Prediction of Coronary Artery Disease Using Pulse Wave Velocity and Retinal Artery Lesions

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Coronary artery disease (CAD) is the leading cause of death worldwide. The prevention and early diagnosis of CAD is important for the treatment of this disease. Since the coronary angiographic examination is not available for every hospital, the convenient, quick and cheap prediction marker is needed for the screening of the suspected CAD patients. The aim of this study was to assess whether the combination of brachial-ankle pulse wave velocity (baPWV) and staging of retinal artery lesions could be a useful approach to predict CAD in symptomatic patients, including atypical chest pain. To prove this question, 472 Chinese patients with suspected CAD underwent coronary angiography, the eye fundus examination and measurement of baPWV. The results show that the frequency of baPWV of 1,400 cm/s or retinal artery atherosclerosis of ≥ Stage 2 is higher in patients with CAD (n = 312) than those without CAD (n = 160, p < 0.001). Both baPWV and retinal artery atherosclerosis are correlated with the presence of CAD with and without typical chest pain (p < 0.001), indicating that the combination of the two indexes is an independent predictor of the presence of CAD (OR: 10.37, 95% CI: 5.72-18.81, p < 0.001). Either baPWV over 1,400 cm/s or retinal artery atherosclerosis of ≥ Stage 2 is a useful marker to predict the presence of CAD even with atypical chest pain. The combination of the two non-invasive methods is also useful for predicting CAD in symptomatic Chinese patients.

Keywords: arterial stiffness; brachial-ankle pulse wave velocity; coronary angiography; coronary artery disease; retinal artery atherosclerosis

Although the modification of conventional vascular risk factors and lifestyle behavior reduce its incidence, coronary heart disease is a main cause of mortality worldwide. Increased arterial stiffness was strongly related to atherosclerosis and was an important risk factor for coronary heart disease (Mitchell et al. 2010). Brachial-ankle pulse wave velocity (baPWV) is a simple and non-invasive method of evaluating arterial stiffness and coronary artery disease (CAD) (Imanishi et al. 2004; Koji et al. 2004; Tanaka et al. 2009). In addition, the retinal arterioles offer an opportunity to noninvasively explore the systemic cardiovascular disease (Borgia et al. 1997; Shantha et al. 2010; Kraljev et al. 2010; Kim et al. 2010). The retinal atherosclerotic changes correlated with the atherosclerotic changes of coronary arteries (Michelson et al. 1979; Ugrica et al. 1989; Tedeschi-Reiner et al. 2005). Kim et al. (2010) and Raicević et al. (2000) found that the coronary arterial stiffness and the retinal artery atherosclerosis over Stage 2 are closely correlated. However, the two markers have not been compared in the same subjects. And it is still unclear whether the combination of baPWV and retinal artery lesions will provide a better prediction marker for the screening of CAD.

The aim of this study was to assess whether the combination of baPWV and retinal artery lesions can be a useful approach to predict CAD in symptomatic Chinese patients, including atypical chest pain.

Methods

Study population
Four hundred and seventy-two consecutive patients, aged 36 to 88 years, were enrolled in this study. All subjects received coronary angiographic examination at Department of Cardiovascular Medicine, Mentougou district hospital between July 2006 and August 2009, including patients with typical chest pain [1, chest pain was induced by fatigue or emotion; 2, chest pain located in precordial or under the lower sternum; 3, chest pain persists 2-3 minutes, not longer than 20 minutes; and 4, symptom relieved soon after the elimination of causes or sublingual nitroglycerin (Jones et al. 2010)] or patients with atypical chest pain, such as chest distress, short breath, a sense of soreness of precordial or backs, and epigastric pain. Smoking habit was defined as active smoking at the present state. High blood pressure...
was defined as a systolic blood pressure ≥ 140 mm Hg and/or a diastolic blood pressure ≥ 90 mmHg or the prescription of antihypertensive drugs. Diabetes mellitus was defined as a fasting blood glucose level ≥ 7.0 mmol/L or the prescription of hypoglycemic agents including oral blood sugar-lowering drugs or insulin. Hyperlipidemia was defined as a total cholesterol level > 5.72 mmol/L or the prescription of hypocholesterolemic drugs such as statins. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m²). The eye fundus examination and baPWV were evaluated in all subjects. Patients were excluded from the study if they had severe nephropathy (serum creatinine > 133 µmol/L), vascular obstruction, previous coronary intervention, limb amputation, acute illnesses or any other condition that was thought to contraindicate coronary angiography (CAG). Also, subjects with atrial fibrillation, aortic aneurysm, low left ventricular ejection fraction (< 40%), or a permanent pacemaker implant were excluded for factors known to influence the baPWV.

Measurement of baPWV

For all the patients baPWV was measured before CAG in the morning. In brief, after the subject had rested in a supine position for more than 5 min, the baPWV was measured with a volume-plethysmographic apparatus (FORM/ABI, Colin Co. Ltd, Komaki, Japan) while the subject was in the same position. This instrument simultaneously records the brachial-ankle PWV and the brachial and ankle blood pressures on the left and right sides, produces an electrocardiogram, and records the heart sounds. The higher baPWV value measured on either side of each patient was used for the analysis. The completed method has been described elsewhere. Patients did not receive their medications on the day of the examination. According to the data from Japanese baseline epidemiological studies, baPWV over 1,400 cm/s was a critical value that indicates the increase of the peripheral main arterial stiffness. The morbidity of CAD is significantly higher in patients with baPWV over 1,400 cm/s than patients with baPWV under 1,400 cm/s. So baPWV over 1,400 cm/s was defined as a risk factor (Imanishi et al. 2004; Koji et al. 2004; Tanaka et al. 2009).

Assessment of retinal artery lesions

The eye fundus examination was done in all patients before CAG by direct ophthalmoscopy performed after pupil dilation. The ophthalmologist did not know the baPWV values about the subjects. In all patients, the upper temporal quadrants and the first 3 arterial branching were analyzed. The extent and severity of atherosclerotic vascular lesions in the retinal arteries were classified according to Scheie (1953). Stage 1 is defined as a broadening of the light reflex from the artery, with minimal or no arteriovenous compression. Stage 2 is defined as changes similar to those in Stage 1, but more prominent. In Stage 3, the arteries have a “copper wire” appearance, the arteriovenous compression is much greater, and serious atherosclerotic changes of the retinal arteries are present. In Stage 4 is the most severe form of atherosclerosis of the retinal arteries. Some studies found that the retinal artery atherosclerosis over Stage 2 and the coronary arterial stiffness are closely correlated (Raicević et al. 2000; Kim et al. 2010). In addition, we found that the prediction ability is good when the retinal artery atherosclerosis over Stage 2 with the best sensibility, specificity, and the biggest area under the ROC curve. So the retinal artery atherosclerosis greater than or equal Stage 2 was defined as a risk factor.

Coronary Angiography

CAG was performed in all patients using a standard Judkins technique (Shah et al. 1975). The degree of diameter stenosis (%) was evaluated by two observers who were blinded to the information regarding brachial-ankle PWV and retinal artery lesions. The percentage of luminal diameter stenosis was evaluated by quantitative coronary analysis in each segment, and CAD was defined as the presence of a greater than 50% narrowing in diameter for each of the three main coronary vessels (left anterior descending coronary artery, left circumflex coronary artery and right coronary artery).

Ethical Statements

This study was approved by the Ethics Committee of Capital Medical University. Informed consent was obtained for all participants and written by themselves.

Statistical Analysis

Baseline characteristics of patients were presented as the means ± standard deviation for continuous variables and the chi-squared test was used for noncontinuous variables. BaPWV over 1,400 cm/s, retinal artery atherosclerosis ≥ Stage 2 and both of two risk factors in CAD and Non-CAD were compared using analysis of the chi-squared test. Multivariate logistic regression analysis was performed to assess the correlation between the presence of CAD and the possible risk factors including age > 65 years, female sex, hypertension, hypercholesterolemia, BMI > 25 kg/m², diabetes, smoking, typical chest pain, BaPWV > 1,400 cm/s, and retinal artery atherosclerosis ≥ Stage 2. Univariate and multivariate logistic regression analyses were performed to determine the association between both of two risk factors and the presence of CAD. A two-sided p value < 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software (version 12.0).

Results

Baseline Characteristics

The average age of the 472 patients was 60 ± 11 years. Table 1 shows the comparison of baseline characteristics of the patients with and without CAD. There were 304 males (64.4%) and 168 females (35.6%). Overall, 75.2% of the subjects had hypertension, 38.1% had hypercholesterolemia, 44.9% had diabetes, and 58.1% were smokers. Patients with CAD (n = 312) were more likely to have diabetes and typical chest pain compared with the patients without CAD (n = 160, p < 0.001, Table 1). However, there was no significant difference in age, gender, hypertension, hypercholesterolemia, body mass index or smoking between two groups. Of patients with hypertension, 82.0% had been taking antihypertensive agents; 72.2% of patients with hypercholesterolemia had been taking cholesterol-lowering drugs, and 64.2% of patients with diabetes had been taking insulin or hyperglycemic agents.

Comparison of BaPWV and Retinal Artery Lesions

The frequency of baPWV > 1,400 cm/s was higher in patients with CAD than those without CAD (p < 0.001). There was a higher incidence of retinal artery atherosclerosis ≥ Stage 2 in patients with CAD (p < 0.001). Moreover,
175 CAD patients (56.1%) had the two risk factors, whereas among 160 non-CAD patients, 20 patients (12.5%) showed the two risk factors. In patients with CAD, the incidence of the two risk factors was higher ($p < 0.001$) (Table 2). For example, though a patient was diagnosed without significant hypertension and diabetes, significant cross-vein pressure was seen in the fundus photography examination with retinal artery atherosclerosis as Stage 2, and the two-vessel disease was seen in the results of coronary angiography (Fig. 1).
Risk factors with CAD

Logistic regression analysis revealed that, among the coronary risk factors evaluated in this study, the presence of CAD was correlated significantly and independently with diabetes and typical chest pain. As the two noninvasive methods used to evaluate CAD, either BaPWV or retinal artery atherosclerosis was significantly correlated with the presence of CAD (Table 3).

A combination of BaPWV and retinal artery atherosclerosis was used to predict the presence of CAD. In univariable analysis, the combination of the two risk factors independently correlated with the presence of CAD (OR: 8.94, 95% CI: 5.32-15.03, p < 0.001). After multivariable adjusting for other important covariates, the combination of the two risk factors remained an independent predictor of the presence of CAD (OR: 10.37, 95% CI: 5.72-18.81, p < 0.001) (Table 4).

Further analysis showed that two non-invasive markers were correlated with the presence of CAD with typical chest pain and without typical chest pain. In univariable analysis, BaPWV and retinal artery atherosclerosis ≥ Stage 2 in the patients with the typical chest pain were useful markers to predict the presence of CAD (Odds Ratio = 5.77, p < 0.001 and Odds Ratio = 4.09, p < 0.001, respectively). These data suggest that both BaPWV and retinal artery atherosclerosis ≥ Stage 2 possess good prediction value in patients with typical chest pain and those with atypical chest pain.

Discussion

Atherosclerosis is a systemic disease and represents in the large arteries, the medium-sized arteries and small arteries. If atherosclerosis exists in the peripheral arteries and arterioles, the likelihood of atherosclerosis in coronary artery will increase. BaPWV is simpler and easier as a non-invasive measure of the stiffness of the peripheral large arteries (Wong et al. 2002). Since the coronary artery is a middle-sized artery, theoretically sclerosis in the coronary artery is highly suspected to occur when atherosclerosis happened in both large and small peripheral arteries. So we want to know whether we can predict the stiffness of middle-sized coronary artery by exploring the early stiffness of the large and small peripheral arteries. Therefore, we determined whether the combination of baPWV and retinal artery lesions can be a useful approach to prediction of

<table>
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<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
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</thead>
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<tr>
<td>Age &gt; 65 years</td>
<td>0.89</td>
<td>0.51 - 1.52</td>
<td>0.658</td>
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<td>Female sex</td>
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<td>2.02 - 6.02</td>
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<td>Smoking</td>
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<td>0.704</td>
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<td>Typical chest pain</td>
<td>7.17</td>
<td>4.12 - 12.50</td>
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<td>BaPWV &gt; 1,400 cm/s</td>
<td>6.49</td>
<td>3.80 - 11.09</td>
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<tr>
<td>Retinal artery atherosclerosis ≥ Stage 2</td>
<td>6.64</td>
<td>3.79 - 11.64</td>
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<th>Odds Ratio</th>
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<th>P Value</th>
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<td>Combination of BaPWV and retinal artery atherosclerosis ≥ Stage 2</td>
<td>10.37</td>
<td>5.72 - 18.81</td>
<td>&lt; 0.001</td>
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CAD in symptomatic (including typical chest pain and atypical chest pain) Chinese patients.

BaPWV, which reflects arterial stiffness, is not only a predictor of cardiovascular events, but also a useful marker to predict the presence and severity of CAD. Many studies reported that baPWV could be used to predict cardiovascular lesions and with increasing interests, various cutoff values have been suggested to assess arteriosclerosis in multiple clinical settings. Yamashina and colleagues reported that baPWV in patients with CAD was significantly higher than those without patients CAD. And they also found that a cutoff value 1,400 cm/s for baPWV was useful for screening patients with atherosclerotic cardiovascular disease (Yamashina et al. 2003). Tso et al. (2005) observed that patients diagnosed as lupus erythematosus with baPWV above 1,400 cm/s had more cardiovascular risk factors. Xu et al. (2008) demonstrated that baPWV above 1,600 cm/s strongly indicated severe coronary atherosclerosis in elderly urban Chinese patients, and Kim et al. (2009) showed cutoff value of 1,635 cm/s was useful for predicting the presence of multiple coronary artery occlusive disease. In the present study we demonstrated that in patients with baPWV over 1,400 cm/s, the number of those diagnosed as CAD is significantly more than those diagnosed as non-CAD. Further, baPWV over 1,400 cm/s was remained an independent predictor of CAD after adjusting conventional vascular risk factors in symptomatic Chinese patients.

Atherosclerotic changes in the retinal arteries are characterized by thickening of the arterial wall and lipid deposition in the intima. Several studies conducted that many patients who had retinal vascular changes most probably had systemic atherosclerosis disease. Michelson et al. (1979) reported that retinal arteriolar changes were indicator of the severity of coronary stenosis in patients without hypertension and diabetes, and Tedeschi-Reiner et al. (2005) also showed that retinal vessel atherosclerosis significantly correlated with atherosclerotic changes of coronary arteries. Moreover, Wong et al. (2002) reported that retinal arteriolar narrowing was related to risk of coronary heart disease in women after adjusting other important risk factors in multivariable analysis. Our study showed there was a higher incidence of retinal artery atherosclerosis over Stage 2 in patients with CAD and it also independently associated with CAD in symptomatic Chinese patients. Moreover, we found that the combination of baPWV over 1,400 cm/s and retinal artery atherosclerosis over Stage 2 were a strong predictor of CAD after adjusting other important risk factors in multivariable analysis (OR: 10.37, 95% CI: 5.72-18.81, p < 0.001). The combination of the two non-invasive tests to estimate the presence of CAD was superior than assessing a single such marker and could be a useful approach to prediction of CAD in symptomatic Chinese patients.

Previous studies showed that both hypertension and dyslipidemia were the most important risk factors for CAD (Sharrett et al. 1994; Giannakoulas et al. 2009). However, hypertension and dyslipidemia were not significantly associated with the presence of CAD in the multivariate analysis in our study. This may be explained by the fact that most of the patients with risk factors had been previously treated.

Conclusions

Either baPWV over 1,400 cm/s or retinal artery atherosclerosis of ≥ Stage 2 is a useful marker to predict the presence of the CAD. The combination of these two non-invasive methods is a useful approach for predicting CAD in symptomatic Chinese patients.

Conflict of Interest

We have no conflict of interest.

References


