Normalization of Coronary Vasomotion After Percutaneous Transluminal Coronary Angioplasty?

Thomas M. Suter, MD; Martin Buechi, MD; Otto M. Hess, MD; Cordula Haemmerli-Saner, BA; Antonio Gaglione, MD; and Hans P. Krayenbuehl, MD

Background. Coronary vasomotion was evaluated at rest and during bicycle exercise in 33 patients (age, 53±7 years) with coronary artery disease. In a first group of patients (n=15), vasomotion was studied before and 4.3±2.3 months (early) after percutaneous transluminal coronary angioplasty (PTCA), whereas in a second group (n=18), exercise coronary arteriography was performed 30±11 months (late) after successful PTCA. Patients with restenosis (percent area stenosis ≥75% or percent diameter stenosis ≥50%) were excluded.

Methods and Results. Luminal areas of a normal segment and the stenotic segment were determined at rest, during supine bicycle exercise, and 5 minutes after sublingual nitrate administration by using biplane quantitative coronary arteriography. Work loads before and early after PTCA were identical in group 1 and similar late after PTCA in group 2. Percent area stenosis decreased from 86% to 36% (p<0.001) in group 1 and from 93% to 46% (p<0.001) in group 2. Normal coronary arteries showed mild vasodilation during exercise before (+3%, NS versus rest), early (+7%, NS versus rest), and late after (+10%, p<0.05 versus rest) PTCA. Administration of sublingual nitrate was associated with significant vasodilation of the normal vessel segment before (+27%, p<0.001 versus rest), early (+31%, p<0.001 versus rest), and late (+21%, p<0.001 versus rest) after PTCA. In contrast, the stenotic vessel segments showed coronary vasoconstriction during exercise before PTCA (−25%, p<0.001 versus rest), whereas minimal vasomotion was observed early (+2%; NS versus rest) as well as late (+5%; NS versus rest) after PTCA. Individual post-PTCA (early and late) exercise data elicited vasodilation in 19, no vasomotion in four, and vasoconstriction in 10 instances. Sublingual administration of nitrate was associated with a significant increase in minimal luminal area before (+18%, p<0.05 versus rest), early (+24%, p<0.01 versus rest), and late (+16%, p<0.001 versus rest) after PTCA. An inverse linear correlation was found between the percent change in minimal luminal area during peak exercise and percent area stenosis at rest (r=0.77, p<0.001).

Conclusions. Exercise-induced stenosis narrowing is observed before PTCA but normal vasomotion is reestablished in two thirds of all patients early and late after PTCA. In one third, an abnormal reaction to exercise (i.e., vasoconstriction) persisted after PTCA, mainly in those patients with a residual area stenosis of 50% (percent diameter stenosis of 30%) or more. Thus, PTCA appears to have a salutary effect on coronary vasomotion during exercise, which, however, remains dependent on the severity of the residual stenosis. (Circulation 1992;85:86–92)

Coronary vasomotion plays an important role in the regulation of coronary blood flow at rest and during physical exercise.1–3 Not only normal but also stenotic coronary arteries show vasomotion during exercise because approximately 70% of all stenotic lesions have a normal musculoelastic wall segment within the stenosis.4,5 Previous studies have indicated that normal coronary arteries dilate during dynamic exercise but stenotic arteries constrict.3 Thus, the purpose of the present study was to evaluate the effect of percutaneous transluminal coronary angioplasty (PTCA) on coronary vasomotion at rest and during exercise in patients with coronary artery disease before, early, and late after the procedure.
Methods

Study Population

Thirty-three male patients (mean age, 53 years; range, 39–68 years) were included in the present study (Table 1). Fifteen of the 33 patients were evaluated before as well as 4.3±2.3 months after PTCA (group 1), whereas the other 18 patients were studied 30±11 months after successful dilatation (group 2). All patients had a history of exercise-induced angina pectoris and 13 had previous myocardial infarction. Bicycle exercise testing was performed in the upright position before cardiac catheterization. ST segment depression of more than 0.1 mV was found in 10 of 15 patients in group 1 (mean, 0.16±0.15 mV) before PTCA; after PTCA, ST segment depression was observed in three of the 15 patients of group 1 and in four of the 18 patients of group 2. Angina pectoris occurred in eight patients before, in three early, and in three late after PTCA, respectively.

Patients were selected on a consecutive basis when the following inclusion criteria were fulfilled: 1) coronary artery stenosis clearly visible on angiography for quantitative evaluation and 2) successful PTCA without restenosis at the follow-up examination (residual area stenosis <75% or residual diameter stenosis <50%).

Cardiac Catheterization

Patients underwent right and left heart catheterization for diagnostic purposes. Informed consent was obtained from all patients. All medication had been stopped at least 24 hours before cardiac catheterization. Because PTCA was performed on another day than the exercise study, no vasoactive drugs such as intravenous nitroglycerin or calcium blockers were administered. Premedication consisted of 10 mg chlordiazepoxide administered orally 1 hour before the procedure. Aortic pressure was measured with an 8F Judkins catheter and pulmonary artery pressure was determined with a 6F pacing catheter with a side lumen for pressure measurements. Biplane left ventricular angiography was performed in all patients followed by diagnostic coronary arteriography.

Study Protocol

An interval of at least 10 minutes was allowed for dissipation of the effect of the nonionic contrast medium (Iopamiro 370 R: iopamidol 755.2 mg/ml, trometamol 1 mg/ml). Simultaneous biplane coronary arteriograms were carried out in two orthogonal projections to guarantee optimal visualization of the stenotic lesion. First, a control arteriogram was performed with the patient's feet attached to the bicycle ergometer (model 380 B, Siemens-Albis AG, Zurich). Exercise was then begun at 50–75 W and was increased every 2 minutes in increments of 25–50 W. Coronary arteriography was carried out at the end of each exercise level with the patient holding his breath during injection of the contrast medium. The exercise test was terminated because of anginal pain, fatigue, or ST segment depression of more than 0.2 mV. The average work load was 103±35 W before and after PTCA in group 1 and 117±17 W late after PTCA in group 2. At the end of the exercise test, 1.6 mg nitroglycerin was administered sublingually in group 1 and one spray (1.25 mg) of oral isosorbidine dinitrate (ISDN) was given in group 2, respectively. Biplane coronary arteriography was repeated 5 minutes after administration of sublingual nitrate. There were no complications related to the study protocol before or after PTCA.

Quantitative Coronary Arteriography

Quantitative evaluation of biplane coronary arteriograms was performed with a semiautomatic computer system. The system is based on a 35-mm film projector (Tagarno A/S, Horsens, Denmark), a slow-scan charge couple device camera (image digitation) developed at the Institute for Biomedical Engineering in Zurich, and a computer workstation (Apollo DN 3000, Apollo Computer AG, Wangen, Switzer-

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**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Age (years)</th>
<th>NYHA</th>
<th>Follow-up (months)</th>
<th>PWC (%)</th>
<th>AP</th>
<th>ST (mV)</th>
<th>Stenosis (% area)</th>
</tr>
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<tbody>
<tr>
<td>Before PTCA</td>
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<tr>
<td>Mean</td>
<td>15</td>
<td>51</td>
<td>2.1</td>
<td>...</td>
<td>93</td>
<td>8/15</td>
<td>0.16</td>
<td>86</td>
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<td>7</td>
<td>0.4</td>
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<td></td>
<td>20</td>
<td></td>
<td>0.15</td>
<td>9</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>15</td>
<td>...</td>
<td>1.4†</td>
<td>4.3</td>
<td>98</td>
<td>3/15</td>
<td>0.04*</td>
<td>36†</td>
</tr>
<tr>
<td>SD</td>
<td>0.6</td>
<td>2.3</td>
<td></td>
<td></td>
<td>16</td>
<td></td>
<td>0.08</td>
<td>17</td>
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<tr>
<td>Late after PTCA</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>18</td>
<td>55</td>
<td>1.3</td>
<td>30</td>
<td>98</td>
<td>3/18</td>
<td>0.04</td>
<td>46</td>
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<tr>
<td>SD</td>
<td>7</td>
<td>0.4</td>
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<td></td>
<td>11</td>
<td></td>
<td>0.08</td>
<td>13</td>
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</tbody>
</table>

NYHA, New York Heart Association functional class; PWC, physical working capacity in percent of the age-, sex-, and height-corrected normal value; AP, angina pectoris during upright bicycle exercise; ST, ST segment depression during upright bicycle exercise; Stenosis, percent area stenosis; SD, standard deviation. *p<0.01; †p<0.001 before vs. early after PTCA.
land) for image storage and processing. Calibration was performed by the isocenter technique, which requires two orthogonal angiographic projections, the exact determination of the focus-image intensifier distance and a reference point in the center of the two image intensifiers (2-mm lead marks). From these data, the exact calibration factor for each point of the image can be determined accurately. Contour detection was carried out in biplane projection (Figure 1) using a geometric densitometric edge detection algorithm. Biplane analysis was performed in 24 of the 48 measurements and monoplane evaluation in the other 24 measurements because of overlapping vessels or because of foreshortening when the analyzed vessel was orthogonal to one of the two projections. Interobserver variability was found to be small, with a standard error of estimate for biplane data of 0.14 mm² (4.1% of the mean vessel area).

The methodology for computerized analysis of coronary arteriograms has been described elsewhere. Briefly, a three-dimensional model of the vessel is constructed by matching center lines of the individual biplane tracings, assuming the vessel cross section to be ellipsoidal. The proximal and distal as well as the minimal luminal area of the vessel segments are calculated and printed out by the computer.

### Statistical Analysis

Statistical comparisons of hemodynamic and angiographic data at rest and during exercise as well as after sublingual nitrate administration were carried out by a two-way analysis of variance for repeated measurements. When the analysis was significant, the Scheffé's procedure was applied. Comparisons before and after PTCA were performed by a paired Student’s t test. Data are reported as mean ± standard deviation if not indicated otherwise.

### Results

**Patient Characteristics**

Functional classification according to the New York Heart Association improved significantly after successful PTCA. Eight of 15 patients suffered from exercise-induced angina pectoris before PTCA; early after successful angioplasty, three of 15 patients had angina pectoris, and three of 18 patients had angina pectoris late after PTCA. Physical working capacity during upright bicycle exercise increased from 93% to 98% (NS) in group 1 and was 98% in group 2 after PTCA. Percent area stenosis was 86% before and 36% after angioplasty in group 1 and 93% and 46%, respectively, in group 2. (See Table 1.)

### Hemodynamic Data

Heart rate increased significantly during exercise before, early, and late after PTCA. Mean aortic pressure increased only slightly (NS) before but significantly early and late after angioplasty. Heart rate remained significantly elevated after administration of sublingual nitrates when compared with rest. Before, early, and late after PTCA, mean aortic and mean pulmonary artery pressure were significantly lower after nitrates than in the resting state. (See Table 2.)

### Angiographic Data

A representative coronary arteriogram in biplane projection is shown before (Figure 1A) and after (Figure 1B) PTCA. (Also see Table 3.)

Normal coronary arteries (Figure 2) showed a mild increase in luminal area during bicycle exercise before (+3%, NS) as well as early after (+7%, NS) PTCA. There was a significant increase in cross-sectional area late after PTCA (+10%, p<0.05). Sublingual administration of nitrate was associated with a significant increase in normal vessel area before (+27%, p<0.001), early (+31%, p<0.001), and late (+21%, p<0.001) after PTCA. There was no significant difference in coronary vasodilation after sublingual nitroglycerin or one spray of ISDN before, early, and late after PTCA.

Stenotic coronary arteries (Figure 2) showed exercise-induced vasoconstriction with a significant reduction in luminal area by 25% (p<0.001) before
FIGURE 1. Panel A: Representative coronary arteriogram in biplane projection (right anterior oblique projection on left, left anterior oblique projection on right) at rest (upper panels, minimal luminal area 0.8 mm$^2$) and during exercise (lower panels, minimal luminal area 0.6 mm$^2$) before percutaneous transluminal coronary angioplasty (PTCA). Contour of the circumflex coronary artery is detected automatically by computer (red contour). Circumflex area stenosis at rest is 96%. Panel B: Representative coronary arteriogram in biplane projection at rest (upper panels, minimal luminal area 4.8 mm$^2$) and during exercise (lower panels, minimal luminal area 5.3 mm$^2$) in the same patient as panel A (2.5 months after PTCA). There is minimal residual stenosis (24% area stenosis) after PTCA.
TABLE 3. Calculated Luminal Areas

<table>
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<tr>
<th></th>
<th>Normal coronary luminal area</th>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Ex</td>
<td>NTG</td>
</tr>
<tr>
<td></td>
<td>mm²</td>
<td>%</td>
<td>mm²</td>
</tr>
<tr>
<td>Before PTCA</td>
<td>Mean 4.6 ± 0.8</td>
<td>100%</td>
<td>Mean 4.8 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>SD 2.4</td>
<td>0%</td>
<td>SD 2.6 ± 0.2</td>
</tr>
<tr>
<td>Early after PTCA</td>
<td>Mean 4.2 ± 0.8</td>
<td>100%</td>
<td>Mean 4.4 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>SD 2.1</td>
<td>0%</td>
<td>SD 2.1 ± 0.2</td>
</tr>
<tr>
<td>Late after PTCA</td>
<td>Mean 7.7 ± 0.8</td>
<td>100%</td>
<td>Mean 8.4 ± 0.6</td>
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<tr>
<td></td>
<td>SD 3.2</td>
<td>0%</td>
<td>SD 3.5 ± 0.2</td>
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TABLE 3. Continued

<table>
<thead>
<tr>
<th></th>
<th>Stenotic coronary luminal area</th>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Ex</td>
<td>NTG</td>
</tr>
<tr>
<td></td>
<td>mm²</td>
<td>%</td>
<td>mm²</td>
</tr>
<tr>
<td>Before PTCA</td>
<td>Mean 1.0 ± 0.6</td>
<td>100%</td>
<td>Mean 0.8 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>SD 0.6</td>
<td>0%</td>
<td>SD 0.6 ± 0.2</td>
</tr>
<tr>
<td>Early after PTCA</td>
<td>Mean 2.7 ± 0.6</td>
<td>100%</td>
<td>Mean 2.7 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>SD 1.3</td>
<td>0%</td>
<td>SD 1.0 ± 0.2</td>
</tr>
<tr>
<td>Late after PTCA</td>
<td>Mean 2.6 ± 0.6</td>
<td>100%</td>
<td>Mean 2.7 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>SD 0.8</td>
<td>0%</td>
<td>SD 1.0 ± 0.2</td>
</tr>
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</table>

Ex, peak exercise; NTG, sublingual nitroglycerin or isosorbide dinitrate (late); mm², luminal area; %, luminal area given in percent of the luminal area at rest; PTCA, percutaneous transluminal coronary angioplasty; SD, standard deviation. *p<0.05 (vs. rest), †p<0.01 (vs. rest), ‡p<0.001 (vs. rest), §p<0.001 (before vs. early after PTCA).

PTCA. A significant increase in minimal luminal area (+18%, p<0.05) was observed after sublingual administration of nitrate. In contrast, vasoconstriction was not observed early (+2%, NS) and late (+5%, NS) after PTCA (Figure 2). However, individual data showed exercise-induced vasodilation in seven, no vasomotion in three, and persistence of exercise-induced vasoconstriction in five patients early after PTCA (Figure 2). Late after PTCA, 12 of the 18 patients showed exercise-induced vasodilation, one showed no vasomotion, and five showed exercise-induced vasoconstriction late after PTCA. Sublingual administration of nitrate was associated with a significant increase in minimal luminal area before (+18%, p<0.05), early (+24%, p<0.01), and late (+16%, p<0.001) after PTCA (Figure 2). There was no significant difference in coronary vasodilation after sublingual nitroglycerin or one spray of ISDN.

The relation between the degree of stenotic area and vasomotion was evaluated with pooled data. There was an inverse linear correlation between percent area stenosis (AST) and exercise-induced change in minimal luminal area (percent change = −0.58% AST + 26; p<0.001) (Figure 4).

Discussion

Blood flow increases three to five times in normal coronary arteries during physical exercise, whereas in stenotic coronary arteries, the increase in blood flow...
is strongly dependent on the severity of the stenotic lesion. Regional coronary blood flow is, however, not solely determined by the stenotic lesion itself but is the result of a complex interplay of hemodynamic, metabolic, and neural factors. Several studies have indicated the presence of both α- and β-adrenergic receptors in animal and human coronary arteries. An increase in α-adrenergic tone has been associated with coronary artery vasoconstriction, whereas β stimulation is accompanied by coronary vasodilation. In the present study as well as in previous reports, a decrease in coronary stenosis area has been observed during exercise in patients with coronary artery disease. The exact mechanism responsible for the decrease in minimal luminal area of the stenotic artery during exercise is not clear but might involve the following mechanisms: 1) active vasoconstriction caused by enhanced sympathetic stimulation, 2) insufficient production of endothelium-derived relaxing factor (EDRF), 3) increased platelet aggregation with release of thromboxane A2 and serotonin, and 4) flow-induced (passive) collapse of the disease-free vessel segment within the stenosis (Venturi mechanism). It seems likely that endothelial dysfunction and enhanced sympathetic stimulation during exercise play an important role in the physiology of exercise-induced vasoconstriction and thus can aggravate myocardial ischemia by augmenting the imbalance between oxygen supply and demand. The purpose of the present study was to evaluate the effect of PTCA on coronary vasomotion early and late after the intervention.

**Coronary Vasomotion Before and After PTCA**

Normal coronary arteries showed coronary vasodilation during dynamic exercise with a significant increase after sublingual administration of nitroglycerin (Figure 2). Exercise-induced vasodilation was mild, but a similar reaction was found before, early, and late after PTCA. The extent of vasodilation was, however, less (+3% before, +7% early, and +10% late after PTCA) than previously reported. This might be due to the fact that the wall of the so-called "normal vessel" was not truly normal although angiography showed no luminal changes. In patients with diseased but nonstenotic coronary arteries, no vasomotion has been found during exercise. In patients with truly normal coronary arteries, large epicardial vessels showed vasodilation during dynamic exercise in the range of 20–30% and even more in small epicardial arteries.

Stenotic coronary arteries showed exercise-induced vasoconstriction before PTCA, with a decrease in minimal luminal area of 25% (Figure 2). Similar data have been reported by Gage and Gordon. Coronary angioplasty was associated with an increase in minimal luminal area from 1.0 mm² to 2.7 mm² in group 1 and a decrease in percent area stenosis from 86% to 36% in group 1 and from 93% to 46% in group 2. The stenotic vessel segments showed on the average no vasodilation during peak exercise early and late after PTCA (Figure 2). However, the individual data revealed coronary vasomotion during exercise in seven of the 15 patients, no vasodilation in three patients, and less but persisting vasoconstriction in five other patients early after PTCA (Figure 3). Similar data were observed late after PTCA: vasodilation in 12 of the 18 patients, no vasodilation in one patient, and persisting vasoconstriction in five patients.

**Pathophysiological Mechanisms**

Several mechanisms might be involved in the regulation of coronary vasomotor tone during exercise. Coronary vasodilation during exercise seems to be dependent on an intact endothelium with adequate production of EDRF. Because the endothelium is not normal in the presence of atherosclerotic changes, it can be assumed that the abnormal response of the stenotic lesion to exercise is mediated, at least in part, by functional abnormalities of the endothelium. Healing after PTCA might lead to re-endothelialization and improvement of endothelial function. Histological examinations of re-endothelialization after PTCA have shown in the experimental animal that the neoendothelium has functional properties similar to the normal endothelium but the cells of the neoendothelium are smaller with a different shape compared with normal cells. Because a direct relation between percent area stenosis and exercise-induced vasomotion was observed (Figure 4), it has to be assumed that the more severe the stenotic lesion is, the less functioning endothelium can be expected to be present. Thus, the lack of EDRF production caused by the reduction in endothelium surface might explain exercise-induced stenosis vasoconstriction. In contrast, restoration of endothelial function, which might be due to the increase in endothelial surface after coronary angioplasty, can explain normalization of coronary vasomotion during exercise that was observed in two thirds of all patients after PTCA. On the other hand, patients with a residual area stenosis of more than 50% (Figure 4) had an abnormal response of the stenotic artery to exercise after PTCA, suggesting that the loss of more than one third of the function-
ing endothelium is associated with an abnormal response of the coronary artery under high-flow situations such as exercise. Thus, from the present data, one can conclude that a 50% area stenosis or more is associated with abnormal coronary vasomotion under high-demand situations such as exercise.

It has been shown in vitro, in situ, and in computer modeling that a flow-induced collapse within tight stenoses (Venturi mechanism) can occur.1 This would be supported by the inverse linear correlation between percent area stenosis and exercise-induced vasomotion (Figure 4); however, it is hard to explain that mild stenoses show coronary vasodilation as a result of a passive phenomenon. Thus, another mechanism must be involved during exercise besides the passive collapse of severe stenoses (more than 50% area stenosis). These two opposing effects—vasoconstriction of severe lesions and vasodilation of mild lesions—can probably be explained by a combined action of different pathophysiological mechanisms.

Coronary vasomotion was similar in the two groups early and late after PTCA, suggesting that re-endothelialization after PTCA21 is achieved early and does not further improve during the later follow-up. However, only two thirds of all patients with successful PTCA showed normal coronary vasomotion early as well as late after PTCA, and vasomotion of one third of all patients remained abnormal irrespective of the time after which the patient was evaluated. Sublingual nitroglycerin and ISDN showed a similar extent of coronary vasodilation at the different time points during the study.

Study Limitations

The accuracy of quantitative coronary arteriography has been established previously in our laboratory.3,6 Brown and coworkers22 reported that the accuracy of quantitative coronary arteriography is within 0.08 mm for measurement of known dimensions and 0.1 mm for minimum diameter estimates. The changes observed in our study, such as the 0.21-mm2 (0.52-mm diameter) decrease in stenosis area at peak exercise, are small but clearly larger than the reported angiographic resolution. Therefore, the observed changes after acute interventions such as exercise can be considered to be representative.

Acknowledgments

We acknowledge the collaboration of Richard Kirkeeide, PhD, and K. Lance Gould, MD, who provided the software and documentation of the accuracy of quantitative coronary arteriography.10

References


Key words: coronary artery disease · percutaneous transluminal coronary angioplasty · stenosis · vasomotion · supine bicycle exercise
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