Role of Renin-Angiotensin System in the Controls of Blood Pressure and Aldosterone in Patients with Cirrhosis and Ascites

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SUMMARY

In an attempt to evaluate the role of renin-angiotensin system in the controls of blood pressure and aldosterone secretion in the patients with cirrhosis and ascites, 7 patients were infused of an antagonist of angiotensin II, Sar-1 Ile-8 angiotensin II, intravenously to inhibit the action of renin-angiotensin system and to observe changes in arterial pressure and plasma aldosterone. In 1 patient with recent onset of severe ascites and high plasma renin activity, blood pressure and plasma aldosterone decreased during the infusion. In contrast, mild rise in blood pressure and various changes in plasma aldosterone were observed in the other 6 patients with normal plasma renin activity.

These results suggest variable angiotensin dependency in the controls of blood pressure and plasma aldosterone in the patients with cirrhosis and ascites according to the stage of the disease, the states of sodium and water balance and/or plasma renin activity.

Additional Indexing Words:

Angiotensin II Angiotensin II analogue Plasma renin activity
Liver disease Edema Secondary aldosteronism

IN an experimental model of hyperaldosteronism secondary to increased plasma renin activity such as chronic sodium depletion or thoracic inferior vena caval constriction, it is well recognized that angiotensin II is critically involved in the maintenances of arterial pressure and aldosterone secretion.¹⁾ Clinically, it is suggested that renin-angiotensin system is activated secondarily to decreased effective plasma volume²⁾⁻⁵⁾ and plays an important role in salt and water retention in the patients with liver cirrhosis and ascites,⁶⁾ however, the role of renin-angiotensin system in the maintenance of arterial pressure has not been clearly defined in these patients.

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The recent availability of an inhibitor of renin-angiotensin system has provided means for more precise analysis of this problem.^{7),8)} The present study was undertaken to elucidate whether the controls of blood pressure and plasma aldosterone in the patients with cirrhosis and ascites are angiotensin-dependent by means of a specific antagonist of angiotensin II (Sar-1 Ile-8 angiotensin II).

SUBJECTS AND METHODS

Seven patients having cirrhosis with ascites were studied as inpatients in the Keio University Hospital. Each had physical and laboratory evidences of cirrhosis, confirmed by biopsy in 3 cases. Clinical and biochemical characteristics in these subjects are presented in Tables I and II. Medication was withdrawn at least 2 weeks before the examination. All subjects were placed on the diet containing 140–180 mEq of sodium and 80–100 mEq of potassium per day. All studies

Table I. Baseline Assessment of Blood Chemistry in the Patients

Patient	Age & Sex	Total protein (Gm/100 ml)	A/G ratio	GOT (U)	GPT (U)	Na (mEq/L)	K (mEq/L)	Cr (mg/100 ml)
K. E.	58M	6.9	0.6	127	74	138	4.2	1.0
S. S.	65M	6.7	1.0	69	85	142	3.5	1.1
T. F.	46M	6.2	1.0	89	53	141	3.7	1.2
S. H.	68F	5.2	1.1	55	25	140	2.5	1.1
T. Y.	42M	5.8	0.7	95	17	138	2.6	2.1
H. A.	50F	5.6	1.0	15	34	139	2.8	1.2
M. K.	60F	7.6	0.8	143	65	140	3.0	1.1

A/G=Albumin/Globulin, GOT=Glutamic oxaloacetic transaminase, GPT=Glutamic pyruvic transaminase, Cr=Serum creatinine

Table II. Responses of Blood Pressure and Plasma Aldosterone in Patients with Cirrhosis and Ascites

Patient	Control PRA (ng/ml/hr)	Blood Pressure (mmHg)		Plasma Aldosterone (ng/100 ml)	
		Control	Infusion	Control	Infusion
K. E.	2.6	122/80	98/68	15.0	9.0
S. S.	0.9	128/72	150/80	0.5	2.0
T. F.	1.2	156/92	178/106	11.2	11.0
S. H.	1.6	118/60	142/78	6.2	3.0
T. Y.	1.4	134/88	140/90	13.4	17.6
H. A.	1.6	100/60	132/80	10.0	13.0
M. K.	1.8	180/90	220/100	8.0	7.0

PRA=Plasma renin activity

were performed in the morning after an overnight fast with the patients having been supine for 10 hours. Graded infusion of Sar-1 Ile-8 angiotensin II (100, 300, 600 ng/Kg/min at intervals of 10 min was performed after a control period of at least 30 min. Blood pressure was measured with sphygmomanometer by a physician every 3 min during the control period and during the infusion. Blood samples for determinations of plasma renin activity and aldosterone were drawn before and after the infusion of the antagonist.

Informed consent was obtained from each patient.

Plasma aldosterone was determined by radioimmunoassay.⁹⁾ Plasma renin activity was measured by the method of Skinner (1968).¹⁰⁾ Normal values in our laboratory are 7.0 ± 5.0 ng/100 ml for aldosterone and 1.7 ± 0.5 ng/ml/hr for renin activity.

RESULTS

The maximum increase or decrease in blood pressure was observed at a infusion rate of 600 ng/Kg/min. Changes in blood pressure and plasma aldosterone are shown in Table II. Baseline plasma renin activity was within normal ranges in 6 patients with pressor response, while it was high in one patient with depressor response. The patient with depressor response (K. E.) had recent clinical onset of severe ascites and edema and showed decrease in plasma aldosterone in response to angiotensin II analogue. In the other patients, slight increase or no change in plasma aldosterone was observed in response to Sar-I Ile-8 angiotensin II.

DISCUSSION

The present study demonstrated that the infusion of Sar-I Ile-8 angiotensin II induced depressor response in 1 of 7 patients with cirrhosis and ascites. Yamamoto et al¹¹⁾ have also reported that blood pressure declined by the same angiotensin II analogue in 1 out of 3 patients with cirrhosis and ascites. By the infusion of another angiotensin II analogue (Sar-1 Ala-8 angiotensin II), Schroeder et al¹²⁾ revealed decrease in blood pressure in 5 out of 7 patients with cirrhosis and ascites and suggested that the control of arterial pressure in these patients was angiotensin-dependent. Observation by Johnson et al¹⁾ has demonstrated that the infusion of Sar-1 Ala-8 angiotensin II decreased the blood pressure of dogs with thoracic caval constriction, which were similar to the patients with cirrhosis and ascites hemodynamically.^{13),14)}

It is worthy to note that most of the patients with cirrhosis and ascites showed pressor response in the studies of Yamamoto et al¹¹⁾ and ours compared with the high incidence of depressor response in the study of Schroeder

et al.¹²⁾ There are several possible explanations for the discrepancy in the incidence of depressor response. One is the difference in the forms of the inhibitor of angiotensin II. Sar-1 Ile-8 angiotensin II, a potent competitive antagonist of angiotensin II in vitro^{15),16)} was employed in our study. It is recognized that this analogue shows depressor effect on patients with renovascular or malignant hypertension with high plasma renin activity¹⁷⁾ and complete blockade of the pressor effect of exogenously infused 1600 ng/Kg of angiotensin II at a rate of 1000 ng/Kg/min in rabbits.¹⁸⁾ However, it induces pressor response in patients with low or normal renin activity because of its partial agonist activity, that has already been observed in the use of Sar-1 Ala-8 angiotensin II.^{19),20)}

Another possibility is the difference in the sodium intake by the patients. The patients in the present study were on normal sodium diet and therefore most of them showed normal or slightly decreased plasma renin activity while the patients of Schroeder et al on the diet containing 10 mEq of sodium had maximally activated plasma renin activity. Since the response to the angiotension II inhibitor is fairly dependent on the states of sodium and water balance and/or plasma renin activity, prior sodium restriction induces the elevation of plasma renin activity and the increase in the incidence of depressor response.^{21)–25)} Thus, the response to the angiotensin II analogue during sodium depletion is an influence of sodium depletion per se rather than a measure of intrinsic angiotensin II dependency of the disease.

The third possibility is the difference in the state of compensation in the process of the disease per se. Watkins et al (1976)²⁶⁾ revealed that renin-angiotensin system played an important role in the maintenance of blood pressure during the initial stage, but not during the later stage of thoracic caval constriction in dogs since the administration of a converting enzyme inhibitor, which blocked the conversion of angiotensin I to angiotensin II²⁷⁾, reduced blood pressure during the initial stage but not in the later stage. In the present study, plasma renin activity of the patient who had depressor response (K.E.) was elevated in spite of normal sodium intake. Because of his recent development of severe ascites, it was assumed that the hemodynamic compensation to decreased effective plasma volume was limited and inadequate and thus plasma renin activity remained elevated when the study was performed. Other patients with pressor response, having longer history of cirrhosis and ascites and showing normal or low plasma renin activity, were supposed to be in the state of compensation. From these results, it is suggested that the difference in the hemodynamic compensation is an important factor to determine the intrinsic angiotensin II dependency in the maintenance of blood pressure in the patients with cirrhosis and ascites.

In the present study, we were unable to demonstrate the angiotensin-dependency of steroidogenesis in the adrenal glands in most of the patients with cirrhosis and ascites in contrast to the study by Schroeder et al. Four humoral changes have been shown to participate in the control of aldosterone.²⁸⁾⁻³²⁾ They are increased concentrations of angiotensin II, adrenocorticotrophic hormone (ACTH), and serum potassium, and reduced level of serum sodium. Among these factors, when renin-angiotensin system is activated by prior sodium depletion to regulate aldosterone secretion exclusively, plasma aldosterone will decline in response to the infusion of an angiotensin II analogue. Since the renin-angiotensin system was not activated by prior sodium restriction in the present study, it is supposed that not only renin-angiotensin system but also other factors were involved in the control of aldosterone secretion and various changes in plasma aldosterone were observed after the infusion of Sar-1 Ile-8 angiotensin II. Further, the duration of infusion of the angiotensin II inhibitor was too short to make clear the intrinsic angiotensin-dependency of aldosterone secretion by the adrenal gland,³³⁾ particularly in the patient with liver cirrhosis associated with a prolonged half-life of aldosterone.³⁴⁾

In summary, the role of renin-angiotensin system for the maintenances of arterial pressure and aldosterone secretion in the patients with cirrhosis and ascites is variable according to the state of sodium and water balance and/or the stage of the disease per se.

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