Effect of endothelial dysfunction on regional perfusion in myocardial territories supplied by normal and diseased vessels in patients with coronary artery disease

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Background. **Endothelium-dependent regulation of coronary tone affects both conduit and resistance coronary arteries. However, little is known about the usefulness of myocardial perfusion imaging in evaluating coronary endothelial function. We evaluated the relation between invasive angiographic measurements of coronary vasomotion in response to intracoronary acetylcholine and the presence of regional perfusion abnormalities assessed by technetium 99m sestamibi imaging.**

Methods and Results. **We studied 11 patients (9 men and 2 women) with suspected coronary artery disease (48 ± 8 years, mean ± standard deviation). We used quantitative coronary angiography to delineate the vasomotor response to increasing doses of acetylcholine given intracoronary. Regional myocardial perfusion was assessed by planar Tc-99m sestamibi imaging during and after the administration of acetylcholine. In the 11 patients, 23 coronary artery territories were analyzed: 13 were angiographically normal, and 10 showed varying degrees of luminal narrowing. Four (31%) of 13 angiographically normal coronary arteries had a positive vasomotor response to acetylcholine (≥20% reduction in luminal diameter) that was associated with a regional perfusion defect. Acetylcholine induced a positive vasomotor response, which was also associated with a regional perfusion defect in 1 of 3 coronary arteries with stenoses of intermediate severity (50% to 69%). Likewise, acetylcholine induced a positive vasomotor response in 6 of 7 coronary arteries with significant luminal narrowing (≥70%), 5 of which showed a corresponding regional perfusion defect.**

Conclusions. **In patients with coronary artery disease, noninvasive measurements of regional myocardial perfusion by Tc-99m sestamibi correlate well with invasive measurements of coronary endothelial function. These findings may have implications for monitoring the effects of interventions designed to improve endothelial function and microvascular function in patients with coronary artery disease. (J Nucl Cardiol 2000;7:199-204.)**

Key Words: Coronary artery disease • endothelial dysfunction • Tc-99m sestamibi imaging

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Endothelial dysfunction plays an important role in the pathogenesis and clinical manifestations of coronary atherosclerosis by modulating the responsiveness of the underlying vascular smooth muscle to a variety of neurohormonal stimuli.[1] The vasodilator response to infused agonists such as acetylcholine as assessed by coronary arteriography has become an accepted method of assessing endothelial function.[2] Selective infusion of acetylcholine causes vasodilation in normal coronary arteries, whereas in

Table 1. Clinical and laboratory findings

Patient	Age	Sex	HTN	Smoker	Family history	Symptom	Serum cholesterol	LDL cholesterol
1	50	M	Yes	Yes	No	CSA	345	263
2	38	M	Yes	Yes	Yes	CSA	214	147
3	49	M	No	Yes	Yes	CSA	255	179
4	37	M	Yes	Yes	No	CSA	210	136
5	45	M	No	Yes	No	Asymp	228	168
6	60	M	No	Yes	Yes	CSA	264	179
7	48	F	Yes	No	No	ROA	466	370
8	52	M	No	No	No	ROA	195	132
9	42	F	Yes	No	Yes	CSA	151	59
10	61	M	Yes	No	Yes	CSA	200	122
11	41	M	No	Yes	No	CSA	216	146
Mean ± SD	48 ± 8						249 ± 87	173 ± 82

HTN, Hypertension; *Asymp*, asymptomatic; *CSA*, chronic stable angina; *ROA*, recent onset angina; *SD*, standard deviation.

diseased vessels it elicits paradoxic vasoconstriction.[2] Although precise, invasive, catheter-based intracoronary investigation of endothelial function in human beings is cumbersome, costly, and not without risk. More importantly, it cannot easily be repeated or performed before coronary angiography becomes clinically necessary.

Endothelium-dependent regulation of vascular tone affects both the conduit and resistance coronary arteries.[3] The latter is particularly important because vasodilation of resistance arteries plays a key role in determining myocardial perfusion.[4] Therefore noninvasive methods that assess myocardial blood flow could play an important role in identifying patients with endothelial dysfunction at risk for coronary atherosclerosis. The objective of this study was to evaluate the relation between invasive angiographic measurements of coronary vasomotion in response to intracoronary acetylcholine and the presence of regional perfusion abnormalities assessed by Tc-99m sestamibi myocardial perfusion imaging.

METHODS

Patient Population

We studied 11 patients with suspected coronary artery disease. Patient selection was based on a history of angina, an abnormal stress test, or diagnostic cardiac catheterization. There were 9 men and 2 women (48 ± 8 years, mean ± standard deviation). Ten patients had stable anginal symptoms, and 1 had an abnormal exercise stress test result. None had prior myocardial infarction. Six patients had a history of hypertension, and 7 patients were active smokers. None had a history of diabetes. The clinical and laboratory characteristics of the patients studied are summarized in Table 1.

Quantitative Coronary Arteriography

The study protocol was approved by the Ethics Committee at Hospital Cosme Argerich, and all participants gave informed consent. All patients underwent diagnostic coronary arteriography by standard technique. All antianginal medications were withheld for 96 hours before the study except for sublingual nitroglycerine. Coronary angiography was performed with the Judkins technique and recorded with a biplane radiographic system (Siemens-Elema Angioskop D40). Nonionic contrast material (Telebrix) was injected by a power injector. An appropriate view that allowed visualization of the artery studied (eg, left anterior descending, circumflex, or right coronary artery) with no overlap of the other coronary arteries was selected to determine percent diameter stenosis. A pacemaker cable was positioned at the tip of the right ventricle in all patients.

The stenosis severity was quantified on the coronary arteriograms with an automated edge detection system. Cineangiographic frames of orthogonal views were digitized and stored in a personal computer system. Stenoses involving the coronary artery under study were outlined with an automated edge detection algorithm with a 2-dimensional search. All traced lesions were corrected for pincushion and magnification distortion. Estimation of percent diameter stenosis was accomplished with a geometric method from biplane orthogonal views of each lesion. Patients with ≥20% reduction (from baseline) in luminal diameter after the highest dose of acetylcholine were considered as having a positive vasomotor response.[5]

Study Protocol. In each patient, cumulative doses of acetylcholine at a rate of 12.5 and 25 μg/min (50 and 100 μg over a 4-minute period) were infused in the left coronary sys-

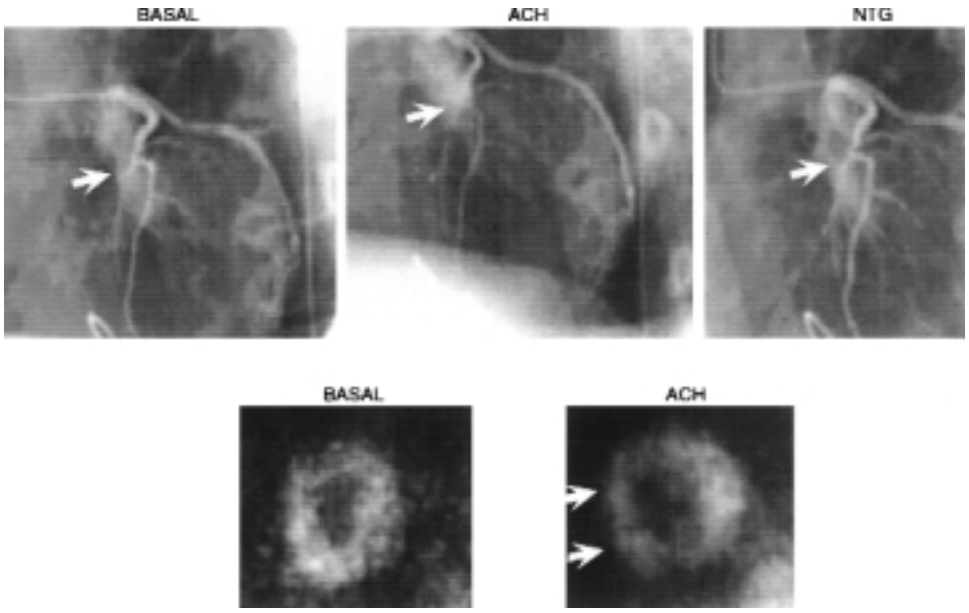

Figure 1. Coronary angiography (*top*) shows a normal left anterior descending coronary artery at baseline. After acetylcholine (*ACH*), there is a positive vasomotor response (*arrow*) that normalizes after the administration of nitroglycerine (*NTG*). The planar Tc-99m sestamibi images (*bottom*) during acetylcholine show a severe perfusion defect throughout the septal and inferoapical regions of the left ventricle (*arrows*), showing complete reversibility.

tem; and 30 seconds after each dose coronary angiography was repeated. In patients with no vasomotor response in the left coronary system, cumulative doses of acetylcholine at a rate of 6.25 and 12.5 μg/min (25 and 50 μg over a 4-minute period) were infused in the right coronary artery; and 30 seconds after each dose coronary angiography was again performed. Systemic blood pressure and a 12-lead electrocardiogram were recorded throughout the study. Intracoronary nitroglycerine (200 μg) was used in patients who had chest pain develop or had ischemic electrocardiogram changes.

Technetium 99m Sestamibi Imaging

All patients received an intravenous injection of 25 mCi of Tc-99m sestamibi 30 seconds after the highest dose of acetylcholine, inducing a vasomotor response. In patients without vasomotor changes, Tc-99m sestamibi was injected after the last dose of acetylcholine. Twenty-four hours after the angiographic procedure, a second dose of 25 mCi of Tc-99m sestamibi was given. Planar imaging was performed within 2 hours of the sestamibi injection (baseline images). Images were acquired with a planar gamma camera (Picker 415) with an all-purpose collimator in standard anterior, 45° left anterior oblique, and 70° left lateral views. Images were interpreted by consensus visual analysis of 3 expert observers who were blinded to the angiographic results. Images were considered normal if no regional defects were visualized. Images with any degree of regional hypoperfusion were classified as abnormal. Patients with reversible defects were subgrouped according to their anatomic location (eg, left anterior descending, circumflex, or right coronary artery territories).

Statistical Analysis

Data are presented as mean ± standard deviation or as simple proportions, as appropriate. Differences between proportions were assessed by Fisher's exact test. A P value < .05 was used to define statistical significance.

RESULTS

Clinical Response to Acetylcholine

During infusion of the highest dose of acetylcholine, three patients had chest pain and ischemic electrocardiogram changes, which were associated with complete atrioventricular block in 1 patient and completely resolved with administration of intracoronary nitroglycerine. In these patients, coronary angiography and sestamibi injection were performed just before nitroglycerine administration.

Concordance Between the Coronary Vasomotor Response and the Presence of Regional Defects on Myocardial Perfusion Imaging

In the 11 patients, there were 33 coronary artery territories, of which 23 received selective injections of acetylcholine followed by angiography. The severity and location of coronary artery stenoses on the baseline angiography in each patient are summarized in Table 2.

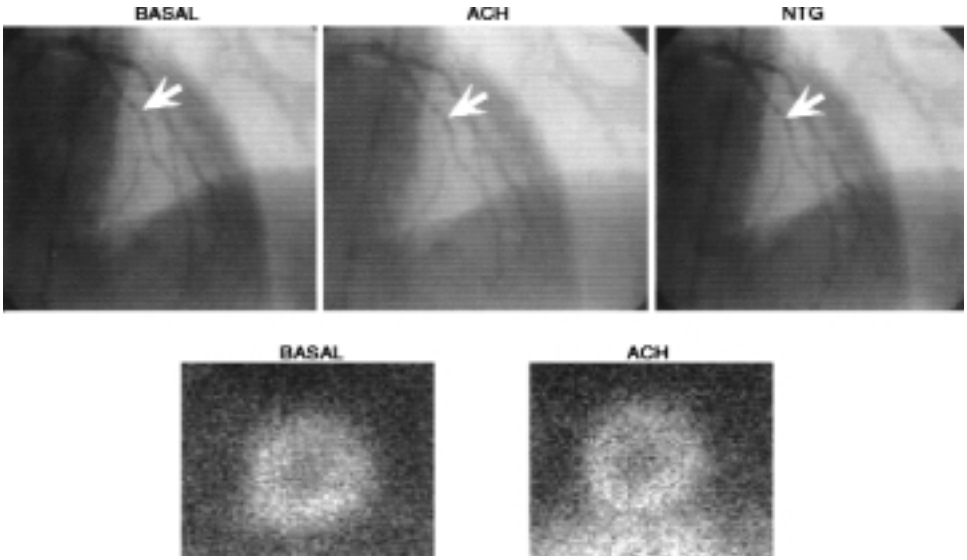

Figure 2. Coronary angiography (*top*) shows a diseased mid-left anterior descending coronary artery at baseline. After acetylcholine (*ACH*), there is a negative vasomotor response (*arrow*) that is unchanged after the administration of nitroglycerine (*NTG*). The planar Tc-99m sestamibi images (*bottom*) show normal regional perfusion throughout the left ventricle at baseline and during acetylcholine.

Among the 23 coronary arteries analyzed, 13 arteries were angiographically normal or had a nonsignificant luminal narrowing (<50%), 3 arteries had stenoses of intermediate severity (50% to 69%), and 7 arteries had significant luminal narrowing (≥70%). Increasing intracoronary injections of acetylcholine were performed in 10 of 11 left main coronary arteries and in 3 right coronary arteries. Overall, 12 coronary arteries showed a vasoconstrictive response to acetylcholine. Of those 12, 11 were considered significant (positive) based on a criterion defined prospectively (≥20%). The average reduction in luminal narrowing among the 11 vessels showing a positive response to acetylcholine was –26.5% ± 11.2%.

Table 2 summarizes the relation between the vasomotor response to acetylcholine and the results of myocardial perfusion imaging. Among the 13 angiographically normal coronary arteries analyzed, 4 (31%) had a positive vasomotor response to acetylcholine infusion associated with a corresponding regional perfusion defect on sestamibi imaging (Figure 1). The remaining 9 normal vessels analyzed had a negative vasomotor response to acetylcholine infusion and showed no regional perfusion defects.

There were 3 coronary arteries with a luminal narrowing of intermediate severity (50% to 69%). Two of these arteries had a negative response to acetylcholine and showed normal myocardial perfusion in the corresponding territory (Figure 2), whereas only 1 had a positive vasomotor response to acetylcholine infusion with a corresponding reversible perfusion defect on sestamibi imaging. Seven of the 23 coronary arteries analyzed had ≥70% diameter stenosis on baseline angiography. Of these, 6 (86%) coronary arteries developed a positive vasomotor response to acetylcholine infusion, 5 of which were associated with a corresponding regional perfusion defect ($P < .01$ vs proportion of normal coronaries with a positive response to acetylcholine). In one patient (patient 6), a positive response to acetylcholine in the left circumflex artery was not associated with a corresponding regional perfusion defect. In the remaining coronary artery (patient 1), there was a vasodilator response to acetylcholine infusion, and myocardial perfusion was normal.

DISCUSSION

This study demonstrates that in patients with coronary artery disease, noninvasive assessment of regional myocardial perfusion with Tc-99m sestamibi imaging may be useful for evaluating endothelium-dependent changes in coronary artery tone. We found that 6 (60%) of 10 coronary arteries with angiographic stenoses of intermediate severity had a positive vasomotor response to increasing doses of acetylcholine, which was associated with a reversible perfusion defect on Tc-99m sestamibi imaging. Likewise, 4 (31%) of 13 angiographically normal coronary arteries showed a positive vasomotor response to acetylcholine that was associated with a regional perfusion abnormality on Tc-99m ses-

Table 2. Relation among the percent coronary stenosis on baseline angiography, the vasomotor response to acetylcholine, and the results of myocardial perfusion imaging

Patient	Baseline coronary angiography and location (% stenosis)			ΔChange after acetylcholine (%)			Location and severity of perfusion defect
	LAD	LCX	RCA	LAD	LCX	RCA	
1	90 (prox)	70 (mid)	0	10.7	–20.0	—	PB, moderate
2	0	70 (mid)	0	11.4	–20.0	—	PB/PL, moderate
3	0	60 (mid)	30 (prox)	–50.0	–20.0	—	S/PL, moderate
4	0	0	0	–27.3	–27.0	—	S/AL, moderate
5	0	0	0	7.9	8.1	7.9	Normal, —
6	90 (prox)	80 (dist)	0	–47.6	–21.1	—	S, severe
7	100 (mid)	70 (dist)	0	—	—	9.8	Normal, —
8	80 (prox)	0	0	–29.3	–14.3	—	S/A, severe
9	50 (prox)	0	0	11.4	12.9	9.8	Normal, —
10	50 (mid)	0	0	4.8	–20.0	—	PB, mild
11	70 (prox)	0	0	–22.2	2.6	—	S, mild

LAD, Left anterior descending coronary artery; *LCX*, left circumflex coronary artery; *RCA*, right coronary artery; *prox*, proximal; *dist*, distal; *PB*, posterobasal segment; *PL*, posterolateral segment; *S*, septal segment; *AL*, anterolateral segment; *A*, apical segment.

tamibi imaging. The latter findings are consistent with those of Hasdai et al[6] in patients with chest pain and angiographically normal coronary arteries. They showed that acetylcholine induced epicardial vasoconstriction and a reduction in coronary blood flow that was associated with regional perfusion defects in 7 of 20 patients without significant left anterior descending coronary artery disease.

Exactly how the intracoronary infusion of acetylcholine may induce a regional defect on myocardial perfusion imaging cannot be determined from this study. However, several potential mechanisms could explain these findings. It is possible that further increases in coronary tone at the site of known angiographic stenoses may have critically increased the resistance to blood flow through the stenotic segment, ultimately leading to a reduction in myocardial perfusion distal to the stenosis and a reversible perfusion defect.[7,8] Another possibility is that vasoconstriction of resistance coronary vessels in response to acetylcholine infusion may have contributed to a reduction in myocardial blood flow and a reversible perfusion defect on Tc-99m sestamibi imaging, especially among the angiographically normal coronary arteries. This is supported by the fact that endothelium-dependent regulation of vascular tone affects both conduit and resistance coronary arteries.[3,6,9,10] The latter is particularly important because vasodilation of resistance arteries plays a key role in determining myocardial blood flow.[4] Furthermore, coronary risk factors, such as hypercholesterolemia,[3,11] smoking,[12] hypertension,[13] and diabetes,[14] have all been associated with impaired endothelium-dependent vasodilation of both conduit and resistance coronary arteries. Among our patients, 64% were active smokers, 55% had hypertension, and 82% had markedly increased LDL cholesterol levels.

Study Limitations

Limitations to this study must be acknowledged. First, this pilot study included a relatively small number of patients. Thus the findings will have to be confirmed in a larger patient population. Second, the relation between the increased vasomotor response of epicardial coronary vessels to acetylcholine infusion and regional myocardial perfusion abnormalities in patients with CAD probably depicts the most severe manifestation of endothelial dysfunction. Because of the relative nature of the assessment of myocardial perfusion, the presence of more modest degrees of microvascular endothelial dysfunction cannot be ruled out, especially among the arteries without angiographic disease.[6] Such abnormalities, which probably occur earlier in the natural history of the disease, can be better characterized noninvasively by absolute measurements of myocardial blood flow, such as those provided by positron emission tomography.[15] Third, the potential role of endothelial dysfunction in response to exercise in the pathogenesis of myocardial ischemia in patients with coronary artery disease was not determined. However, previous studies have shown that coronary endothelial dysfunction cor-

relates well with the presence of regional perfusion abnormalities as assessed by exercise thallium scintigraphy.[9] Fourth, nonquantitative planar imaging rather than quantitative SPECT was used, which may have limited our ability to detect small changes in myocardial perfusion.

Clinical Implications

Endothelial dysfunction occurs in patients with atherosclerosis[2] and is considered an early event in atherogenesis.[16] Previous studies have demonstrated the importance of the vascular endothelium in modulating the responsiveness of the underlying coronary smooth muscle to a variety of neurohormonal stimuli.[11,17,18] Noninvasive assessment of regional myocardial perfusion with Tc-99m sestamibi imaging correlates well with invasive measurements of coronary vasomotion in response to the endothelium-dependent dilator acetylcholine. However, whether or not these findings can be reproduced with more physiologic tests of endothelial function, such as those that increase sympathetic stimulation,[18] will have to be demonstrated in future studies. Nevertheless, these findings suggest that there may be a role for myocardial perfusion imaging in monitoring the effects of interventions designed to improve endothelial function and microvascular function in patients with coronary artery disease.

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