Impaired Hyperemic Response of Forearm Vessels in Patients with Coronary Artery Disease

A Non-Invasive Evaluation

Osamu Hirono, MD, Isao Kubota, MD, Ryoko Shiga, MD, Shuichi Abe, MD, Kyoko Terashita, MD, and Hitonobu Tomoike, MD

SUMMARY

The blood flow velocity of the right brachial artery was measured noninvasively by pulsed Doppler flowmetry in 50 patients with angina pectoris. Reactive hyperemia was induced by a 2-minute occlusion of the artery by a tourniquet. We assessed the peak velocity ratio (PVR) and 50% recovery time (RT) which were defined as the ratio of maximal to baseline systolic peak velocity and as the interval from the resumption of arterial flow to 50% decline of the increased systolic peak velocity, respectively. Multiple regression analysis for determinants of PVR and 50% RT was performed with 7 variables which were age, sex, hypertension, diabetes mellitus, smoking, total cholesterol level, and the number of diseased coronary arteries. Multiple R was 0.649 (p < .01) for PVR and 0.682 (p < .01) for 50% RT. There were significant inverse correlations between PVR and the number of diseased vessels (t-value; -3.34), hypertension (-2.43) and smoking (-2.38). The 50% RT was inversely correlated with the number of diseased vessels (t-value; -4.45), feminine gender (-2.75) or smoking (-2.12). Stepwise regression analysis revealed that the number of diseased vessels was the only significant variable for the determination of PVR or 50% RT. An impairment of reactive hyperemia at the forearm vessel correlated with the severity of coronary artery disease in patients with angina pectoris. This finding suggests the presence of some identical mechanisms which are detrimental to both vascular beds. Observation of the hyperemic response at the brachial artery will provide a clue for noninvasive estimation of the extent of coronary artery disease. (Jpn Heart J 1996; 37: 837-846)

Key words: Angina pectoris Coronary artery disease Ultrasound Doppler

From the First Department of Internal Medicine, Yamagata University School of Medicine, Yamagata, Japan.
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Address for correspondence: Isao Kubota, MD, The First Department of Internal Medicine, Yamagata University School of Medicine, Iida-Nashi 2-2-2, Yamagata 990-23, Japan.
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The presence of coronary stenosis of more than 50% diameter narrowing is accompanied by the reduction of coronary flow reserve. The level of coronary flow reserve is limited not only by the epicardial coronary narrowing but also by the presence of microvascular diseases. Alterations of flow reserve have been estimated by reactive hyperemia and/or pharmacological interventions. In cases of coronary circulation, invasive techniques such as cardiac catheterization or transesophageal pulsed Doppler echocardiography are needed. However, it has become possible to evaluate the reactive hyperemia at the forearm artery noninvasively using a high-resolution ultrasound device.

We postulated that reactive hyperemic response of the peripheral circulation might be impaired in patients who have severe coronary artery disease. Since there are correlations in the levels of atherosclerosis among various arterial beds, it is plausible that patients with coronary artery disease have atherosclerotic changes in their peripheral arteries. However, little is known about the relationship between changes in the reactive hyperemic response of peripheral vessels and the extent of coronary artery disease. The purposes of this study were to examine the characteristics of reactive hyperemia at the brachial artery in patients with angina pectoris using a percutaneous pulsed Doppler technique and to correlate the hyperemic response with the angiographic findings in coronary arteries.

Methods

Subjects: This study population consisted of fifty patients who underwent coronary arteriography at our institution under the clinical diagnosis of angina pectoris but not of myocardial infarction (Table I). They were 28 men and 22 women. Mean age was 67 ± 10 (range 39–87) years. Of these patients, hypertension (> 140/90 mmHg) was present in 24 (48%), diabetes mellitus in 11 (22%), smoking in 27 (54%) and hypercholesterolemia (> 220 mg/dl) in 20 (40%). Smoking level was rated using Brinkman’s index (the number of cigarettes smoked per day multiplied by the number of years of smoking). Significant coronary narrowing, defined as > 50% diameter stenosis, was found in 39 patients (78%); 15 (30%) had one-vessel disease, 12 (24%) had two- and 12 (24%) had three-vessel disease. The other 11 patients had no significant coronary narrowing (zero-vessel disease, 22%). Multivessel disease was defined as two- or three-vessel disease. None of the patients had clinical evidence of vascular disease of the upper extremities or ultrasound evidence of arterial narrowing of the vessel studied.

Measurement of brachial artery blood flow velocity: All studies were done in the early morning with the patients in a supine position and in a fasting state.
Blood flow velocity measurements were performed using the pulsed Doppler technique, the ROI (region of interest) was guided by two-dimensional images (L738 transducer, Acuson 128XP, Acuson, Mountain View, California). The carrier frequency of the Doppler system was 5 MHz. For fixing the transducer position properly during this study, we used a transducer-holding apparatus. An incident angle was less than 45 degree to flow. Reactive hyperemia was induced by an inflation of a pneumatic tourniquet placed around the forearm to a pressure of 300 mmHg and then release of occlusion. The arterial flow velocity was continuously recorded on super-VHS videotape. The diameter of the vessel at the peak of the R wave on the ECG was measured just before the Doppler study on two-dimensional images, with a 7.0 MHz linear array mode of the same transducer.

**Preliminary study:** To determine the general characteristics of the reactive hyperemic response at the brachial artery, we performed a preliminary study in six normal volunteers (all men, mean age 25.3 years). Interruptions of blood flow for four different durations (12, 36, 120 and 360 seconds) were conducted in each subject. Before and after the cuff occlusion, systolic peak velocity and mean velocity were measured in each cardiac cycle and recorded on a strip chart. Mean velocity was calculated by planimetry. The ratio of maximal systolic peak velocity during reactive hyperemia to baseline systolic peak velocity (ratio of systolic peak velocity) and the ratio of maximal to baseline mean velocity (ratio of mean velocity) were calculated.

Figure 1A shows the relationship between the ratio of systolic peak velocity and the ratio of mean velocity. A linear correlation was observed. We then
measured the interval from the resumption of blood flow to 50% decline of increased systolic peak velocity (50% recovery of systolic peak velocity) and the interval from the resumption of flow to 50% decline of increased mean velocity (50% recovery of mean velocity). Figure 1B shows the relationship between 50% recovery of systolic peak velocity and 50% recovery of mean velocity. This figure demonstrated that the 50% recovery of systolic peak velocity is almost identical to 50% recovery of mean velocity.

**Study for patients:** Based on the results of the preliminary study, we measured...
the systolic peak velocity instead of the mean velocity. Since it became difficult to keep the arm at the fixed position as the ischemic duration increased, we adopted a 120-second tourniquet occlusion in the study for patients. With regard to the reactive hyperemic response of 120-second ischemia, the ratio of systolic peak velocity and 50% recovery of systolic peak velocity were designated peak velocity ratio (PVR) and 50% recovery time (50% RT), respectively.
Figure 2 shows examples of pulsed Doppler waveforms recorded before a 2-minute occlusion (Figure 2A) and just after the resumption of the arterial flow (Figure 2B) of the brachial artery.

**Statistical analysis:** Statistical analysis was conducted using StatView 4.0 for Macintosh (Abacus Concepts, Inc., California). Comparison of patient characteristics and Doppler parameters between patients with and without multivessel (2 or 3 vessel) disease was performed by unpaired t test. Multiple regression analysis and stepwise multiple regression analysis for determinants of PVR and 50% RT were performed with 7 variables; age (years), sex (male 0, female 1), absence (0) or presence (1) of hypertension and diabetes mellitus, Brinkman’s index, total cholesterol level (mg/dl), and the number of diseased vessels (0, 1, 2 or 3). When performing stepwise multiple regression analysis, the entry criterion used was 4.000 of the F-value, and the removal criterion used was 3.996 of the F-value. Comparisons of PVR and 50% RT among patient groups of 0-, 1-, 2- and 3-vessel diseases were made by ANOVA followed by Bonferroni t test. Differences were considered significant at $p < 0.05$.

**RESULTS**

All recordings were appropriate for the calculation of PVR and 50% RT. Out of 50 patients, 24 had multivessel disease. Patients with multivessel disease had a significantly higher mean age than those without ($p = 0.044$, Table I). There were no significant differences in sex ratio, percentages of hypertension, diabetes mellitus, smoking and hypercholesterolemia, Brinkman’s index, total cholesterol level, and vessel diameter between multivessel and non-multivessel patients. At the baseline, systolic peak velocity in patients with multivessel disease

| Table II. Multiple Regression Analysis of Determinants of PVR and 50% RT for Risk Variables |
|----------------------------------------------|----------------|----------------|
| Variable                        | Coefficient | t-value | Coefficient | t-value |
| Age (years)                     | -0.523      | -0.541  | 0.014       | 0.277   |
| Sex (male 0, female 1)          | -8.220      | -0.377  | -3.119      | -2.750**|
| Hypertension                    | -43.704     | -2.432* | -0.296      | -0.317  |
| Diabetes mellitus               | -3.768      | -0.175  | -1.116      | -0.997  |
| Brinkman’s index                | -0.050      | -2.381* | -0.002      | -2.166* |
| Total cholesterol (mg/dl)       | -0.028      | -0.179  | 0.017       | 2.091*  |
| Number of diseased vessels     | -28.950     | -3.335**| -2.008      | -4.450**|

Hypertension and diabetes mellitus were assigned 0 (absent) or 1 (present), and number of diseased vessels was assigned 0, 1, 2 or 3. PVR, peak velocity ratio; 50% RT, 50% recovery time. *$p < 0.05$, **$p < 0.01$. 

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Table III. Stepwise Regression of Number of Vessel Disease for Determinants of PVR and 50% RT

<table>
<thead>
<tr>
<th></th>
<th>PVR</th>
<th>50% RT (second)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>0.513</td>
<td>0.541</td>
</tr>
<tr>
<td>R squared</td>
<td>0.263</td>
<td>0.292</td>
</tr>
<tr>
<td>F-value</td>
<td>17.147</td>
<td>19.839</td>
</tr>
<tr>
<td>p-Value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Coefficient</td>
<td>−33.427</td>
<td>−1.906</td>
</tr>
</tbody>
</table>

Only the number of diseased vessels was selected as a determinant of both PVR and 50% RT. PVR, peak velocity ratio; 50% RT, 50% recovery time.

was 0.61 ± 0.13 m/sec, which was significantly faster than 0.49 ± 0.13 m/sec in patients without (p = 0.003). At the peak hyperemic state, the maximal systolic peak velocity was 1.03 ± 0.25 and 1.14 ± 0.34 m/sec in patients with multivessel and non-multivessel disease (NS), respectively. PVR and 50% RT in patients with multivessel disease were significantly (p < 0.001) lower than those in patients without multivessel disease (Table I).

Table II summarizes the results of multiple regression analysis for determinants of PVR and 50% RT. Significant inverse correlations were noted between PVR and the number of diseased vessels (t-value; −3.335), hypertension (−2.432), and Brinkman’s index (−2.381). Similar correlations were noted between 50% RT and the number of diseased vessels (−4.450), feminine gender (−2.750), and
Brinkman’s index (~2.266). Note that a significant positive correlation existed between 50% RT and total cholesterol level (t-value 2.091). Age and diabetes mellitus were not associated with alterations in PVR or 50% RT.

Using stepwise regression analysis, only the number of diseased vessels was considered as a significant variable for determining the levels of both PVR and 50% RT (Table III). Inclusion of other parameters did not significantly improve the level of the regression coefficient.

Figure 3 shows the comparison of mean values of PVR (A) and 50% RT (B) among groups of patients with 0-, 1-, 2- and 3-vessel diseases. Both PVR and 50% RT became smaller as the number of diseased vessels increased.

**DISCUSSION**

Basal blood flow and reactive hyperemic response were measurable noninvasively at the brachial artery using a percutaneous pulsed Doppler method. We found that the PVR and 50% RT of reactive hyperemia following a 2-minute interruption of blood flow in patients with angina pectoris were attenuated in proportion to the number of diseased coronary arteries. This finding clearly demonstrates that the reactive hyperemia at the brachial artery is impaired in patients with severe coronary artery disease, and the degree of the impairment and the extent of coronary atherosclerosis correlate with each other. It is suggested that there are some identical mechanisms which are detrimental to both vascular beds.

In the present study, there were no stenotic lesions at the brachial artery studied, since local narrowing and turbulence were not detected on two-dimensional vascular and flow images, respectively. Therefore, the attenuation of reactive hyperemia associated with the severity of epicardial coronary artery disease might depend on changes in proximal arteries such as the aorta as well as in the distal forearm vessels. The baseline systolic peak velocity was greater in cases with multivessel disease than in those with non-multivessel disease, which suggests the presence of stiffening of the conduit vessels. Functional disorders of the resistance vessels but not of arterial occlusions may also alter the hyperemic response or flow reserve at the forearm vessel, as reported on coronary flow reserve in patients with syndrome X or microvascular angina.

The endothelial function is shown to deteriorate in patients with cardiovascular disease. The presence of endothelial dysfunction reduces the hyperemic response through the reduced production of nitric oxide, which is one of the determinants of reactive hyperemia in human forearm vessels. Since hypertension, diabetes mellitus, smoking habit or hypercholesterolemia causes endothelial dysfunction of the forearm vessels, we examined whether these coronary
risk factors influence the appearance of reactive hyperemia. Multiple regression analysis demonstrated a negative effect of smoking and hypertension on the reactive hyperemic response, although they were less influential than the number of diseased vessels. On the other hand, total cholesterol level showed a positive correlation with 50% RT. Stepwise multiple regression analysis did not reveal any significant contribution of these risk factors to the reactive hyperemic response in addition to the number of diseased vessels. Apart from nitric oxide, prostaglandins, adenosine, and ATP-sensitive K+ channels may play a role in reactive hyperemia of forearm vessels. Further study will be needed to investigate the contribution of these agents to the impaired forearm reactive hyperemia in patients with coronary artery disease.

In this study, we evaluated the reactive hyperemia as the ratio of the maximal to baseline blood velocity according to the previous studies using ultrasound Doppler. On the other hand, the maximal blood flow per se was used as an index of reactive hyperemia in a study using strain-gauge plethysmography. Further study will be needed to determine the best index for reactive hyperemia assessed by ultrasound Doppler. In addition, we made use of only the blood flow velocity to evaluate the reactive hyperemic response. The change in vessel diameter must be taken into consideration to calculate the actual blood flow. It is unlikely that the flow-mediated dilatation has a critical effect on our estimation of PVR and 50% RT, since flow-mediated dilation of the brachial artery after 4.5 minutes of arterial occlusion is as much as 10%.

In conclusion, this study demonstrates for the first time that there is a significant correlation between the impairment of reactive hyperemia at the brachial artery and the extent of coronary artery disease in patients with angina pectoris. Further study will be required to clarify the mechanisms of the altered reactive hyperemic response of the forearm vessels in patients with severe coronary artery disease. Practically, measuring the reactive hyperemia at the brachial artery by a pulsed Doppler technique will provide a clue for noninvasive estimation of the severity of coronary artery disease.

REFERENCES


