Postischemic Left Ventricular Dysfunction Is Abolished by Alpha-Adrenergic Blocking Agents

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Objectives. We sought to evaluate the efficacy of alpha-adrenergic blocking agents in counteracting left ventricular (LV) dysfunction occurring after transient ischemia in humans.

Background. The mechanisms underlying postischemic LV dysfunction are largely unknown.

Methods. Percutaneous transluminal coronary angioplasty (PTCA) provides a clinical model of ischemia and reperfusion. In 50 patients undergoing coronary stenting for 77 ± 5% stenosis, LV function was monitored by transesophageal echocardiography during and 30-min after PTCA. Fifteen minutes after stenting, 15 patients received 12 μg/kg body weight of the alpha-blocker phentolamine and urapidil increased global LV shortening from 34 ± 9% to 45 ± 8% and to 49 ± 8%, respectively (p < 0.05). After the administration of propranolol combined with phentolamine, LV dysfunction remained unchanged (34 ± 6%), as in control subjects.

Conclusions. LV dysfunction occurs after PTCA, as described in animal models after ischemia. Alpha-blockers abolished LV, macrocirculatory and microcirculatory dysfunction, whereas the alpha-blocker effect was prevented by combining alpha- and beta-blockers. The evidence of diffuse rather than regional dysfunction, together with the opposite effects of alpha- and beta-blockade, supports the hypothesis of neural mechanisms eliciting postischemic LV dysfunction.

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In 1935 brief periods of myocardial ischemia in open chest dogs (1) were reported to impair systolic shortening. In 1975 Heyndrickx et al. (2) described, in conscious dogs, that brief periods of myocardial ischemia, too brief to cause necrosis, were followed by a long-lasting impairment of contractile function and of regional blood flow (3), a phenomenon that was later called myocardial “stunning” (4). In humans percutaneous transluminal coronary angioplasty (PTCA), clinically accompanied by an increase in coronary resistance and diffuse vasoconstriction. Alpha-blockers counteracted LV dysfunction and coronary resistance and the increase in vasoconstriction. Phentolamine and urapidil increased global LV shortening from 34 ± 9% to 45 ± 8% and to 49 ± 8%, respectively (p < 0.05). After the administration of propranolol combined with phentolamine, LV dysfunction remained unchanged (34 ± 6%), as in control subjects.

Conclusions. LV dysfunction occurs after PTCA, as described in animal models after ischemia. Alpha-blockers abolished LV, macrocirculatory and microcirculatory dysfunction, whereas the alpha-blocker effect was prevented by combining alpha- and beta-blockers. The evidence of diffuse rather than regional dysfunction, together with the opposite effects of alpha- and beta-blockade, supports the hypothesis of neural mechanisms eliciting postischemic LV dysfunction.

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hypothesis that, in humans, transient myocardial ischemia, as induced by PTCA, is followed by LV dysfunction. As an additional goal we assessed whether counteracting post-PTCA reflex coronary artery constriction and the simultaneous increase in coronary vascular resistance by means of alpha-blockers (10), thus allowing for a fuller restoration of flow, might prove beneficial to LV performance (2,3).

Table 1. Effects of Procedure and Drugs on Coronary Diameters

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>No. of Pts</th>
<th>Pre-PTCA Diameter (mm)</th>
<th>Percent Stenosis</th>
<th>Diameter Soon After Stenting (mm)</th>
<th>Diameter 15 min After Stenting (mm)</th>
<th>Percent Change</th>
<th>Drug Effect (mm)</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentolamine, 12 μg/kg ic</td>
<td>15</td>
<td>3.19 ± 0.6</td>
<td>—</td>
<td>3.23 ± 0.5</td>
<td>2.73 ± 0.4*</td>
<td>−13 ± 9*</td>
<td>3.56 ± 0.6*</td>
<td>12 ± 7*</td>
</tr>
<tr>
<td>PTCA vessel, normal reference</td>
<td>15</td>
<td>0.65 ± 0.2</td>
<td>80 ± 4%</td>
<td>3.27 ± 0.5*</td>
<td>3.14 ± 0.6*</td>
<td>—</td>
<td>3.36 ± 0.5*</td>
<td>—</td>
</tr>
<tr>
<td>PTCA vessel, distal level</td>
<td>15</td>
<td>1.80 ± 0.5</td>
<td>—</td>
<td>1.88 ± 0.4</td>
<td>1.45 ± 0.4*</td>
<td>−19 ± 6*</td>
<td>2.17 ± 0.3*</td>
<td>21 ± 8*</td>
</tr>
<tr>
<td>Control vessel, distal level</td>
<td>12</td>
<td>1.92 ± 0.4</td>
<td>—</td>
<td>1.94 ± 0.4</td>
<td>1.52 ± 0.3*</td>
<td>−21 ± 6*</td>
<td>2.20 ± 0.3*</td>
<td>15 ± 6*</td>
</tr>
<tr>
<td>Propranolol, 1.2 mg ic, plus phentolamine, 12 μg/kg ic</td>
<td>10</td>
<td>3.36 ± 0.9</td>
<td>—</td>
<td>3.31 ± 0.9</td>
<td>2.80 ± 0.7*</td>
<td>−17 ± 4*</td>
<td>2.92 ± 0.5*</td>
<td>−11 ± 11*</td>
</tr>
<tr>
<td>PTCA vessel, normal reference</td>
<td>10</td>
<td>0.73 ± 0.2</td>
<td>78 ± 6%</td>
<td>3.22 ± 0.9*</td>
<td>3.18 ± 0.8*</td>
<td>—</td>
<td>3.18 ± 0.8*</td>
<td>—</td>
</tr>
<tr>
<td>PTCA vessel, distal level</td>
<td>10</td>
<td>2.34 ± 0.8</td>
<td>—</td>
<td>2.21 ± 0.7</td>
<td>1.94 ± 0.6*</td>
<td>−12 ± 4*</td>
<td>1.84 ± 0.6*</td>
<td>−21 ± 9*</td>
</tr>
<tr>
<td>Control vessel, distal level</td>
<td>9</td>
<td>2.18 ± 0.7</td>
<td>—</td>
<td>1.96 ± 0.5</td>
<td>1.74 ± 0.6*</td>
<td>−20 ± 6*</td>
<td>1.69 ± 0.6*</td>
<td>−23 ± 10*</td>
</tr>
<tr>
<td>Urapidil, 600 μg/kg iv</td>
<td>15</td>
<td>2.99 ± 0.5</td>
<td>—</td>
<td>2.94 ± 0.4</td>
<td>2.54 ± 0.5*</td>
<td>−15 ± 9*</td>
<td>3.34 ± 0.4*</td>
<td>12 ± 10*</td>
</tr>
<tr>
<td>PTCA vessel, normal reference</td>
<td>15</td>
<td>0.74 ± 0.5</td>
<td>75 ± 4%</td>
<td>2.89 ± 0.4*</td>
<td>2.90 ± 0.4*</td>
<td>—</td>
<td>2.95 ± 0.4*</td>
<td>—</td>
</tr>
<tr>
<td>PTCA vessel, distal level</td>
<td>15</td>
<td>1.95 ± 0.4</td>
<td>—</td>
<td>1.89 ± 0.5</td>
<td>1.52 ± 0.4*</td>
<td>−23 ± 9*</td>
<td>2.34 ± 0.6*</td>
<td>20 ± 12*</td>
</tr>
<tr>
<td>Control vessel, distal level</td>
<td>8</td>
<td>1.67 ± 0.2</td>
<td>—</td>
<td>1.67 ± 0.2</td>
<td>1.42 ± 0.2*</td>
<td>−15 ± 7*</td>
<td>1.94 ± 0.2*</td>
<td>17 ± 9*</td>
</tr>
<tr>
<td>Saline, 5 ml ic</td>
<td>15</td>
<td>3.02 ± 0.4</td>
<td>—</td>
<td>2.99 ± 0.4</td>
<td>2.59 ± 0.4*</td>
<td>−14 ± 6*</td>
<td>2.47 ± 0.4*</td>
<td>−18 ± 8*</td>
</tr>
<tr>
<td>PTCA vessel, normal reference</td>
<td>15</td>
<td>0.78 ± 0.2</td>
<td>74 ± 6%</td>
<td>2.93 ± 0.4*</td>
<td>2.95 ± 0.4*</td>
<td>—</td>
<td>2.95 ± 0.4*</td>
<td>—</td>
</tr>
<tr>
<td>PTCA vessel, distal level</td>
<td>10</td>
<td>2.02 ± 0.3</td>
<td>—</td>
<td>1.95 ± 0.3</td>
<td>1.67 ± 0.2*</td>
<td>−15 ± 4*</td>
<td>1.64 ± 0.3*</td>
<td>−19 ± 6*</td>
</tr>
<tr>
<td>Control vessel, distal level</td>
<td>9</td>
<td>1.97 ± 0.6</td>
<td>—</td>
<td>1.94 ± 0.6</td>
<td>1.64 ± 0.5*</td>
<td>−17 ± 6*</td>
<td>1.64 ± 0.5*</td>
<td>−17 ± 6*</td>
</tr>
</tbody>
</table>

*p < 0.05 as compared with diameter before PTCA. Data presented are mean value ± SD or number of patients (Pts). Coronary diameter measurements were obtained by means of quantitative coronary angiography (Artrek) in the basal condition (before PTCA), soon after stenting, 15 min after stenting and at the time of the maximal effect of the drugs (10 min after urapidil and phentolamine, 15 min after the combination of phentolamine and propranolol or saline). A significant reduction in vessel diameter occurred 15 min after stenting, except inside the stent. The intrastent diameter increased somewhat with the Wallstent implantation. Phentolamine and urapidil induced a significant vasodilation, whereas the combined injection of propranolol and phentolamine or saline did not. ic = intracoronary; iv = intravenous; PTCA = percutaneous transluminal coronary angioplasty.

Methods

Patients. We studied 50 patients (9 women and 41 men, mean age 61 ± 11 years) undergoing coronary dilation followed by coronary stenting for 77 ± 5% (mean ± SD) epicardial vessel stenosis. Vessel diameters were measured by quantitative coronary angiography (Artrek) (17). Three diameters were prospectively chosen on the basal angiogram along the PTCA vessel (stenosis, normal reference and distal level) and one at the distal level of the control vessel (Table 1), following the schema previously reported by us as well as by other investigators (8–10). The same diameters were subsequently measured in the following conditions. Thirty patients had left anterior descending coronary artery (LAD) stenosis, and 12 had right coronary artery (RCA) and 8 had left circumflex lesions. All patients were admitted to the Clinique Pasteur for recurrent or unstable angina. All gave written, informed consent to the study, which had been approved by the Clinique Pasteur Ethical Committee.

Medical treatment. All patients were pretreated with conventional antianginal drugs such as nitrates, calcium antago-
nists (diltiazem, 180 to 360 mg/day) and antiplatelet drugs (aspirin, 250 mg/day for at least 7 days, and ticlopidine, 250 mg twice daily for the preceding 72 h). If it was part of the ongoing therapy, beta-blockers were withdrawn 72 h before the study. At the beginning of the dilation procedure patients received neuroleptic analgesia with droperidol (2 to 10 mg intravenously) and phenoperidine (0.6 to 1 mg intravenously) (10). The doses were adjusted during the study to keep the patient sedated. Heparin, 150 U/kg, was used for anticoagulation. Nitric oxide donors, linsidomine (1 mg) and isosorbide dinitrate (1.5 mg) were injected before balloon inflation to make the final stent expansion match, in diameter, with the lesion in a state of dilation. Nitric oxide donors were always administered after obtaining baseline coronary diameters and predilation LV function.

**Measurements of LV function.** Beginning 10 min before the dilation procedure and continuously throughout the study, up to 30 min after stent deployment, LV function was continuously monitored by means of transesophageal echocardiography (TEE) (18) using a 5.0-MHz multiplane probe (SONOS 2500, Hewlett Packard Co.). Before positioning the guiding catheter, with the patient already sedated, the TEE probe was introduced and a transgastric view of the left ventricle at the level of papillary muscles was obtained (short-axis view). The images were acquired on a SVHS Panasonic videotape recorder and subsequently analyzed by means of a Freeland-TomTec Imaging System with Integrated Cardiac Analysis Software, Version 5, to obtain quantitative analysis. Starting 40 ms after the electrocardiographic (ECG) R wave, eight frames through a single cardiac cycle were automatically selected and digitized. Afterward the frames with maximal and minimal LV area were selected and diastolic and end-systolic endocardial borders were manually traced. Global and regional LV function were automatically calculated as percent fractional area change (FAC) and percent systolic wall thickening (WTH), respectively, according to the following formulas:

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

\[
\text{WTH} (%) = \frac{\text{Systolic} - \text{Diastolic wall thickness}}{\text{Diastolic wall thickness}} \times 100.
\]

LV diastolic area was also used as an indirect index of preload (19).

For regional LV analysis, diastolic and systolic wall thicknesses and WTH were assessed from the short-axis view at 0, 3, 6 and 9 o’clock, with zero representing the posterior wall (RCA-supplied region), 3 the lateral wall (region supplied by left circumflex coronary artery), 6 the anterior wall (LAD-supplied region) and 9 the mid-septum (LAD-supplied region or RCA-supplied region in case of a dominant RCA). In the final evaluation, regions were also defined as PTCA and non-PTCA, depending on the vessel that underwent dilation.

FAC and WTH were calculated in 1) the basal condition (before PTCA); 2) soon after coronary stenting; 3) 15 min after coronary stenting (i.e., when coronary artery constriction has been described [8–10]); and 4) 5 to 15 min after pharmacologic intervention.

Intraobserver variability was assessed by having one observer (G.B.A.) remeasure FAC and WTH twice in 10 subjects at all phases of the study. To assess interobserver variability in 15 subjects, the same indexes were measured also by a second observer (M.K.) at all phases of the study.

**Coronary blood flow velocity.** Phasic and mean coronary blood flow velocity (CBFV, cm/s) were obtained with a pulsed Doppler flow meter (Triton Technology, model 100-1000-20C) and 3F Doppler catheters (Nyros-Sorin) that were positioned ~10 mm above the stenosis, as previously described (10). The technique has been fully validated (20). The Doppler catheter was withdrawn during coronary dilation and reinserted over the wire in the same position after coronary stenting. Two ECG leads were continuously recorded. Arterial blood pressure was measured through the guiding catheter at the coronary ostium. Cross-sectional area (CSA) was obtained with the aid of quantitative coronary angiography (Artrek) (17). Coronary blood flow (CBF) (m/min) and a calculated index of coronary vascular resistance (CVR) were obtained as previously described (21). In view of the approximations inherent in this procedure, we report only directional and relative variations as percent changes (mean ± SD) from pre-PTCA values.

**Coronary stenting.** Two or three balloon inflations of 3 min, each followed by 2 min of reperfusion, were performed to predilate the artery before inserting the stents. A single stent or multiple stents (Palmaz-Schatz, GT-Roubin II or Wall-Stent) were implanted in the lesion to properly reconstruct the anatomy of the vessel. Stents were deployed with a 20/30-s balloon inflation followed by other high pressure inflations (3 to 5 inflations at 18 to 22 atm for 30/60 s) to expand the struts up to the nominal normal reference vessel diameter (Table 1). The smallest guiding catheter size compatible with the type of stent was chosen, and the tip of the guiding catheter was slightly withdrawn from the coronal ostium, when not required by the procedure, to avoid flow reductions.

**Pharmacologic interventions.** Fifteen minutes after coronary stenting and after documenting LV function, 15 patients received 12 µg/kg of phentolamine intracoronarily (nonselective alpha-blocker: Regitin, 10-mg vials, Novartis, Switzerland), 15 patients received 600 µg/kg of urapidil (24,25) intravenously (from 35 to 48 mg intravenously) (alpha1-selective blocker: Ebrantil, 50-mg vials, Byk Gulden, Germany) and 10 patients received the combination of 12 µg/kg of phentolamine and 1.2 µg of propranolol (nonselective beta-sympathetic blocker: Inderal, 5-mg vials, Zeneca) intracoronarily. As the alpha1-blocker we chose urapidil because this drug induces a central serotoninergic activation of brain 5HT1A receptors, which may be responsible for the smallness of reflex tachycardia, despite the pronounced vasodilatation (22,23). The doses of alpha- and beta-blockers were lower than those used in other studies (24) and were titrated to obtain an alpha- or beta-blocking effect without decreasing blood pressure (10). In 10 control subjects, 5 ml of warm saline was
injected intracoronarily. The short-axis view was monitored by TEE for an additional 15 min to assess the effects of different pharmacologic interventions. All study investigators, except the one responsible for drug dilution, were unaware of the administered agent. All off-line measurements were performed in a blinded manner.

**Statistical analysis.** The results are expressed as the mean value ± SD. One- or two-way analysis of variance for repeated measures was performed with a commercial package, as appropriate. To assess statistical significance between the groups, the Scheffé $F$ test was applied, with a value of $p < 0.05$ as significant. In view of the large interindividual variability of the absolute values, multiple comparisons between the groups were performed with normalized data (%). Regression analysis was performed by the least squares technique. Agreement between the readings performed by two observers was evaluated by estimating the consistent bias between readings, as recommended by Bland and Altman (25) for the comparison of two methods of clinical measurements.

**Results**

**Effect of coronary stenting on LV function and on coronary diameters.** Fractional area change and end-diastolic area measured at various conditions are shown in Figure 1. Coronary stenting slightly increased FAC from $41 ± 9\%$ to $43 ± 7\%$ (mean of all patients). After stenting, myocardial function progressively worsened in all myocardial regions, reaching its lowest level 15 min later, as indicated by a decrease in FAC from $43 ± 7\%$ soon after stenting to $34 ± 9\%$ 15 min after coronary stenting ($p < 0.05$ vs. before PTCA) (Fig. 1). Also, LV diastolic area significantly increased 15 min after coronary stenting. The changes in regional function are more clearly shown in Figure 2 and Table 2. Soon after coronary stenting, systolic thickening significantly increased in the myocardium supplied by the dilated vessel, whereas no changes were observed in normally perfused regions. Surprisingly, 15 min later, the reduction in thicknesses and in systolic thickening occurred not only in PTCA regions but also in surrounding territories that did not undergo transient ischemia (non-PTCA regions). Figure 3 represents the computer printouts of systolic and diastolic LV endocardial contour of two different patients—one receiving urapidil and the other a combination of phentolamine and propranolol 15 min after coronary stenting. Both patients showed a clear increase in percent systolic thickening soon after stenting and severe worsening 15 min after coronary stenting.

![Figure 1](image1.png)

**Figure 1.** Left ventricular FAC (top) (% mean ± SD) and diastolic area (cm$^2$) (bottom) obtained from the endocardial diastolic and systolic contours (TomTec) before PTCA (Pre-PTCA), soon after coronary stenting (Post-Stent), 15 min after stenting (15 min Post-S) and after pharmacologic interventions. Phentolamine and urapidil significantly increased FAC and decreased diastolic area. When alpha- and beta-blockers combined or saline was injected, no effects on FAC or diastolic area were observed. No changes in diastolic area were observed after drug administration versus pre-PTCA condition. 5 min Phe = 5 min after intracoronary (ic) phentolamine injection; Phe = phentolamine; Pro = propranolol; 5 min Ura = 5 min after urapidil intravenous injection; 15 min Saline = 15 min after saline.
later. The occurrence of LV global dysfunction corresponded to diffuse coronary artery constriction (Table 1). In fact, 15 min after stenting, a $-20 \pm 7\%$ and $-18 \pm 7\%$ reduction in coronary diameter, as compared with the diameter before PTCA ($p < 0.05$), was measured at the distal level of the dilated and control vessel, respectively.

Intraobserver variabilities for FAC and WTH were 4.2 $\pm 2.1\%$ and 4.4 $\pm 3.0\%$, respectively. Interobserver variabilities for the same indexes were 5.7 $\pm 3.0\%$ and 5.3 $\pm 3.2\%$, respectively. A plot of the difference between the two observers for each measurement versus the mean of the two measurements showed a mean difference of 0.14 $\pm 2.63\%$ and $-0.25 \pm 2.55\%$, respectively, with good agreement because all points but two were within $\pm 2\ SD$ (Fig. 4).

**Figure 2.** Systolic wall thickening (mean $\pm SD$) measured in myocardial regions undergoing coronary dilation (top) and in regions not subtended by the dilated vessel (bottom). Systolic wall thickening significantly increased soon after coronary stenting only in PTCA regions, whereas 15 min after dilation a significant reduction occurred in myocardium both subtended and not subtended by the dilated vessel. Five minutes after the injection, phentolamine and urapidil significantly increased systolic thickening. When the combination of propranolol and phentolamine was simultaneously injected or saline was administered to control subjects, the impairment in systolic thickening was still present. Pro + Phe = propranolol combined with phentolamine.

<table>
<thead>
<tr>
<th>Time</th>
<th>Pre-PTCA</th>
<th>Soon after Stenting</th>
<th>15 min after Stenting</th>
<th>3–5 min after Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DWT</td>
<td>SWT</td>
<td>WTH</td>
<td>DWT</td>
</tr>
<tr>
<td>Pre-PTCA</td>
<td>121 ± 0.1</td>
<td>129 ± 0.1</td>
<td>93 ± 0.1</td>
<td>93 ± 0.1</td>
</tr>
<tr>
<td>Soon after Stenting</td>
<td>134 ± 0.2</td>
<td>132 ± 0.2</td>
<td>103 ± 0.1</td>
<td>103 ± 0.1</td>
</tr>
<tr>
<td>15 min after Stenting</td>
<td>142 ± 0.2</td>
<td>138 ± 0.2</td>
<td>110 ± 0.1</td>
<td>110 ± 0.1</td>
</tr>
<tr>
<td>3–5 min after Drugs</td>
<td>142 ± 0.2</td>
<td>138 ± 0.2</td>
<td>110 ± 0.1</td>
<td>110 ± 0.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>PTCA regions</th>
<th>Non-PTCA regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urapidil, 600 µg/kg</td>
<td>15 ± 0.92</td>
<td>15 ± 0.91</td>
</tr>
<tr>
<td>Pro + Phe, 1.5 mg</td>
<td>10 ± 0.91</td>
<td>10 ± 0.89</td>
</tr>
<tr>
<td>Phentolamine, 2 µg/kg</td>
<td>10 ± 0.89</td>
<td>10 ± 0.87</td>
</tr>
<tr>
<td>Saline, 5 ml</td>
<td>10 ± 0.87</td>
<td>10 ± 0.85</td>
</tr>
</tbody>
</table>

*p < 0.05 as compared with values before percutaneous transluminal coronary angioplasty (PTCA). Data presented are mean value $\pm SD$. Intracoronary (ic) phentolamine (Phe) and intravenous (iv) urapidil significantly increased diastolic wall thickness (DWT), systolic wall thickness (SWT) and percent systolic wall thickening (WTH), whereas after the combined injection of propranolol (Pro) and phentolamine or saline, DWT, SWT and WTH remained unchanged. Myocardial thickness and thickening of regions subtended by vessels undergoing or not undergoing angioplasty are reported as PTCA and non-PTCA regions, respectively.
Effect of stenting on CBF and CVRi. The effects of coronary stenting on blood flow measurements obtained in the proximal dilated coronary vessel are reported as normalized mean (±SD) values in Figure 5. Average basal CBFV was 9.2 ± 2 cm/s; CSA was 11.3 ± 4 mm²; CBF was 61.7 ± 23 ml/min; and CVRi was 1.69 ± 0.5 U. With the condition before drug injections (before PTCA, soon after and 15 min after stenting) similar in all groups, the data were grouped together. Soon after stent implantation no changes were observed in CBFV, CSA, CBF and CVRi. In fact, CBFV increased by 15.3 ± 12% (p = NS), CSA by 2.5 ± 6% (p = NS) and CBF by 18.3 ± 16% (p = NS), whereas CVRi decreased by −15.4 ± 11% (p = NS). Fifteen minutes after coronary stenting, CBFV decreased by −23.6 ± 16%, CSA by −18.5 ± 12% and CBF by −38.4 ± 15% (p < 0.05), whereas CVRi increased by 66.2 ± 13% (p < 0.05) (Fig. 5).

Hemodynamic effects of drugs. The intravenous injection of urapidil transiently (1 to 2 min) decreased mean (±SD) arterial pressure (from 87 ± 8 to 73 ± 9 mm Hg, p < 0.05) and did not change heart rate. The intracoronary injection of 12 µg/kg of phenolamine significantly affected blood pressure and heart rate.

Effects of drugs on LV dysfunction. Thirty minutes after PTCA a diffuse reduction in fractional systolic shortening and thickening and significant coronary artery constriction were persisting in patients who received intracoronary saline (Fig. 1 and 2, Tables 1 and 2). Both the alpha₁-adrenergic blocker urapidil and the nonselective alpha-blocker phenolamine significantly improved SWT and counteracted coronary artery constriction (Tables 1 and 2, Fig. 2). When the beta-sympathetic blocker propranolol was combined with phenolamine, no significant changes in SWT or in coronary diameters, as compared with 15 min after stenting, were observed. In fact, LV dysfunction and vasoconstriction were persisting, as in patients receiving saline. As shown in Figure 3, LV dysfunction was abolished by the intravenous injection of urapidil (top right panel), whereas it persisted after the administration of propranolol and phenolamine (bottom right panel).

Effect of drugs on CBF and coronary vascular resistance. The intracoronary administration of phenolamine or urapidil significantly increased CBF by 74.8 ± 21% and 51.9 ± 19%, respectively, and decreased CVRi by −46 ± 11% and −35 ± 9%, respectively (p < 0.05) (Fig. 5). The combined administration of propranolol and phenolamine, as well as saline, did not change CBF or CVRi, as compared with 15 min after coronary stenting, when a condition of global LV dysfunction was present.

Discussion

Our study provides clear evidence that coronary stenting, despite the removal of a flow-limiting stenosis, is followed by a significant impairment of LV myocardial function (2–4), which is associated with a significant reduction in flow. The beneficial
Effect of intracoronary alpha-blockers suggests a causative role of reflex sympathetic interaction.

Effect of coronary stenting on LV function. The observation that coronary stenting is followed by LV dysfunction is in agreement with a previous report by Sheiban et al. (7), who described the occurrence of myocardial stunning in patients undergoing 5-min balloon inflations. In our study, two inflations of 3 min were performed to predilate the coronary artery, but additional inflations followed by very short reperusions were carried out to deploy the stent. These additional high pressure inflations may have further increased the artery stretching, which has been demonstrated, in animal studies, to activate cardiac sympathetic afferent fibers (14–16,26,27) and may have exerted a cumulative ischemic effect. Our observation is at variance with the results of other studies (5,6) that assessed ventricular function during a shorter interval from the end of the last inflation (5) or after a single 1-min inflation (6). In contrast to previous reports, in our study LV function was assessed with the aid of continuous TEE, which has been shown to allow reliable quantitative measurement of LV global and regional function (18,19). In fact, the TEE short-axis view displays in sequence systolic and diastolic excursions and simultaneously allows measurement of systolic and diastolic thickness, as well as thickening in myocardial wall sectors supplied by different coronary rami.

Effect of coronary stenting on flow and resistance. The occurrence of global LV dysfunction corresponded in timing and time course to the angiographic phenomenon of coronary artery constriction, which is also a diffuse phenomenon involving both dilated and nonmanipulated control vessels, as previously observed by us (10) and other investigators (28). Moreover, vasoconstriction was also demonstrated to occur after PTCA along renal (27) and limb (29) vessels. The reduction in epicardial coronary artery diameter was followed by a simultaneous microvascular constriction. Both these phenomena are abolished by alpha-adrenergic blockade (10). For this study, we selected a cohort of patients who, because of the irregular anatomy of their plaques, would be better treated by coronary stenting, which allows for complete dilation of the lesion and removes the mechanical obstruction to flow. This is, to our knowledge, the first demonstration, in humans, that flow reductions occur simultaneously with LV dysfunction, although the relation between the reduction in regional coronary perfusion and cardiac function has been demonstrated for a long time in animal studies (3,30). Indeed, in our patients, the reduction in systolic shortening and the evidence of macrovascular and microvascular perfusion abnormalities were more sensible indexes of postischemic LV dysfunction (31), as compared with ECG changes, which were negligible 15 min after stenting.

LV dysfunction. Regional rather than global contractile LV dysfunction is commonly believed to occur as a consequence of regional ischemia, with sparing of areas not involved in the ischemic process (2–4,31). This observation comes from animal studies, in particular from conscious dog models in which a close correlation between regional blood flow and regional contractile function was found after transient myocardial ischemia (2–4,31–33). In particular, in animal models, an increase in regional vascular resistance and a reduction of vasodilator responsiveness to intravenous adenosine and papaverine were observed to occur simultaneously with the presence of LV dysfunction (32,33). In contrast, we have

Figure 5. CBFV, CSA, CBF and CVRi calculated as percent changes from basal values (average ±SD basal values 9.2 ± 0.7 cm/s, 11.3 ± 4.2 mm², 61.7 ± 23 ml/min and 1.69 ± 0.5 U, respectively). Because the conditions before drug injections (Soon After Stent and 15 min After Stent) were similar in all groups, these data were grouped together. Coronary stenting did not affect CBFV, CSA or CBF. Fifteen minutes after the end of the dilation procedure, a significant increase in CVRi was observed. Phentolamine and urapidil reduced CVRi, whereas no effects were observed after the combination of propranolol and phentolamine. *p < 0.05 versus pre-PTCA values.
observed that in humans, brief coronary balloon occlusions induce LV dysfunction, which also occurs in regions not undergoing transient ischemia. In contrast to previous reports (5–7) that did not observe global LV dysfunction, our observation may have been favored by acquiring images by means of TEE. Our observation is in agreement with the recent finding that remote regional dysfunction is present in patients with myocardial infarction and single-vessel disease (34). Our findings are also consistent with evidence of an altered vasodilator reserve and metabolism in the myocardium supplied by apparently normal coronary arteries (35,36) in patients with single-vessel disease or in patients with coronary spastic angina (37). In fact, our data suggest that coronary artery constriction, a reduction in CBF and an increase in coronary vascular resistance are different facets simultaneously accompanying LV dysfunction. The apparently smooth aspect of the coronary tree on the angiogram does not exclude the presence of a diffusely altered endothelium (21,38) or of subendothelial plaques (39), which cause the artery to react paradoxically to physiologic vasodilator stimuli such as acetylcholine (40,41), serotonin (40,42–44), adenosine (13,45) and others (40). The discrepancies observed in our study as compared with previous reports may also be ascribed to a diffusely altered endothelium.

Myocardial dysfunction is usually thought to reflect an adjustment of coronary flow to preserve the perfusion contraction matching in several acute and chronic ischemic states (4), including coronary vasospasm (46) occurring in the absence of a flow-limiting stenosis, and is often considered a protection mechanism (47) by which the ischemic myocardium slows the rate of adenosine triphosphate utilization (48) and preserves its cells from an energy supply reduction by a decrease of energy demand (2–4). Adrenergic vasocostriction might be beneficial in the presence of ischemia by lessening transmural steal during myocardial hypoperfusion (47). Obviously, this interpretation must be at least partly revised as a consequence of the observation that LV dysfunction also occurs in parts of the myocardium that are not ischemic and have not undergone a transient restriction of blood flow during the PTCA procedure.

Role of alpha-adrenoreceptors in LV dysfunction. The observation that the myocardium not exposed to transient flow standstill undergoes mechanical dysfunction suggests that neural mechanisms may play a major role in this phenomenon. Cardio-cardiac sympathetic reflexes, which have been described in animals (14–16,28,47,48) and hypothesized in humans (10,29,30), may represent the link between the area subjected to transient ischemia and other LV regions and exaggerate the effects of mechanisms such as “oxyradical” production (32,33,49), calcium overload (32,50,51) or release of endothelial factors (52). In fact, experimental studies suggest that impaired calcium homeostasis, resulting in a transient calcium overload, might be involved in myocardial stunning (7,50,51). All of our patients were pretreated with full doses of calcium antagonists, which attenuate myocardial stunning in case of pretreatment (51). This treatment might have reduced the occurrence of LV dysfunction. Although coronary stenting is likely to extensively damage the endothelium of the dilated vessel, endothelial factors might have contributed to the delayed occurrence of vasoconstriction. Local nitric oxide release, likely following wall shear stress changes induced by stenosis removal, may be responsible for the significant increase in systolic thickening, which soon after dilation was observed only in regions supplied by the dilated vessel. In addition, endothelin release might have influenced the changes in vessel diameter (52). Indeed, in vivo shear stress–dependent tone or nitric oxide–induced vasodilation is modulated by inhibition of the adrenergic vasoconstriction (53,54). Although we did not measure total peripheral resistance, the hypothesis that the effect of alpha-blockers might in part be ascribed to an unloading of the LV is made unlikely by the observation that significant changes in blood pressure or in LV diastolic area did not occur at the time of post-drug measurements. Indeed, in our patients, the injection of alpha-blockers increased SWT and myocardial shortening after infusion (55), counteracting LV dysfunction and the abnormalities in macrocirculatory and microcirculatory coronary flow, whereas the simultaneous administration of beta- and alpha-blockers blunted the effect of alpha-blockers alone, unmasking the presence of a betasympathetic inotropic and vasodilator tone (56). After coronary stenting, mechanical, contractile, macrocirculatory and microcirculatory adjustments take time. This might be due to the fading effect on cardiac contractility (57) of nitrates administered intracoronarily to better adjust the final stent size to a diluted vessel, or it may be due to shear stress mechanisms occurring soon after coronary dilation (8,57). Indeed, in humans, at variance with experimental models in which a sympathetic reflex occurs in seconds, the sympathovagal interaction is reported to be impaired 2 weeks after acute myocardial infarction (58). The inotropic effect of phentolamine on reduced LV performance in acute myocardial infarction was reported previously by Walinsky et al. (59), who hypothesized a reflex increase in sympathetic tone 48 h after acute myocardial infarction. In line with this previous study (59), our data suggest the testable hypothesis that the administration of alpha-blockers might be beneficial in improving LV dysfunction after PTCA.

Conclusions. Coronary stenting corrects the mechanical obstruction to flow but does not induce an immediate recovery of LV function. Conductance and resistance artery constriction occurred simultaneously with global LV dysfunction as interrelated functional and clinical facets of the same phenomenon. Alpha-sympathetic blockers counteract LV dysfunction, inducing a better perfusion, whereas the combination of alpha- and beta-blockers has the opposite effect. Neural mechanisms are most likely regulating these phenomena by cross-talk interaction. These observations may open potential and promising therapeutic perspectives.

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