Conclusions

The response of the coronary arteries after PTCA is abnormal after administration of various pharmacological agents and generally results in coronary vasoconstriction in the animal model and in humans. This indicates a depressed protective role of the endothelium against vasoconstrictor influences. Thus, the purpose of the present study was to evaluate the influence of PTCA on coronary vasoconstriction in normotensive and hypertensive patients. Specifically, we wanted to know whether dynamic exercise has a different effect on coronary vasoconstriction of the dilated vessel in patients with normal and with high blood pressure.

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).

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.

Study Population

Thirty-nine men (mean age, 53±8 years) with coronary artery disease were included in this prospective analysis. Twenty-one normotensive (mean age, 54±7 years) and 18 were hypertensive (mean age, 52±9 years) before and 9±3 months after PTCA. The 21 patients, who were studied on a prospective basis, were asked by written informed consent to undergo repeated angiography 6 to 12 months after PTCA.

All patients were selected from a group of subjects undergoing bicycle exercise and coronary arteriography on the basis of the following inclusion criteria: (1) stable, exercise-induced angina pectoris in patients with coronary artery disease; (2) written informed consent to undergo the exercise study; (3) clearly visible coronary arteries with a normal and a stenotic vessel segment (2 different vessels) for quantitative evaluation; (4) successful PTCA without restenosis at the follow-up examination (residual area stenosis <75% or residual diameter stenosis <50%); and (5) exercise coronary arteriography before and after PTCA.

Exclusion Criteria

Patients were excluded when there was severe or unstable angina pectoris, diffuse 3-vessel disease, inability to perform exercise angiography, recent myocardial infarction (<1 month), large infarcts with hypokinetic or akinetic regions, and renal or hepatic disease.

Definition of Arterial Hypertension

Hypertension was defined according to World Health Organization criteria as a history of high blood pressure (diastolic pressure

Key Words: coronary disease ■ vasodilation ■ endothelium ■ hypertension ■ angioplasty

Coronary vasomotion plays an important role in the regulation of coronary blood flow at rest and during physical exercise. Arterial hypertension is associated with morphological and functional alterations of the endothelium that may cause abnormal coronary vasomotion. Hypertensive patients, especially in the presence of coronary atherosclerosis, show reduced vasodilator capacity during exercise compared with normotensive subjects.


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≥95 mm Hg and/or systolic values ≥160 mm Hg) requiring long-term therapy and a sustained blood pressure elevation documented during hospitalization in a drug-free period (drugs discontinued 24 hours before cardiac catheterization). Patients were considered to have normal blood pressure if continuous blood pressure readings showed diastolic values <90 mm Hg and systolic values <140 mm Hg. Patients with secondary causes of hypertension and evidence of damage to end organs were excluded.

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.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.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. Cinefilm was used as a data carrier (filming rate, 50 frames per second). PTCA was carried out according to current indications and techniques. Patients with large dissections, stenting, insufficient results, or restenosis at follow-up were excluded from the study. Area stenosis before and after PTCA were calculated according to standard methods used in our laboratory.

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. Angelograms at maximum exercise level were used for analysis of coronary vaso-motor. The exercise test was terminated because of angina pectoris, dyspnea, or ST-segment depression ≥0.2 mV. At the end of the exercise test, 1.6 mg nitroglycerin was administered sublingually. Biplane coronary arteriography was repeated 5 minutes thereafter. There were no complications related to the study protocol. The whole procedure was repeated 9±3 months after PTCA. All patients gave written informed consent for the second evaluation.

Quantitative Coronary Arteriography
Quantitative evaluation of biplane coronary arteriograms was performed with a semiautomatic computer system, which has been described previously.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 a 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 (ΔEx, percent change compared with rest =100%) and after administration of sublingual nitroglycerin (ΔNg, 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 Scheffe’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 (26±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 (211±24%) and hypertensives (220±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 (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>
<tr>
<td>Supine bicycle exercise (during catheterization)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workload (2 min), W</td>
<td>94±32</td>
<td>115±31</td>
</tr>
<tr>
<td>Workload, % of normal</td>
<td>63±15</td>
<td>76±20</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 normoten-
sives (+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 com-
pared with normotensive subjects. Second, hypertensive and
normotensive patients show exercise-induced vasoconstric-
tion 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.22-25
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 vaso-
motion. 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.7-8
In the present analysis, however, blunted coronary vasodila-
tion 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 pharmacologi-
cal 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 nitroglyc-
erin 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 endo-
thelium-dependent regulation of the epicardial coronary ar-
teries in hypertensive patients with coronary artery disease.

Stenotic Vessel
Exercise-induced vasoconstriction of the stenotic vessel seg-
ments 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 precipi-
tate coronary vasoconstriction during exercise. Because in
hypertension a diminished release of nitric oxide has been
reported,26,27 hypertensive patients may elicit more pro-
nounced vasoconstrictory effects that may have been at least
partially counterbalanced by the increase in perfusion pres-
sure 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.28
Third, enhanced platelet aggregation with release of
thromboxane A2 and serotonin may cause focal vasoconstric-
tion of diseased epicardial arteries.29 In vivo, serotonin
induces paradoxical vasoconstriction in the presence of cor-
onary atherosclerosis.30
Finally, a flow-induced (passive) collapse of the athero-
sclerosis-free vessel wall within the stenosis (Venturi mech-
anism) may induce coronary vasoconstriction during exer-
cise. 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.1,31

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 diluted vessel segments.12,23 Endo-
vascular 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 func-
tion.24 Histological examinations of reendothelialization late
after PTCA have shown in the experimental animal that the

![Figure 1. Luminal area change during exercise (ΔEx, %) of nor-
mal coronary arteries before and after PTCA in normotensive
and hypertensive patients. Values are mean±SEM.](Image 1)

![Figure 2. Luminal area change during exercise (ΔEx, %) of ste-
notic vessel segments before and after PTCA in normotensive
and hypertensive patients. Values are mean±SEM.](Image 2)
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 serotoninergic 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 relationship between the vessel area recovered by neuroendothelial 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 α-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


![Diagram](image_url)
Percutaneous Transluminal Coronary Angioplasty Reverses Vasoconstriction of Stenotic Coronary Arteries in Hypertensive Patients
Jürgen Frielingsdorf, Philipp Kaufmann, Thomas Suter, Rosy Hug and Otto M. Hess

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