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Hyperkalemia due to Hyporeninemic Hypoaldosteronism with Liver Cirrhosis and Hypertension

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A 49-year-old man with liver cirrhosis and hypertension was found to have hyperkalemia out of a degree of renal insufficiency and metabolic acidosis with low to normal anion gap, aggravated by volme contraction with diarrhea and medications (captopril, spironolactone and atenolol) interfering with potassium homeostasis. Plasma renin activity and serum aldosterone levels of this patient on a regular diet after discontinuation of medications were very low compared to those of five other cirrhotic patients with normokalemia as controls. Also, the renin-aldosterone stimulation testing on this patient performed by sodium restrieted diet and furosemide, upright position and by angiotensin converting enzyme inhibition (captopril, 50 mg) showed the blunted renin and aldosterone responses to each of these stimuli, almost no changes from baseline renin and aldosterone levels, It was concluded that the underlying defect responsible for hyperkalemia in this case was hyporeninemic hypoaldosteronism and this was aggravated by other factors or drugs affecting potassium homeostasis.

Key Words: *Hyperkalemia, Liver Cirrhosis, Hypertension, Hyporeninemic Hypoaldosteronism*

INTRODUCTION

In the absence of laboratory error or pseudohyperkalemia and extracellular potassium shift due to acute acidosis or hyperosmolality, impaired renal excretion of potassium would be the answer for sustained hyperkalemia (Oh and Carroll, 1989). Among the variety of underlying causes responsible for the impaired renal excretion of potassium without advanced renal insufficiency (GFR>20 ml/min)or oliguria, the hyporeninemic hypoaldosteronism is the most common cause of chronic hyperkalemia (Oh and Carroll, 1989, Defronzo, 1980). The hyperkalemia, low aldosterone level and hyperchloremic metabolic acidosis with normal anion gap resulting from impaired renal potassium and net acid excretion are unique characteristics of hyporeninemic hypoaldosteronism (Sebastian et al., 1977, Sehambelan et al., 1980, Perez et al., 1972). Most patients are over 50 years of age and have hypertension. However, the patients who suffer from hyporeninemic hypoaldosteronism are often able to maintain serum potassium within the normal range with liberal salt intake, but usually develop hyperkalemia by variable accompanied factors, such as by reduction in sodium intake, gastrointestinal salt, heart failure, or drugs that interfere with renin or aldosterone production (e.g., indomethacin, heparin, angiotensin converting enzyme inhibitors) or with renal blood flow (Pence et al., 1985, Phelps et al., 1980, Carlsson et al., 1978, Tan et al., 1979). This case report with liver eirrhosis, hypertension and hyperkalemia revealed the full-blown evidence of hyporeninemic hypoaldosteronism, which, to our knowledge, has not been reported in association with liver cirrhosis and showed the amelioration of degree of hyperkalemia after the correction with liver cirrhosis and showed the amelioration of degree of hyperkalemia after the correction of the other accompa-

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nied precipitating factors including drugs for the potassium derangements in hyporeninemic hypoaldosteronism.

CASE HISTORY

The patient is a 49-year-old oriental man with a history of essential hypertenstion and liver cirrhosis for the last 8 years. He had a history of alcohol abuse and (+) hepatitis surface antigenemia. on Jan. 27, 1993, he was admitted under the gastrointestinal service of Hanyang university hospital because of weakness, diarrhea and intractable ascites with anasarca on medications of captopril (25mg, Bid), furosemide (20 mg, Bid), spironolactone (25 mg, Bid). Blood pressure was 170/100 mmHg; pulse was 90/min and regular; respiratory rate was 20/min; body weight 91 kg. He had the stigmata of advanced liver disease with anasarca and huge ascites. As shown in table 1, with adding atenolol 50mg, hs, and perdipine 60mg, Tid on day 4 in hospital, dosages of captopril and furosemide were increased to 25mg, Tid and 40 mg, Bid on day 5 in hospital for hypertension and ascites, respectively. Serum potassium value was found to be 6.2 mEq/L on admission, which remained elevated (range, 5, 6 to 6.4 mEq/L) in spite of oral potassium exchange resin and Shohl's solution intake. The admission serum creatinine value was 0.8 mg/dL and BUN 40 mg/dL. Anion gap ranged from 3 to 12 mEq/L with low serum albumin, 2.5 g/dL. Twenty four hour urine for protein was 1.5gm. Arterial blood gas analysis was not performed on initial hospital days. There was no clinical evidence of adrenal insufficiency, and his 24-hour urinary 17-hydroxycorticoid excretion was normal. On day 7, renal consultation was asked to evaluate the persistent hyperkalemia. All the medications was discontinued with sodium unrestrieted diet on that day.

METHODS

After discontinuation of all medications, he was kept on 6 days of dietary adjustment with unrestrieted regular diet to ensure a constancy of sodium-potassium balance before the renin/aldosterone stimulating testing. During the last 3 days before the stimulation testing, daily blood samples for baseline plasma renin activity and serum aldosterone levels were obtained at 8 A.M. with the patient still supine after overnight recumbency. Also, daily measurements of serum electrolytes, arterial blood gases, urine PH and 24-hour urine samples for sodium, potassium, and creatinine clearance were performed. PRA and serum aldosterone levels were compared to those of five cirrhotic male patients of similar ages (45 to 55 year old) with ascites and edema, whose serum potassium values were within normal range on a regular diet and without medications affecting the renin-angiotensin-aldosterone system. The renin/aldosterone sysem was stimulated on tow separate days by converting enzyme inhibition with 50 mg of captopril orally on regular diet and by 2 days of low salt diet and oral furosemide intake 20 mg Bid followed by upright position for two hours. The blood samples for stiumlated PRA and aldosterone levels were drawn 3 hours afters oral captopril intake and after two hours in upright position on a low salt diet and oral furosemide intake and after two hours in upright position on a low salt diet and oral furosemide intake for the preceding 2 days, respectively. The specific radioimmunoassays (kits from abbott laboratory) were used to measure PRA and serum aldosterone levels. Electrolytes and creatinine were measured by autoanalyzer.

RESULTS

Baseline profiles of a cirrhotic patient with hyperkalemia before renin/aldosterone stimulation test (Table 2). Though the degree of hyperkalemia ranging between 0.4 and 0.6 meq/L after discontinuation of medications affecting the renin-angiotensin system became less than that of the initial hospital days on medications ranging between 0.8 and 1.4 mEq/L (Table 1), serum potassium values still remained hyperkalemic (> 5.0 mEq/L). Creatinine clearance measured twice was 54 and 61 ml/min. With these mild degrees of hyperkalemia and mild to moderate renal insufficiency (>20 ml/min), hyperchloremic metabolic acidosis with low to normal anion gap ranging between 3 and 8 mEq/L, and acidic urine pH, 5 were observed during this time. Urinary sodium excretions in 24 hours on a sodium unrestricted diet were lower than expected with ranges between 16 to 49 mEq, being suggestive of continued sodium avidity in the kidneys. PRA was less than 0.5 ng/ml/hr and serum aldosterone levels were less than 90 pg/ml (normal values on supine position and sodium unrestrieted diet-PRA, 1.02±0.34 ng/ml/hr; Aldosterone, 122±72 pg/ml).

Baseline meaurements of PRA and serum aldos-

Table 1. Baseline characteristics, serum electrolytes, blood chemistries and medications on initial hospital dyas

Date	1/27/93	1/28/93	1/29/93	1/30/93	1/31/93	2/193
Diet	Regular	Regular	Regular	Regular	Regular	Regular
Diarrhea	(+)	(+)	(+)	(+)	(+)	(+)
Weight (kg)	91	90	89.6	89.5	88.4	87
Bp (mmHg)	175/100	180/100	150/90	160/90	160/100	150/90
Na (mEq/L)	142	137	139	138	144	138
K (mEq/L)	6.2	6.2	6.4	5.8	6.4	6
Cl (mEq/L)	119	115	115	114	114	111
CO2(mEq/L)	20	18	19	14	18	20
BUN/Crea.(mg/dl)	40/0.8	42/1.4	42/1.3	-	-	40/1.4
Albumin (gm/dl)	2.5	-	-	-	-	2.5
Captopril	25 mg Bid →				25 mg Tid →	
Furosemide	20 mg Bid →				40 mg Bid	
Spironolactone	25 mg Bid	D/C				
Nicardipine				20 mg Tid →		
Atenolol				50 mg hs →		
K-resin		5 gm Tid →				10 gm Tid
Shohl's soln				20 ml Tid →		

Na, Sodiumk; K, potassium; Cl, ehloride; CO2, carbon dioxide; Crea., creatinine; D/C, discontinue

K-resin, potassium exchange resin

terone levels (Fig.1, Fig.2). The basal PRA values were markedly lower in our cirrhotic patient with hyperkalemia than in the other 5 cirrhotic patients with normokalemia (range, 0.2 to 0.4 vs. 1.2 to 5ng/ml/hr) (Fig. 1). The basal serum aldosterone levels were also markedly lower in this patient than in the other 5 cirrhotic patients with normokalemia (range, 74 to 82 vs. 185 to 800 pg/ml) (Fig.2).

Effect of captopril on PRA and serum aldosterone level (Fig.3). The renin/aldosterone stimulations test in our cirrhotic patient with hyperkalemia by oral intake of converting enzyme inhibitor, 50 mg of captopril, were shown at baseline and after 3 hours. PRA (ng/ml/hr) was 0.2, at baseline and 0.3 at 3 hours. Aldosterone level(pg/ml) was 74 at baseline and 73 at 3 hours.

Effect of low salt diet and furosemide followed by upright position on PRA and serum aldosterone levels(Fig.4). The renin/aldosterone stimulation test in our cirrhotic patient with hyperkalemia by low salt diet (2 gm salt) and by oral intake of furosemide, 40mg/day for 2 days for 2 days and then by upright position for 2 hours was performed, respectively. PRA (ng/ml/hr) was 0.3 at baseline, increased slightly to 0.6 by low salt diet and furosemide intake, and then to 0.7 by upright position. Aldosterone level (pg/ml) was 74 at baseline and without change by low salt diet and furosemide intake, and then inereased slightly to 85 upright position.

DISCUSSION

This 49 year-old man with cirrhosis and hypertension described herein was brought to our attention because of persistent hyperkalemia during his initial dyas in hospital. Subsequent studies including renin/aldosterone stimulation testing exhibited mild to moderate renal insufficiency. mild hyperchloremic metabolic acidosis with normal to low anion gap, still acidic urine pH and sustained hyperkalemia even after discontinuation of medications affecting th renin angiotensin-aldosterone system, those of which are known features of hy-

Table 2. Baseline profiles of electrolytes and chemistry of blood and urine, arterial blood gas analysis, PRA and serum aldosterone levels of a cirrhotic patient with hyperkalemia after discontinuation of medications and before renin/aldosterone stimulation lest

Date		2/4/93	2/5/93	2/6/93
Serum	Na (mEq/L)	138	132	138
	K (mEq/L)	5.6	5.6	5.4
	Cl(mEq/L)	114	109	115
ABG	HCO_3^- (mEq/L)	16	19	20
	pH/pCO_2	7.29/34	7.37/34	7.37/35
Anion gap	(mEq/L)	8	4	3
Urine pH		5	5	5
24-hour urine	Na(mEq)	16	21	49
	K (meq)	27	28	29
Ccl	(ml/min)	54		61
PRA	(ng/ml/hr)	0.2	0.3	0.4
Aldosterone	(pg/ml)74	67	82	

Na, sodium; K, potassium; Cl, chloride; HCO_3^-, bicarbonate

ABG, arterial blood gas; Ccl, creatinine clearance; PRA, plasma renin activity

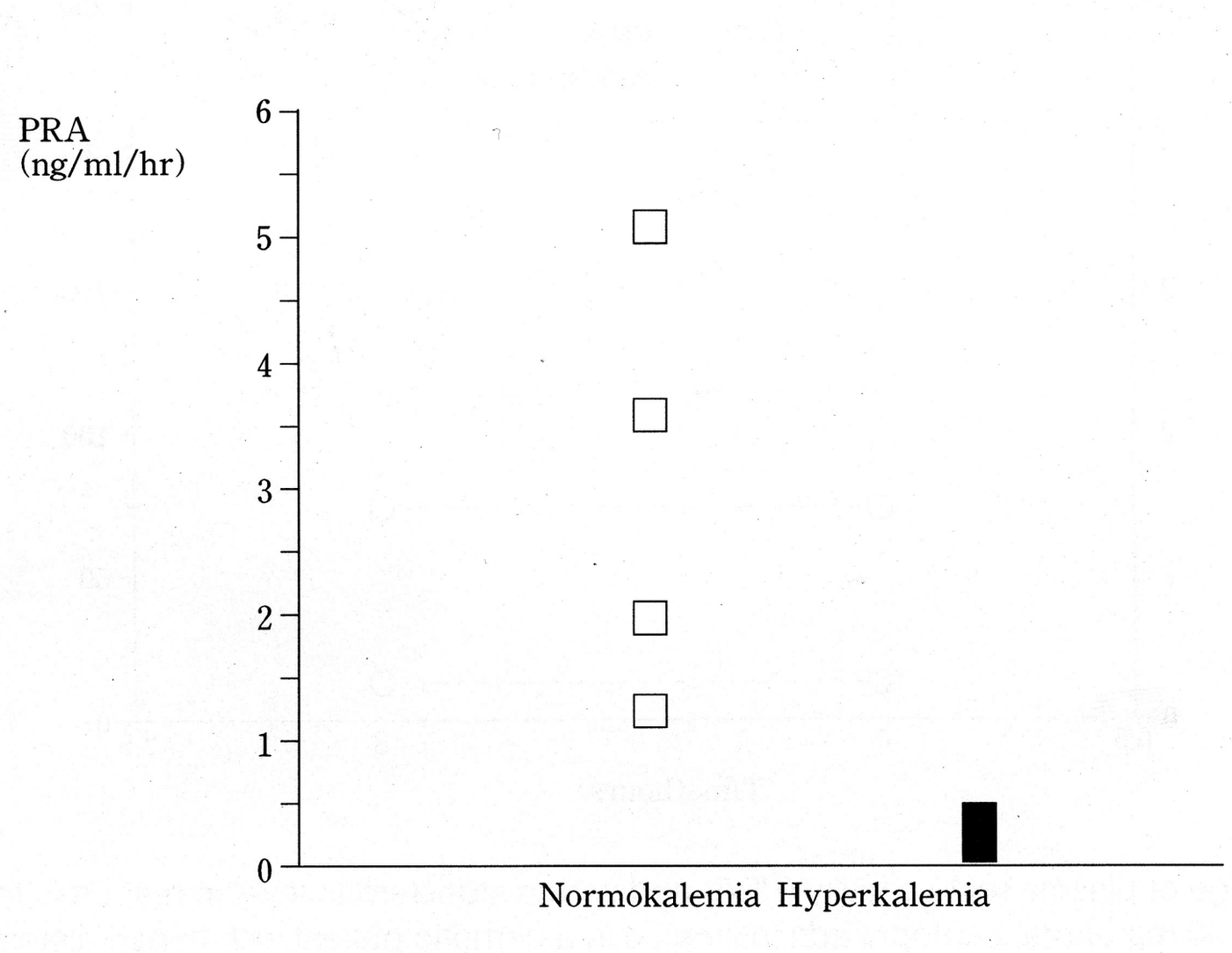

Fig. 1. Plasma renin activity(PRA) on regular diet in 5 cirrhotic patients with normokalemia(open square) and a cirrhotic patient with hyperkalemia(closed square, measured 3 times).

poreninemichypoaldsteronism(Phellpsetal., 1980). Adrenal insufficiency was unlikely in view of clinical evidence including the presence of hypertension and the absence of hyperpigmentation, and normal 24-hour urinary 17-hydroxycorticoid exeretion. Baseline aldosterone levels when compared to five other normokalemic cirrhotic patients were very low, especially for the degree of hyperkalemia (Defronzo, 1980); the latter is known to be a potent independent stimulus of aldosterone secretion

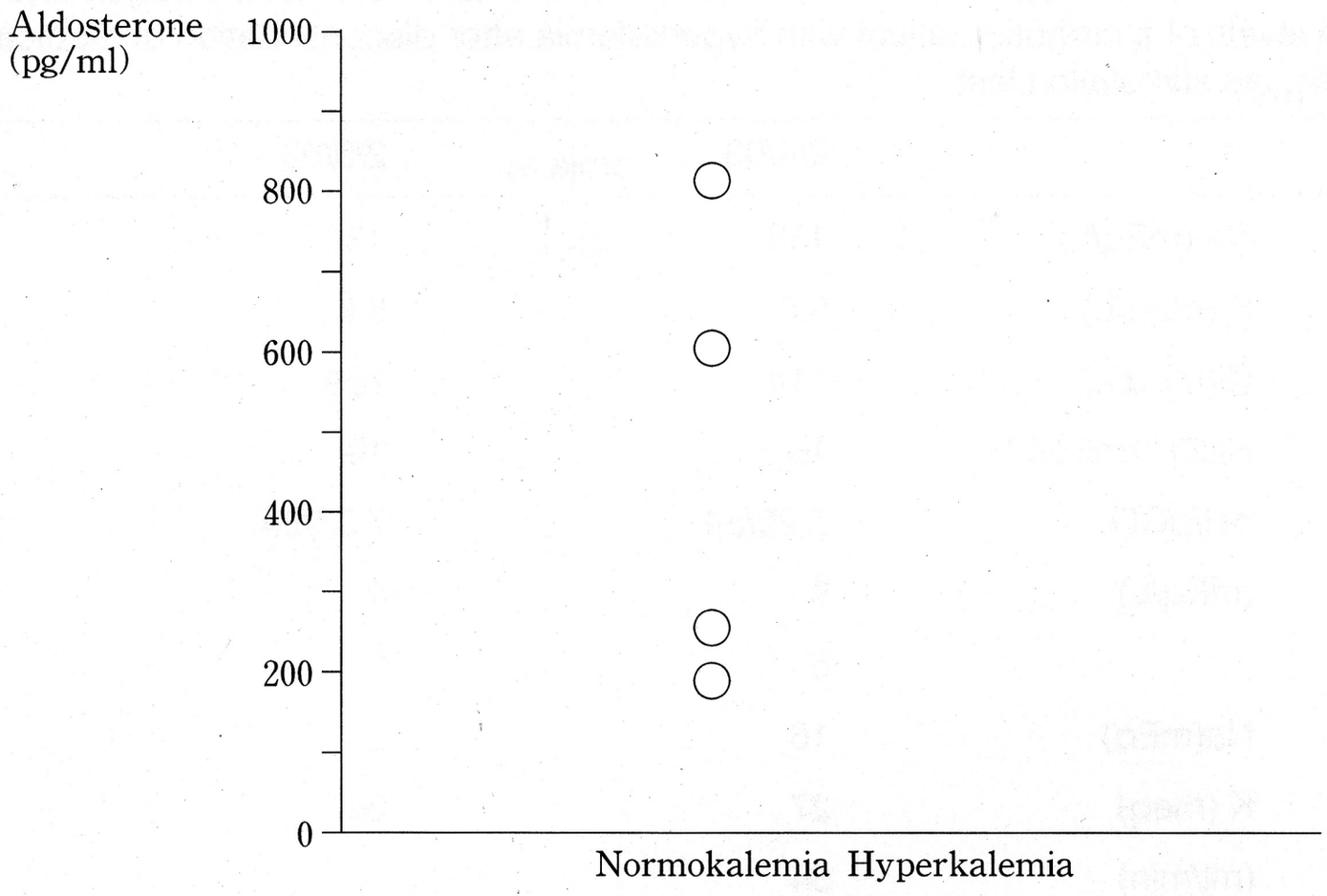

Fig. 2. Serum aldosterone levels on regular diet in 5 cirrhotic patients with normokalemia(open circle) and cirrhotic patient with hyperkalemia (closed circle, measured 3 times).

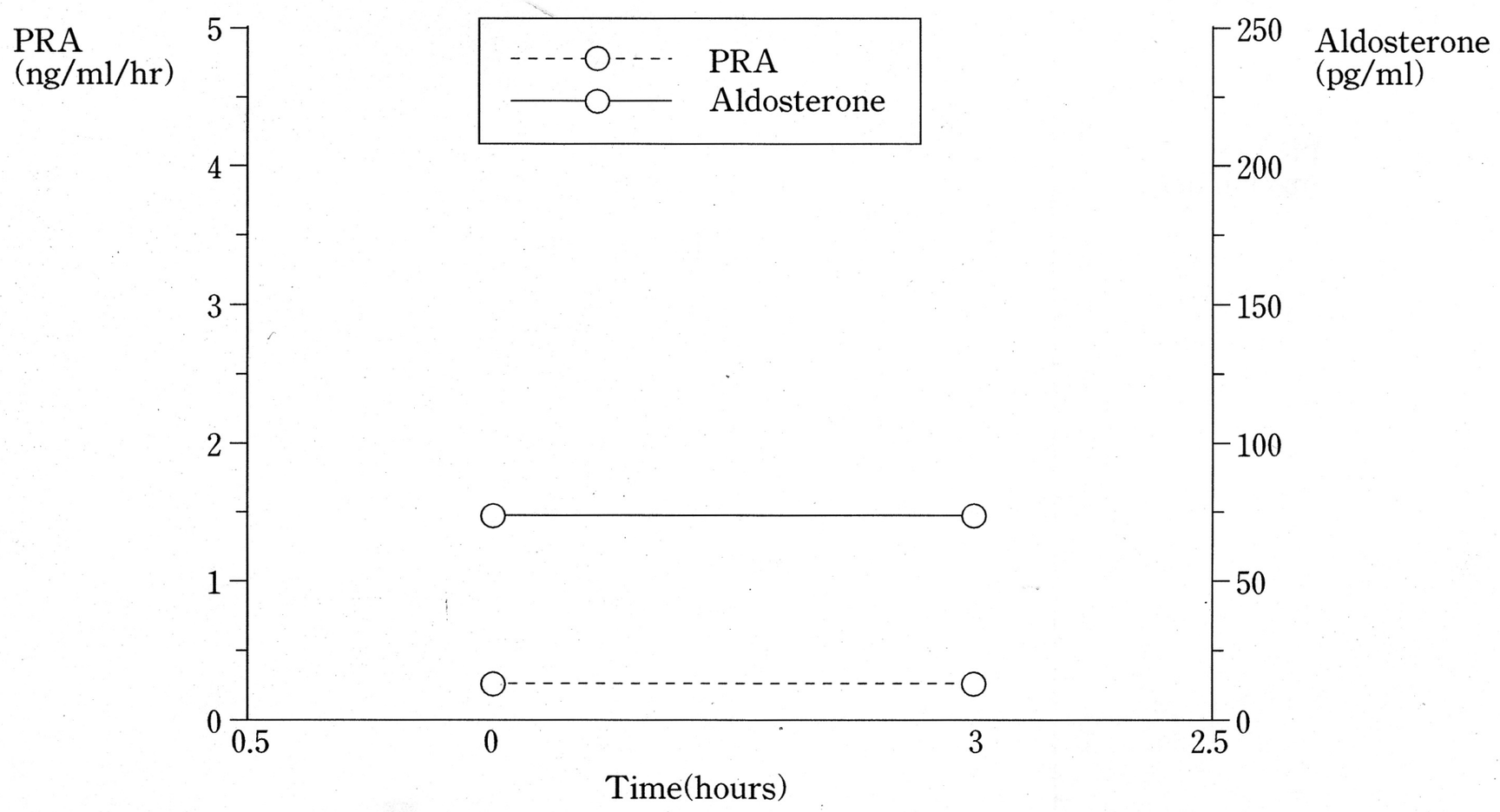

Fig. 3. Change of plasma renin activity (PRA) and serum aldosterone level in response to 3 hours after 50 mg of oral captopril administration in a cirrhotic patient with hyperkalemia..

(Laragh, 1973). We obtaind further insights into this selective aldosterone deficiency by renin/aldosterone stimulation studies. Both the PRA and aldosterone levels at base line were low and failed to rise adequately after stimulation with low salt and furosemide intake, upright posture and captopril intake, respecitively. These data were consistent with the first report suggesting that the aldosterone deficiency of hyporeninemic hypoaldosteronism under consideration was a secondary rather than a primary phenomenon to a deficiency of renin production (Sehambelan et al., 1972).

The previously proposed caused for the hyporeninemia of hyporeninemic hypoaldosteronism include damage to juxtaglomerular appratus (Schindler and Sommers, 1966), impaired conver-

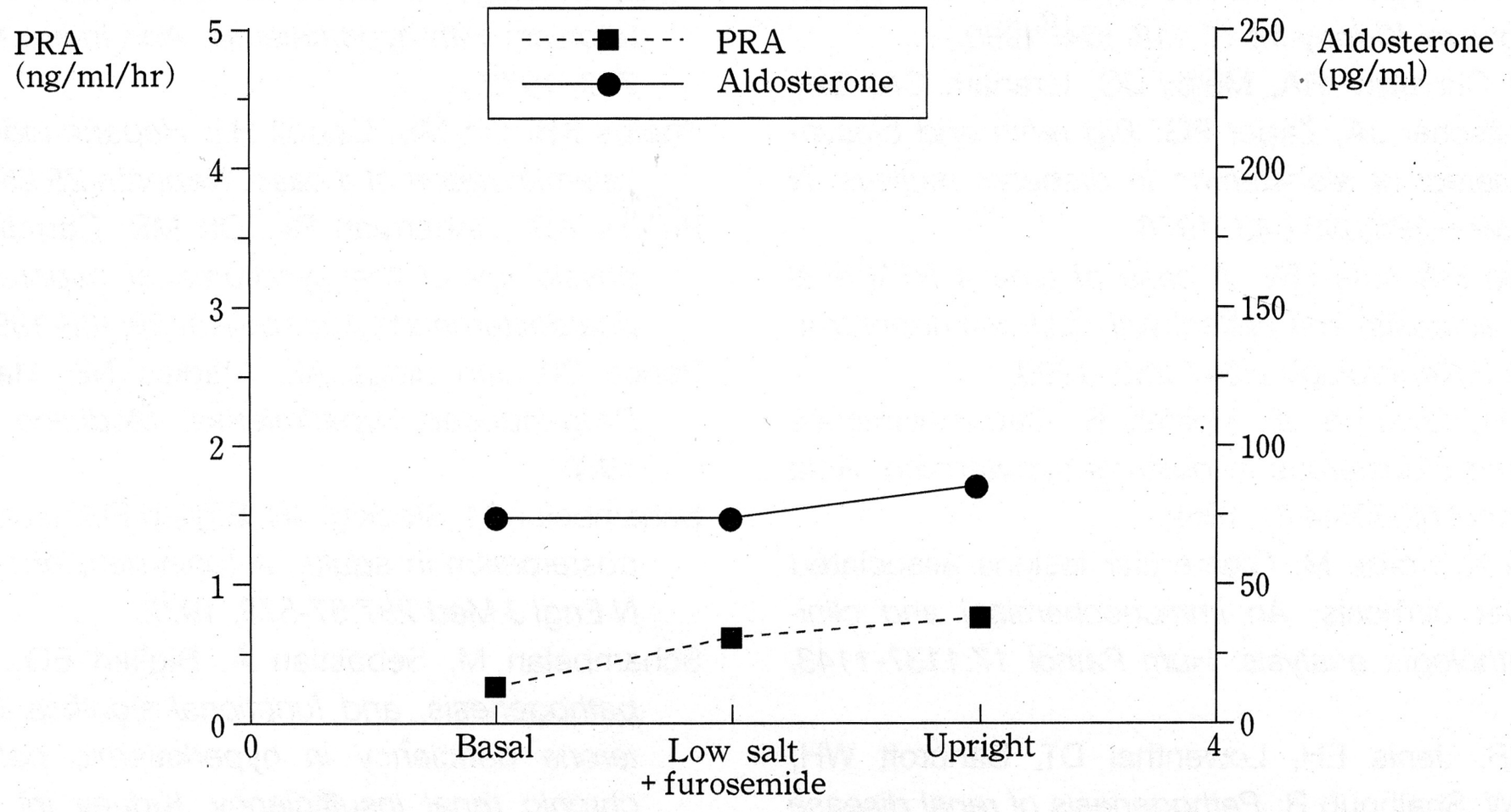

Fig. 4. Changes of PRA and serum aldosterone after stimulation tests by restricted salt diet and furosemide, 40 mg/d for 2 days, followed by two hours of upright posture in a cirrhotic patient with hyperkalcmia.

sion of precursors of renin to the active hormone (Deleiva et al., 1976), insufficient sympathetic stimulation of renin producing cells (Hedeland et al., 1969), physiologic inhibition of renin release by volume expansion (Oh et al., 1974), and altered synthesis of renal prostaglandins (Tan et al., 1979). The liver cirrhosis and hypertension of our patient could potentially play a role in any of these mechanisms.

Following the description of a series of patients manifesting with hyperkalemia and hyperchloremic acidosis in chronic pyelonephritis in 1964 by Carroll HJ et al., hyporeninemic hypoaldosteronism has become widely appreciated in the past decades. Also, there have been few scattered reports of hyporeninemic hypoaldosteronism in Korea (Song et al., Do et al., 1990, Park et al., 1991). More than half of the patients with hyporeninemic hypoaldosteronism have diabetic nephropathy, and the remainder have one of many varieties of predominantly, obstructive uropathy, hypertensive renal disease, sickle cell nephropathy (Oh and Carroll, 1989, DeFronzo, 1980). Though the presence of a history of hypertension, liver cirrhosis and hepatitis surface antigenemia in our patient, which was unrecognized as far as we know as underlying diseases with hyporeninemic hypoaldosteronism, would have implications for the development of hyporeninemic hypoaldosteronism in this case. Certainly, severe chronic liver disease of almost any type occasionally may be associalted with diffuse glomerular sclerotic process, often refered to as cirrhotic glomerular sclerosis (Kawaguchi and Koibe, 1986). Furthermore, many reports have documented the development of renal involvements with vasculitis of glomerulonephritis in patients with hepatitis B infection (Knieser et al., 1974, Sergent et al., 1976, Nagy et al., 1978).

Superimposed on impaired renal potassium excretion by hyporeninemic hypoaldosteronism in our ease, the presence of a marked reduction in effective arterial volume with decompensated liver cirrhosis, diarrhea and poor dietary salt intake could impair further potassium secretion by reducting the delivery of sodium to the distal nehron (DeFronzo et al., 1980). Furthermore, medications by diuretics including, especially potassium sparing diuretic (Spironolactone), captopril, and adrenergic beta blocker (atenolol) aggravated the degree of hyperkalemia in the initial hospital days. Follwoing simple discontinuation of these medications later in the course of treatment into other regular regimens for hyperkalemia ameliorated the degree of this severe hyperkalemia.

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