Endothelial Function

Early Dysfunction and Long-Term Improvement in Endothelium-Dependent Vasodilation in the Infarct-Related Artery After Thrombolysis

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OBJECTIVES

This study assessed the degree of endothelial dysfunction in post-acute myocardial infarction (AMI) and its subsequent status in the infarct-related artery (IRA) in patients treated with thrombolysis.

BACKGROUND

Coronary flow reserve alterations in the IRA after thrombolysis have been described, but the endothelium-dependent vasomotion has not been investigated, to date.

METHODS

Endothelial function in patients after thrombolysis was assessed by infusion of acetylcholine (ACh) at increasing doses in the IRA. Diameter changes in the distal segments were evaluated using quantitative coronary angiography. Patients with coronary atherosclerosis constituted the control group. Clinical variables, electrocardiography and biochemical markers were used to determine the timing of reperfusion and the extent of the infarct. Patients in the AMI group were re-evaluated one year later.

RESULTS

In the initial assessment, 16 patients showed a vasoconstriction response to ACh in the IRA compared to the control group (20 ± 21% vs. 4 ± 4%; p < 0.01). Significant correlations between the degree of vasoconstriction and maximum value of the creatine kinase-MB fraction and number of new Q waves were observed. Of the 12 patients re-evaluated, 4 had complete occlusion of the IRA. In the remaining eight patients with patent artery, an improvement in response to ACh was observed relative to the initial study (11% vs. 19 ± 15%, p < 0.05).

CONCLUSIONS

In patients with AMI treated with thrombolysis, severe endothelial dysfunction in the IRA is observed early. In patients who retain patency of the IRA, the endothelial dysfunction improves during the follow-up and suggests a component of stunned endothelium in the first few days post-AMI. (J Am Coll Cardiol 2002;40:257–65) © 2002 by the American College of Cardiology Foundation

Endothelial dysfunction is an initial event in the development of atherosclerosis and can contribute to the progression of the disease (1,2). The endothelium plays a predominant role in circulatory homeostasis via the liberation of various vasoactive substances such as nitric oxide, prostacyclins and endothelins (3). Nitric oxide, apart from its vasodilation action, inhibits plaque aggregation, adhesion of leukocytes and the proliferation of smooth muscle cells (4).

The functional reaction of the vascular endothelium under determinate conditions of ischemia is complex. In animal models, the presence of endothelial dysfunction during episodes of ischemia and reperfusion has been documented (5,6). In post-acute myocardial infarction (AMI) patients with thrombolytic treatment, alterations in coronary flow reserve have been noted (7,8). However, to date, there have been no studies that have evaluated the state of endothelial function in the infarct-related artery (IRA) after thrombolysis, and whether there is a relationship with the extent of the infarct and the timing of reperfusion. Studies have documented that the coronary endothelial function can improve in different situations (9–13), but it is not known whether endothelial dysfunction after ischemia reperfusion is a transient phenomenon.

The present study was conducted in a series of patients with AMI treated with thrombolytic agents to assess the state of endothelial function early in the IRA, its relationship with the extent of the infarct and the timing of reperfusion, and the coronary endothelial function at one year of follow-up.

METHODS

Patients. Initially, 29 consecutive patients who presented with an AMI with indication of fibrinolysis and who were admitted into the coronary care unit of our hospital were included in the study. All were treated with aspirin and streptokinase (1.5 × 10^6 IU) or recombinant tissue-type plasminogen activator (100 mg in an accelerated manner) plus intravenous heparin. Exclusion criteria were a prior...
history of myocardial infarction (MI) in the same coronary territory, previous coronary revascularization, insulin-dependent diabetes mellitus, renal insufficiency or severe hypertension. The protocol of the study was approved by the ethics committee of our institution, and all patients provided informed written consent.

Serial electrocardiograms (ECGs) pre-, immediately post-, and at 2, 6, 12, 24 and 48 h after thrombolysis were performed. At baseline and at 15, 30 and 60 min and 2, 4, 6, 12, 24 and 48 h following thrombolysis, the levels of MB fraction of creatine kinase (CK-MB) and myoglobin were determined. A questionnaire evaluated the moment of pain remission. The appearance of post-AMI angina necessitating vasodilator agents was considered an exclusion criterion. Coronary angiography and the assessment of endothelial function were scheduled for between 7 and 10 days post-AMI.

Estimation of reperfusion. INFARCT SIZE. The time intervals between pain onset, implementation of thrombolysis and pain remission were recorded. Normalization of the ST-segment and the appearance of new Q-waves were analyzed in the serial ECGs. Appearance of arrhythmias on the ST-segment and the appearance of new Q-waves were recorded. To assess endothelium-dependent coronary vasomotor function, the saline infusion was replaced by intracoronary infusion of serial doses of acetylcholine (ACh), with estimated intracoronary final concentrations of $10^{-8}$ mol/l to $10^{-6}$ mol/l. Because ACh causes endothelium-dependent vessel relaxation in experimental models and in humans, a paradoxical vasoconstriction after the infusion of this substance is an indicator of endothelial dysfunction (2). The duration of each infusion was 2.5 min and, at each stage, an angiogram was taken. All angiograms were performed with identical views and radiographic characteristics. All infusions were delivered at a rate of 2 ml/min using a precision pump injector (Harvard, Southnatick, Massachusetts). The final blood concentrations of ACh were estimated with the assumption that blood flow in the coronary artery was 80 ml/min (17).

Finally, to evaluate endothelium-independent vasomotor response, NTG bolus (2 mg) was administered through the guiding catheter, and an angiogram identical to the others was performed (2). Throughout the procedures, heart rate, systemic arterial pressure and ECG were monitored continuously. All details of the catheterization and radiography were recorded so as to ensure duplication of the procedures at the proposed follow-up.

Quantitative coronary analysis. Quantitative coronary angiography was performed after the infusion of the saline solution, at the end of each infusion of ACh and after NTG bolus. Angiograms were performed in the two orthogonal projections that best showed the artery of interest, without overlapping of side branches and with less foreshortening. Angiograms were obtained on a real-time digital image acquisition and processing system (Digitron-3, Siemens). Images were acquired at 25 frames/s with a $512 \times 512$ pixel matrix with 10-bit depth for subsequent computer analysis. End-diastolic frames were taken for quantification. This system is based on a modular, fully automated border-detection algorithm developed by Pope et al. (18) and described in detail elsewhere. Variability of this method has been previously reported (19).

Calibration of the system was based on dimensions of the guiding catheter not filled with contrast medium. Mean luminal diameters of the segments distal to the lesion...
RESULTS

Of the 29 patients initially included in the study, 1 died after thrombolysis and 7 were excluded because of postinfarct angina that necessitated vasodilator drugs. Of the remaining 21 patients, the coronary angiography demonstrated a TIMI flow grade <3 in 4 patients and a severe lesion in the left main coronary artery in 1 patient. Endothelial function was assessed in the remaining 16 patients.

The baseline characteristics of patients and control group are presented in Table 1. No statistically significant differences existed between the groups with respect to age, gender, prevalence of risk factors and extent of coronary disease. In the study group, thrombolysis was performed within 140 ± 60 min from the onset of chest pain. The IRA was the anterior descending artery in 10 patients (63%), right coronary artery in 5 (31%) and circumflex in 1 patient (6%). The left ventricular ejection fraction was greater in the control group.

Initial study of endothelial function. Assessment of endothelial function was conducted within 9 ± 2 days of the infarct in the study group. The mean diameter of the arterial segments analyzed was 2.5 ± 0.5 mm in the post-AMI group and 2.4 ± 0.5 mm in the control group (p = NS). Intracoronary infusion of ACh produced a significant vasoconstriction response indicative of endothelial dysfunction in the IRA in the group of post-AMI patients (Fig. 1, Table 2). At the maximum concentration of ACh, there was a mean vasoconstriction of the artery in the group of post-AMI patients compared to a mean vasodilation response in the control group (−20 ± 21% vs. 4 ± 4%; p < 0.01). Nitroglycerin provoked a similar grade of vasodilation in both groups (16 ± 3% vs. 11 ± 4%; p = NS), suggesting that the nonendothelial-dependent vasodilation was conserved. No significant changes occurred in arterial pressure or in cardiac rate in the course of ACh administration. No clinical complications were seen during the procedures.

Correlates of endothelium-dependent vasodilation. The severity of endothelial dysfunction did not correlate with vessel size (r = 0.12; p = NS). The status of endothelial function of the IRA did not correlate significantly with any of the following variables measured to determine the timing of reperfusion: value of myoglobin at 90 min (r = 0.35; p = NS), ratio and relative increment of CK-MB (r = −0.23; p = NS and r = −0.25; p = NS, respectively) and ratio and relative increment of myoglobin (r = −0.30; p = NS and r = −0.30; p = NS, respectively). Conversely, the initial endothelial dysfunction correlated significantly with parameters indicative of the extent of infarct. The percentage of diameter change at the maximum dosage of ACh correlated with the maximum value of the CK-MB (r = −0.53; p < 0.05), the AUC of CK-MB (r = −0.49; p < 0.05) and with the number of new “Q” waves (r = −0.62; p = 0.04).

Reassessment study of endothelial function in the IRA in follow-up. During the follow-up, patients were asked to follow secondary prevention measures, and all patients were
treated with aspirin. Additionally, two had angiotensin-converting enzyme (ACE) inhibitors, four had beta-blockers and three had hypolipidemic drugs prescribed. Cholesterol levels were 5.46 mmol/l and 5.20 mmol/l in the first and second study, respectively.

Of the 16 patients in whom we had performed the initial endothelial function study, 4 asymptomatic patients decided not to participate in the second study. Of the 12 remaining patients, the second study showed complete occlusion of the IRA in 4 patients. As such, the reevaluation of endothelial function was performed in 8 patients at 12 months post-AMI. The ejection fraction was 51 ± 12% (p = NS vs. the first study). In those patients who retained permeability of the artery, a significant improvement in the grade of Table 1. Baseline Characteristics of the Patients With AMI and the Control Group (Percentages of the Overall Study Group in Parentheses)

<table>
<thead>
<tr>
<th>Post-AMI Patients (n = 16)</th>
<th>Control Group (n = 12)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>65 ± 8</td>
<td>61 ± 6</td>
</tr>
<tr>
<td>Male</td>
<td>14 (87)</td>
<td>11 (91)</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>7 (44)</td>
<td>8 (66)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (37)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Noninsulin-dependent diabetes</td>
<td>3 (19)</td>
<td>2 (16)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>4 (25)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Number of diseased vessels</td>
<td>1.2 ± 0.7</td>
<td>1.1 ± 0.4*</td>
</tr>
<tr>
<td>Arteries assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descending anterior artery</td>
<td>10 (63)</td>
<td>10 (83)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>5 (31)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Circumflex artery</td>
<td>1 (6)</td>
<td></td>
</tr>
<tr>
<td>Stenosis (%)</td>
<td>62 ± 30</td>
<td>31 ± 6</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>50 ± 17</td>
<td>62 ± 10</td>
</tr>
<tr>
<td>Site of the AMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior-lateral</td>
<td>10 (63)</td>
<td></td>
</tr>
<tr>
<td>Inferior-posterior</td>
<td>6 (37)</td>
<td></td>
</tr>
<tr>
<td>Thrombolytic agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue plasminogen activator</td>
<td>11 (69)</td>
<td></td>
</tr>
<tr>
<td>Streptokinase</td>
<td>5 (31)</td>
<td></td>
</tr>
<tr>
<td>Time to thrombolysis (min)</td>
<td>140 ± 60</td>
<td></td>
</tr>
<tr>
<td>Maximum value of CK-MB (µkat/l)</td>
<td>6.05 ± 3.21</td>
<td></td>
</tr>
<tr>
<td>Maximum value of myoglobin (µkat/l)</td>
<td>3608 ± 3021</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. *Six months before the endothelial function study. AMI = acute myocardial infarction; CK-MB = MB fraction of creatine kinase.

Figure 1. Percent change in arterial diameter in response to different doses of acetylcholine (ACh) in post-acute myocardial infarction (AMI) patients and the control group. At the maximum concentration of ACh the post-AMI patients showed a considerable vasoconstriction response in the infarct-related artery, indicative of endothelial dysfunction, while the control group showed a slight vasodilation response. Both groups exhibited a vasodilation response to nitroglycerin (NTG), suggesting that the nonendothelium-dependent vasodilation is conserved.
endothelial dysfunction was observed (Fig. 2). In the first study and at the maximum concentration of ACh, an intense vasoconstriction response was noted, whereas in the second study and at the same concentration of ACh, a vasodilation response was observed (19/1100219/1100615% vs. 3/1100611%; p<0.04), similar to the response noted in the control group at the first study (4/1100617/110064%; p=NS; Fig. 3). No significant correlations existed between endothelial function at follow-up and the initial parameters of reperfusion or the extent of the infarct. Neither was there any relationship observed between the type and number of drugs received by each patient during follow-up and the improvement in the endothelial function. Figure 4 shows the response of the IRA in one of the patients at the maximum concentration of ACh in the initial study and in the reevaluation. Five patients who presented with angina and/or ischemia induced in an exercise tolerance test were scheduled for angioplasty at the end of the endothelial function assessment.

**DISCUSSION**

Our study demonstrates that in the first few days of an AMI treated with thrombolytic therapy, the IRA has a considerable degree of endothelial dysfunction compared to a control group of patients with coronary artery disease but who had not experienced a previous infarct. The initial endothelial dysfunction correlated significantly with parameters indicative of the size of infarct. In patients who retained patency of the artery, the endothelial function underwent a significant improvement in the follow-up year.

To date, there have not been any studies evaluating endothelial function status in the IRA following thrombolysis. Okamura et al. (20) observed a significant vasoconstriction response to ACh in the IRA between 1 and 24 months after AMI in patients who had not been treated with thrombolytic agents. Bridges et al. (21), using factor VIII von Willebrand factor antigen as a marker of endothelial dysfunction, observed a significant increase in plasma levels of the marker in a series of patients following thrombolytic therapy; this suggested that the ischemia-reperfusion in patients with AMI would cause a lesion on the endothelium.

Studies in experimental animals indicate that abnormal vasomotor response after a myocardial infarct could be related to the liberation of serotonin, thromboxane A or thrombin, which would induce constriction of the smooth muscle around the site of the thrombosis or in the distal segments (22). In contrast, models of ischemia-reperfusion show that occlusion of the epicardial arteries with subsequent reestablishment of the flow can produce a migration of neutrophils toward the endothelium and the elastic lamina (23), an accumulation of mastocytes (24) and the production of superoxide anions.

Human cells are altered substantially during exposure to hypoxia. Transient expression of preformed proteins stored within the endothelium promotes leukocyte endothelial cell interaction and coagulation. Alternatively, in response to

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**Table 2. Coronary Vasomotor Response (Mean Luminal Diameter in mm)**

<table>
<thead>
<tr>
<th></th>
<th>Post-AMI Patients (n = 16)</th>
<th>Control Group (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.55 ± 0.5</td>
<td>2.48 ± 0.5</td>
</tr>
<tr>
<td>ACh 10⁻⁸</td>
<td>2.46 ± 0.4</td>
<td>2.56 ± 0.4</td>
</tr>
<tr>
<td>ACh 10⁻⁷</td>
<td>2.43 ± 0.4</td>
<td>2.54 ± 0.5</td>
</tr>
<tr>
<td>ACh 10⁻⁶</td>
<td>2.01 ± 0.5*†</td>
<td>2.57 ± 0.4</td>
</tr>
<tr>
<td>NTG</td>
<td>2.95 ± 0.5†</td>
<td>2.76 ± 0.5</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. *p < 0.001 with respect to control group. †p < 0.001 with respect to baseline values.

ACh = acetylcholine; NTG = nitroglycerin.

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**Figure 2.** Individual changes in post-acute myocardial infarction patients, in response to the maximum concentration of acetylcholine (ACh) at the time of the initial study (9 ± 2 days) and one year later. *p = 0.04; IRA = infarct-related artery. Data are expressed as mean ± SEM.
tumor necrosis factor, interleukin-1 and interleukin-6, transcriptional activation of several genes is initiated in the endothelial cells, and translation of specific transcripts into protein products on the endothelial surface is completed over the course of several hours. These proteins include leukocyte adhesion molecules, tissue factor and leukocyte activators. In this situation there is an increase of adherence of leukocytes to endothelial cells (25), an up-regulation of intercellular adhesion molecule, and release of interleukin-1-alpha, E-selectin and interleukin-8.

Free radicals may induce significant functional alterations in endothelial cells that promote and extend the inflammatory reaction (26). In particular, free radicals stimulate platelet-activating factor release from the endothelium, which in turn can further activate cells in the growing neutrophil infiltrate in an amplifying feedback loop (27).

**Figure 3.** Response to the maximum concentration of acetylcholine (ACh) in post-acute myocardial infarction (AMI) patients who retained infarct-related artery (IRA) patency and in the control group. Initial study was at 9 ± 2 days following infarct, and the follow-up was 12 ± 3 months later. A significant improvement in the endothelial function in the IRA was observed on follow-up. Endothelial function in the IRA at one-year follow-up was similar to the response detected initially in the control group. Data are expressed as mean ± SEM.

**Figure 4.** Assessment of endothelial function in the infarct-related artery at 10 days and 9 months in the same patient post-acute myocardial infarction. At the initial assessment (A), there was a considerable vasoconstriction response to the maximum dose of acetylcholine, which indicates a marked endothelial dysfunction. In the second assessment (B), a vasodilation response to the acetylcholine was observed, which indicates a significant improvement in the grade of endothelial dysfunction in the infarct-related artery at follow-up.
Endothelial dysfunction occurs moments after reperfusion following regional ischemia, and it progresses with time (29). Endothelium may be more vulnerable to injury than the myocyte or endothelial injury that might precede myocyte injury (30). When rendered hypoxic and reoxygenated, endothelial cells become activated to express pro-inflammatory properties, pro-coagulant factors and vasoconstrictive agents that increase vasomotor tone (26). These changes may contribute to the myocardial dysfunction. Heart failure per se can influence endothelial function due to a reduced ability of endothelium to synthesize or release nitric oxide (31). However, it was unlikely in our patients because the ejection fraction did not change during the follow-up and, in contrast, the endothelial dysfunction improved significantly during this period. Also, the reduction in the ejection fraction was modest, and no patient showed signs of heart failure during the study.

**Endothelial dysfunction changes at follow-up.** In the patients who retained patency of the artery, the endothelial dysfunction in the IRA had improved dramatically in the year post-AMI and demonstrated an ACh response similar to that documented in the noninfarct control group. Our study demonstrated the capacity of the human endothelium to recover its function after an episode of ischemia-reperfusion.

Using positron emission tomography, Uren et al. (7) investigated 9 patients at one and six months' postinfarction who were treated with thrombolysis. They observed that the severe vasodilator abnormality initially detected, involving resistant vessels in the infarcted myocardium, improved during the follow-up. Ishihara et al. (28) documented that the coronary flow reserve improves during follow-up in patients after MI. It has also been observed that endothelial dysfunction induced by the ischemia-reperfusion processes can be minimized by specific interventions. Ischemic preconditioning in humans (32) and pharmacologic treatment with ibopamine, captopril and heparin (33,34), prior exposure to peroxinitrite (35) and hepatic hydroxymethylglutaryl-coenzyme A reductase inhibitors (36) have been shown to preserve endothelial function in animal models. No specific interventions during follow-up were conducted in our patients except for the general secondary prevention measures in patients post-AMI. No significant correlations were observed between any of these measures and the grade of improvement in response to ACh and which was, in general, superior to the improvement documented in studies with hypolipidemic agents or ACE inhibitors (10–12).

Mechanisms proposed for the improvement in endothelial function during follow-up in patients with patent arteries are speculative. Following brief periods of ischemic insult to the myocardium, considerable alterations in the coronary vasodilation responsiveness without changes in the structure of the coronary small vessels have been described (37). Bhagat et al. (38) define endothelial stunning as a transient endothelial dysfunction that persists after the injury and takes a long period to recover. Sheridan et al. (39) documented a reversible dysfunction of pulmonary vasorelaxation through stunning of vascular endothelial and smooth muscle cells.

**Study limitations.** To assess endothelial function in the IRA accurately, we excluded those patients with TIMI flow grade <3 as well as those who, for post-AMI angina, were under vasodilator treatment. These criteria could imply that the patients included in the study represented a very selected subgroup of postthrombolysis patients. Nevertheless, these patients represent 55% of a consecutive series of patients with AMI treated with thrombolytic agents. Furthermore, the expected frequency of a patent artery at nine days’ post-AMI despite a noneffective thrombolysis has been reported as being between 4% to 22% (40,41). Although we had not used very early angiographic evaluation for determining the timing of reperfusion (40) we had, nevertheless, used a series of noninvasive parameters that have been validated recently (14–16).

It could be argued that the considerable endothelial dysfunction that we observed early in the IRA was already present pre-AMI (42). Endothelial dysfunction is more prevalent in the setting of acute coronary syndrome than in chronic coronary artery disease. In patients with unstable angina, severe endothelial dysfunction has been described in the culprit lesion. However, the coronary artery downstream from the culprit lesion in these patients shows minor degrees of vasoreactivity in response to exercise, with a magnitude similar to the distal segments of patients with stable angina (43). In contrast, our post-AMI patients showed a severe endothelial dysfunction downstream from the culprit lesion, with important differences compared to the response shown in the distal segments of the control group, which consisted of patients with stable coronary artery disease. Furthermore, the documented reversibility during the follow-up period would also suggest that the dysfunction was secondary to the infarct.

The relatively reduced number of patients could be a limitation of the study. Nevertheless, the endothelial response in our group of patients was uniform in the initial assessment and in the assessment at follow-up. To demonstrate a definite relationship between IRA patency and endothelial dysfunction, improvement would require a much larger number of patients. Likewise, even though no correlation was found, no definite conclusion can be drawn regarding the influence of the medication received during the follow-up and improvement in the endothelial function.

**Clinical implications.** In this study we demonstrate that, in post-AMI patients treated with thrombolytic agents and with patent IRA artery, there is severe endothelial dysfunction and, as such, it is an attractive model in which to evaluate different forms of intervention so as to preserve...
endothelial function. Aspects that may be addressed could include hypoxic endothelial cell injury contribution to the no-reflow phenomenon (26), relationship between the endothelial-dependent vasodilation in the epicardial arteries during follow-up, and the endothelium function of the micro-circulation and its influence in the long-term ventricular dysfunction, as has been suggested previously (44).

Conclusions. In patients with AMI treated with thrombolytic agents, an important degree of initial endothelial dysfunction that correlates with the extent of infarct is observed. In those patients who retain a patent IRA, the endothelial dysfunction improves during the follow-up period, which suggests a component of stunned endothelium in the first few days post-AMI.

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