Baroreflex Sensitivity in Patients with Takayasu's Aortitis

Akira Takeshita, M.D, Senichi Tanaka, M.D., Yasuhiro Orita, M.D., Hideo Kanaide, M.D., and Motoomi Nakamura, M.D.

SUMMARY Takayasu's aortitis is an arterial inflammatory disease of arteries of unknown etiology. Fainting is a common symptom and has been attributed to hypersensitivity of the baroreflex. We studied baroreflex sensitivity in 11 patients with Takayasu's aortitis and compared it with that of eight control subjects of comparable age. Baroreflex sensitivity was assessed by determining the slope of a regression line relating the rise of systolic arterial pressure to the prolongation of the R-R interval of the electrocardiogram during a transient rise of arterial pressure induced by an intravenous injection of phenylephrine. The average baroreflex slope of patients with Takayasu's aortitis (4.0 ± 0.8 msec/mm Hg) was significantly less than that of control subjects (10.7 ± 0.8 msec/mm Hg, P < 0.001). Reduced baroreflex sensitivity in patients with Takayasu's aortitis may be due to the hardening of the arteries where baroreceptors lie, or to hypertension and/or cardiac disease which was present in most of the patients included in the study. Patients with Takayasu's aortitis who complained of fainting also showed the reduced baroreflex sensitivity. This indicates that fainting in this disease is not likely to be caused by the hyperreactivity of the baroreceptors as is commonly postulated.

TAKAYASU'S AORTITIS is an arterial inflammatory disease of unknown etiology, which most commonly affects the aorta and its large branches, and the pulmonary artery.1,5 Pathological examinations usually reveal extensive granulomatous lesions and/or cellular infiltration in the middle and outer layers of the arterial wall in the early stage of the disease. In the chronic stage, these processes lead to stenosis or obstruction of the involved arteries, mainly due to severe intimal fibrosis.6 This type of aortitis commonly affects young women.

It appears that there is some controversy in the literature regarding whether the baroreflex is hypersensitive or shows impaired function in patients with Takayasu's aortitis. Fainting, a common symptom of Takayasu's aortitis,6,7 is postulated to be caused by hypersensitivity of the baroreflex because profound response to carotid sinus massage has occurred in these patients.6 However, a recent study has suggested that paroxysmal hypertension which may occur in patients with Takayasu's aortitis may be due to impaired baroreflex function.6 In fact, the hardening of the arteries where baroreceptors lie has been shown to be associated with reduced responsiveness of baroreceptors to a transient change of blood pressure.6,7

Baroreflex function in Takayasu's aortitis has not been studied using a method which enables comparison of the reflex function between patients with aortitis and control subjects. The present study was undertaken to examine the baroreflex function in patients with Takayasu's aortitis using the method of Smyth, Bristow and co-workers which assesses baroreflex function by the prolongation of R-R interval per unit change of blood pressure induced by bolus injections of phenylephrine6,8 and to compare it with that in control subjects.

Methods

Eleven patients with Takayasu's aortitis and eight control subjects, at a comparable age, were studied. The study was done with unsedated subjects in the supine position. An intra-arterial cannula was inserted into a brachial or femoral artery and connected to a Statham pressure transducer. The artery was chosen when there was no significant stenotic lesion on the angiogram proximally to the place where the cannula was inserted. Arterial pressure and the electrocardiogram were recorded simultaneously on a multichannel oscillographic recorder at a paper speed of 50 mm/sec. A second cannula was inserted in an antecubital vein, through which repeated bolus injections of phenylephrine were given. The sensitivity of the baroreflex was calculated by plotting the R-R interval of each beat against the systolic pressure of the preceding beat when blood pressure was raised acutely and transiently by an intravenous injection of phenylephrine. Plotting was started at the beginning of blood pressure change and proceeded to the peak of the rise of blood pressure. These points were then analyzed for linear correlation. The reflex sensitivity was expressed as the slope of the regression line. The slope was used for further comparisons only if the correlation coefficient was more than 0.80.

Patients with Takayasu's aortitis included eight female and three male patients (table 1). Their age ranged from 19 to 52 years (average 33.6 ± 3.1 years). All patients were hospitalized in Kyushu University Hospitals and the diagnosis of Takayasu's aortitis was made on the basis of clinical findings and aortography. Most of the patients had symptoms and signs of arterial obstruction and/or evidence for inflammation in the arterial wall, including fever, absent peripheral pulses, vascular bruits or pain along the involved arteries. Three patients (H.W., K.T., M.H.) had fainting as one of their chief complaints at the time of the study. One patient (M.M.) had a prior history of severe fainting attacks and obtained relief from a bypass graft placed between the aortic arch and the right carotid artery (table 1). One patient (K.Y.) had typical angina pectoris and ischemic ST-segment depression with exertion, but did not have a history or electrocardiographic evidence for myocardial infarction.

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Six patients had increased sedimentation rate and more than 2+ positive C-reactive protein. Gamma-globulin was increased in seven patients. In five patients mild to moderate aortic insufficiency was present, but none had symptoms or signs of congestive heart failure. The severity of aortic incompetence was assessed by the pulse pressure, chest X-ray, electrocardiogram, and angiography. Cardiomegaly (cardiac silhouette greater than 50% of cardiothoracic ratio) was noted in three patients and left ventricular hypertrophy with ST-T changes on electrocardiogram was present in four patients.

Diagnostic aortography was performed in all patients to evaluate the thoracic and abdominal aorta as well as their large branches, and in three patients pulmonary angiography was also performed. In all patients but one (M.Y.) angiography revealed stenosis or obstruction of the carotid arteries, and irregularity and thickening of the wall of the aortic arch. Four patients with a history of fainting had severe stenosis or obstruction in at least three of the four carotid and vertebral arteries. One patient (K.Y.) had atypical coarctation of the descending thoracic aorta with proximal hypertension.13 Three patients (K.T., M.Y., N.Y.) had more than 50% stenosis at the renal artery, but only one of the three (M.Y.) had diastolic hypertension. The ascending thoracic aorta was markedly dilated in four patients (H.Y., T.O., K.T., K.Y.) who had moderate aortic insufficiency or atypical coarctation.

Control subjects consisted of eight men with an age range of 19 to 60 years (average 35.6 ± 5.8 years); the age was comparable to that of our patients with Takayasu's aortitis. No cardiovascular abnormality, except for occasional premature atrial contractions seen in subjects T.K. and Y.F., was noted on history and physical examination. Electrocardiograms and chest X-rays, which were obtained on subjects older than 27 years, were within normal limits.

The study was explained to the patients and informed consent was obtained from all participants. Statistical analysis was done using the Student's t-test.

### Results

Arterial pressure, heart rate at the time of the study, and the baroreflex slope assessed by the prolongation of R-R interval per unit change of blood pressure induced by intravenous phenylephrine are shown in table 2.

Heart rate in patients with Takayasu's aortitis was not significantly different from that of control subjects (table 2). Seven of 11 patients with Takayasu's aortitis had systolic blood pressure greater than 150 mm Hg, but diastolic hypertension (greater than 90 mm Hg) was noted in only two patients (table 2). The average systolic pressure was significantly higher in patients with aortitis than in the control group, but diastolic pressures were similar in the two groups (table 2).

The baroreceptor slope in patients with Takayasu's aortitis was significantly lower than that in the age-matched control subjects (table 2 and figure 1). Figure 2 depicts the relationship between age and the baroreflex slope in patients with Takayasu's aortitis and in control subjects. The baroreflex slope was significantly lower (P < 0.001) in patients with aortitis than in control subjects. This difference could not be attributed to the effects of aging since the two groups were of comparable age. The relationship between systolic blood pressure and baroreflex slope is shown in figure 3. In four patients with Takayasu's aortitis whose systolic blood pressure was normal, the baroreflex slope was still lower than that in control subjects with comparable systolic blood pressure. This suggests that the abnormality in baroreflex was not related solely to systolic hypertension. However, three of these four patients had cardiac disease as...
TABLE 2. Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>S BP (mm Hg)</th>
<th>D BP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>Baroreceptor slope (msec/mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K.Y.</td>
<td>190</td>
<td>60</td>
<td>93</td>
<td>1.4</td>
</tr>
<tr>
<td>M.T.</td>
<td>194</td>
<td>66</td>
<td>91</td>
<td>0.8</td>
</tr>
<tr>
<td>M.M.</td>
<td>120</td>
<td>60</td>
<td>64</td>
<td>3.4</td>
</tr>
<tr>
<td>H.Y.</td>
<td>140</td>
<td>40</td>
<td>71</td>
<td>1.9</td>
</tr>
<tr>
<td>A.M.</td>
<td>126</td>
<td>56</td>
<td>70</td>
<td>5.1</td>
</tr>
<tr>
<td>K.Y.</td>
<td>206</td>
<td>100</td>
<td>73</td>
<td>4.5</td>
</tr>
<tr>
<td>M.Y.</td>
<td>182</td>
<td>114</td>
<td>88</td>
<td>4.4</td>
</tr>
<tr>
<td>T.O.</td>
<td>178</td>
<td>115</td>
<td>71</td>
<td>7.9</td>
</tr>
<tr>
<td>N.Y.</td>
<td>156</td>
<td>80</td>
<td>79</td>
<td>5.4</td>
</tr>
<tr>
<td>K.T.</td>
<td>180</td>
<td>78</td>
<td>60</td>
<td>1.1</td>
</tr>
<tr>
<td>M.H.</td>
<td>150</td>
<td>64</td>
<td>85</td>
<td>8.5</td>
</tr>
<tr>
<td>Mean</td>
<td>160.2</td>
<td>70.0</td>
<td>76.8</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Control

T.K.    | 140          | 82           | 71             | 9.2                           |
H.G.    | 102          | 58           | 88             | 7.8                           |
Y.F.    | 125          | 78           | 71             | 10.4                          |
M.I.    | 120          | 64           | 57             | 9.4                           |
S.T.    | 132          | 78           | 80             | 8.6                           |
H.Y.    | 125          | 65           | 72             | 13.5                          |
P.K.    | 135          | 77           | 63             | 12.4                          |
T.K.    | 117          | 64           | 63             | 14.0                          |
Mean    | 124.5        | 70.8         | 70.6           | 10.7                          |

= SE ± 4.2* ± 3.2 ± 3.5 ± 0.5**

*Aortitis vs control (P <.001)
**Aortitis vs control (P <.001)

Abbreviations: S and D BP = systolic and diastolic blood pressure; HR = heart rate.

The results of this study indicate that Takayasu's aortitis is associated with reduced responsiveness of the baroreflex to a transient rise of blood pressure as assessed by the prolongation of R-R interval per unit change of blood pressure.

Discussion

The attenuation of baroreflex sensitivity was noted even in patients with fainting.

Our findings contrast with previous concepts which postulate that Takayasu's aortitis is associated with hypersensitivity of the baroreflex that accounted for fainting, a common symptom in patients with Takayasu's aortitis. This assumption was based on the finding that carotid sinus massage produced marked sinus bradycardia and/or hypotension in some of these patients. Based on the response to carotid sinus massage, it was postulated that baroreceptors are hyperreactive in Takayasu's aortitis because of inflammation or ischemia in the arterial wall where baroreceptors lie. However, carotid sinus massage is not a quantitative, reproducible way to evaluate baroreflex sensitivity. Moreover, when cerebral blood flow is compromised by severe stenosis of carotid and vertebral arteries, as it is commonly in Takayasu's aortitis, carotid sinus massage may cause further reduction of cerebral blood flow. The resulting cerebral ischemia may influence vasomotor response.

FIGURE 1. Baroreflex slope in a patient with Takayasu's aortitis (A.M.) and in a control subject (H.Y.). The baroreflex slope was assessed by the prolongation of R-R interval per unit change of systolic blood pressure as blood pressure was raised by intravenous phenylephrine. The baroreflex slope is reduced in the patient with aortitis.

FIGURE 2. Relationship between the baroreflex slope and age in patients with Takayasu's aortitis (open circle) and in control subjects (solid dots). The baroreflex slope in the patients with aortitis is reduced in comparison to that in control subjects at any comparable age.

FIGURE 3. Relationship between the baroreflex slope and systolic blood pressure. Open circles represent patients with Takayasu's aortitis and solid dots control subjects. Asterisk (*) indicates the presence of cardiac disease as evidenced by aortic insufficiency, cardiomegaly, or electrocardiographic findings suggestive of left ventricular hypertrophy. Patients with Takayasu's aortitis whose systolic blood pressure was normal showed the reduced baroreflex slope, but only one of these patients with normal systolic pressure and depressed baroreflex sensitivity had no evidence of cardiac involvement.
centers and possibly the reflex response to activation of the baroreflex since it has been shown that central autonomic interaction can modulate the baroreflex.15-14

The method employed in this study was devised by Smyth and co-workers for evaluating the baroreflex sensitivity quantitatively.9 Using this technique alterations of the baroreflex have been studied in man in various physiological and pathological conditions. Attenuation of baroreflex sensitivity has been noted in man during exercise and anesthesia,14 and in patients with hypertension8, 6, 17 and various cardiac diseases.18 Dogs with myocardiopathy and heart failure have also been shown to have disturbance of the baroreflex response.19 The attenuation of the baroreflex sensitivity during exercise or with heart failure is thought to be due to an inhibition of the reflex by a higher center in the nervous system,20, 21 while that in established hypertension or in arteriosclerosis is considered to be caused by the increased stiffness of the arteries in which baroreceptors lie.2 The central nervous system may also be contributing to the reduced baroreflex sensitivity in patients with hypertension, particularly in young patients with borderline hypertension.17 The concept that the increased stiffness of the arteries reduces baroreflex sensitivity appears to be supported by the experimental results of Angell-James that less distensible aortas of the arteriosclerotic rabbits are associated with less sensitive baroreflex.7 The stiffness has a splinting action and protects receptors from the stretch normally caused by the rise of arterial pressure, so that baroreceptors respond to a given pressure rise with a reduced afferent nerve activity.

Takayasu’s aortitis most frequently involves the aortic arch and its major branches including carotid arteries where baroreceptors lie. Therefore, one might speculate that the reduced baroreflex sensitivity in Takayasu’s aortitis may be due to the increased stiffness of the arteries. However, it is also possible that hypertension or cardiac disease associated in Takayasu’s aortitis have contributed to this alteration. Seven of the 11 patients with Takayasu’s aortitis had systolic hypertension and seven patients had aortic insufficiency, cardiomegaly, or electrocardiographic findings compatible with left ventricular hypertrophy or myocardial ischemia. Only one patient (M.M.) had neither hypertension nor evidence of cardiac disease (fig. 2). Age and control heart rate, which are also known to affect the baroreflex sensitivity assessed by the method used in this study,6, 86 were comparable between patients with Takayasu’s aortitis and control subjects (fig. 3). Our control subjects were all men and patients with Takayasu’s aortitis were mostly women; however, we are not aware of any study suggesting that the baroreflex slope may be affected by sex.

Reduced responsiveness of the baroreflex was noted in patients with fainting as well as in others. This finding suggests that fainting in these patients is not likely caused by hypersensitivity of the baroreceptors as currently postulated. Rather, it is likely that fainting results from reduced cerebrovascular blood flow caused by severe stenotic lesions of the carotid and vertebral arteries. In patients with fainting, severe or total obstruction was present in at least three of the four of carotid and vertebral arteries.

Patients with Takayasu’s aortitis not infrequently show an abrupt rise of blood pressure with minimum physical exercise or mental excitement.8 While loss of the wind kessel effect may explain this finding, reduced function in the baroreflex may also be responsible.

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References

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