diltiazem; none of these medications were in a sustained-release form). Patients used sublingual nitroglycerin as needed for angina, but no patient was included who had used nitroglycerin within 3 hours of study. All patients were taking 325 mg/d aspirin. All studies were performed with patients in a fasting postabsorptive state. Throughout the study, heart rate, femoral arterial pressure via a femoral sheath, and surface ECG leads I, II, and V5 were monitored and recorded continuously on analog tape (Racal Store-14). After completion of diagnostic angiograms, an optimal view was chosen to visualize the left coronary artery and minimize overlap. A small multipolar pacing catheter was advanced to the right ventricle via the femoral vein and connected to a standby pacer set at 60 beats per minute.

The study was divided into three periods: first, a control infusion of 0.9% saline; second, infusions of increasing syringe concentrations of acetylcholine at 10⁻⁴, 10⁻³, and 10⁻² mol/L (the highest dose of acetylcholine corresponds to an estimated blood concentration of 6.6×10⁻⁷ mol/L assum-
ioring a blood flow in left coronary artery of 150 mL/min; and third, a bolus infusion of 200 μg of nitroglycerin. Infusions were administered into the left coronary artery at room temperature through a 7F left Judkins catheter at a rate of 1 mL/min for 2 minutes using a syringe pump (IVAC Corp, San Diego, Calif). Before each infusion was started, the catheter was primed by a premeasured volume of infusate to fill in the dead space so that when the infusion starts, the infusate is delivered into the left main coronary artery. At the end of each infusion, coronary angiograms were performed using injections of 8 to 10 mL of Hypaque 76 (Winthrop). The time elapsed between the end of acetylcholine infusion and repeat coronary angiography was between 12 and 15 seconds. Two minutes elapsed between the last acetylcholine infusion angiogram and injection of nitroglycerin, unless either chest pain or ST-segment changes occurred and nitroglycerin was given immediately. To prevent bolus administration of acetylcholine, before each angiogram, the catheter was emptied of infusate by rapidly withdrawing it into a syringe until blood appeared in the manifold at the stopcock holding the withdrawal syringe, and the stopcock was then turned, connecting the contrast-filled syringe. All patients received ascending concentrations of acetylcholine infusion unless chest pain or signs of myocardial ischemia occurred or the largest dose (10−4 mol/L) was reached. No changes were made in patient position or tube-to-patient distance during the three study periods, and all angiograms were done using 6- or 7-in cineimage intensification filmed at a speed of 30 frames per second. Data for heart rate and blood pressure analysis were obtained during the last 15 seconds of each infusion.

Quantitative Coronary Angiography

Quantitative coronary angiography was done using a cinevideodensitometric technique (Vanguard Instrument Corp, XR-70).1-15 End-diastolic frames from each angiogram were selected by a cardiologist and analyzed by a technician. Nonstenotic coronary arterial segments identified between easily visualized branch points were selected for analysis in the anterior descending and circumflex arteries. At least 6 coronary segments were identified in any given patient, and the same segments were analyzed after each intervention in all study periods. To establish the reproducibility of the method, 24 segments, 8 from the proximal, 8 from the middle, and 8 from the distal segment, were analyzed by a blinded observer. Repeat analysis of the same segments was performed at remote intervals by the same observer. The exact location and cineframe were identified by Polaroid photograph made at the previous measurement setting. There was no significant difference in the coefficients of repeated analysis (F coefficient = 0.1±0.3, P = 0.6, 95% confidence limits for the difference ±2 SD [±0.15 mm]). To define a segmental constrictor or dilator change in response to acetylcholine, a value of ≥10% diameter change compared with control was used. No significant direct effect of the contrast agent on luminal caliber was observed.16

Statistical Analysis

All data were summarized and expressed as mean±SEM. The data were analyzed using repeated-measures ANOVA to compare the difference in absolute response of different segment diameters to saline and acetylcholine and the response of diameters of the same segments in the control period. A value of P<.05 was considered to indicate statistical significance.

Results

Responses of Coronary Arteries

Two patterns of response were observed at the maximal acetylcholine dose. In 21 patients (group 1), the response was only constriction. In 7 other patients (group 2), the response was patchy, with some adjacent segments showing dilation and others showing constriction.

Response to saline. Intracoronary infusion of saline was not associated with significant change in lumen diameter in any patient. These measurements were used as control values.

Group 1. Intracoronary infusion of acetylcholine was associated with dose-dependent reduction in diameter (constriction) of all analyzed segments compared with control. At an infused concentration of 10−4 mol/L, the proximal, middle, and distal segments of the left anterior descending artery constricted by 15±3%, 17±4%, and 21±3%, respectively (all P<.01 versus control diameter) and dilated after nitroglycerin by 13±3%, 24±4%, and 20±5%, respectively (all P<.01 versus control diameter). The proximal, middle, and distal segments of the circumflex artery constricted by 17±3%, 21±4%, and 26±5%, respectively (all P<.01 versus control diameter) and dilated after nitroglycerin by 20±3%, 27±4%, and 29±5%, respectively (all P<.01 versus control diameter). No symptoms or important ECG changes were noted at any infused concentration.

Group 2. The patients’ individual segmental responses to acetylcholine and nitroglycerin are summarized in Fig 1.

In the 30 left anterior descending artery segments analyzed, 10−4 mol/L acetylcholine caused constriction in 14 segments by 37±9% compared with control (P<.01) and dilation in 16 segments by 25±5% compared with control (P<.01). Nitroglycerin induced dilation by 15±4% and 38±9%, respectively, compared with control (both P<.01). There was no significant difference in the response to maximum acetylcholine dose between proximal, middle, and distal segments. Of the 7 proximal segments, 3 constricted by 13±5% and 4 dilated by 11±2%; of the 7 middle segments, 4 constricted by 53±19% and 3 dilated by 9±8%; and of the 7 distal segments, 3 constricted by 45±27% and 4 dilated by 36±8%.

In the 28 circumflex artery segments analyzed, 10−4 mol/L acetylcholine caused constriction in 16 segments by 31±6% compared with control (P<.01) and a dose-dependent dilation in 12 segments by 34±10% compared with control (P<.01). Nitroglycerin induced dilation by 21±5% and 33±10%, respectively, compared with control (P<.01). There were significant differences in the response to maximum acetylcholine dose between proximal, middle, and distal segments. All 6 proximal segments constricted by 20±9%, and all 5 middle segments constricted by 46±9% (P<.02 versus proximal), while all 5 distal segments dilated by 36±9% (P<.01 versus proximal and middle). Fig 2 shows the segmental responses to acetylcholine and nitroglycerin in a representative group 2 patient. Changes in coronary diameter in response to intracoronary infusion of saline, three ascending doses of acetylcholine (10−6, 10−3, and 10−4 mol/L), and nitroglycerin are shown in Table 2 for all group 2 patients. One group 2 patient (Fig 3, top) had transient occlusion of left anterior descending artery with chest pain and ST-segment changes that was quickly reversed by nitroglycerin after an angiogram was obtained. Coronary angiograms from two patients in this group are shown in Fig 3.
Observations have led with obstructive coronary arteries with patients who may dysfunction subjects in recent years, Vita et al demonstrated that acetylcholine-induced coronary dilatation is present despite the coexistence of obstructive atherosclerosis and coronary artery disease risk factors.

Ludmer et al first showed that acetylcholine causes coronary constriction in patients with angina and documented coronary atherosclerosis and coronary dilatation in subjects with chest pain atypical for angina and angiographically normal coronary arteries. Werns et al demonstrated that acetylcholine causes constriction of angiographically normal coronary artery branches in patients who exhibit angiographic signs of atherosclerosis in one or more remaining coronary branches. More recently, Vita et al and Zeiher et al demonstrated that acetylcholine causes coronary constriction even in patients with angiographically normal or near normal coronary arteries if they exhibit one or more risk factors for coronary atherosclerosis. These important observations have led to the hypothesis that endothelial dysfunction may be an early marker of coronary atherosclerosis and that a constriction response to intracoronary infusion of acetylcholine identifies this abnormality. It is currently believed that in patients with early atherosclerosis, or with risk factors only, acetylcholine causes coronary constriction because its direct muscari

**Hemodynamic parameters.** There was no significant change in either heart rate or systolic arterial blood pressure associated with either saline or incremental concentrations of acetylcholine in any patient.

**Discussion**

This study demonstrates that in a subset of patients with obstructive coronary artery disease, intracoronary infusion of acetylcholine induces vasodilator and constrictor responses in adjacent segments of the same coronary artery. These findings show for the first time that acetylcholine-inducible coronary dilatation is present despite the coexistence of obstructive atherosclerosis and coronary artery disease risk factors.

Fig 1. Plot showing left coronary artery segment responses. Diameters of 30 left anterior descending (top) and 28 circumflex (bottom) artery segments from seven patients (group 1) during control, after $10^{-4}$ mol/L acetylcholine (ACh max), and after nitroglycerin (NTG). Note that the responses to acetylcholine range from constriction to dilation within the same patients. Patients are identified with the use of the same symbols throughout.

**FIG 1.** Plot showing left coronary artery segment responses. Diameters of 30 left anterior descending (top) and 28 circumflex (bottom) artery segments from seven patients (group 1) during control, after $10^{-4}$ mol/L acetylcholine (ACh max), and after nitroglycerin (NTG). Note that the responses to acetylcholine range from constriction to dilation within the same patients. Patients are identified with the use of the same symbols throughout.

**FIG 2.** Plot showing example of dilation (above 0) and constriction (below 0) responses in one group 2 patient. Changes in segments of the left coronary artery in response to ascending doses of acetylcholine and nitroglycerin. Note that in the same artery (circumflex), two segments dilated (distal and proximal obtuse marginal) while the other three segments constricted (proximal, mid, and mid obtuse marginal).
Acetylcholine, 

...medicated smooth-muscle constrictor effect is not opposed by acetylcholine-induced release of sufficient endothelium-derived relaxing factor from dysfunctional endothelium. Alternatively, EDRF could be inactivated at sites of dysfunctional endothelium. Conversely, in patients without risk factors for coronary atherosclerosis, acetylcholine causes coronary dilation because the dilating effect of acetylcholine-induced release of endothelium-derived relaxing factor from normal endothelium prevails over direct muscular constrictor effects.

Our results suggest that the relation between coronary atherosclerosis and endothelial function is much more complex than previously appreciated. We have identified a subset of patients with coronary artery disease risk factors, stable angina, and obstructive coronary atherosclerosis who exhibit both coronary dilation and constriction in response to the same dose of acetylcholine. Of note, constriction and dilation were observed frequently in adjacent segments of the same coronary artery branch. Since these findings were observed in 25% of a population of patients with stable angina and obstructive coronary atherosclerosis, we conclude that the hypothesis that diffuse endothelial dysfunction is an early marker of coronary atherosclerosis may not apply to a sizable proportion of patients with angina. Our results suggest, instead, that there are at least two patterns of endothelial dysfunction: (1) a diffuse pattern involving most vessels throughout their course and (2) a patchy pattern that results in the coexistence of coronary segments with acetylcholine-inducible dilation and of coronary segments with dysfunctional endothelium.

It is worth noting that in our patients with patchy distribution of endothelial dysfunction, we did not observe any apparent consistent relation between the latter and angiographically detectable coronary obstructions. Indeed, as shown in Fig 3A, no constriction in response to acetylcholine was noted at the site of severe stenosis at the mid circumflex artery, while severe constriction that almost totally obliterated the lumen occurred in the angiographically normal proximal segment of the left anterior descending artery.

Since all these patients had one or more risk factors for coronary atherosclerosis, our findings suggest that risk factors per se may not be the only contributor to endothelial dysfunction and that some other factors important to determining the response to acetylcholine exist in certain patients. They also suggest that (1) local factors may be important in determining endothelial dysfunction and (2) the local factors leading to obstructive atherosclerosis may be different, at least in some patients, from those leading to endothelial dysfunction. For example, the endothelium produces vasodilators such as prostacyclin and nitric oxide, as well as vasoconstrictors such as leukotriene (LTC₄) and endothelin, and it is also involved in the production of growth factors and inhibitors (for endothelial and smooth muscle cells) and metabolism of circulating substances such as vasoconstrictor catecholamines and platelet products. All these factors are involved in the blood cell/vessel wall interactions occurring during thrombus formation in patients with unstable angina and myocardial infarction.

Possible explanations for the differences between the results of this and previous studies could be related to differences in the methodology used. For instance, some studies³,⁷ infused acetylcholine subselectively into the left anterior descending artery, which could have obscured any differential change that might have taken place in the other vessel. The use of a bolus injection of acetylcholine instead of continuous infusion in other studies⁴,⁵ is another factor to be accounted for. In addition, the time elapsed between end of acetylcholine infusion and angiography is another important factor that has a direct bearing on how much effect remains visualized, depending on the timing of angiography and taking into account the very short half-life of acetylcholine. In our study, this time was not more than 15 seconds.

Yasue et al⁴ described heterogeneity in the response of coronary arteries to acetylcholine with regard to coronary segments and age of patients. They described 49 patients with angiographically normal coronary arteries, of whom 23 were older than 30 years of age, and
25 patients with atherosclerotic coronary arteries. Acetylcholine constricted most segments of angiographically normal coronary arteries in the older group and also in patients with coronary artery disease. This constrictor response was greater in the proximal than distal segments of both left anterior descending and circumflex arteries. They concluded that proximal segments are more susceptible to endothelial injury or atherosclerosis than distal segments in the coronary arteries. The heterogeneity described by Yasue et al relates to degrees of constriction between proximal and distal segments and did not refer to dilator versus constrictor responses as is the case in our patients. In our study, proximal and middle segments of the left anterior descending artery showed dilator responses to acetylcholine, in contrast with the circumflex artery, in which proximal and middle segments showed constrictor responses, reflecting heterogeneity and complexity in predicting a particular response. Moreover, these findings emphasize the difficulty encountered in attempts to use the response to a single dose of acetylcholine to predict the degree of response. Of note, in no patient was dilation seen at one dose and constriction seen at another dose in the same segment.

Coronary angiography provides a limited assessment of coronary atherosclerosis because in most cases the threshold for detection is relatively high; at best, it indicates only whether obstruction may be present. More recently, intravascular ultrasound has been used to measure lumen size, wall thickness, and plaque composition, and this technique has shown the patchy distribution of atherosclerosis.10

There is abundant evidence that the severity of coronary atherosclerosis, as assessed by coronary angi-
ography, does not predict the evolution toward the total occlusion responsible for acute coronary syndromes in many patients.\textsuperscript{23} It is also well recognized that the anticoagulant factors synthesized by the endothelium play an important role in determining the local hemostatic equilibrium. Therefore, it might well be the case that apparently angiographically "normal" coronary segments with endothelial dysfunction rather than stenotic coronary segments might be more susceptible to the plaque rupture and disruption and perhaps even metabolic dysfunction that results in acute coronary events.

Conclusions

In patients with advanced atherosclerosis and multiple risk factors, the existence of coronary segments with functioning endothelium indicates that the latter is not irreversibly and diffusely lost in atherosclerotic coronary arteries. A better understanding of the mechanisms responsible for preservation of endothelial function in this setting might advance efforts directed at preventing or even reversing endothelial dysfunction present in some coronary segments. The role played by coronary segments with dysfunctional endothelium regarding the clinical manifestations of coronary atherosclerosis remains to be established.

Acknowledgment

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References


Constrictor and dilator responses to intracoronary acetylcholine in adjacent segments of the same coronary artery in patients with coronary artery disease. Endothelial function revisited.

H el-Tamimi, M Mansour, T J Wargovich, J A Hill, R A Kerensky, C R Conti and C J Pepine