Relationship between Aortic Stiffness and Coronary Flow Reserve in Patients with Coronary Artery Disease

Running Title: Aortic Stiffness and CFR

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Abstract

Objectives: Recent studies have demonstrated that aortic stiffness is predictive of cardiovascular morbidity or mortality. Alteration of phasic coronary flow has been demonstrated in experimental models with stiffen aorta. In this study, we investigated the relationship between aortic stiffness and coronary flow reserve (CFR) in patients with coronary artery disease (CAD).

Design: An observational study

Setting: Coronary care unit of primary care hospital

Patients: 192 consecutive patients who underwent coronary angiography

Main outcome measure: Brachial-ankle pulse wave velocity (ba-PWV), CFR and severity of coronary artery disease

Results: According to the angiographic findings, patients were divided into 4 sub-groups, patients without significant stenosis (NCA group, n=28), and those with 1-vessel disease (1VD group, n=92), 2-vessel disease (2VD group, n=50) or 3-vessel disease (3VD group, n=22). Ba-PWV increased as did the number of diseased vessels and showed a significant correlation with the number of diseased vessels (NCA group vs. 1VD group vs. 2VD group vs. 3VD group: 1481±252 vs. 1505±278 vs. 1577±266 vs. 1727±347 cm/s, p<0.001). CFR showed a significant negative correlation with ba-PWV (r=-0.45, p<0.0001). The diastolic-to-systolic velocity ratio obtained in 45 patients also showed a significant correlation with ba-PWV (r=-0.35, p<0.05). Multiple regression analysis showed that ba-PWV was independent determinants of CFR (p<0.01).

Conclusions: We demonstrated the alteration of coronary flow with stiffen aorta in patients with CAD. Our results suggest one possible mechanism for recent reports showing aortic stiffness is one of the key cardiovascular risk factors.

Key words: aortic stiffness, coronary artery disease, coronary circulation
**Introduction**

Several studies have suggested that aortic stiffness may be predictive of cardiovascular morbidity or mortality.[1][2] Actually, aortic stiffness has been shown to relate to the degree of epicardial coronary artery disease (CAD) assessed by coronary angiography,[3][4] although coronary angiography provides information only about the epicardial coronary artery.

The aim of this study, therefore, was to investigate the relationship between aortic stiffness and the coronary circulation. In this study, we performed brachial-ankle pulse wave velocity (ba-PWV) measurement, as a known marker of aortic stiffness,[5][6] and compared them to the results of coronary angiography and flow velocity measurement with a coronary Doppler guidewire.
Methods

Patient Enrollment

Our patient population comprised 192 consecutive patients who were admitted to the Osaka City University Hospital to be examined for CAD. The exclusion criteria were as follows: 1) patients with an ankle-to-brachial blood pressure (BP) ratio <0.9; 2) patients with atrial fibrillation or flutter, 3) patients with valvular disease, cardiomyopathy or congenital heart disease; 4) patients with acute coronary syndrome, 5) patients who had undergone coronary artery bypass graft surgery, 6) patients with end-stage renal disease on hemodialysis.

Pulse Wave Velocity Measurements

All patients underwent ba-PWV measurement as a marker of aortic stiffness prior to coronary angiography. Measurements were performed using an automatic waveform analyzer (form PWV/ABI, Colin, Komaki, Japan) as previously reported.[7][8][9] In this study, the average of right and left ba-PWV was used for analysis.

Coronary Angiography

Coronary angiography was performed using a standard technique.[10] All patients initially received a bolus injection of 3,000IU of heparin and an intracoronary isosorbide dinitrate (2mg) prior to angiography. In this study, coronary angiograms were reviewed separately by two independent observers blinded to the results of the ba-PWV measurements and angiographically detected >75% stenosis in the major coronary vessel was defined as significant stenosis. The number of diseased vessels was determined from the number of major coronary arteries with significant stenosis or with a history of any intervention.

Intracoronary Blood Flow Velocity Measurements

Coronary flow velocity measurements were taken in a total 79 patients whom angiography confirmed had stenosis less than 25% diameter stenosis, stenosis length <10 mm and no collateral flow. In this study, we did not perform flow velocity measurements in a coronary artery with a history of myocardial infarction or prior intervention. After completion of diagnostic coronary angiography, we performed coronary flow velocity measurement using a 0.014-inch coronary Doppler guidewire as described our previous paper.[11] In this study, 30 μg of intracoronary adenosine triphosphate were administered over 10 seconds to obtain maximal hyperemia. Diastolic-to-systolic velocity ratio (DSVR) (time-averaged diastolic peak velocity divided by time-averaged systolic peak velocity) was also calculated. In this study, DSVR in right coronary artery was excluded because of its specific perfusion character.[12]

Statistical Analysis

Values are expressed as mean±SD. Categorical data were compared using χ² analysis of
Fisher's Exact Test. Analysis of variance with Bonferroni/Dunn correction was used to test for differences in continuous variables between groups. Correlation between the number of diseased vessels and ba-PWV or number of coronary risk factors was assessed by Spearman’s correlation coefficient by rank. Multiple regression analysis was performed for several parameters, predicting ba-PWV and CFR. We examined the sensitivity and specificity of ba-PWV for CFR using receiver operating characteristic (ROC) curves. A p value <0.05 was considered statistically significant.
Results

Clinical Backgrounds of Patients

A total of 192 patients (165 men, 62.1 ± 9.2 years old) were enrolled in this study. Ba-PWV measurement was successfully completed in all. From the results of coronary angiography, patients were divided into 4 subgroups; patients without significant stenosis (NCA group, n=28), patients with 1-vessel disease (1VD group, n=92), patients with 2-vessel disease (2VD group, n=50) and patients with 3-vessel disease (3VD group, n=22). Patient characteristics are summarized in Table 1.

There were no significant differences in gender and age between the 4 groups. However, incidence of hypertension and diabetes mellitus tended to increase as did the number of diseased vessels. And the number of prevalent coronary risk factors was also increased as did the number of diseased vessels (NCA vs. 1VD vs. 2VD vs. 3VD; 2.1 ± 1.2 vs. 2.3 ± 1.0 vs. 2.7 ± 1.2 vs. 3.0 ± 1.3, p<0.001).

Aortic Stiffness and Epicardial Coronary Artery Stenosis

In terms of differences between the 4 groups, systolic BP of patients in the 3VD group was significantly higher than that of patients in both the NCA group (p<0.05) and the 1VD group (p<0.05). Also, diastolic BP was significantly lower in 3VD group than in the NCA group (p<0.05) and the 1VD group (p<0.05). Patients in the 3VD group also showed significantly higher pulse pressure (PP) than patients in the NCA group (p<0.05) and the 1VD group.

Table 1. Clinical Backgrounds of Patients

<table>
<thead>
<tr>
<th></th>
<th>NCA (n=28)</th>
<th>1VD (n=92)</th>
<th>2VD (n=50)</th>
<th>3VD (n=22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>62.0±9.4</td>
<td>61.1±9.5</td>
<td>63.2±8.0</td>
<td>64.0±10.2</td>
<td>0.44</td>
</tr>
<tr>
<td>Male</td>
<td>22 (79)</td>
<td>80 (87)</td>
<td>44 (88)</td>
<td>19 (86)</td>
<td>0.68</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (43)</td>
<td>48 (52)</td>
<td>30 (60)</td>
<td>18 (82)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (18)</td>
<td>23 (25)</td>
<td>21 (42)</td>
<td>10 (45)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypercholesterolemia (&gt;220mg/dL)</td>
<td>12 (43)</td>
<td>46 (50)</td>
<td>25 (50)</td>
<td>11 (50)</td>
<td>0.92</td>
</tr>
<tr>
<td>Smoking</td>
<td>15 (54)</td>
<td>44 (48)</td>
<td>26 (52)</td>
<td>13 (59)</td>
<td>0.79</td>
</tr>
<tr>
<td>Family history of coronary artery disease</td>
<td>8 (29)</td>
<td>15 (16)</td>
<td>18 (35)</td>
<td>5 (23)</td>
<td>0.07</td>
</tr>
<tr>
<td>Obesity (body mass index&gt;25kg/m²)</td>
<td>6 (21)</td>
<td>33 (36)</td>
<td>14 (28)</td>
<td>10 (45)</td>
<td>0.25</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>123.2±11.5</td>
<td>121.9±15.6</td>
<td>124.2±17.3</td>
<td>125.9±13.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>76.0±7.3</td>
<td>75.0±8.8</td>
<td>72.4±8.1</td>
<td>71.9±7.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>48.0±8.0</td>
<td>47.2±11.0</td>
<td>48.8±11.7</td>
<td>54.9±11.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Pulse wave velocity, cm/sec</td>
<td>1481±252</td>
<td>1505±278</td>
<td>1577±266</td>
<td>1727±347</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data are presented as mean ±SD or numbers (%).
NCA; normal coronary artery, 1VD; 1 vessel disease, 2VD; 2 vessel disease, 3VD; 3 vessel disease.
(p<0.01), as shown in Table 1 and Figure 1-A~C. Similarly, patients in the 3VD group showed significant higher ba-PWV than patients in the NCA group (p<0.01), the 1VD group (p<0.01) and the 2VD group (p<0.05), as shown in Table 1 and Figure 1-D. Furthermore, ba-PWV showed a significant correlation with the number of diseased vessels (p<0.001). Multiple regression analysis was performed for several parameters (male gender, age and coronary risk factors) to predict ba-PWV. This model indicated that ba-PWV was independently correlated with age (p<0.0001), hypertension (p<0.01) and diabetes mellitus (p<0.01).

**Aortic Stiffness and Coronary Microcirculation**

In this study, CFR was obtained in a total of 79 patients (NCA group; 25, 1VD group; 37, 2VD group; 17). CFR of the 2VD group (2.6 ± 0.4) was significantly lower than that of the NCA group (3.3 ± 0.8, p<0.01) and 1VD group (3.1 ± 0.7, p<0.01). From those 79 patients, a total of 45 patients underwent flow velocity measurements in the left coronary artery were therefore eligible for DSVR measurement. 34 patients were excluded from DSVR measurement (24 patients; flow velocity measurements were performed in right coronary artery, and 10 patients; we were unable to obtain satisfactory wave-patterns). The results of DSVR measurements was follows; NCA group: 2.0 ± 0.3, 1VD group: 1.7 ± 0.3, 2VD group: 1.73 ± 0.3 (p<0.05). Both CFR and DSVR had significant correlation with ba-PWV (CFR; r=-0.45, p<0.0001, and DSVR; r=-0.35, p<0.05) as shown in Figure 2-A and B. From the univariate analysis, CFR also correlated significantly with age, and DSVR correlated significantly with systolic BP. However, there was no significant correlation between DSVR and CFR. Furthermore, we performed multiple regression analysis to predict CFR. As independent variables, age, male gender, coronary risk factors, systolic and diastolic BP, the number of diseased vessels and ba-PWV were used. This model showed that ba-PWV was an independent determinants for CFR (standard regression coefficient; -0.44, p<0.01). From the ROC curve, the value of ba-PWV >1600 cm/sec provided the best combination with a sensitivity 75% and specificity 76.1%.
Discussion

In this study, we demonstrated that aortic stiffness relates to not only epicardial coronary artery stenosis but also impaired coronary microcirculation. Atherosclerosis of the aorta and coronary artery is reported to develop in parallel.[13] However, to our knowledge, very few studies have investigated the relationship between aortic stiffness and the coronary microcirculation in humans.[14][15][16]

Aortic Stiffness and Coronary Microcirculation

Atherosclerotic changes in the epicardial coronary artery plays a central role in the pathogenesis of CAD, so early detection of atherosclerotic change is of great importance. However conventional angiography provides only a silhouette of the vascular lumen, so it is difficult to assess the early stage of atherosclerosis by this method alone. One approach might be to monitor CFR, since a decrease in CFR is reported to precede epicardial coronary artery stenosis progression.[17][18][19] Adenosine-induced CFR is thought to represent, at least in part, endothelial function.[20][21] Previously, Nemes A et al investigated the relationship between CFR and aortic stiffness obtained by transesophageal echocardiography in patients with CAD, although it is thought to be rather invasive.[15] So use of ba-PWV as a marker of aortic stiffness may well be one useful non-invasive method of assessing coronary artery endothelial function in patients with CAD.

Furthermore, our results of multiple regression analysis showed that ba-PWV was an independent determinant for CFR. In this model, however, age did not come out as a significant predictor of CFR. This may be because of the small number of patients and the strong relation between age and PWV. As described in several papers, CFR as well as aortic stiffness was reported to be impaired by several coronary risk factors.[17][18] [22] [23][24][25] [26] Therefore, it may be difficult to ascertain whether aortic stiffness has a clear cut causative role in inducing the observed impairment of CFR. Meanwhile, there are several studies, investigating the relationship between aortic stiffness and coronary circulation, which suggest potential role of aortic stiffness on the reduction of coronary circulation. Aortic stiffening leads to left ventricular hypertrophy and altering coronary perfusion. Indeed, LV hypertrophy may cause an impairment of CFR through the increase of microvessel resistance in the coronary bed.[27] Furthermore, in previous papers, aortic stiffness decreases coronary flow and an additive effects on myocardial ischemia.[28][29] Kass et al have reported that basal myocardial flow can actually be enhanced under experimental bypass model of aortic stiffening.[30][31] even at matched work loads, primarily due to augmentation of coronary flow during systole. Their results may support our findings that aortic stiffness showed a weak negative correlation with DSVR and that CFR did not correlate with DSVR. Indeed, Kingwell
et al have recently reported that aortic stiffness is a predictor of ischemic threshold of patients with coronary artery disease.[29] The alteration of coronary flow, as we demonstrated in our study, may be one possible mechanism that explains their results.

Aortic stiffness is now held to be one of the most important cardiovascular risk factors, and several recent studies have indeed demonstrated that aortic stiffness is predictive of vascular morbidity or mortality.[1][2] Our own results suggesting that not only epicardial coronary artery stenosis but also microcirculatory dysfunction are possible mechanisms for aortic stiffness correlating to cardiovascular events in humans.

Limitations

Our study may be said to have several limitations. First, there were methodological limitations in PWV measurement. We used equation to assess the vessel path length, although unfolding of the aorta with increasing age may make such approximation less reliable. Second, assessment of the coronary microcirculation was performed only in coronary arteries without significant stenosis, or in other words, patients with 3VD was excluded. So our results may not be applicable for all patients with coronary artery disease. Furthermore, we did not perform intravascular ultrasound analysis. There was the possibility that atheromatous plaque in the artery without angiographical significant stenosis reduced coronary flow. Thirdly, in this study, we used only one dose of adenosine (30µg) to obtain CFR. Our dose might not be sufficient to obtain maximal hyperemia. Finally, our patient population was small, and a large-scale study is required to confirm the validity of our results.

Conclusion

In this study, we demonstrated the decrease of CFR and DSVR in concert with increased aortic stiffness. This is one of the first studies demonstrating that aortic stiffness is an independent predictor of coronary microcirculation dysfunction in patients with CAD. We think that use of ba-PWV may well be one useful non-invasive method of assessing coronary artery endothelial function. Also, our result may be one possible mechanism which explains recent reports showing that aortic stiffness is one of the important cardiovascular risk factors.
Figure Legends

Figure 1. Relationship between the Number of Diseased Vessels and Aortic Stiffness

In the 4 groups, patients in the 3VD group showed significantly higher systolic blood pressure (BP) and lower diastolic BP than patients in the NCA and 1VD groups (p<0.05, respectively), as shown in A, B. Patients in the 3VD group also showed significantly higher pulse pressure than patients in the NCA group (p<0.05) and the 1VD group (p<0.01), as shown in Figure C. Also, patients in the 3VD group showed significant higher PWV than patients in the NCA group and in the 1VD group (p<0.01, respectively) and the 2VD group (p<0.05), as shown in D. Moreover, ba-PWV showed a significant correlation with the number of diseased vessels (p<0.001).

Figure 2.

A) Correlation between Aortic Stiffness and Coronary Flow Reserve

Coronary flow reserve showed a significant negative correlation with brachial-ankle pulse wave velocity (r=-0.45, p<0.0001).

B) Correlation between Aortic Stiffness and Diastolic-to-Systolic Velocity Ratio

Diastolic-to-systolic velocity ratio showed a significant negative correlation with brachial-ankle pulse wave velocity (r=-0.35, p<0.05).
References


Figure 1

A) Systolic blood pressure, mmHg

B) Diastolic blood pressure, mmHg

C) Pulse pressure, mmHg

D) Averaged ba-PWV, cm/sec

p<0.05; median; 75 percentile; 90 percentile
Figure 2

A) The scatter plot shows the relationship between coronary flow reserve and averaged ba-PWV, cm/sec. The correlation coefficient is $r = -0.45$, and the p-value is $p < 0.0001$.

B) The scatter plot shows the relationship between diastolic-to-systolic velocity ratio and averaged ba-PWV, cm/sec. The correlation coefficient is $r = -0.35$, and the p-value is $p = 0.02$.

Legend:
- △: normal coronary artery group
- ○: 1-vessel disease group
- □: 2-vessel disease group
Relationship between aortic stiffness and coronary flow reserve in patients with coronary artery disease
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