Abnormality of Circulatory Reflex and Aldosterone Response during Head-up Tilting in Patients with Primary Aldosteronism

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SUMMARY

Abnormality of the circulatory reflexes has been reported in patients with primary aldosteronism. However, changes in blood pressure, heart rate, plasma renin activity (PRA), and plasma aldosterone concentration (PAC) after head-up tilting in primary aldosteronism have not yet been reported. Seven patients with primary aldosteronism were tilted to a 65 degree head-up position which was maintained for 30 min. Systolic blood pressure decreased significantly 5 min after tilting and remained at this level during the period of tilting. Diastolic blood pressure did not change during the tilting. Heart rate increased after 5 min of tilting and this level of heart rate was maintained for 30 min. Plasma renin activity was low and did not change during tilting. However, plasma aldosterone concentration increased significantly 20 min after tilting. Plasma cortisol concentration and plasma ACTH concentration also increased significantly. These results suggest that primary aldosteronism causes abnormalities of the circulatory reflexes. The increase of endogenous ACTH may increase plasma aldosterone concentration in patients with primary aldosteronism.

Additional Indexing Words:

Primary aldosteronism Aldosterone Tilting Renin

THE head-up tilt test has been used to evaluate the mechanism of blood pressure maintenance in patients with hypertension^{1),2)} and in patients with orthostatic hypotension.³⁾⁻⁵⁾ Increased plasma norepinephrine,²⁾⁻⁵⁾ increased PRA,⁶⁾⁻¹⁰⁾ and increased plasma aldosterone¹¹⁾ were reported during tilting in normal subjects. These factors may represent the mechanisms of

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blood pressure maintenance in response to the decrease in cardiac output during tilting. Increased aldosterone secretion is considered to be caused by a potentiated renin-angiotensin system in this situation.¹¹⁾

In primary aldosteronism, it is believed that aldosterone increases sodium reabsorption in the renal tubules which increases circulatory plasma volume. PRA is usually suppressed and does not respond to any renin stimulation test in patients with primary aldosteronism. Biglieri et al¹²⁾ reported abnormalities of the circulatory reflexes in primary aldosteronism. They reported that the hypertensive responses and reflex bradycardia to Valsalva's maneuver were minimal or absent in patients with primary aldosteronism. The present study was carried out to evaluate whether there are some abnormalities of the blood pressure controlling mechanism in patients with primary aldosteronism. The effect of the head-up tilt test on aldosterone secretion was also studied in patients with primary aldosteronism.

MATERIALS AND METHODS

Seven patients with primary aldosteronism (1 male, 6 females, aged from 24 to 51) were studied (Table I). They had hypertension ($190 \pm 22/112 \pm 14$ mmHg), hypokalemia (2.6 ± 0.4 mEq/L), low PRA (<0.1 ng/ml/hr), and high PAC (>300 pg/ml). Diagnosis of primary aldosteronism was also confirmed retrospectively at surgery in all of these patients. Hypertension and hypopotassemia improved after removal of the aldosteronoma. All subjects were admitted to hospital and all drugs were withheld. A normal sodium diet (12 g/day) was given for more than 7 days. The head-up tilt test was performed after 30 min supine rest on the table in the morning, the patients having fasted. The table was tilted abruptly to a 65 degree head-up position which was maintained for 30 min. Arterial blood pressure was

Table I. Clinical Findings in 7 Patients with Primary Aldosteronism

No.	Patient	Age (yo)	Sex	Blood Pressure (mmHg)	Serum (mEq/L)			K Clearance (ml/min)	TBK (%)	PRA (ng/ml/hr)	PAC (pg/ml)	Adenoma Side
					Na	K	Cl					
1	TN	24	M	168/104	147	3.2	102	32	105	<0.1	314	R
2	KS	28	F	174/110	142	2.7	106	58	77	0.1	311	L
3	FN	28	F	214/138	148	2.7	100	51	78	0.1	660	L
4	MK	28	F	218/110	141	2.1	100	33	72	0.1	506	R
5	KM	30	F	180/106	147	2.8	102	46	94	<0.1	686	L
6	MM	41	F	210/120	143	3.0	108	48	(—)	0.1	346	L
7	SK	51	F	172/94	146	2.0	93	33	80	<0.1	556	L

Fig. 1. Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) during tilting are shown. N=7, * $p < 0.05$.

measured by sphygmomanometry. Venous blood samples were collected before and during tilting (0, 10, 20, and 30) for the measurement of PRA, plasma aldosterone concentration (PAC), plasma cortisol concentration (PCC), and plasma ACTH concentration (ACTH). PRA was measured by radioimmunoassay using CIS kits. Plasma samples (1 ml) were incubated with 20 μ l of 8-hydroxyquinoline sulphate 0.13% and 6 μ l of 2,3 dimercapto-propanol. After incubation for 1.5 hours at 37°C, the samples were transferred to an ice bath, and 50 μ l aliquots were taken for radioimmunoassay of generated angiotensin I. PAC was measured by radioimmunoassay using CIS kits. One ml of plasma sample and 4 ml of dichlormethane were mixed and shaken for 10 min and centrifuged. Two ml of the dichlormethane layer were obtained and dried using nitrate gas, and the resultant sediment was dissolved in 0.1 ml of phosphate buffer, pH 7.4. Radioimmunoassay of aldosterone was done using a CIS kit. PCC was measured using an Eiken Immunochemical kit (Osaka, Japan) and ACTH was measured using a

Fig. 2. Changes of PRA, PAC, PCC, and ACTH during tilting are shown. Statistical difference from the control value (0 min) is given above each column (N=7, * $p < 0.05$, NS=not significant).

CIS kit.

Statistical analysis was performed by the paired t-test with log transformation. Significance was defined as a p value of less than 0.05.

RESULTS

Fig. 1 shows the changes in systolic blood pressure, diastolic blood pressure, and heart rate during tilting. Systolic blood pressure decreased significantly 5 min after tilting and this level of systolic blood pressure was maintained for 30 min. Diastolic blood pressure increased more than 5 mmHg during tilting for 30 min. However, changes in diastolic pressure during tilting in these subjects were not significant. Heart rate increased significantly

5 min after tilting and this level of heart rate was maintained for 30 min.

Fig. 2 shows the changes in PRA, PAC, PCC, and ACTH during tilting. PRA was very low and did not change during tilting. PAC, PCC, and ACTH all increased significantly 20, 30, and 20 min after tilting, respectively.

DISCUSSION

It has been reported that abnormalities of the circulatory reflexes exist in patients with primary aldosteronism.¹²⁾ In this report, the circulatory reflex was evaluated using head-up tilting in patients with primary aldosteronism. Our previous report¹³⁾ suggested that diastolic blood pressure increased significantly in healthy normal volunteers. Thus, the present study showing that diastolic blood pressure did not increase during tilting in most of our subjects with primary aldosteronism supports the hypothesis that circulatory reflex abnormalities do exist in this population. It was considered that the mechanisms of blood pressure maintenance after tilting were the sympathetic nervous system,^{2),5),8),9)} the renin-angiotensin system,^{6)–10)} and aldosterone.¹¹⁾ However, other factors may contribute to the control of blood pressure after tilting. In primary aldosteronism, it may be possible that the renin-angiotensin system is markedly suppressed and does not contribute to blood pressure regulation. Our results showing that PRA did not increase during tilting in patients with primary aldosteronism indicate that the renin-angiotensin system does not contribute to the maintenance of blood pressure during tilting in patients with this disease. On the other hand, PAC increased during tilting, indicating that this response of aldosterone was not caused by the renin-angiotensin system. Since PCC and ACTH also increased during tilting, this increase of PAC may have been caused by the endogenous increase of ACTH. The possibility that hypokalemia contributed in this abnormality of the circulatory reflex in patients with primary aldosteronism cannot be excluded in this study since hypokalemia was present in all of these subjects and head-up tilting was not performed after surgery.

A recent report¹⁴⁾ suggests that aldosterone secretion in primary aldosteronism is controlled by ACTH since the diurnal variation of PAC in primary aldosteronism is suppressed by dexamethasone administration, and ACTH administration increased PAC in this disease. Furthermore, Nicholls et al¹⁵⁾ reported that a low dose of ACTH stimulated aldosterone secretion in healthy subjects. Our results, showing that PAC increased during tilting, support these findings.

These results suggest that patients with primary aldosteronism have

abnormalities of the circulatory reflexes. The increase of endogenous ACTH increases PAC in subjects with primary aldosteronism during tilting.

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