α-Adrenergic Blockade Improves Recovery of Myocardial Perfusion and Function After Coronary Stenting in Patients With Acute Myocardial Infarction

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**Background**—AMI reperfusion by thrombolysis does not improve TIMI flow and LV function. The role of infarct-related artery (IRA) stenosis and superimposed changes in coronary vasomotor tone in maintaining LV dysfunction must be elucidated.

**Methods and Results**—Forty patients underwent diagnostic angiography 24 hours after thrombolysis. Seventy-two hours after thrombolysis, the culprit lesion was dilated with coronary stenting. During angioplasty, LV function was monitored by transesophageal echocardiography. Percent regional systolic thickening was quantitatively assessed before PTCA, soon after stenting, 15 minutes after stenting, and after phentolamine 12 mg/kg IC (n = 10), the α1-blocker urapidil 600 μg/kg IV (n = 10), or saline (n = 10). Ten patients pretreated with β-blockers received urapidil 10 mg IC. Coronary stenting significantly improved thickening in IRA-dependent and in non–IRA-dependent myocardium (from 27±15% to 38±16% and from 40±15% to 45±15%, respectively). Simultaneously, TIMI frame count decreased from 39±11 and 40±11 in the IRA and non-IRA, respectively, to 23±10 and 25±7 (P < 0.05). Fifteen minutes after stenting, thickening worsened in both IRA- and non–IRA-dependent myocardium (to 19±14% and 28±14%, P < 0.05), and TIMI frame count returned, in both the IRA and non-IRA, to the values obtained before stenting. Phentolamine and urapidil increased thickening to 36±17% and 41±14% in IRA and to 48±11% and 49±17% in non-IRA myocardium respectively, and TIMI frame count decreased to 16±6 and to 17±5, respectively. Changes were attenuated with β-blocker pretreatment.

**Conclusions**—Our finding that α-adrenergic blockade attenuates vasoconstriction and postischemic LV dysfunction supports the hypothesis of an important role of neural mechanisms in this phenomenon. (*Circulation*. 1999;99:482-490.)

**Key Words:** myocardial infarction ■ nervous system, autonomic ■ vasoconstriction ■ regional blood flow ■ receptors, adrenergic, alpha

The use of thrombolysis in acute myocardial infarction (AMI) has changed its natural history, reducing mortality by 30%,1–3 but no improvement in ventricular function was reported to occur after thrombolysis in numerous trials.2–8 This paradox was first observed by the TIMI study group,1 who proposed a TIMI blood flow grade to indicate the relationship between angiographic evidence of vessel patency and myocardial perfusion. In fact, coronary patency is observed at angiography in 85% of patients 90 minutes after the beginning of thrombolytic treatment,2,3 but despite evidence of an open infarct-related artery (IRA), a “mismatch” between patency and flow is frequently reported.3–8 This enigma led Lincoff and Topol9 to speculate that the angiographic patency may greatly overestimate the success of thrombolysis. The persisting contractile dysfunction observed after thrombolysis may be due to irreversible myocardial injury (necrosis), to reversible myocardial injury (stunning),10–12 but also to microcirculatory perfusion abnormalities. Surprisingly, PTCA performed soon after thrombolysis is not reported to substantially improve left ventricular (LV) function,13,14 which correlates highly with long-term survival.15,16

See p 468

The present study was based on the hypothesis that in addition to the benefit of an “open artery,”17 the restoration of myocardial perfusion would improve LV function. Accord-
ingly, 3 different approaches interfering with different mechanisms responsible for the sequelae of AMI were undertaken: (1) soon after AMI reflow was restored by means of thrombolysis, (2) the flow-limiting stenosis was dilated and a stent was implanted (72 hours after thrombolysis), and (3) an α-adrenergic blocker was given with the aim of normalizing microcirculatory perfusion and consequently attenuating LV dysfunction. In fact, we have previously demonstrated that vasoconstriction and LV dysfunction occur 15 minutes after coronary stenting and that these phenomena are related to sympathetic mechanisms. Indeed, the injection of α-adrenergic blocking drugs counteracted the development of LV dysfunction.

Methods

Patients
We studied 40 patients (mean age, 60±13 years), among them 4 women, who were treated with thrombolysis as outpatients within 90 minutes after the onset of acute MI symptoms and were then referred to the Clinique Pasteur for further treatment.

Thrombolysis
To shorten reperfusion time, patients were treated as soon as the outside cardiologist validated the diagnosis. Forty consecutive patients receiving different fibrinolytic treatments were included in the study, irrespective of the type of thrombolytic agent given, but after documented reflow by coronary angiography 24 hours after AMI.

Adjunct Medical Treatment
After thrombolysis, conventional antiangiural drugs, such as nitrates and calcium antagonists, were administered. Ten patients were pretreated with β-adrenergic blockers (atenolol 50 mg/d), and this therapy was not withdrawn. Twenty-four hours after thrombolysis, aspirin 250 mg/d and ticlopidine 250 mg BID were given, and the dilation procedure was performed when fibrinogen had returned to the lower level of normal values.

Coronary Angiography
Coronary angiography was performed 24 hours after the onset of pain to check coronary artery patency and to look for the presence of significant flow-limiting lesions requiring angioplasty. The angiographic images were acquired with a Philips-Integris H 3000 single-plane system at a cine rate of 25 frames/s. Meglumine ioxaglate (64 g iodine/200 mL) was used as a nonionic contrast medium. Vessel diameters were measured by quantitative coronary angiography (QCA Artrek), as previously reported. Three diameters were considered along the IRA vessel (stenosis, next to lesion normal reference, and distal level) and 1 at a distal level of the non-IRA. In 25 patients, the IRA was the left anterior descending coronary artery (LAD), in 5 the right coronary artery (RCA), and in 10 the left circumflex coronary artery (LCx).

Coronary Dilation Procedure
At the beginning of the dilation procedure, patients received neuroleptic analgesia with droperidol 2 to 10 mg IV and phenoperidine 0.6 mg IV. The doses were adjusted during the study to keep the patient sedated. After the baseline LV function measurement had been acquired, the NO donor isosorbide dinitrate 1.5 mg was given by intracoronary (IC) injection to evaluate the diameter of the dilated normal reference vessel and to match the final stent diameter with that of a dilated reference vessel accordingly. Heparin 100 IU/kg was given intravenously as anticoagulation.

All patients gave written informed consent to the following study, which had previously been approved by the Ethical Committee of the Clinique Pasteur.

Two or 3 balloon inflations of 3 minutes each followed by 2 minutes of reperfusion were performed to predilate the artery before either a Palmaz-Schatz, a GT-Roubin II, or a Wallstent was inserted, or 2 of them. The type of stent was chosen to make the size, struts, and flexibility of the stent match the anatomy of the lesion (stenosis, 78±5%; mean±SD) and reconstruct the proper shape of the vessel. The stents were deployed with a 20-second balloon inflation followed by repeated high-pressure inflations (18 to 22 atm for 30 to 40 seconds).

TIMI Frame Count Assessment
The TIMI flow grading classifies successful reperfusion, but although it is largely accepted, it lacks precision, being a visual, subjective method. Accordingly, to obtain quantitative indices of blood flow velocity, we assessed TIMI flow by the corrected frame-counting method recently suggested by Gibson et al. Briefly, the number of cine frames required for the contrast material to reach a given distal level of the IRA or of a non-IRA was calculated by means of the cine-frame counter of a Tagaro 35-AX cine viewer. The number of frames was subsequently multiplied by 30 and divided by 25 frames to report a cine-frame count in accordance with standard methods. During the dilation procedure, the cine-frame count was assessed only in the IRA, and a non-IRA was used as control. Anatomic distal landmarks were used for TIMI frame count, and in the case of the LAD, the number of frames was divided by 1.7 to obtain the “corrected” TIMI frame count.

LV Function
LV function was continuously monitored by means of transesophageal echocardiography (TEE) (SONOS 2500, Hewlett Packard Co). With the patient already sedated, the probe was introduced to acquire a short-axis view of the LV at the level of the papillary muscles. The images were stored on an SVHS Panasonic videotape recorder and subsequently analyzed by a Freeland-TomTec Imaging System to obtain quantitative data. LV images, selected in each specific phase of the study, were digitized and stored in the TomTec Imaging System. Starting 40 ms after the ECG R wave, 8 frames through a single cardiac cycle were automatically captured. The frames with maximal and minimal LV area were selected, and the end-diastolic and end-systolic endocardial borders were manually traced. Global and regional LV function were automatically calculated as percent fractional area changes (FAC%) and systolic wall thickening (%Th), according to the following formulas:

\[
\text{FAC} \% = \frac{\text{LV end-diastolic area} - \text{LV end-systolic area}}{\text{LV end-diastolic area}} \times 100;
\]

\[
\text{Th} \% = \frac{\text{end-systolic wall thickness} - \text{end-diastolic wall thickness}}{\text{end-diastolic wall thickness}} \times 100.
\]

For regional LV analysis, the short-axis view was divided into 4 quadrants corresponding to the posterior wall (RCA-supplied region), the lateral wall (LCx-supplied region), the anterior wall (LAD-supplied region), and the midseptum (LAD-supplied region or RCA-supplied region in case of a dominant RCA). In the final evaluation, LV regions were also defined as IRA and non-IRA, depending on the location of the MI. Fractional area changes and systolic wall thickening were calculated in (1) the basal condition (before PTCA); (2) soon after coronary stenting (after stent); (3) 15 minutes after coronary stenting (15 minutes after stent), ie, at the time when LV dysfunction was observed; and (4) 5 minutes after pharmacological interventions (drugs) or up to 15 minutes after saline administration, respectively. All indices of LV function were measured by 1 observer (G.B.A.), and in 15 subjects they were remeasured also by a second observer (M.K.). Intraobserver variability for fractional area changes and systolic wall thickening were 4.2±2.1% and 4.4±3.0%, respectively. A plot of the difference between the 2 observers in each measurement against the mean of the 2 measurements showed a mean difference of 0.14±2.63% and −0.25±2.55%, respectively.
TEE Coronary Blood Flow Velocity

After introduction of the TEE into the esophagus, the proximal part of the LAD was visualized just above the semilunar aortic valves. The sample volume of pulsed Doppler was placed into the proximal third of the LAD or above the LAD stenosis, and the spectral Doppler signal of coronary flow was obtained. The angle between the ultrasound beam and the direction of the LAD was maintained as close to 0° as possible and never exceeded 30°. A two-dimensional image showing the position of Doppler sample volume in the LAD was stored in the cine-loop memory and was repeatedly retrieved during the study to ensure that the coronary flow velocity was always measured at the same level. The flow velocity in the LAD was measured in the following stages: (1) before PTCA, (2) soon after coronary stenting, (3) 15 minutes after coronary stenting, and (4) after the different drugs or saline administration, with the aim of acquiring the peak effect of the drugs on coronary flow velocity. For the purpose of the study, the average instantaneous spectral peak velocities during diastole (ADV) are reported at different steps of the study, rather than maximal diastolic velocity, because ADV corresponds better to volume flow rate. The reproducibility and validity of this method compared with the intracoronary flow wire were tested in previous studies. Reported values of flow velocity represent an average of 5 cardiac cycles. Because with TEE, Doppler flow velocity can be reliably monitored in the LAD artery only, measured ADVs express the flow velocity in non-IRA vessels in the case of the IRA being the LCx or RCA. Because the trend of the flow changes at different stages of the study was similar in the IRA and non-IRA vessels, the ADV values in Table 1 represent the flow velocity in both the IRA and non-IRA vessels.

**Pharmacological Interventions**

Fifteen minutes after coronary stenting and after LV dysfunction had been documented, 10 patients received phentolamine 12 mg/kg IC (nonselective α-adrenergic blocker, Regitin, 10-mg vials, Novartis). Ten other patients were given urapidil 600 mg/kg IV (from 36 to 46 mg IV) (α1-selective blocker, Ebrantil, 50-mg vials, Byk Gulden).

### TABLE 1. TIMI Frame Count and ADV

<table>
<thead>
<tr>
<th>Time</th>
<th>IRA (n=10)</th>
<th>Non-IRA (n=10)</th>
<th>ADV (n=10)</th>
<th>IRA (n=8)</th>
<th>Non-IRA (n=7)</th>
<th>ADV (n=10)</th>
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</thead>
<tbody>
<tr>
<td>24 h after thrombolysis</td>
<td>51.6±15</td>
<td>60.4±20</td>
<td>30±15</td>
<td>49.6±13</td>
<td>42.7±14</td>
<td>48.7±29</td>
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<tr>
<td>72 h after thrombolysis</td>
<td>41.5±16</td>
<td>43.9±6</td>
<td>39±10</td>
<td>37.7±12</td>
<td>35.9±9</td>
<td>38.2±20</td>
</tr>
<tr>
<td>Soon after stenting</td>
<td>25.2±16</td>
<td>27.6±2</td>
<td>22.8±8</td>
<td>25.5±6</td>
<td>20.7±6</td>
<td>23.7±10</td>
</tr>
<tr>
<td>15 min after stenting</td>
<td>45.8±20</td>
<td>50.0±12</td>
<td>31.8±7</td>
<td>38.1±10</td>
<td>39.5±11</td>
<td>30.9±4</td>
</tr>
<tr>
<td>5 min after drug</td>
<td>16.3±6</td>
<td>18.6±4</td>
<td>47.1±11</td>
<td>28.8±13</td>
<td>31.5±10</td>
<td>36.1±3</td>
</tr>
</tbody>
</table>

Corrected TIMI frame count (mean±SD) measured in IRA and non-IRA. ADV obtained by TEE.

*P<0.05 between times.
†P<0.05 72 h vs 24 h after thrombolysis.

### TABLE 2. Diastolic and Systolic Wall Thickness; % Systolic Thickening

<table>
<thead>
<tr>
<th>Time and Region</th>
<th>Phenolamine 12 μg/kg IC</th>
<th>Oral β-Blockade+Urapidil 10 mg IC</th>
<th>Urapidil 600 μg/kg IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before PTCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRA</td>
<td>0.73±0.1±1</td>
<td>0.93±0.3±2</td>
<td>0.91±0.1±1</td>
</tr>
<tr>
<td>Non-IRA</td>
<td>0.86±0.2±2</td>
<td>1.20±0.3±3</td>
<td>0.96±0.1±1</td>
</tr>
<tr>
<td>Soon after stent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRA</td>
<td>0.74±0.1±1</td>
<td>1.00±0.3±2</td>
<td>0.92±0.1±1</td>
</tr>
<tr>
<td>Non-IRA</td>
<td>0.91±0.2±2</td>
<td>1.35±0.3±3</td>
<td>0.99±0.1±1</td>
</tr>
<tr>
<td>15 min after stent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRA</td>
<td>0.69±0.1±1</td>
<td>0.82±0.2±2</td>
<td>0.92±0.1±1</td>
</tr>
<tr>
<td>Non-IRA</td>
<td>0.82±0.1±1</td>
<td>1.07±0.2±2</td>
<td>0.91±0.1±1</td>
</tr>
<tr>
<td>5 min after drug</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRA</td>
<td>0.76±0.1±1</td>
<td>1.05±0.2±3</td>
<td>0.95±0.1±1</td>
</tr>
<tr>
<td>Non-IRA</td>
<td>0.91±0.1±1</td>
<td>1.35±0.2±3</td>
<td>0.93±0.1±1</td>
</tr>
</tbody>
</table>

Diastolic and systolic wall thickness (DWT, SWT) and percent systolic thickening (%Th) (mean±SD) measured in IRA-dependent and non–IRA-dependent myocardium.

*P<0.05 between-within times and IRA or non-IRA.
As an α₁-blocker, we chose urapidil because this drug induces a central serotoninergic activation, which may be responsible for the lack of pronounced reflex tachycardia, despite the pronounced vasodilation. Ten other patients had an ongoing chronic β-blocking treatment (atenolol 50 mg/d) that was not discontinued and received urapidil 10 mg IC. In 10 patients who served as controls, 5 mL warm saline was injected IC. The short-axis TEE view of the LV was monitored for an additional 15 minutes to assess the effects of the different pharmacological interventions. Only 1 investigator (L.G.) was aware of the drug administration. Both the interventional cardiologists and echocardiographers who performed the study and evaluated the results were blinded to drug administration.

**Statistical Analysis**

The results are expressed as mean±SD. One-way or 2-way ANOVA for repeated measures was performed with the commercially available package SPSS version 6.1, SPSS Inc, as appropriate. To assess statistical significance between groups, Scheffe F tests were applied, and a value of P<0.05 was considered significant. Agreement between the 2 readings performed by 2 observers was evaluated by the presence of chronic β-blockade. The changes in wall thickening in the urapidil and the saline groups and the estimating the consistent bias between readings, as recommended by Bland and Altman.²⁸

**Results**

Twenty-four hours after thrombolysis, the IRA was patent in all patients, although a 77.5±5% coronary stenosis was present.

**TIMI Frame Count**

Corrected TIMI frame count is shown in Table 1. Twenty-four hours after thrombolysis, the TIMI frame count was slowed compared with normal values,²¹ to 47.9±15 and 50.2±25 in the IRA and non-IRA, respectively. Seventy-two hours after thrombolysis, the frame count decreased to 38.5±11 and 39.6±11 frames, respectively. Also in this condition, the flow was similarly slowed in both the IRA and non-IRA. Coronary dilation further decreased the frame count to 23.0±10 and to 25.3±7, respectively, whereas 15 minutes after coronary stenting, the frame counts returned to the values observed before dilation (39.1±13 and 41.1±14 in the IRA and non-IRA, respectively. The α-nonselective and the α₁-selective adrenergic blockade reduced the IRA frame count to 16.3±6 and 16.9±5, respectively, and to 18.6±4 and 18.9±6 in the non-IRA, respectively. In patients treated with β-blockers and receiving IC urapidil, the frame count decreased less than in patients receiving only α-blockers. No changes were observed in patients receiving saline.

**Average Diastolic Flow Velocity**

ADV data are reported in Table 1. The ADV measurements showed the same trend as the TIMI frame count. In fact, 15 minutes after stent implantation, a significant decrease in diastolic flow velocity occurred compared with soon after coronary dilation (from a mean value of 38.0±7 to 29.9±6 cm/s). Selective and nonselective α-adrenergic blockade increased the ADV significantly, to 47.1±11 and 42.8±10 cm/s, respectively, whereas in patients chronically treated with β-blockers, the increase in flow velocity was less pronounced (from 30.9±4 to 36.1±3 cm/s) than after α-blockers alone.

**Effect of Coronary Stenting and Drugs on LV Function**

The effects of the procedure and of drug administration on LV function are shown in Tables 2 and 3 and in Figures 1 and 2. Before angioplasty, the systolic thickening was 26.6±15% and 39.8±15% (Table 2, mean of all patients) in IRA-dependent and non–IRA-dependent myocardium, respectively. Coronary stenting briefly improved thickening in IRA-dependent myocardium (to 37.5±16%, P<0.05). Fifteen minutes later, systolic thickening worsened to 19.0±14% and 27.6±14% in IRA and non-IRA myocardium, respectively (P>0.05). The administration of phentolamine and urapidil significantly improved thickening, to 36.0±17% and 41.4±14% in IRA-dependent and to 48.3±11% and 48.5±17% in non–IRA-dependent myocardium, respectively (Table 2). The effects of α-adrenergic blockers were attenuated by the presence of chronic β-blockade. The changes in wall thickening in the urapidil and the saline groups and the

### Table 1. Continued

<table>
<thead>
<tr>
<th></th>
<th>IRA (n=40)</th>
<th>Non-IRA (n=35)</th>
<th>AVD (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Values Before Drugs</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td><strong>DVT</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
</tr>
<tr>
<td>IRA 5 mL IC</td>
<td>0.8±0.1</td>
<td>1.09±0.2</td>
<td>27.1±14</td>
</tr>
<tr>
<td>Non-IRA 5 mL IC</td>
<td>0.97±0.1</td>
<td>1.39±0.1</td>
<td>42.3±7</td>
</tr>
<tr>
<td>AVD</td>
<td>0.86±0.1</td>
<td>1.20±0.2</td>
<td>39.2±16</td>
</tr>
<tr>
<td>IRA 5 mL IC</td>
<td>1.01±0.1</td>
<td>1.44±0.1</td>
<td>44.1±12</td>
</tr>
<tr>
<td>Non-IRA 5 mL IC</td>
<td>0.76±0.1</td>
<td>0.95±0.2</td>
<td>24.0±9</td>
</tr>
<tr>
<td>AVD</td>
<td>0.93±0.1</td>
<td>1.19±0.1</td>
<td>28.3±5</td>
</tr>
<tr>
<td>IRA 5 mL IC</td>
<td>0.75±0.1</td>
<td>0.97±0.2</td>
<td>22.0±9</td>
</tr>
<tr>
<td>Non-IRA 5 mL IC</td>
<td>0.92±0.1</td>
<td>1.15±0.1</td>
<td>25.3±7</td>
</tr>
<tr>
<td>AVD</td>
<td>0.83±0.1</td>
<td>1.09±0.2</td>
<td>27.1±14</td>
</tr>
</tbody>
</table>
simultaneous TIMI flow count calculated as % changes are clearly shown in Figure 1.

In all patients, coronary dilation significantly increased fractional area change (Table 3 and Figure 2), whereas in patients treated with β-blockers, a smaller improvement was observed (38.4±7% to 41.4±6%). Global LV function progressively worsened after stent implantation, reaching a nadir 15 minutes later, as indicated by a decrease in fractional area changes from 40.1±9% to 27.1±10% (P<0.05). No changes were seen after saline.

**Typical Example**

Figure 3 shows the digitized short-axis-view printouts, fractional area change, and corresponding angiograms of a patient with a non–Q-wave AMI. Urapidil 34 mg IV counteracted the diffuse vasoconstriction and diffuse LV dysfunction present 15 minutes after coronary stenting.

### Coronary Diameters and Hemodynamic Effects of the Drugs

Coronary diameter changes were in line with the other measurements (Table 4). The injection of α-blockers transiently (1 to 3 minutes) reduced mean arterial pressure by ~10 mm Hg (P<0.05), but at the time of functional measurements, arterial pressure had returned to control values. No change in heart rate was observed in our sedated patients during the procedure.

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**TABLE 3. Fractional Area Change (%)**

<table>
<thead>
<tr>
<th></th>
<th>Phentolamine 12 µg/kg IC</th>
<th>Oral β-Blockade + Urapidil 10 mg IC</th>
<th>Urapidil 600 µg/kg IV</th>
<th>Saline 5 mL IC</th>
<th>Before-Drugs Mean Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before PTCA</td>
<td>30.2±12</td>
<td>38.4±7</td>
<td>38.4±6</td>
<td>33.2±11</td>
<td>34.9±10</td>
</tr>
<tr>
<td>Soon after stent</td>
<td>35.4±10</td>
<td>41.4±6</td>
<td>44.1±7</td>
<td>39.4±12</td>
<td>40.1±9</td>
</tr>
<tr>
<td>15 min after stent</td>
<td>22.9±8</td>
<td>27.9±8</td>
<td>31.9±11</td>
<td>25.5±12</td>
<td>27.1±10</td>
</tr>
<tr>
<td>5 min after drug</td>
<td>39.3±7</td>
<td>39.0±8</td>
<td>48.4±9</td>
<td>29.8±19</td>
<td></td>
</tr>
</tbody>
</table>

Fractional area changes (mean±SD) quantified by means of the TomTec Imaging System and by drawing in short-axis view the diastolic and systolic endocardial contours.

*P<0.05 vs times.

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**Figure 1.** Percent TIMI frame count changes (±SD) calculated vs 72 hours after thrombolysis (TIMI), ie, before coronary dilation, in both IRA (open bars) and non-IRA (shaded bars). Conditions soon after stent, 15 minutes after stent, and after urapidil or saline treatment are shown. Percent systolic wall thickening measured in IRA-dependent and non–IRA-dependent myocardium is represented in lower panels. No significant differences were observed in TIMI frame count between IRA and non-IRA. Urapidil significantly decreased TIMI frame count in both IRA and non-IRA and improved % thickening, whereas no changes were induced by saline injection. *P<0.05 vs 72 hours TIMI. †P<0.05 between IRA and non-IRA.
Discussion

This study shows that α-adrenergic blockade normalizes TIMI flow and attenuates coronary constriction and LV dysfunction, which occur in patients treated with thrombolysis and IRA stenting. After successful thrombolysis, a significant flow-limiting coronary lesion was evident in all patients, a lesion that, together with the ≤90 minutes of severe ischemia, had reduced contractile function. The profound reduction in antegrade epicardial coronary flow and the sustained LV dysfunction recovered simultaneously after coronary dilation. Several mechanisms may have contributed to the observed improvement in contractile function. Removal of the flow-limiting stenosis per se and an additional flow-mediated, endothelium-dependent attenuation of coronary vasomotor tone, in particular sympathetic vasomotor tone,29,30 may have initially improved microcirculatory perfusion and consequently, contractile function. The improvement in contractile function after reperfusion was short-lasting, because 15 minutes later, a reduced TIMI frame count rate and a diffuse reduction in LV systolic thickening occurred. We have previously observed such a delayed occurrence of LV dysfunction after coronary artery stretch and transient ischemia induced by coronary stenting in patients with no history of MI.19

A no-reflow or slow-flow phenomenon is thought to be due to microvascular constriction31–33 and is reported to occur not only after thrombolysis4–7 but also as a sequela of angioplasty.31–33 In a previous study,18 we showed that the increase in coronary vascular resistance occurring 30 minutes after conventional angioplasty is counteracted by the injection of phenolamine 16 μg/kg IC. Such reduction of coronary vascular resistance by selective α₁-adrenergic blockers was described previously in normal subjects34 and in patients with stable angina.35

In the present study, we investigated LV function with TEE, which in humans provides an adequate measure of regional and global myocardial function.19,22 In fact, the short-axis view permits the simultaneous investigation of IRA-related and non–IRA-related systolic thickening. Our observation is in agreement with the data obtained by magnetic resonance myocardial tagging in patients 5 days after an AMI,36 demonstrating that even remote noninfarcted regions had reduced intramyocardial shortening. In our patients treated with thrombolysis after an AMI, 2 indirect indices of perfusion were measured: TIMI frame count21 and TEE ADV.24,25 Both of these techniques, although indirect and semiquantitative compared with the intracoronary Doppler guide wire,37 are used extensively in trials38,39 and have been validated.25,37 In our study, a slow TIMI flow was observed both in the IRA and in the non-IRA. This observation is in agreement with recent reports by other investigators.38,39

Emphasis is usually put on a local rather than diffuse decrease in coronary blood flow velocity, because only the regions subtended by the IRA are assumed to be involved in the ischemic process. In fact, in animals, when a coronary

Figure 2. Mean (±SD) percent fractional area changes obtained by TomTec Imaging System. Phe indicates phentolamine; β+Ura, chronic α-blocker treatment combined with urapidil (Ura 10 mg ic). Fifteen minutes after coronary stenting, a reduction in fractional area changes (FAC) occurred in all patients. Phenolamine and urapidil significantly increased FAC 5 minutes after injection. In case of combined β- and α-blockade, FAC did not increase compared with pre-PTCA values, but it increased compared with 15 minutes After Stent, when LV dysfunction occurred.
artery is occluded by a snare, myocardial shortening increases in nonischemic regions, and accordingly, a compensatory vasodilation occurs in the surrounding, normally supplied territories. In our patients, non-IRA vessels also were involved in the slow-flow phenomenon, indicating microvascular disturbances in apparently unaffected vessels as well and suggesting diffuse atherosclerosis.

In our study, the observed angiographic, hemodynamic, and functional responses to coronary stretch and additional transient ischemia presented as intimately linked, ie, epicardial and microvascular constriction, and LV dysfunction occurred simultaneously. The persistence of a residual obstruction to flow at the level of the dilated vessel was demonstrated to reduce the ratio of proximal to distal coronary flow velocity and is thought to contribute to the lack or small magnitude of coronary flow normalization after balloon dilation. In our patients, no residual stenosis was quantified inside the stent, and a progressive stent diameter improvement was observed at 15 minutes in the case of self-expandable Wallstent implantation. Accordingly, the presence of the slow flow most likely reflects diffuse microvascular dysfunction.

Coronary stretch and ischemia are known to reflexly increase the cardiac sympathetic nerve activity by the stimulation of cardiac ventricular and coronary receptors.

An intense α-adrenergic vasoconstriction can result and then reduce myocardial perfusion and consequently ventricular function. This hypothesis is in agreement with the observed increase in coronary resistance after angioplasty. No changes in heart rate or in blood pressure were observed during the study in our sedated patients. Also, in experimental animal studies, reflex sympathetic excitation can occur by a local cardiocardiac reflex with increased sympathetic vasoconstriction but in the absence of heart rate and arterial pressure changes.

The release of a vasoactive substance, such as serotonin, by activated platelets might have added to vasoconstriction.

In our patients pretreated with calcium antagonists and with the combination of ticlopidine and aspirin, which decreases intracoronary serotonin release, serotonin probably played a minor role. In addition, platelets possess mainly α2-adrenergic receptors, whereas the effects on vasomotor tone and on LV function were also present after the injection of the selective α1-adrenergic antagonist urapidil.

The observation of a diffuse reduction in LV function suggests the involvement of neural trigger mechanisms, and in particular, the presence of cardiocardiac sympathetic reflexes, with resulting aortic arch and microvascular constriction, and LV dysfunction. The administration of α-adrenergic blockers counteracted the vasoconstriction, the slow TIMI flow present in IRA- and non-IRA–supplied myocardium, and the resulting LV dysfunction. In patients with an ongoing chronic β-blocking treatment, the injection of urapidil in low doses did not completely counteract LV dysfunction, possibly indicating the presence of an effective β-adrenergic blockade.

The observation that the decrease in systolic thickening induced by transient coronary occlusion was less evident in patients pretreated with β-adrenergic blockers than in patients receiving other treatment is in line with the observation obtained in animals by Theroux et al.

Merely “getting the artery open mechanically” by removing the flow-limiting stenosis apparently does not preclude the occurrence of a persistent increase in α-adrenergic vasoconstrictor tone, which reduces cardiac function and impairs blood flow at the epicardial and microvascular levels. This observation is in contrast with the widely held opinion that coronary stenting may completely reduce poor distal runoff.

Conclusions

In patients with MI treated with thrombolytic, coronary stenting may salvage reversibly impaired myocardium. The presence of diffuse LV dysfunction, together with the diffuse, α-adrenergic macrovascular and microvascular vasoconstriction, suggests that neural mechanisms supervise and modulate other local phenomena. The administration of α-adrenergic blockers might be beneficial in improving reversible postischemic LV dysfunction.

Acknowledgments

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TABLE 4. Effects of Procedure and Drugs on Coronary Diameters

<table>
<thead>
<tr>
<th></th>
<th>Before-PTCA Diameter, mm</th>
<th>Percent Stenosis</th>
<th>Diameter Soon After Stent, mm</th>
<th>Diameter 15 min after stent, mm</th>
<th>Percent Change</th>
<th>Drug</th>
<th>Drug Effect, mm</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRA, normal reference</td>
<td>3.49±0.8</td>
<td>-</td>
<td>3.44±0.6</td>
<td>2.91±0.3</td>
<td>-13.9±11*</td>
<td>Phentolamine 12 µg/kg IC</td>
<td>3.87±0.8*</td>
<td>+11.6±5*</td>
</tr>
<tr>
<td>IRA, stenosis level</td>
<td>0.76±0.3</td>
<td>78.8±4</td>
<td>3.48±0.5*</td>
<td>3.50±0.5*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRA, distal level</td>
<td>1.86±0.4</td>
<td>-</td>
<td>1.90±0.5</td>
<td>1.55±0.4</td>
<td>-16.4±6*</td>
<td>Saline 5 mL IC</td>
<td>2.19±0.3</td>
<td>+19.2±10*</td>
</tr>
<tr>
<td>Control vessel, distal level</td>
<td>1.90±0.4</td>
<td>-</td>
<td>1.90±0.4</td>
<td>1.55±0.3</td>
<td>-18.4±4*</td>
<td></td>
<td>2.20±0.3</td>
<td>+18.2±11*</td>
</tr>
<tr>
<td>IRA, normal reference</td>
<td>3.55±0.8</td>
<td>-</td>
<td>3.53±0.9</td>
<td>3.30±0.7</td>
<td>-7.1±6</td>
<td>Chronic β-blockade, urapidil 10 mcg IV</td>
<td>3.60±0.5</td>
<td>+2.0±10</td>
</tr>
<tr>
<td>IRA, stenosis level</td>
<td>0.71±0.2</td>
<td>79.7±5</td>
<td>3.45±0.9*</td>
<td>3.37±0.8*</td>
<td></td>
<td></td>
<td>3.38±0.8</td>
<td></td>
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<tr>
<td>IRA, distal level</td>
<td>2.51±0.7</td>
<td>-</td>
<td>2.45±0.7</td>
<td>2.25±0.6</td>
<td>-10.4±1*</td>
<td></td>
<td>2.62±0.6</td>
<td>+4.2±10</td>
</tr>
<tr>
<td>Control vessel, distal level</td>
<td>2.40±0.6</td>
<td>-</td>
<td>2.36±0.5</td>
<td>2.27±0.7</td>
<td>-5.4±5</td>
<td></td>
<td>2.57±0.8</td>
<td>+7.1±11</td>
</tr>
<tr>
<td>IRA, normal reference</td>
<td>3.15±0.5</td>
<td>-</td>
<td>3.05±0.3*</td>
<td>2.65±0.5*</td>
<td>-15.8±9*</td>
<td>Saline 600 µg/kg IV</td>
<td>3.48±0.6*</td>
<td>+10.6±8*</td>
</tr>
<tr>
<td>IRA, stenosis level</td>
<td>0.80±0.2</td>
<td>73.7±4</td>
<td>3.01±0.5*</td>
<td>3.01±0.5*</td>
<td></td>
<td></td>
<td>3.10±0.5</td>
<td></td>
</tr>
<tr>
<td>IRA, distal level</td>
<td>1.96±0.5</td>
<td>-</td>
<td>1.88±0.6</td>
<td>1.51±0.5*</td>
<td>-23.7±10*</td>
<td></td>
<td>2.42±0.7*</td>
<td>+23.5±12*</td>
</tr>
<tr>
<td>Control vessel, distal level</td>
<td>1.73±0.2</td>
<td>-</td>
<td>1.67±0.2</td>
<td>1.38±0.1*</td>
<td>-20.2±6*</td>
<td></td>
<td>2.03±0.2</td>
<td>+17.3±9*</td>
</tr>
<tr>
<td>IRA, normal reference</td>
<td>3.59±0.7</td>
<td>-</td>
<td>3.50±0.6</td>
<td>2.99±0.8</td>
<td>-16.7±6*</td>
<td></td>
<td>2.67±0.4*</td>
<td>-25.5±10*</td>
</tr>
<tr>
<td>IRA, stenosis level</td>
<td>0.85±0.2</td>
<td>75.0±7</td>
<td>3.40±0.6*</td>
<td>3.34±0.4*</td>
<td></td>
<td></td>
<td>3.34±0.4</td>
<td></td>
</tr>
<tr>
<td>IRA, distal level</td>
<td>2.73±0.9</td>
<td>-</td>
<td>2.53±0.7</td>
<td>2.16±0.7</td>
<td>-20.9±9*</td>
<td></td>
<td>2.16±0.7</td>
<td>-20.9±8*</td>
</tr>
<tr>
<td>Control vessel, distal level</td>
<td>2.28±0.9</td>
<td>-</td>
<td>2.20±0.9</td>
<td>1.82±0.8*</td>
<td>-20.2±4*</td>
<td></td>
<td>1.80±0.8</td>
<td>-21.6±3*</td>
</tr>
</tbody>
</table>

Coronary diameters (mean± SD) obtained by quantitative angiography (QCA Artrek) in basal conditions (before PTCA), soon after stenting, 15 min after stenting, and at the time of the maximal effect of the drugs.

*P<0.05 vs before-PTCA diameter.

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LV Dysfunction After Thrombolysis and Stenting


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