INTRODUCTION

Percutaneous transluminal coronary angioplasty (PTCA) is an important method for the treatment of coronary artery disease. However, stent implantation restenosis develops in approximately 30% of patients within 6 months of PTCA, mainly because of coronary intimal hyperplasia. Several complex interactions between cellular and extracellular factors that could contribute to restenosis have been identified. Previous studies have demonstrated the potential

Effect of Chlamydia pneumoniae Infection on Coronary Flow Reserve and Intimal Hyperplasia After Stent Implantation in Patients With Angina Pectoris

Takahiro TANAKA, MD
Masashirou MATSUSHITA, MD
Yukiko OKA, MD
Toshikatsu SADA, MD
Yuji KIRA, MD

Abstract

Objectives: Chlamydia pneumoniae, C. pneumoniae has been detected in tissue from coronary atherosclerotic vascular lesions and may be involved in the pathogenesis of atherosclerosis. However, the effect of prior C. pneumoniae infection on coronary intimal hyperplasia after stent implantation and on coronary microvascular function is unknown.

Methods: Seventy-three patients with stable angina pectoris and a single de novo coronary lesion were studied prospectively. All patients underwent successful coronary angioplasty and stent implantation for the stenotic lesion. Blood samples were tested for prior C. pneumoniae infection before the procedure, and patients were divided into two groups: Seropositive and seronegative. Coronary flow reserve was measured in the non-stenotic coronary vessel before angioplasty, and quantitative coronary arteriography was performed at the stent implantation site before angioplasty and 6 months later in all patients.

Results: Coronary flow reserve in the non-stenotic vessel was significantly lower in the seropositive group than in the seronegative group (2.51 ± 0.35 vs 2.76 ± 0.43, p < 0.05). The minimum lumen diameter was smaller and late loss was greater in the seropositive group than in the seronegative group (minimum lumen diameter: 1.52 ± 0.59 vs 1.91 ± 0.79 mm, p < 0.05, late loss: 1.17 ± 0.55 vs 0.76 ± 0.55, p < 0.05). However, there was no significant difference in the restenosis rate or target lesion revascularization rate between the two groups.

Conclusions: Prior C. pneumoniae infection may accelerate intimal hyperplasia after stent implantation and impair coronary microvascular function in the non-stenotic coronary vessels.

Key Words

- Atherosclerosis
- Intravascular Doppler
- Restenosis
- Stent
- Microcirculation coronary flow reserve
- Infectious disease Chlamydia pneumoniae
Coronary angioplasty and angiography.

Ethics Committee of the Showa General Hospital.

Ten informed consent to a protocol approved by the
months after the procedures. All patients gave writ-
tion were scheduled for follow-up angiography 6

All patients undergoing PTCA and stent implant-
tion were studied prospectively. All patients had single vessel
stenotic lesion were de novo

Coronary angioplasty and stent implantation were performed using a standard method. A bal-
loon catheter of appropriate size was advanced over a

guide wire through a 6F or 7F guiding catheter and positioned at the site of stenosis. After suf-
cient predilation, coronary stent implantation was

performed in all patients. After stent implantation,

100 mg of aspirin and 200 mg of ticlopidine a day

were given to all patients as antiplatelet therapy

until follow-up angiography. Quantitative coronary

angiography (QCA) data were analyzed using a

computerized QCA system (QCA-CMS, Medical

Imaging System Co., Ltd.) before and immediately

after PTCA and stent implantation, and after a

mean follow-up of 6 months. The minimum lumina-
diameter, reference diameter, and length length

were measured, and the late loss was calculated as

the minimum luminal diameter at follow-up minus

the minimum luminal diameter immediately after

sten implantation. The rate of restenosis (%) > 50%

stenosis at the target lesion and the target lesion

revascularization rate were also analyzed.

Coronary flow reserve measurement

Left and right coronary angiography were performed

using a standard method after intracoronary

injection of 150 to 200 μg of nitroglycerin. Before

coronary angioplasty, a 0.014-inch Doppler flow

wire (FloWire, Cardiometrics, Mountain View) was

advanced into the coronary artery without the

stenotic lesion through a guiding catheter. The flow

velocity pattern was monitored on a video display.

The coronary flow velocities were determined from

single-frame images (Flomap, Cardiometrics, Mountain View) Doppler velocities were recorded

under steady state conditions and coronary flow

velocity measurements were obtained at baseline

and at peak hyperemia after bolus intracoronary

injection of adenosine 25 to 50 μg. The coronary

flow reserve was calculated as the ratio of hyper-

cemic to baseline averaged peak velocity. The blood

pressure, heart rate, and surface electrocardiogra-

phy were continuously monitored.

Blood samples and laboratory analysis

Blood was taken under standardized conditions,

and all laboratory determinations were performed

in a blinded fashion. Specific antibodies against C.

pneumoniae were identified by a microimmunoflu-

orescence method. Blood samples were used to
determine the C. pneumoniae IgG titer. Patients

were divided into two groups, seropositive and


J Cardiol 2001 Dec; 38(6): 311–317
seronegative patients, based on the titer. Patients were considered seropositive when the IgG titer was ≥ 0.9.

Statistical analysis

Values in the two groups were compared by the unpaired t-test or the χ² test for categorical variables. All measurements are expressed as the mean ± SD, and a p value < 0.05 was considered statistically significant.

RESULTS

C. pneumoniae serostatus and patient characteristics

C. pneumoniae IgG serum antibody titer was positive in 47 patients (64%) and negative in 26 patients (36%). In the study population, seropositive and seronegative individuals showed similar basic characteristics, hemodynamic parameters, risk factors for coronary artery disease, and drug treatment (Table 1).

PTCA and QCA data

The angiographic findings, the calculated parameters at baseline, immediately after PTCA, and at the 6-month follow-up, the target vessel, lesion type, and stents used are listed in Table 2. There were no differences between the two groups with respect to the reference diameter, minimal luminal diameter, percentage diameter stenosis, and lesion length before angioplasty. There were no differences in the minimum luminal diameter and percentage diameter stenosis just after the stent implantation between the two groups. No differences between the two groups were found with respect to the target vessel, lesion type, or type of stent used. Although the left anterior descending artery was treated more frequently than the other two vessels and multi-link stents were used in most patients, there were no significant differences between the two groups.

Based on the follow-up QCA data, the minimum luminal diameter was smaller in the seropositive group than in the seronegative group (1.52 ± 0.59 vs 1.91 ± 0.79 mm, p < 0.05), and the late loss was greater in the seropositive group than in seronegative group (1.17 ± 0.55 vs 0.76 ± 0.67 mm, p < 0.05). However, there were no significant differences between the two groups with respect to the restenosis rate or the target lesion revascularization.

Table 1  Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Seropositive (n = 47)</th>
<th>Seronegative (n = 26)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63 ± 10</td>
<td>67 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>30/8</td>
<td>24/5</td>
<td>NS</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>77 ± 12</td>
<td>72 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>136 ± 12</td>
<td>140 ± 23</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79 ± 15</td>
<td>82 ± 19</td>
<td>NS</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>99 ± 18</td>
<td>104 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (38)</td>
<td>11 (42)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>21 (44)</td>
<td>11 (42)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17 (36)</td>
<td>10 (38)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>16 (32)</td>
<td>9 (35)</td>
<td>NS</td>
</tr>
<tr>
<td>Drug treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>4 (94)</td>
<td>2 (88)</td>
<td>NS</td>
</tr>
<tr>
<td>ACE-inhibitor</td>
<td>18 (38)</td>
<td>8 (30)</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>21 (44)</td>
<td>9 (35)</td>
<td>NS</td>
</tr>
<tr>
<td>Lipid-lowering agent</td>
<td>17 (36)</td>
<td>9 (35)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Continuous values are mean ± SD (%). Seropositive = positive Chlamydia pneumoniae titer; Seronegative = negative Chlamydia pneumoniae titer; ACE = angiotensin converting enzyme.
tion rate. No correlation was recognized between the *C. pneumoniae* IgG serum antibody titer and minimum luminal diameter or late loss.

**Coronary flow data**

The basal averaged peak velocity did not differ between the two groups, but coronary flow reserve was lower in the seropositive group than in the seronegative group (2.51 ± 0.35 vs 2.76 ± 0.43, p < 0.05; Table 3).

**DISCUSSION**

The results of the present study indicate that *C. pneumoniae* infection might accelerate intimal hyperplasia after coronary stent implantation. We also found that *C. pneumoniae* infection might alter coronary microvascular function, as reflected by impaired coronary flow reserve.

Restenosis after coronary stent implantation is a serious complication due to its effect on secondary coronary morbidity. Despite considerable efforts, the results of various pharmacologic and interventional approaches to prevent restenosis after stent implantation have been unsatisfactory. In the present study, *C. pneumoniae* infection was found not to be a risk factor for restenosis or indicator for target lesion revascularization, although the incidence of intimal hyperplasia represented by late loss was significantly greater in seropositive than in seronegative patients. The most likely reason for

Table 2 PTCA and QCA findings

<table>
<thead>
<tr>
<th>Before angioplasty</th>
<th>Seropositive (n = 47)</th>
<th>Seronegative group (n = 26)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference diameter (mm)</td>
<td>2.84 ± 0.34</td>
<td>2.88 ± 0.28</td>
<td>NS</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>0.72 ± 0.22</td>
<td>0.70 ± 0.29</td>
<td>NS</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>74.1 ± 12.7</td>
<td>75.0 ± 13.3</td>
<td>NS</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>6.9 ± 4.4</td>
<td>8.0 ± 5.4</td>
<td>NS</td>
</tr>
<tr>
<td>Post stent implantation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>2.79 ± 0.25</td>
<td>2.81 ± 0.40</td>
<td>NS</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>4.1 ± 0.23</td>
<td>3.3 ± 0.39</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>1.52 ± 0.59</td>
<td>1.91 ± 0.79</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>41.5 ± 18.0</td>
<td>34.0 ± 20.6</td>
<td>NS</td>
</tr>
<tr>
<td>Late loss (mm)</td>
<td>1.17 ± 0.55</td>
<td>0.76 ± 0.67</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Restenosis rate (%)</td>
<td>1 (26%)</td>
<td>7 (27%)</td>
<td>NS</td>
</tr>
<tr>
<td>TLR (%)</td>
<td>0 (19%)</td>
<td>0 (23%)</td>
<td>NS</td>
</tr>
<tr>
<td>Target vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>29</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Cx</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>9</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Lesion type (ACC/AHA)</td>
<td></td>
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<td>NS</td>
</tr>
<tr>
<td>Type A</td>
<td>15</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Type B</td>
<td>27</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Type C</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Stent used</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>GFX</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Multi-link</td>
<td>39</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>NIR</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

PTCA = percutaneous transluminal coronary angioplasty, QCA = quantitative coronary angiography, MLD = minimum luminal diameter, TLR = target lesion revascularization, LAD = left anterior descending artery, Cx = left circumflex artery, RCA = right coronary artery, ACC/AHA = American College of Cardiology/American Heart Association. Other abbreviations as in Table 1.
Table 3  Coronary flow data

<table>
<thead>
<tr>
<th></th>
<th>Seropositive group (n = 47)</th>
<th>Seronegative group (n = 26)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline APV (cm/sec)</td>
<td>18.8 ± 18.7</td>
<td>14.9 ± 16.6</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary flow reserve</td>
<td>2.51 ± 0.35</td>
<td>2.76 ± 0.43</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

APV = averaged peak velocity. Other abbreviations as in Table 1.

this discrepancy is that the angiographic differences in the minimum luminal diameter and late loss between the two groups were so small. As a result, the restenosis rate and target lesion revascularization rate were not reflected by the minor luminal changes.

Preliminary studies have examined the relationship between C. pneumoniae infection and restenosis after coronary intervention, but the results are controversial. C. pneumoniae was detected in tissue specimens obtained from coronary atherosclerotic vascular lesions by coronary atherectomy and was implicated as a contributing pathogenic factor. C. pneumoniae was detected in a larger number of specimens obtained from restenotic tissue than from primary lesions. However, the difference did not reach statistical significance. Recent in vitro studies have indicated that C. pneumoniae can infect and reproduce in human endothelial cells, smooth muscle cells, and macrophages. Based on these studies, C. pneumoniae infection may affect the intimal hyperplasia that occurs after stent implantation.

The present study indicated that C. pneumoniae infection might impair coronary microvascular function. Coronary flow reserve was significantly lower in seropositive patients than in seronegative patients. The baseline coronary flow velocity was equivalent in the two groups, so the mechanism responsible for the impairment of coronary flow reserve in C. pneumoniae seropositive patients might involve restricted diastolic function at the coronary microvascular level. Serologic evidence for C. pneumoniae infection precedes both the development of early and advanced atherosclerotic lesions, suggesting that C. pneumoniae infection might have an atherogenic effect on both the coronary conduit vessels and on the microvascular vessels. Based on these factors, C. pneumoniae seropositive patients might have a lower ischemic threshold than seronegative patients with coronary artery disease. Ongoing trials of pharmacologic therapy will determine whether anti-chlamydial antibiotics such as azithromycin can prevent the acceleration of atherosclerosis associated with C. pneumoniae infection. In the near future, these antibiotics may reduce intimal hyperplasia after stent implantation and coronary microvascular dysfunction.

There are a few limitations to the present study. First, the study population was so small that the restenosis rate and target lesion revascularization rate could not be shown to be statistically different. Second, this study did not include a control group, so our results only permit comparisons between patients with or without demonstrated C. pneumoniae infection and with coronary artery disease. We could not determine the exact time when patients were infected with C. pneumoniae, so it is impossible to demonstrate that C. pneumoniae infection induced coronary atherosclerosis. To solve these problems, we must include patients with C. pneumoniae seropositive or seronegative but without coronary artery disease. Third, only C. pneumoniae IgG titers were measured in the present study, but we must examine other parameters, including C. pneumoniae IgA, IgM, and C. pneumoniae DNA in the future. Fourth, intravascular ultrasonography is a more specific diagnostic method to evaluate intimal hyperplasia than coronary angiography. However, intravascular ultrasonography was not used in the follow-up examination of coronary vessels, so a further study is necessary to acquire more accurate data on the intimal hyperplasia after stent implantation.

**CONCLUSIONS**

Our data indicate that C. pneumoniae infection affects coronary artery intimal hyperplasia and impairs coronary microvascular function. These results may support the beneficial effect of antimicrobial therapy for the treatment of coronary artery disease.
狭心症患者における冠動脈ステント留置後の冠血流予備能と内膜増殖
及びChlamydia pneumoniae感染の影響
田中 茂博 松下幸男他 通 由紀子

目的: 冠動脈の動脈硬化症治療にChlamydia pneumoniae(C. pneumoniae)の病理学的影響を指摘されて以来、C. pneumoniae感染が冠動脈硬化の一因との提唱がある。しかしながら、C. pneumoniae先行感染が冠動脈ステント留置後の内膜増殖に与える影響についての報告はない。そこで、C. pneumoniae感染の冠動脈ステント留置後の内膜増殖におよぶ影響を検討した。

方法: 30例の冠動脈ステント留置術後1ヶ月以内に行った267例の狭心症患者を対象とする。臨床経過を観察し、C. pneumoniaeの感染の有無を確認し、臨床症状、検査成績、治療経過を観察した。

結果: C. pneumoniaeの感染の有無は內膜増殖に与えないと報告されている。しかし、内膜増殖の増加はC. pneumoniaeの感染に伴うことが示唆された。

結論: C. pneumoniaeの感染は内膜増殖の増加に影響を与えるが、その詳細なメカニズムは今後の研究に待たれる。

References


Circulation 1998; 98: 628 - 633