HEMODYNAMIC AND VOLUME CHARACTERISTICS, 
AND PERIPHERAL PLASMA RENIN ACTIVITY 
IN TAKAYASU'S ARTERITIS

SHOTARO YONEDA, TADAATSU NUKADA, MASATOSHI IMAIZUMI, 
MOTONOBU MIYAI, HIROSHI ABE

Hemodynamic and volume characteristics, and/or peripheral plasma renin activity were investigated in 19 patients with Takayasu's arteritis who included 8 hypertensive patients with renal arterial disease and 11 normotensive patients.

In hypertensive patients, mean arterial pressure had an inverse correlation with cardiac index, a direct correlation with total peripheral resistance index and no correlation with blood volume.

These hemodynamic and volume characteristics were different from those of hypertension with renal arterial disease previously reported.

High plasma renin activity was presented in not only hypertensive patients with renal arterial disease but normotensive patients. The investigation of high plasma renin activity in Takayasu's arteritis must be also directed to the mechanism except renal arterial lesions.

TAKAYASU's arteritis includes wide varieties of manifestations which are caused by inflammatory lesions of unknown etiology. The renal artery is frequently involved and among Japanese thirty percent of renovascular hypertension is caused by Takayasu's arteritis. It is well known that the patients with Takayasu's arteritis with hypertension had poor prognosis.

Many studies of the hemodynamics and plasma renin activity levels in hypertension with renal arterial disease have been reported previously. No study, however, was presented about the hemodynamics and blood volume and there were few reports about plasma renin activity in hypertension with renal arterial disease caused by Takayasu's arteritis.

This study was concerned with the hemodynamics, blood volume and peripheral plasma renin activity of patients with Takayasu's arteritis.

METHODS AND MATERIALS

The study was based on data from 19 patients with Takayasu's arteritis diagnosed by physical examinations, laboratory findings and aortographies. Age of patients averaged 33.3 years, with a range of 14 to 49 years. All patients except one normotensive case were female. The hemodynamic indices and blood volume in 6 hypertensive and 6 normotensive patients, and peripheral plasma renin activity in 8 hypertensive and 11 normotensive patients were presented in Table I and II.

All hypertensive patients had renal arterial

Key Words:
Takayasu's arteritis
Peripheral plasma renin activity
Hemodynamics
Blood volume

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### TABLE I  HEMODYNAMIC INDICES AND BLOOD VOLUME IN TAKAYASU'S ARTERITIS

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Blood Pressure (mmHg) S/D</th>
<th>Cardiac Index (ml/min/m²)</th>
<th>TPR Index (dynes sec/cm² m²)</th>
<th>Blood Volume (ml/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Hypertension with Renal Arterial Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>238/110</td>
<td>153</td>
<td>2068</td>
<td>3100</td>
</tr>
<tr>
<td>2</td>
<td>174/118</td>
<td>137</td>
<td>3490</td>
<td>1411</td>
</tr>
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<td>3</td>
<td>174/ 80</td>
<td>111</td>
<td>4230</td>
<td>872</td>
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<tr>
<td>4</td>
<td>176/ 82</td>
<td>113</td>
<td>4750</td>
<td>903</td>
</tr>
<tr>
<td>5</td>
<td>160/ 80</td>
<td>111</td>
<td>4535</td>
<td>969</td>
</tr>
<tr>
<td>6</td>
<td>180/ 90</td>
<td>120</td>
<td>5136</td>
<td>786</td>
</tr>
<tr>
<td>mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>124 ± 17</td>
<td>4035 ± 1111</td>
<td>1340 ± 889</td>
<td>26.0 ± 3.1</td>
<td></td>
</tr>
<tr>
<td>B. Normotension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>90/ 70</td>
<td>77</td>
<td>4147</td>
<td>801</td>
</tr>
<tr>
<td>10</td>
<td>110/ 70</td>
<td>83</td>
<td>3054</td>
<td>1076</td>
</tr>
<tr>
<td>11</td>
<td>120/ 68</td>
<td>85</td>
<td>3559</td>
<td>825</td>
</tr>
<tr>
<td>12</td>
<td>110/ 60</td>
<td>77</td>
<td>2857</td>
<td>931</td>
</tr>
<tr>
<td>13</td>
<td>102/ 72</td>
<td>82</td>
<td>4090</td>
<td>853</td>
</tr>
<tr>
<td>14</td>
<td>116/ 66</td>
<td>88</td>
<td>4370</td>
<td>796</td>
</tr>
<tr>
<td>mean ± SD</td>
<td></td>
<td></td>
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<tr>
<td>82 ± 4</td>
<td>3680 ± 624</td>
<td>880 ± 108</td>
<td>23.5 ± 2.8</td>
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</table>

S: Systolic  
D: Diastolic  
TPR: Total Peripheral Resistance  
*: Significant difference (p < 0.005) between normotensive and hypertensive groups

Disease caused by Takayasu's arteritis. The diagnosis of renal arterial disease was based on the angiographic demonstration of stenosing vascular lesions. The stenosing lesions were observed in the main renal artery in all cases, and the unilateral lesion was presented in 4 cases and bilateral lesions were shown in 4 cases. The degree of stenosis of intraluminal diameter observed angiographically ranged from moderate (25 to 50 percent) to complete occlusion. No renal arterial disease was observed in normotensive patients (Table II).

None of the patients had malignant hypertension or any evidence of cardiac decompensation. The patients with aortic regurgitation and coarctation of the aorta were excluded.

Pulmonary scintigraphy was performed in 11 out of 19 patients at the same time of hemodynamic measurement. All 11 patients had only minor pulmonary vascular lesions on pulmonary scintigram.

Measurement of blood pressure was performed in supine position. The criteria for hypertension were based on the World Health Organization criteria (systolic 160 and/or diastolic 95 mmHg) and if there was stenotic or occlusive lesion in the right subclavian artery, blood pressure in the left upper extremity was accepted.

Hemodynamic indices and blood volume were measured under basal condition.

Cardiac output was determined by radioisotope ($^{131}$I-labelled human serum albumin, 50μCi) dilution method and an external counter sited over precordium. Dilution curve obtained was analysed by MacIntyre technique.

Mean arterial blood pressure (MABP) was calculated as the sum of diastolic pressure plus one-third of pulse pressure.

Total peripheral resistance was calculated by dividing MABP by cardiac output.

Total blood volume was determined from volume of distribution of $^{131}$I-labelled human serum albumin ($^{131}$I-RHSA, 5 μCi) and from extrapolation to zero time of values obtained at 5 and 10 minutes after injection of $^{131}$I-RHSA.

Cardiac output and total peripheral resistance were divided by body surface area and expressed as cardiac index and total peripheral resistance.
<table>
<thead>
<tr>
<th>Case No.</th>
<th>MABP (mmHg)</th>
<th>PRA (ng/ml/hour)</th>
<th>Radiographic Degree of Stenosis</th>
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<tr>
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<td>A. Hypertension with Renal Arterial Disease</td>
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</tr>
<tr>
<td>1</td>
<td>153</td>
<td>6.00</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>137</td>
<td>3.58</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>111</td>
<td>4.93</td>
<td>25</td>
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<tr>
<td>4</td>
<td>113</td>
<td>6.38</td>
<td>50 - 75</td>
</tr>
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<td>5</td>
<td>111</td>
<td>6.68</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>120</td>
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<tr>
<td>8</td>
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<td>4.60</td>
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<tr>
<td>mean ± SD</td>
<td>130 ± 18</td>
<td>5.43 ± 1.03</td>
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</tr>
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<td>B. Normotension</td>
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</tr>
<tr>
<td>9</td>
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<td>3.94</td>
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</tr>
<tr>
<td>mean ± SD</td>
<td>84 ± 6</td>
<td>4.84 ± 1.90</td>
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</table>

MABP: Mean Arterial Blood Pressure  
PRA: Peripheral Plasma Renin Activity

(TPR) index, respectively. Total blood volume was divided by height and expressed as blood volume\(^{10}\).

Peripheral plasma renin activity was measured in the recumbent state for one hour in the morning. The patients were put on a regular diet containing excess 150 mEq of sodium for more than 4 days. Plasma renin activity was determined by radioimmunassay for angiotensin I (AI) using a kit of CEA (Commissariat a l’Energie Atomique Department des Radioelements, France)-IRE (Institut National des Radioelements c/o CEN-SCK, Belgique)-SORIN (Centro Ricerche Bio- mediche Gruppo Radiochimica, Italia) and was calculated as the difference between the immunoreactive AI formed during a 1.5-hour plasma incubation at 37°C and that present in an incubated plasma sample at 4°C.

Blood samples were collected in pre-chilled tubes containing 1mg EDTA-Na\(_2\) per ml blood and the plasma was rapidly separated by centrifugation at about 2000 rpm for 10 minutes at 4°C, and stocked at -20°C until assayed.

Blocking of converting enzyme was achieved by a mixture of 3.5 mM 2, 3-dimercaptopropranol and 2 mM 8-hydroxyquinoline sulfate. The addition of this buffered mixture to the plasma samples yielded a final pH of 5.6 to 5.7.

Each sample was divided into aliquots of the same volume; one aliquot was incubated at 37°C for 1.5 hours, and the other was kept refrigerated at 2-4°C (blank sample). The incubation mix-
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ture consisted of: 0.1 ml of $^{125}$I-angiotensin solution: 0.1 ml of standard solution of angiotensin I or of plasma sample: 0.1 ml of antisemum: 0.025 M tris buffer, pH 7.4 containing 0.2% lysozyme to a total volume of 1 ml.

The incubation was performed at 4°C for 24 hours. A 0.1 ml of the solution of lyophilized serum was added to the tubes of the standard curve, and a 0.1 ml of tris buffer was added to all the other tubes.

The separation of antibody-bound from free AI was achieved by adsorbing the latter of dextran-coated charcoal suspension 0.5 ml of a suspension containing homogenized powdered mixture (10:1) of charcoal Norit 211F.O.P. and dextran 70, and after centrifugation at 2000g for 10 minutes and decantation the radioactivity of supernatants was counted.

All forms of antihypertensive therapy were discontinued at least 2 weeks before the study.

RESULTS

1. Hemodynamic indices and blood volume

Hemodynamic indices and blood volume were measured in 6 hypertensive and 6 normotensive patients. Mean arterial blood pressure (MABP) was significantly higher in hypertensive group than in normotensive group (p < 0.005, Table I). The patients with hypertension had high average levels in cardiac index, total peripheral resistance (TPR) index and blood volume, however, no significant differences were found between the two groups (Table I).

A significant inverse correlation between cardiac index and MABP was shown in the hypertensive group (p < 0.02, Fig. 1). Among hypertensive patients, MABP significantly correlated with TPR index (p < 0.02), meanwhile the normotensive patients had no relationship (Fig. 2).

No correlation was found between blood volume and MABP in the two groups (Fig. 3).

2. Peripheral plasma renin activity

Peripheral plasma renin activity was determined in 8 hypertensive patients with renal arterial disease and 11 normotensive patients without renal arterial disease. Plasma renin activity (PRA) in 8 hypertensive patients averaged 5.43 ng/ml/hour, with a range of 3.58 to 6.68 ng/ml/hour. In 11 normotensive patients, the mean value was 4.84 ng/ml/hour, with a range of 2.45 to 7.72 ng/ml/hour (Fig. 4, Table II). Although the PRA in hypertensive group revealed high average value, there was no statistically significant difference between the two groups. The PRA in patients with unilateral and bilateral renal arterial stenoses were 5.66 ± 0.89 and 5.21 ± 1.24 ng/ml/hour, respectively. No difference was observed between the unilateral and bilateral stenoses groups. The mean value of the

Fig. 1. A significant inverse relationship between mean arterial pressure and cardiac index in 6 hypertensive patients (solid circles, p < 0.02). No relationship between mean arterial pressure and cardiac index in 6 normotensive patients (open circles).

Fig. 2. A significant direct correlation between mean arterial pressure and total peripheral resistance index in 6 hypertensive patients (solid circles, p < 0.02). No correlation between mean arterial pressure and total peripheral resistance index in 6 normotensive patients (open circles).

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PRA of the age matched control was 2.71 ng/ml/hour, with a range of 0.93 to 4.51 ng/ml/hour. The higher PRA than 4.51 ng/ml/hour (high PRA) was exhibited in 7 of 8 hypertensive and 6 of 11 normotensive patients (Fig. 4).

DISCUSSION

Among Japanese, the large part of renovascular hypertension is caused by Takayasu’s arteritis. There were, however, no reports about the hemodynamics of Takayasu’s arteritis. In this study, the hemodynamics, blood volume and plasma renin activity (PRA) in Takayasu’s arteritis were investigated.

The criteria for hypertension in this study were followed by “official” criteria of the World Health Organization. Although the use of these criteria in patients with Takayasu’s arteritis might not be appropriate, there are no other sufficient criteria.

In hypertensive patients with renal arterial disease, cardiac index was not higher value than that in normotensive patients and total peripheral resistance (TPR) index was significantly higher. Mean arterial blood pressure (MABP) had a direct correlation with TPR index and had an inverse correlation with cardiac index.

Recent study confirmed that in hypertensive patients with renal arterial disease of the fibrosing and atherosclerotic types, cardiac index and TPR were significantly higher than in the normotensive group, and the direct correlation between MABP and cardiac index and between MABP and TPR was significant.

Hemodynamic changes in this study were different from the results of the previous study in hypertension with renal arterial disease.

As previously reported hypertensive women with renal arterial stenosis had significantly lower plasma volume than normotensive group, but had no significant relationship between volume and pressure.

In our results, hypertensive patients had not lower blood volume than normotensive ones. And no correlation was presented between blood pressure and blood volume in 6 hypertensive women.

Meanwhile in essential hypertension, a significant direct correlation between MABP and TPR was presented. And no correlation between MABP and cardiac index was reported. Some reports however, described that cardiac index was lower in severe essential hypertension than in mild essential hypertension, and that cardiac index in advanced essential hypertension over 50 years was lower than that in early essential hypertension. There was no correlation between diastolic pressure and plasma volume in women with essential hypertension.

Hemodynamic and volume characteristics in patients with renal arterial stenosis caused by Takayasu’s arteritis were rather than similar to those in essential hypertension. All hypertensive
patients had stenotic and/or occlusive lesions of the other parts of the aorta and its branches. These differences of hemodynamic and volume characteristics between this study and previous reports might be caused by these stenotic and/or occlusive lesions.

The measurement of PRA in this study during states of 150 mEq sodium diet for more than 4 days and recumbency for one hour might certainly not maximize any differences if renal artery stenosis was a significant stimuli. Most reports on peripheral PRA levels have shown a large number of normal values in patients with renal artery stenosis, and augmentation of PRA have indicated a hyperresponsiveness in patients with curable disease. Even in these suppressive states, however, six of 11 normotensive patients had high PRA and the PRA in normotensive patients with Takayasu's arteritis was significantly higher value than in control group. Mean value of the hypertensive group was higher than the normotensive group. However, there was no statistically significant difference in the PRA between the hypertensive and normotensive groups. This result suggests that the mechanism other than renal arterial stenosis also played a role for high PRA of the patients with Takayasu's arteritis.

In experimental one-kidney Goldblatt hypertension, the blood pressure is not renin-dependent and does not fall when renin is inhibited by antagonist. On the other hand, some investigation were reported high peripheral PRA in the patients with bilateral renal artery stenoses. In this study of a small number of the patients, there was no difference in the peripheral PRA between the unilateral and bilateral renal artery stenoses.

It is well known that three major groups of mechanism are involved in the control of renin release. These include the intrarenal receptors, the renal sympathetic nerves and a number of humoral agents. In Takayasu's arteritis, the carotid and vertebral arteries are frequently involved. Several different groups evaluated the effect of bilateral carotid arterial occlusion on plasma levels of renin. The results of the experiments led to the hypothesis that baroreceptor present within the carotid artery is capable of reflexly altering plasma renin levels. However, the other groups concluded that changes in carotid sinus pressure did not affect plasma renin levels. The most recent study presented the evidence that carotid sinus hypotension produced an increase in PRA. Ueda et al reported that high PRA was observed after experimental vertebral artery embolism and it was known that stimulation of the medulla oblongata near the obex increased PRA.

In this series, PRA in 10 patients without carotid arterial stenoses were 5.49 ± 1.38 ng/ml/hour and PRA in 9 patients with carotid arterial stenoses were 4.64 ± 1.75 ng/ml/hour. There was no statistically significant difference between these two groups. In these patients except 2 cases, carotid stenosis was not severe and two cases had also unilateral carotid stenosis. Our result could not find the relation between PRA and carotid arterial lesions. Plasma renin activity in 9 patients without vertebral arterial stenosis was 5.05 ± 1.18 ng/ml/hour and PRA in 10 patients with vertebral arterial stenosis was 5.12 ± 1.94 ng/ml/hour. There was no significant difference between these two groups.

Many humoral agents affected the level of PRA. The effect of estrogen on the renin-angiotensin system has also been studied. Many investigators have confirmed the increase of PRA by estrogen. And a high level of urinary excretion of estrogen was found in patients with Takayasu's arteritis. In this study, the measurement of estrogen was not performed. The precise mechanism responsible for high PRA in Takayasu's arteritis remains undefined. Further investigations into high PRA in Takayasu's arteritis are necessary.

REFERENCES

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