Percutaneous Transluminal Coronary Angioplasty Reverses Vasoconstriction of Stenotic Coronary Arteries in Hypertensive Patients

Jürgen Frielingsdorf, MD; Philipp Kaufmann, MD; Thomas Suter, MD; Rosy Hug, BA; Otto M. Hess, MD

**Background**—Endothelial dysfunction of coronary arteries with impaired vasodilation has been reported in patients with arterial hypertension. However, the effect of dynamic exercise on coronary vasomotion of a stenotic vessel segment before and after PTCA has not yet been evaluated in these patients.

**Methods and Results**—Coronary vasomotion of a normal and a stenotic vessel segment was studied in 39 patients with coronary artery disease during supine bicycle exercise before and 9 ± 3 months after PTCA. Luminal area changes were determined by biplane quantitative coronary arteriography. There were 21 normotensive and 18 hypertensive patients who did not differ with regard to clinical characteristics. Percent area stenosis decreased after PTCA from 90% to 39% (P < 0.001) in normotensive and from 86% to 33% (P ≤ 0.001) in hypertensive patients. Exercise-induced vasomotion of the normal vessel segment was significantly different between normotensives and hypertensives before (+19% versus +1%, P < 0.01) and after (+16% versus +3%, P < 0.01) PTCA. In contrast, stenotic vessel segments showed vasoconstriction in both normotensive and hypertensive patients (Δexercise, −11% versus −20%, P = NS), which was reversed after PTCA (+3% versus +2%, P = NS).

**Conclusions**—Normal coronary arteries show reduced vasodilation during exercise in hypertensive patients that may be explained by the presence of endothelial dysfunction. Stenotic vessels demonstrate paradoxical vasoconstriction during exercise in both normotensive and hypertensive patients. PTCA reverses vasoconstriction by elimination of the flow-limiting stenosis and prevention of coronary stenosis narrowing during exercise in normotensive and hypertensive patients. (Circulation. 1998;98:1192-1197.)

**Key Words:** coronary disease ■ vasodilation ■ endothelium ■ hypertension ■ angioplasty
Area stenosis before and after PTCA were calculated according to results, or restenosis at follow-up were excluded from the study.

**Definition of Coronary Risk Factors**

Coronary risk factors such as hypercholesterolemia, cigarette smoking, family history (coronary artery disease in 1 patient’s parents or sibling < 60 years), and obesity (body mass index ≥28 kg/m²) were evaluated in the present analysis. There were no patients with diabetes mellitus. Serum cholesterol was considered to be normal if it was ≥200 mg/dL, according to the definition of the National Cholesterol Education Program.\textsuperscript{16}

**Cardiac Catheterization**

Informed consent was obtained from all patients. Medication was stopped ≥24 hours before cardiac catheterization. Pressure measurements in the aorta and pulmonary artery were performed in all patients, which has been described previously.\textsuperscript{17} Diagnostic coronary angiography was carried out according to the Judkins technique. Quantitative coronary angiography was performed in the right and left anterior oblique projections, but in some patients, craniocaudal angiography was carried out according to the Judkins technique.

**Study Protocol**

At the end of diagnostic catheterization, biplane coronary arteriography was carried out at rest with the patient’s feet attached to the bicycle ergometer (Siemens-Elema AG, model 380B). Exercise was begun at 50 to 75 W and was increased every 2 minutes in increments of 25 to 50 W. Coronary arteriography was carried out at the end of each exercise level with the patient holding his or her breath during injection of the contrast medium. Angiograms at the end of each exercise level with the patient holding his or her breath during injection of the contrast medium. Arteriograms at maximum exercise level were used for analysis of coronary vasomotion. The exercise test was terminated because of angina pectoris, fatigue, or ST-segment depression. The exercise test was terminated because of angina pectoris, fatigue, or ST-segment depression.

**Quantitative Coronary Arteriography**

Quantitative evaluation of biplane coronary arteriograms was performed with a semiautomatic computer system, which has been described previously.\textsuperscript{20,21} Interobserver and intraobserver variabilities for this system are 4.1% and 2.1%, respectively. Quantitative analysis was performed in a normal vessel segment chosen from a nonstenosed artery unaffected by luminal irregularities, and the stenosed vessel segment was taken from a diseased artery with localized stenosis of >50% (quantitatively assessed). The stenosed vessel segments (culprit lesion) were chosen only from the proximal two thirds of the respective artery. Measurement sites were selected on the basis of the following criteria: (1) sufficient filling of the vessel with radiographic contrast medium, (2) high-quality end-diastolic cineframe without motion artifacts, (3) straightness of the vessel segment to be analyzed, and (4) biplane x-ray views. Angiograms were measured with the investigator blinded to the variables of interest and actual study sequence (rest, exercise, or nitroglycerin). Luminal area changes were determined during exercise (\( \Delta Ex \)), percent change compared with rest(100%) and after administration of sublingual nitroglycerin (\( \Delta Ntg \), percent change compared with rest(100%)) before (baseline) and after successful PTCA.

**Statistical Analysis**

Between-group comparisons with regard to clinical, hemodynamic, and angiographic data were performed by 1-way ANOVA for continuous variables, followed by Scheffé’s procedure if the probability value was significant (\( P<0.05 \)). Fisher’s exact test was used for categorical variables, and a paired \( t \) test was used for data before and after PTCA. All values in text and tables are expressed as mean±SD and in figures as mean±SEM.

**Results**

**Patient Characteristics**

Baseline values were evenly distributed between normotensive and hypertensive patients, as shown in Table 1. Follow-up examination 9±3 months after PTCA showed similar blood pressure (Table 3) and levels of cholesterol values (normotensives, 231±66 mg/100 mL; hypertensives, 245±41 mg/mL) compared with baseline. After successful PTCA, functional NYHA classification improved significantly in normotensives (2.0±0.6 before versus 1.4±0.5 after PTCA, \( P<0.01 \)) and hypertensives (1.8±0.5 before versus 1.4±0.6 after PTCA, \( P<0.01 \)).

**Exercise and Hemodynamic Data**

Exercise workload and percent workload (percent of the age-, sex-, and height-corrected normal value) in patients in the upright and supine positions before PTCA were higher in hypertensive compared with normotensive patients, although this difference was statistically not significant (Table 2).
After PTCA, exercise-induced ST-segment depression was significantly reduced in all patients.

Heart rate and mean pulmonary artery pressure at rest and during exercise were comparable in all groups (Table 3). Among normotensives and hypertensives, left ventricular end-diastolic volume index (75±17 versus 81±22 mL/m², P=NS), left ventricular ejection fraction (61±6 versus 65±6%, P=NS), and left ventricular mass index (77±6 versus 84±6 g/m², P=NS) were similarly distributed.

**Coronary Angiographic Data**

**Normal Coronary Arteries**

The increase in coronary artery luminal area during exercise (ΔEx, change in percent of control value) differed significantly between normotensive and hypertensive patients before (+19±15% versus +1±9%, P<0.01) (Figure 1) and after (+16±11% versus +3±9, P<0.01) PTCA. Administration of 1.6 mg sublingual nitroglycerin at the end of exercise was associated with a significant increase in mean vessel area in normotensive and hypertensive patients before (126±19% versus 29±14%, P<NS) and after (+23±12% versus 30±13%, P=NS) (Figure 3) PTCA.

**Stenotic Coronary Arteries**

Percent area stenosis decreased after PTCA from 90±25% to 39±9% (P<0.001) in normotensives and from 86±9% to 33±15% (P<0.001) in hypertensives. The inner surface (endothelium) of the stenotic vessel segment increased after PTCA from 2.3±1.6 to 5.8±3.5 mm (P<0.001) in normotensives and from 2.2±1.9 to 6.1±3.7 mm (P<0.001) in hypertensives. At baseline, there was a nonsignificant difference in exercise-induced vasoconstriction of the stenotic vessel segment between normotensives (−11±24%) and hypertensives (−20±19%) (Figure 2). After administration

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**TABLE 2. Exercise Data Before (Upright Position) and During (Supine Position) Catheterization Before and 9±3 Months After PTCA***

<table>
<thead>
<tr>
<th></th>
<th>Before PTCA</th>
<th>After PTCA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotensives</td>
<td>Hypertensives</td>
</tr>
<tr>
<td>Upright bicycle exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(before catheterization)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workload (3 min), W</td>
<td>129±30</td>
<td>143±33</td>
</tr>
<tr>
<td>Workload, % of normal</td>
<td>86±17</td>
<td>95±19</td>
</tr>
<tr>
<td>ST-segment depression, mV</td>
<td>0.15±0.14</td>
<td>0.13±0.13</td>
</tr>
</tbody>
</table>

*P=NS for all comparisons between normotensive and hypertensive patients before and after PTCA unless otherwise indicated.

**TABLE 3. Hemodynamic Data During Angiography Before and 9±3 Months After PTCA in Normotensives and Hypertensives***

<table>
<thead>
<tr>
<th></th>
<th>Before PTCA</th>
<th>After PTCA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotensives</td>
<td>Hypertensives</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>64±11</td>
<td>68±11</td>
</tr>
<tr>
<td>Exercise</td>
<td>111±20</td>
<td>119±19</td>
</tr>
<tr>
<td>MPAP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>22±6</td>
<td>21±6</td>
</tr>
<tr>
<td>Exercise</td>
<td>40±9</td>
<td>40±7</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>90±13</td>
<td>105±15</td>
</tr>
<tr>
<td>Exercise</td>
<td>98±16</td>
<td>119±16</td>
</tr>
</tbody>
</table>

MPAP indicates mean pulmonary artery pressure; MAP, mean aortic pressure.

*P=NS for all comparisons between normotensive and hypertensive patients before and after PTCA unless otherwise indicated.
of nitroglycerin, vasodilation occurred in both groups (+14±17% versus +15±20%, P=NS). After PTCA, exercise-induced coronary vasoconstriction was abolished, and exercise-induced vasodilation was similar in normotensives (+3±11%) and hypertensives (+2±13%). Again, after administration of nitroglycerin, there was vasodilation in normotensives (19±9%) and hypertensives (25±14%) (Figure 3).

Discussion

The present study is the first to assess the effect of PTCA on coronary vasomotion in hypertensive patients. There were 3 important findings. First, hypertensive patients with angiographically documented coronary artery disease reveal a blunted vasodilatory response of the normal vessels compared with normotensive subjects. Second, hypertensive and normotensive patients show exercise-induced vasoconstriction of stenotic vessel segments. Third, successful PTCA reverses the constrictive response of the stenotic coronary arteries to exercise in patients with coronary artery disease.

Nonstenotic Vessel

Coronary vasodilation during exercise is dependent on an intact endothelium with adequate production of nitric oxide. Recent human data indicate that endothelial dysfunction occurs very early in the development of atherosclerosis, even before the appearance of stenotic lesions, resulting in an abnormal coronary vasomotor response to acetylcholine. The present study compared the vasomotor response to exercise of angiographically “normal” vessels in patients with coronary artery disease. In normotensive subjects, these normal vessel segments dilated during exercise by 16%, whereas hypertensive patients did not show coronary vasomotion. Hypertension has direct structural and functional effects on the coronary vessel wall, leading to endothelial dysfunction with vasoconstriction of angiographically normal coronary arteries in response to intracoronary acetylcholine. In the present analysis, however, blunted coronary vasodilation but not vasoconstriction of normal coronary vessels was observed during exercise, which is probably due to the more complex effects of a physiological stimulus such as bicycle exercise on coronary vasomotion than that of pharmacological compounds. A major difference between the 2 stimuli is certainly that blood pressure (coronary driving pressure) rises during exercise but falls with pharmacological vasodilation. The endothelium-independent dilator capacity after nitroglycerin was maintained in both hypertensive and normotensive patients. This suggests a preserved function of the smooth vasculature but makes likely a primary defect of the endothelium-dependent regulation of the epicardial coronary arteries in hypertensive patients with coronary artery disease.

Stenotic Vessel

Exercise-induced vasoconstriction of the stenotic vessel segments was observed in hypertensives that was, however, similar to that in normotensives. The exact mechanism responsible for the decrease in minimal luminal area of the stenotic artery during exercise is not clear but might involve different interacting mechanisms:

First, an impaired production of nitric oxide may precipitate coronary vasoconstriction during exercise. Because in hypertension a diminished release of nitric oxide has been reported. Hypertensive patients may elicit more pronounced vasoconstrictory effects that may have been at least partially counterbalanced by the increase in perfusion pressure during exercise.

Second, an increase in α-adrenergic tone during exercise has been associated with coronary artery vasoconstriction, whereas an increase in β-receptor tone is accompanied by coronary vasodilation. Third, enhanced platelet aggregation with release of thromboxane A2 and serotonin may cause focal vasoconstriction of diseased epicardial arteries. In vivo, serotonin induces paradoxical vasoconstriction in the presence of coronary atherosclerosis. Finally, a flow-induced (passive) collapse of the atherosclerosis-free vessel wall within the stenosis (Venturi mechanism) may induce coronary vasoconstriction during exercise. It has been shown under in vitro and in vivo conditions and in computer models that a flow-induced collapse within tight stenoses can occur and may aggravate a preexisting coronary lesion.

Effect of PTCA

In the acute phase after PTCA, the reaction of the coronary arteries to this procedure is complex and generally results in vasoconstriction of the dilated vessel segments. Endovascular interventions such as PTCA expand the artery lumen, resulting in an increased laminar shear stress that tends to enhance endothelial cell migration and thereby facilitate the reendothelialization and improvement in endothelial function. Histological examinations of reendothelialization late after PTCA have shown in the experimental animal that the
neendothelium has functional properties similar to the normal endothelium but that the cells of the neendothelium are smaller with a different shape and alignment compared with normal cells. The physiological response of the coronary arteries to different pharmacological substances in a late phase after the intervention results in vasoconstriction in the animal model and in humans. This response indicates that in the chronic regenerated state, the protective role of endothelial cells against vasoconstriction is depressed, which may favor the reaction to aggregating platelets, the activation of serotonergic receptors, and/or less production of endothelium-derived relaxing factors. In 1 study, long-term administration of l-arginine, the precursor of nitric oxide, enhanced neendothelium-dependent relaxation of injured rabbit iliac arteries. Furthermore, the extent of anatomical recovery of the endothelium after denudation plays an important role in restoring coronary vasodilation after PTCA. Hayashi et al demonstrated in the animal model a direct correlation between the vessel area recovered by neendothelial cells at the denuded site and percent recovery of reactive vasodilation.

In the present study, coronary vasomotion of the dilated segment was improved in normotensive and hypertensive patients; thus, partial restoration of endothelial function, which might be due to a quantitative increase in endothelial surface after the coronary artery is enlarged by angioplasty, can be assumed but is speculative because no direct measurements of endothelial function have been performed. However, this study did not reveal any vasoconstriction at the site of PTCA. This may be due either to the more complex effects of the physiological stimulus such as bicycle exercise on coronary vasomotion or to the longer time period studied between PTCA and follow-up than in other studies, which probably allows more complete reendothelialization.

Conclusions
In the present study, exercise-induced coronary vasodilation is blunted in hypertensive patients with normal coronary artery segments compared with normotensive subjects. In agreement with previous findings, this observation is compatible with the presence of endothelial dysfunction in essential hypertension. However, the behavior of stenotic vessels during exercise is not affected by the presence or absence of arterial hypertension either before or after PTCA. This is probably due to complex interrelated mechanisms such as impaired production of nitric oxide, increased $\alpha$-adrenergic stimulation, enhanced platelet aggregation, and flow-induced collapse of the disease-free vessel wall within the stenosis during high-flow situations such as physical exercise. Mechanical reduction of the coronary stenosis by PTCA prevents exercise-induced vasoconstriction of the stenotic vessel segment in normotensive and hypertensive patients, probably because of partial restoration of endothelial function and attenuation of the vasoconstrictory effects. Thus, successful PTCA improves myocardial function by 2 mechanisms: (1) elimination of the flow-limiting stenosis and (2) prevention of coronary vasoconstriction during exercise.

References


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