Original Article

The Timing of the Reflected Wave in the Ascending Aortic Pressure Predicts Restenosis after Coronary Stent Placement

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It has been reported that the reflection waveform in the ascending aortic pressure is associated with systemic arterial stiffness. Stiffening of the aortic walls leads to a decrease in coronary perfusion and an increase in restenosis rate. The purpose of this study was to evaluate whether the reflection waveform in the ascending aortic pressure could be used to predict restenosis after percutaneous coronary stenting. One hundred and three patients who underwent percutaneous coronary stenting were enrolled in this study. We measured the inflection time and augmentation index (AIx) to determine the reflection waveform in the ascending aortic pressure at angioplasty. We then prospectively investigated the effect of inflection time and AIx in relation to the subsequent risk of restenosis after coronary stenting. After adjustments for age, gender, smoking habits, hypertension, type 2 diabetes, hypercholesterolemia, stent size, and heart rate, the odds ratio of restenosis in inflection time was 4.62 (95% confidence interval (CI), 1.39 to 15.4) for the lowest tertile of the inflection time level compared with the highest tertile level. As for AIx, the odds ratio of restenosis was 6.96 (95% CI, 1.93 to 25.1) for the highest tertile of the AIx level compared with the lowest tertile level. Inflection time and AIx are related to restenosis after percutaneous coronary stenting.

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Key Words: inflection time, augmentation index, predictor, restenosis, stent

Introduction

Compared with conventional balloon angioplasty, coronary stenting reduces restenosis and has a more favorable clinical outcome (1, 2). Other, more recent studies have further confirmed the safety and efficacy of coronary stenting (3–5). Nonetheless, there remains some risk of restenosis after coronary stenting.

Kastrati et al. (6) reported that diabetes mellitus, placement of multiple stents and smaller final minimal lumen diameter are predictors of restenosis after coronary stent placement.

Recent studies have demonstrated that pulse wave velocity is a predictor of coronary artery disease (7, 8). Nakamura et al. (9) reported that pulse wave velocity was useful for estimating aortic damage and was a useful predictor of vascular morbidity and mortality. The ascending aortic pressure waveform would provide much more useful information for patients with cardiac diseases. Because the reflection waveform in the ascending aortic pressure reflects large artery function and systemic arterial stiffness, it is related to the degree of arteriosclerosis (10). Inflection time and augmentation index (AIx) are closely related to reflection in the arterial...
al system and large artery function. These indices are simple to measure and make attractive tools for understanding the arterial system. Furthermore, we recently reported that the inflection point of the ascending aortic waveform is a useful tool to predict restenosis after conventional balloon angioplasty (11). Therefore, we hypothesized that the restenosis rate after stenting is associated with the reflection waveform, and prospectively investigated the effect of inflection time and AIx in relation to the subsequent risk of restenosis after coronary stenting in view of vascular mechanics. Our results showed that inflection time and AIx were related to restenosis after coronary stenting. These indices may thus be useful for reducing cardiac events after coronary stenting.

Methods

Study Subjects

The subjects consisted of 103 consecutive patients aged from 34 to 82 years, who were admitted to the Ishikiriseiki Hospital between August 1997 and October 2001 for revascularization due to coronary artery disease and were subsequently diagnosed as having angina pectoris or acute myocardial infarction. The enrollment criteria for this study included successful coronary stenting, aortic pressure measurements made at angioplasty, and coronary angiography performed 6 months after angioplasty. The protocol was in accordance with our Institutional Guidelines for Human Research, and each patient provided a written statement of informed consent for the diagnostic and therapeutic procedures performed, stating that the results could be used for prospective studies.

Measurement of Hemodynamic Variables

Hemodynamic measurements were made with the patient in the supine position at angioplasty. Aortic pressure was measured using a fluid-filled system (5F pig-tail catheter) at the ascending aorta. A hard copy was made of the pressure tracing using a chart recorder (Nihon Kohden Surgical Monitoring System; Nihon Kohden, Tokyo, Japan) at a paper speed of 100 mm/s. We defined inflection time as the time interval from the initiation of systolic pressure waveform to the inflection point and measured inflection time and AIx (the ratio of the peak above the inflection point to the pulse pressure) in patients with and without restenosis (Fig. 1). Inflection time and AIx were measured by the same experienced observer who was blinded to the clinical status of patients, angiographic data and follow-up results. Inflection time and AIx were calculated from the data of three sequential waveforms.

Procedure

Coronary stent placement was performed according to standard techniques. All patients received 200 mg/day of ticlopidine for 1 month and 162 mg/day of aspirin for 6 months after angioplasty.

Measurement of Angiographic Variables

Coronary angiography was performed at follow-up 6 months after angioplasty. Optimal views of the target lesions from all technically suitable angiograms were analyzed using a handheld electronic digital caliper (Mitutoyo Corp., Tokyo, Japan) (12), and measurements were made of the maximal narrowing of the target lesion and a noninvolved segment. Angiographic measurements were calibrated using the guiding catheter as the reference dimension. The absolute values for minimal lumen diameter (MLD) were measured at end-diastole. Procedural success was defined as successful stent placement at the desired position with $<20\%$ residual stenosis and thrombolysis in myocardial infarction (TIMI) flow grade 3. In-stent restenosis was defined as a diameter of stenosis of $>50\%$ at the stented site on the follow-up angiogram.

Statistical Analysis

Values were expressed as the mean $\pm$ SD. Categoric variables were compared using the $\chi^2$ test. Differences in the mean values between the two groups were compared using an unpaired t-test. Values of $p<0.05$ were considered statistically significant. Multiple logistic regression analysis was used to evaluate the simultaneous effects of inflection time,
Table 1. Baseline Clinical Characteristics of Study Patients

<table>
<thead>
<tr>
<th></th>
<th>No restenosis (n = 67)</th>
<th>Restenosis (n = 36)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.6 ± 9.0</td>
<td>64.4 ± 8.0</td>
<td>0.133</td>
</tr>
<tr>
<td>Male sex (n)</td>
<td>58 (86.6%)</td>
<td>22 (61.1%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36 (53.7%)</td>
<td>21 (58.3%)</td>
<td>0.835</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>24 (35.8%)</td>
<td>14 (38.9%)</td>
<td>0.833</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>39 (58.2%)</td>
<td>22 (61.1%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Current smoker</td>
<td>44 (65.7%)</td>
<td>18 (50.0%)</td>
<td>0.137</td>
</tr>
<tr>
<td>Old myocardial infarction</td>
<td>9 (13.4%)</td>
<td>6 (16.7%)</td>
<td>0.772</td>
</tr>
<tr>
<td>Echocardiography evidence of LVH</td>
<td>10 (14.9%)</td>
<td>7 (19.4%)</td>
<td>0.585</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>35 (52.2%)</td>
<td>14 (38.9%)</td>
<td>0.220</td>
</tr>
</tbody>
</table>

Status after 6 months follow-up

<table>
<thead>
<tr>
<th></th>
<th>No restenosis (n = 67)</th>
<th>Restenosis (n = 36)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>10 (14.9%)</td>
<td>9 (25.0%)</td>
<td>0.286</td>
</tr>
<tr>
<td>FPG&gt;125 mg/dl or HbA1c&gt;7%</td>
<td>11 (16.4%)</td>
<td>7 (19.4%)</td>
<td>0.787</td>
</tr>
<tr>
<td>TCHO&gt;220 mg/dl</td>
<td>17 (25.4%)</td>
<td>5 (13.9%)</td>
<td>0.214</td>
</tr>
<tr>
<td>Continued smoking</td>
<td>1 (1.5%)</td>
<td>1 (2.8%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Medications

<table>
<thead>
<tr>
<th></th>
<th>No restenosis (n = 67)</th>
<th>Restenosis (n = 36)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-inhibitors</td>
<td>26 (38.8%)</td>
<td>8 (22.2%)</td>
<td>0.123</td>
</tr>
<tr>
<td>ARB</td>
<td>2 (3.0%)</td>
<td>4 (11.1%)</td>
<td>0.180</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>16 (23.9%)</td>
<td>8 (22.2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Oral nitrates</td>
<td>54 (80.6%)</td>
<td>31 (86.1%)</td>
<td>0.568</td>
</tr>
<tr>
<td>Inflection time (ms)</td>
<td>106.9 ± 25.6</td>
<td>91.0 ± 26.4</td>
<td>0.004</td>
</tr>
<tr>
<td>Augmentation index</td>
<td>0.282 ± 0.131</td>
<td>0.348 ± 0.157</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Values are mean ± SD or No. of patients. LVH, left ventricular hypertrophy; FPG, fasting plasma glucose; TCHO, total cholesterol; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers.

Results

Baseline Clinical and Angiographic Characteristics

The baseline clinical characteristics of the study group are summarized in Table 1. Age, the presence of hypertension, diabetes mellitus, hypercholesterolemia, smoking status, and previous myocardial infarction were similar between the two groups. The proportion of men was smaller among patients with restenosis than among those without restenosis (p<0.01). Inflexion time was shorter in patients with restenosis than in those without restenosis (91.0 ± 26.4 and 106.9 ± 25.6 ms, respectively, p = 0.004). AIx was higher in patients with restenosis than in those without restenosis (0.348 ± 0.157 and 0.282 ± 0.131, respectively, p = 0.025).

The baseline angiographic characteristics and results are summarized in Table 2. Stent size was smaller in patients with restenosis than in those without restenosis, but this difference was not statistically significant.

Correlation of the Variables Influencing Inflection Time and AIx

Inflexion time was significantly related to mean pressure (r = -0.220, p = 0.025), and tended to be related to systolic pressure (r = -0.174, p = 0.079). AIx was significantly related to systolic pressure (r = 0.213, p = 0.031), and tended to be related to mean pressure (r = 0.191, p = 0.053). Multi-vessel disease was significantly related to inflexion time (r = -0.223, p = 0.024), and tended to be associated with AIx (r = 0.164, p = 0.097) (Table 3).

Multivariate Analysis of the Risk for Restenosis

To examine whether inflexion time and AIx were associated with the risk of restenosis after coronary stenting in this study population, all patients were classified into tertiles of inflexion time and AIx level. The crude cumulative incidence rates of restenosis were 52.9% for the lowest (46–87 ms), 28.6% for the middle (88–107 ms), and 23.5% for the highest tertile (108–180 ms) of inflexion time. The crude OR of restenosis was 1.25 (95% CI, 0.42 to 3.69) among the populations of tertile 2 and 3.52 (95% CI, 1.24 to 9.97) among those of tertile 3 compared to among those of tertile 3.
After adjustment for age, gender, smoking status, hypertension, diabetes mellitus, hypercholesterolemia, stent size, and heart rate, inflection time was associated with an increased risk of restenosis after coronary stenting.

The multiple-adjusted OR of restenosis after coronary stenting was 1.76 (95% CI, 0.52 to 5.92) for the middle tertile of the inflection time and 4.62 (95% CI, 1.39 to 15.4) for the lowest tertile of the inflection time compared with the highest tertile (p = 0.013 for trend).

To further quantify the effect of inflection time on restenosis after coronary stenting, we modeled inflection time as a continuous variable. The results suggested that the multiple-adjusted OR for restenosis after coronary stenting was increased by 34% when the inflection time was decreased by 10 ms (OR, 1.34; 95% CI, 1.10 to 1.63).

As for AIx, the crude cumulative incidence rates of restenosis were 20.6% for the lowest (0.0553–0.2322),
34.3% for the middle (0.2323–0.3673), and 50.0% for the highest tertile (0.3674–0.8154) of the AIx levels. The crude OR of restenosis was 2.10 (95% CI, 0.71 to 6.25) among the populations of tertile 2 and 3.86 (95% CI, 1.32 to 11.2) among those of tertile 3 compared to among those of tertile 1 ($p = 0.013$ for trend).

The multiple-adjusted OR of restenosis after coronary stenting was 2.68 (95% CI, 0.76 to 9.43) for the middle tertile of the AIx level and 6.96 (95% CI, 1.93 to 25.1) for the highest tertile of the AIx level compared with the lowest tertile ($p = 0.003$ for trend). The multiple-adjusted OR for restenosis after coronary stenting was increased by 70% when AIx was increased by 0.1 (OR, 1.70; 95% CI, 1.16 to 2.48).

**Discussion**

This study showed that inflection time and AIx were related to restenosis after coronary stenting.

**Mechanisms by Which the Reflection Waveform Predicts the Occurrence of Restenosis after Coronary Stenting**

Recent studies have demonstrated that neointimal tissue proliferation is the major cause of in-stent restenosis (13, 14). Komatsu et al. (15) found that the sequence of events leading to neointima formation after implantation of stents was very similar to that observed in the post-percutaneous transluminal coronary angioplasty (PTCA) repair processes. They suggested that the initial event was formation of a thrombus located adjacent to the stent struts and composed of abundant macrophages, and that mural thrombosis with macrophage infiltration at the earliest stage after stenting might be crucial for the recruitment of smooth muscle cells from the arterial wall.

The reflection waveform derived from an ascending aortic pressure waveform reveals the stiffness of the systemic arterial system (16). The pulse pressure increases when the reflection wave is early (17). In the ascending aorta with stiffening arterial walls, the perfusion pressure and coronary flow during diastole decrease. In contrast, in a compliant ascending aorta, the reflection wave is slow, and the perfusion pressure and coronary perfusion during diastole increase. When the reflection wave is early, coronary perfusion decreases, and thrombus formation adjacent to the stent struts may be promoted. This effect might lead to a greater propensity for neointimal tissue proliferation.

Nurnberger et al. (18) reported that AIx was associated with cardiovascular risk. In other studies, higher AIx and shorter inflection time (10, 19) have been associated with an increased risk for coronary artery disease. In this study, inflection time and AIx were associated with coronary artery disease. The increase in restenosis may thus be due to enhanced progression of arteriosclerosis as a result of the early reflection wave.

These results indicate that inflection time and AIx are associated with the occurrence of restenosis after coronary stenting.

**Clinical Implications**

Coronary stenting leads to a greater reduction in restenosis than balloon angioplasty. However, the problem of restenosis after coronary stenting has not been resolved. Several predictors of in-stent restenosis have been identified in recent studies and include smaller vessel size (20), longer stent length (21), final MLD (22) and diabetes mellitus (23). Prati et al. (24) found that the amount of residual plaque burden after stent implantation was strongly associated with in-stent neointimal proliferation, and Moussa et al. (25) reported that directional atherectomy followed by coronary stenting reduced the need for repeated coronary interventions. Our method of analysis would thus be useful not only to predict restenosis but also to determine the need for procedures such as surgical treatment or combined directional coronary atherectomy and stenting in cases with early reflection wave.

**Study Limitations**

There are several limitations to this study. First, we analyzed a limited number of patients. To generalize the results of this study, studies involving a large number of patients are essential.

Second, we used a fluid filled system to record ascending aortic pressure. If we had used a high fidelity pressure transducer, the recorded pressure waveform would have been more accurate.

Third, we did not use computerized angiographic analysis. We used handheld electronic digital caliper measurement to determine the percentage of diameter reduction as an index of stenotic severity. If we had used quantitative analysis by an automated computer-based system, our angiographic measurements would have been more accurate.

**Acknowledgements**

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**References**


