Endothelial Dysfunction in Patients With Chest Pain and Normal Coronary Arteries

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Background. A subgroup of patients with chest pain and angiographically normal epicardial coronary arteries have reduced dilator response to metabolic or pharmacological stimuli, but the mechanisms responsible for this reduced dilator response are unknown. In this study, we have investigated whether microvascular endothelial dysfunction is a cause of the observed reduced vasodilator reserve.

Methods and Results. The functional response of the microvasculature was studied with rapid atrial pacing at 150 beats per minute. Fifty-one patients, 20 hypertensive and 31 normotensive, with chest pain and normal epicardial coronary arteries (<10% stenosis) were studied. Endothelial function was tested with incremental infusions of acetylcholine to achieve estimated intracoronary concentrations ranging from 10^{-7} M to 10^{-3} M. Endothelium-independent smooth muscle vasomotion was measured using intracoronary sodium nitroprusside. Endothelial dysfunction of epicardial coronary arteries, demonstrated as severe (>50%) constriction with <10^{-3} M acetylcholine concentration, was evident in five patients (10%). In the remaining 46 patients, coronary blood flow increased with acetylcholine (mean, 78±43%) and atrial pacing (mean, 51±37%), and coronary vascular resistance decreased by 35±16% and 29±14%, respectively, but the responses were heterogeneous. There was a correlation between the coronary resistance change with acetylcholine and the change with atrial pacing: r = 0.68, p < 0.001 in these 46 patients. Thus, patients with depressed dilation with atrial pacing had reduced endothelium-dependent dilation with acetylcholine, and vice versa. However, the microvascular dilation caused by sodium nitroprusside was not significantly different between patients with and those without reduced dilation with atrial pacing, indicating that the vasodilator defect was not caused by smooth muscle dysfunction. There were no differences in the vasodilator responses with atrial pacing, acetylcholine, or nitroprusside between normotensive and hypertensive patients. Multivariate regression analysis was performed to determine whether age, sex, serum cholesterol level, hypertension, presence of mild epicardial vessel atherosclerosis, resting left ventricular function, change in left ventricular ejection fraction with exercise, vasodilation with acetylcholine, and vasodilation with sodium nitroprusside were independently related to the vasodilator response to atrial pacing. Only the change in coronary vascular resistance with acetylcholine was independently correlated with the change in resistance with atrial pacing: R^2 = 0.46, p < 0.0001.

Conclusions. Patients with chest pain, normal epicardial coronary arteries, and reduced vasodilation in response to atrial pacing appear to have associated endothelial dysfunction of the coronary microcirculation. Thus, microvascular endothelial dysfunction may contribute to the reduced vasodilator reserve with atrial pacing and anginal chest pain in these patients. (Circulation 1992;86:1864–1871)

Key Words • endothelium-derived relaxing factor • angina • microcirculation • vasodilation

A subgroup of patients with chest pain and angiographically normal epicardial coronary arteries have a reduced vasodilator response to metabolic stimuli such as exercise and atrial pacing or to pharmacological vasodilators such as dipyridamole. The mechanisms responsible for chest pain and the reduced vasodilator capacity with atrial pacing are unknown. Among the potential mechanisms are a primary disorder of microvascular medial smooth muscle, enhanced neurally mediated sympathetic tone, or abnormal humorally mediated vasoconstrictor influences. Other possible mechanisms include metabolic abnormalities in substrate handling by the myocardium or reduction in the number of microvessels caused by fibrosis.

Short-acting endothelium-derived relaxing factors (EDRFs), one of which is believed to be nitric oxide, modulate vascular smooth muscle function in response to a variety of pharmacological and physiological stimuli. Normal endothelium exerts a tonic vasodilator influence by releasing EDRFs, and endothelial dysfunction can cause abnormalities in vascular vasomotor function. Studies assessing the role of the endothelium in modulating the tone of coronary arteries in humans have been largely limited to epicardial coronary arteries. Abnormal epicardial coronary artery vasomotion has been demonstrated in patients with coronary atherosclerosis and with hypercholesterolemia, with acetylcholine used as a probe for testing endothelial function. It was the purpose of the present investigation...
to determine whether dysfunction of the coronary microvascular endothelium contributes to the impaired microvascular vasomotor responses in patients with chest pain and normal coronary arteries.

**Methods**

**Patients**

Fifty-one patients referred to the Cardiology Branch of the National Heart, Lung, and Blood Institute for evaluation of anginal chest pain in the presence of angiographically normal epicardial coronary arteries were included in the study. Forty-four patients had no angiographically visible atherosclerosis, whereas the remaining seven had some minor plaquing (<10% narrowing) in at least one major branch of the coronary tree. Twenty patients had long-standing (>5 years) hypertension with blood pressure >145/95 and were on long-term antihypertensive medications.

There were 21 men and 30 women; mean age, 51±11 years. All patients were in sinus rhythm, and one patient had a history of previous myocardial infarction despite normal epicardial coronary arteries. Left ventricular function was measured at rest and with exercise by radionuclide ventriculography in 48 patients; all but six patients had normal resting left ventricular function (≥40% ejection fraction at rest). With exercise, 15 patients (31%) had an abnormal response (failure of left ventricular ejection fraction to increase with exercise).

All medications were withdrawn for 1 week before hospital admission. All patients underwent routine M-mode and two-dimensional echocardiography, and left ventricular mass was assessed by the method of Devereux and Reichek.²² Left ventricular mass index of >125 g/m² was used to define presence of left ventricular hypertrophy. The study was approved by the Institutional Review Board of the National Heart, Lung, and Blood Institute, and patients gave informed consent before cardiac catheterization.

**Cardiac Catheterization**

Patients received diazepam (10 mg p.o.) 1 hour before catheterization. After routine left ventriculography and coronary arteriography were performed, a thermodilution pacing catheter²² (Baim Elecath, Rahway, N.J.) was introduced via the right internal jugular vein into the coronary sinus and advanced to the great cardiac vein, which drains an estimated 90% of blood flowing through the left anterior descending coronary artery. The thermodilution method of determining great cardiac vein blood flow has been described previously.²³ Coronary vascular resistance was calculated as mean arterial pressure divided by great cardiac vein blood flow. Coronary sinus flow measurements were not recorded because of concern for right atrial reflux. Pulmonary capillary wedge pressure and cardiac output were measured with a Swan Ganz thermodilution catheter. A 7F Judkins catheter was advanced into the ostium of the left coronary artery. ECG leads I, III, and either lead V₅ or V₆ were continuously monitored in all patients. Blood samples were obtained simultaneously from the great cardiac vein and the artery for measurement of oxygen content. Oxygen content was measured with a Lex-O₂-Con-TL oxygen analyzer (Lexington Instruments, Waltham, Mass.).

**Acetylcholine Infusion**

Left coronary arteriography was performed after baseline hemodynamic measurements were made of the cardiac output, blood pressure, wedge pressure, and great cardiac vein blood flow. Infusions of intracoronary acetylcholine (dissolved in 5% dextrose) were given in incremental doses into the left main coronary artery for 2 minutes each at a rate of 1–1.5 ml/min before blood flow measurements were performed.

The delivered concentration of acetylcholine was adjusted for both the baseline great cardiac vein flow and the dominance or nondominance of the left coronary artery in each patient so that the estimated intracoronary concentration was similar in all patients. Thus, in the presence of a dominant left coronary artery system, the dose delivered into the left main was equal to desired concentration times great cardiac vein blood flow times 2, whereas in the presence of a nondominant left coronary artery, the delivered dose was equal to desired concentration times great cardiac vein blood flow times 1.5.

During a preliminary study in four patients, a dose-response curve was obtained with intracoronary acetylcholine, which was infused at 10⁻⁷ M, 10⁻⁶ M, 2.5x10⁻⁶ M, 5x10⁻⁶ M, 7.5x10⁻⁶ M, 10⁻⁵ M, and 5x10⁻⁵ M concentrations. The coronary blood flow increases at the 2.5x10⁻⁶ M and 7.5x10⁻⁶ M concentrations were not significantly different from the response to 5x10⁻⁶ M, and the response to 10⁻⁵ M was not different from that to 5x10⁻⁵ M. Therefore, we performed dose-response curves in all patients using intracoronary acetylcholine administered in the following concentrations: 10⁻⁷ M, 10⁻⁶ M, 5x10⁻⁶ M, and 10⁻⁵ M. Because of minimal increases in blood flow with the 10⁻⁷ M concentration, this dose was given to only 22 patients. The 10⁻⁵ M concentration was not administered if vasoconstriction occurred at a lower concentration. At the end of each 2-minute infusion, hemodynamic and great cardiac vein blood flow measurements and a left coronary angiogram were obtained.

To overcome inaccuracies that might result from left main coronary artery delivery while blood flow was measured in the left anterior descending coronary artery territory, we compared the results of selective infusion into the left anterior descending coronary artery using a 2.5F infusion catheter with infusion of a similar estimated concentration of acetylcholine into the left main coronary artery in four patients. No significant differences in blood flow response were found between the two infusions.

**Atrial Pacing**

When all measurements returned to baseline levels, rapid atrial pacing was initiated at 150 beats per minute for 4 minutes, and all hemodynamic and great cardiac vein blood flow measurements were repeated. Nine patients developed second-degree atrioventricular block with pacing and were given intravenous atropine (0.6 mg).

**Sodium Nitroprusside Infusion**

Intracoronary infusions of sodium nitroprusside were given for 2 minutes each to attain estimated intracoronary concentrations of 12 and 24 µg/100 ml in 25
patients. Six patients were also given 36 μg/100 ml of sodium nitroprusside, but this dose resulted in systemic effects (reduction in arterial blood pressure) without any further decrease in coronary vascular resistance. Thus, the maximum vasodilation observed at the 24 μg/100 ml dose of sodium nitroprusside is reported.

Coronary Angiography

Left coronary angiograms were obtained in the best projection to estimate epicardial coronary artery diameter at baseline and after each infusion of acetylcholine. Coronary artery diameter changes were measured with ARTREK software (Quantim 2000 l, StatVIEW, ImageComm Systems, Inc.) without knowledge of the coronary flow data.26,27 Coronary diameter was measured over 1-in. sections of proximal, mid, and distal left anterior descending coronary artery. Four digitized cine frames of the desired segments were averaged, and mean diameter was measured. The greatest constrictor effect of acetylcholine, when it occurred, was in the distal segment of the left anterior descending coronary artery, and these results are reported in this article.

Statistical Analysis

All group data are reported as mean±SD. Continuous variables were compared by two-tailed Student’s t test for paired or unpaired data as appropriate. Discrete data were analyzed by the χ² test. Univariate correlation coefficients (Pearson’s r) were determined for variables as indicated. Statistical significance was defined as a value of p<0.05.

We performed a multivariate stepwise regression analysis to investigate whether the microvascular vasodilator response to atrial pacing was determined by any clinical, biochemical, or hemodynamic responses that were measured in these patients. The variables examined were age, sex, serum cholesterol level, hypertension, presence of left ventricular hypertrophy, presence of epicardial coronary atherosclerosis, resting left ventricular ejection fraction, exercise ejection fraction, change in left ventricular ejection fraction with exercise, and coronary vascular resistance change with acetylcholine and with nitroprusside.

Results

Atrial Pacing

With atrial pacing at a rate of 150 beats per minute, coronary blood flow increased by 51±37% and coronary vascular resistance decreased by 29±14%; however, the response was heterogeneous (Figure 1). Mean arterial pressure decreased by 2.2% (p=0.02), postpacing wedge pressure increased by 1.2 mm Hg (p<0.002), and cardiac output remained unchanged. None of the patients produced lactate in the coronary venous blood during pacing.

Acetylcholine Study: Effects on Epicardial Coronary Arteries

The epicardial coronary artery diameter changes induced by acetylcholine measured in the distal segment of the left anterior descending coronary artery (maximum reduction, 14±25%) are shown in Figure 2. Compared with baseline, 25 patients had vasoconstriction at 10⁻⁶ M acetylcholine, another 11 at 5×10⁻⁶ M, and all but four had constriction at 10⁻⁵ M acetylcholine.

Five patients developed severe (>50%) diffuse constriction of the epicardial coronary arteries, three at 10⁻⁶ M acetylcholine and two at 5×10⁻⁶ M acetylcholine. Because of excessive constriction of epicardial vessels at low concentrations and its contribution to limiting the blood flow increase, the microvascular response to acetylcholine could not be determined in these patients. We therefore excluded these five patients from analysis assessing microvascular endothelial function.

Mean arterial blood pressure, heart rate, cardiac output, and wedge pressure were not significantly dif-

![Figure 1](https://example.com/figure1.png) **FIGURE 1.** Graphs showing percentage increase in coronary blood flow and reduction in coronary vascular resistance compared with baseline during atrial pacing at 150 beats per minute.

![Figure 2](https://example.com/figure2.png) **FIGURE 2.** Graphs showing change in great cardiac vein blood flow, coronary vascular resistance, arteriovenous (A-V) oxygen difference, and distal left anterior descending coronary artery diameter with increasing concentrations of intracoronary acetylcholine.
different from baseline with increasing concentrations of acetylcholine (Table 1).

**Acetylcholine Study: Effects on Coronary Blood Flow**

There was a progressive, dose-related increase in great cardiac vein blood flow, reduction in coronary vascular resistance, and narrowing of the arteriovenous oxygen difference with incremental concentrations of acetylcholine (Figure 2). Great cardiac vein blood flow increase ranged from a mean of 17% at $10^{-7}$ M to a mean of 47% at $5 \times 10^{-6}$ M acetylcholine (Figure 2). However, as with the atrial pacing response, the vasodilator response to acetylcholine was heterogeneous (Figure 3). The maximum flow response was at the $10^{-7}$ M concentration in one patient, at $10^{-6}$ M in 15 patients, at $5 \times 10^{-6}$ M in 24 patients, and at $10^{-5}$ M in seven patients.

**Comparison of Acetylcholine Response With Atrial Pacing**

The relation between the change in coronary vascular resistance with atrial pacing and the maximum change in coronary vascular resistance with acetylcholine is shown in Figure 4. There was a correlation between the maximum change in coronary vascular resistance in response to acetylcholine and the change with atrial pacing: $r=0.68$, $p<0.001$. Similarly, the maximum increase in great cardiac vein blood flow induced with acetylcholine correlated with the increase in blood flow caused by atrial pacing: $r=0.65$, $p<0.01$ (Figure 4). Also, the blood flow increase with atrial pacing correlated with the maximum change in arteriovenous oxygen difference (an independent measure of change in blood flow) with acetylcholine: $r=0.41$, $p<0.01$.

**Sodium Nitroprusside Study**

Mean great cardiac vein blood flow increased by 61% (range, 3–174%), and coronary vascular resistance decreased by 39% (range, 16–65%) after administration of nitroprusside at 24 $\mu$g/100 ml (Figure 5). Mean arterial pressure fell by a mean of 6% with sodium nitroprusside infusion, but the heart rate and cardiac output were not significantly different.

**Comparison of Pacing and Acetylcholine Responses With Sodium Nitroprusside**

Diminished acetylcholine-induced vasodilation could result from either endothelial dysfunction or dysfunc-

**TABLE 1. Hemodynamic Changes During Intracoronary Acetylcholine Infusions**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>$10^{-7}$ M</th>
<th>$10^{-6}$ M</th>
<th>$5 \times 10^{-6}$ M</th>
<th>$10^{-5}$ M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>111±19</td>
<td>114±18</td>
<td>111±19</td>
<td>110±16</td>
<td>107±17</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>83±15</td>
<td>81±16</td>
<td>82±15</td>
<td>80±13</td>
<td>76±20</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>5.8±1</td>
<td>5.6±1</td>
<td>5.6±1</td>
<td>5.5±1</td>
<td>5.4±1</td>
</tr>
<tr>
<td>Wedge pressure (mm Hg)</td>
<td>10±4</td>
<td>10±5</td>
<td>11±5</td>
<td>12±4</td>
<td>12±5</td>
</tr>
</tbody>
</table>

bpm, Beats per minute.

Figure 3. Graphs showing maximum percentage increase in coronary blood flow and reduction in coronary vascular resistance compared with baseline during intracoronary infusion of acetylcholine.

Figure 4. Graphs showing relation between the change in coronary blood flow (top panel) and coronary vascular resistance (bottom panel) during atrial pacing and the maximum endothelium-dependent change during intracoronary acetylcholine infusion.
tion of medial smooth muscle. To elucidate whether patients with a diminished coronary blood flow response to acetylcholine (and also to atrial pacing) did not also have dysfunction of the medial smooth muscle layer, the coronary flow response to an endothelium-independent vasodilator, sodium nitroprusside, was compared with acetylcholine. No correlation was present between the vasodilator response either to acetylcholine or to atrial pacing and the dilator response to nitroprusside (Figure 5).

Comparison of Hypertensive and Normotensive Patients

There were no significant differences in vasodilation in response to atrial pacing at 150 beats per minute between normotensive (mean decrease in resistance, 33±16%) and hypertensive patients (mean, 27±12%) (Figure 1). Excessive epicardial coronary constriction compared with baseline (>50% constriction at <10^{-5} M acetylcholine) occurred in two (6%) of 31 normotensive and three (15%) of 20 hypertensive patients (p=NS). In the remaining patients in whom microvascular dilation with acetylcholine could be measured, there was no significant difference in the maximal increase in coronary blood flow with acetylcholine between the two groups; peak reduction in coronary vascular resistance with acetylcholine in normotensive patients was 33±17% and in hypertensive patients was 39±15% (p=NS) (Figure 3). There was a correlation between the blood flow increase with atrial pacing and the increase with acetylcholine in both groups of patients (r=0.67, p<0.001 in normotensive patients and r=0.66, p<0.02 in hypertensive patients; Figure 4). Similarly, in both patient groups, there was a lack of correlation between the dilator response with nitroprusside and the response to either atrial pacing or acetylcholine (Figure 5).

Nine patients with hypertension had left ventricular hypertrophy by echocardiogram. The reduction in coronary vascular resistance with acetylcholine in patients with hypertrophy compared with those without hypertrophy was not statistically significant (Table 2).

Relation Between Age, Serum Cholesterol, Epicardial Coronary Atherosclerosis, Left Ventricular Function, and Inducible Ischemia and the Microvascular Response to Acetylcholine

There was no correlation between total serum cholesterol level, age, left ventricular function at rest, or the change in left ventricular function with exercise and the microvascular response to intracoronary acetylcholine (Table 2). Six patients had mild (<10% narrowing) plaqing of epicardial vessels; however, its presence did not influence the magnitude of epicardial or microvascular response to acetylcholine.

Multivariate Analysis

Multivariate stepwise regression analysis was performed to investigate whether any clinical, radionuclide
parameters, or coronary hemodynamic responses to endothelium-dependent or endothelium-independent dilators were independently related to the vasodilator response of the coronary vasculature to atrial pacing in these patients. Only the coronary resistance change with acetylcholine correlated independently with the atrial pacing response: \( R^2 = 0.46, p < 0.0001 \).

**Discussion**

Chest pain in patients with angiographically normal epicardial coronary arteries could result from either cardiac or noncardiac causes. Using rapid atrial pacing in previous studies, we have reproduced typical chest pain and determined that the coronary flow response to the increased myocardial metabolic demands is inadequate in some patients.\(^2,3,5\) This is often accompanied by metabolic, ECG, or other evidence of ischemia. These observations led us and other investigators to suggest that some patients with angiographically normal epicardial coronary arteries develop anginal chest pain as a result of myocardial ischemia caused by microvascular dysfunction.

Although inadequate vasodilation to metabolic or pharmacological stimuli characterizes these patients, little is known of the underlying defect in the coronary microvessels that produces this abnormality in vasodilator reserve. Flow-dependent release of EDRF by the endothelium, believed to be secondary to increased endothelial shear stress, has been demonstrated in both conductance and resistance peripheral vessels and in coronary conduit vessels of animals and of humans.\(^28-32\) Inhibition of nitric oxide synthesis with N-monomethyl-L-arginine reduces both resting blood flow\(^33\) and hyperemia-induced increases in blood flow.\(^34\) These observations suggest that the EDRF–nitric oxide system is critical in determining not only resting blood flow but also, to some extent, the increases in blood flow resulting from changes in demand. The hypothesis we examined in the present investigation was that endothelial dysfunction of the coronary microvasculature, resulting in reduced release of EDRF in response to increased coronary flow rates, can play a pathophysiological role in the reduced coronary vasodilator reserve manifested by a subgroup of patients who have chest pain and normal epicardial coronary arteries.

To determine whether the capacity of the coronary microvascular endothelium to release EDRF was impaired in patients with chest pain and normal coronary arteries, we compared the coronary flow response with atrial pacing and the flow response with acetylcholine, an agent that dilates vessels by stimulating the endothelium to release EDRF.\(^7,8\) We found a concordance between these responses; there was a linear correlation between the coronary flow response with acetylcholine and that to atrial pacing. Thus, patients with reduced response to atrial pacing had a reduced endothelium-dependent response to acetylcholine, and vice versa. Although this reduced response to acetylcholine is compatible with impaired endothelial release of EDRF, it could alternatively reflect an intrinsic impairment of the capacity of smooth muscle cells to relax. To distinguish endothelial dysfunction from intrinsic smooth muscle dysfunction, we infused sodium nitroprusside, an endothelium-independent vasodilator.\(^35\) Sodium nitroprusside causes smooth muscle relaxation directly by increasing intracellular cyclic GMP levels of smooth muscle cells.\(^36,37\) Our results demonstrated that the response to sodium nitroprusside was similar in patients with and in those without reduced vasodilatation to pacing and to acetylcholine (Figure 5).

Thus, a subset of patients with chest pain, normal coronary arteries, and reduced vasodilator response to atrial pacing also appear to have endothelial dysfunction of the coronary microvasculature. Although we cannot definitively conclude that this correlation signifies causality, a reasonable interpretation of our data is that endothelial dysfunction contributes to the impaired vasodilator response in some patients. Whether this is a result of a reduced release of EDRF in response to atrial pacing or of an increased release of constrictors\(^38,39\) needs further study.

Our study does not permit us to identify the exact site of the endothelial abnormality. Analysis of the results of microvascular dysfunction in our previous studies, however, suggested that the prearteriolar vessels were probably the site of dysfunction.\(^40\) Interestingly, a study by Griffith et al.\(^41,42\) of distribution of release of EDRF from rabbit ear microvessels led to a similar conclusion; the prearteriolar vessels in the rabbit ear were also the site of greatest EDRF activity.

The action of acetylcholine on the coronary vasculature is complex and paradoxical. Acetylcholine causes dilation of vascular smooth muscle by releasing EDRF but is capable of causing vasoconstriction if applied directly to smooth muscle. Thus, the net effect of acetylcholine on blood vessels is a balance between endothelium-dependent vasodilation and direct constriction. Low concentrations of acetylcholine cause vasodilation, but when endothelial dysfunction is present, similar concentrations of acetylcholine produce vasoconstriction.\(^14,43-47\) At higher concentrations, endothelium-dependent vasodilation can be overridden by the direct actions of acetylcholine, even with normal endothelium.\(^46,47\) Microvascular endothelial function can be assessed, as demonstrated in this study, by administering acetylcholine at estimated intracoronary concentrations ranging between \(10^{-6}\) and \(10^{-3}\) M. Difficulties in interpretation can arise, however, because of the drug’s dual action and narrow dose-response range; thus, below \(10^{-6}\) M, there is minimal dilation of microvessels, and at \(10^{-5}\) M there is often evidence of microvascular constriction.

The use of intracoronary acetylcholine to assess microvascular endothelial function is further complicated by the drug’s effects on the epicardial coronary arteries. Previous studies have demonstrated that low concentrations (\(10^{-9}\) to \(10^{-7}\) M) of acetylcholine can cause mild vasodilation of epicardial coronary arteries with intact endothelium, whereas in the presence of atherosclerosis, hypercholesterolemia, hypertension, or aging, there is often vasoconstriction.\(^14,21\) Higher concentrations (\(\geq 10^{-5}\) M) constrict epicardial coronary arteries in most patients.\(^45\) The concentration of acetylcholine required to test endothelial function in the epicardial coronary arteries is one to two orders of magnitude lower than the concentrations required to test endothelial function in the coronary microvessels. Whether this reflects a decreased sensitivity of microvessels in releasing EDRF compared with epicardial vessels needs to be further investigated. In our study,
some degree of epicardial vasoconstriction was present in 71% of patients at 5×10⁻⁸ M acetylcholine; however, this was not of a degree that would limit blood flow in itself, except in five patients who had severe diffuse epicardial constriction (≥50%). Therefore, our study demonstrated that in a population of patients with chest pain and normal coronary arteries, 10% had marked endothelial dysfunction of the epicardial coronary arteries.

In contrast to the depressed response of the epicardial coronary arteries in hypercholesterolemia, hypertension, and aging described previously, there was no independent correlation between serum cholesterol level, presence of hypertension, or age and the microvascular response to acetylcholine in our study. However, the group of patients with cholesterol level >280 mg/100 ml was very small; furthermore, many of the remaining patients may have had endothelial dysfunction secondary to as yet unidentified factors.

Critique

Concern has been expressed in the past about the validity of great cardiac vein blood flow measurement by thermodilution. During acetylcholine and sodium nitroprusside infusions, when myocardial oxygen consumption remained relatively constant (no significant change in rate-pressure product), great cardiac vein blood flow and narrowing of the arteriovenous oxygen difference were measured and found to be closely correlated (r=0.94), suggesting that the changes in great cardiac vein blood flow within the range of responses studied were directionally accurate. Also, the change in arteriovenous oxygen difference with acetylcholine, an independent measure of increase in blood flow, also correlated with the atrial pacing response.

We also limited our analysis to the percentage change in blood flow with different interventions rather than to absolute changes. This is important, because baseline great cardiac vein blood flow depends on the relative dominance of the left anterior descending coronary artery and its venous drainage and on the size of the muscle mass drained by the great cardiac vein, which often varies between individuals. Thus, by measuring a percentage change in blood flow relative to the baseline, we hoped to have overcome this interindividual variation.

For ethical reasons, we do not have a control group of subjects with normal epicardial coronary arteries and without chest pain to compare with patients included in this study. Thus, an unequivocally normal response to acetylcholine, to sodium nitroprusside, and to pacing has not as yet been defined. However, we have had experience with atrial pacing in more than 200 patients with chest pain and normal epicardial coronary arteries. Patients without any evidence of ischemia (absence of chest pain, ST segment depression, widening of the arteriovenous oxygen difference, lactate production, or an increase in wedge pressure during rapid atrial pacing) were considered to have no dysfunction of their coronary vasculature. These subjects had a mean reduction in coronary vascular resistance of 38±14%. Using a 24% (38%±1 SD) decrease in vascular resistance in response to atrial pacing as the lower limit of normal pacing-induced resistance decrease, we were able to define 45% of the patients studied in this investigation as having reduced dilation with atrial pacing; these patients also had reduced endothelial-dependent vasodilation. Thus, we believe that our investigation provides strong evidence indicating that endothelial dysfunction of the coronary microvasculature plays a role in the reduced vasodilator reserve to pacing in patients with chest pain and normal coronary arteries.

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References

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