Plasma ADH Level in Patients with Chronic Congestive Heart Failure

YÔKO YAMANE[†]

Plasma ADH levels in patients with chronic congestive heart failure were determined. In about half cases with moderate to severe right heart failure, ADH increased and it normalized after the cardiac function had improved. There were some cases where ADH increased in response to decreased circulating blood volume. In chronic congestive heart failure, ADH seems to play a rôle in edema formation together with aldosterone or change in the renal circulation.

IN 1940, ROBINSON and FARR¹ reported the presence of antidiuretic activity in the urine of patients with chronic congestive heart failure. This work was confirmed by BERCU et al.² After that, DECHIOS et al.³ and PERRY et al.⁴ observed an increased antidiuretic substance in blood of patients with heart disease who had edema. But none of these assay methods for antidiuretic substance was specific or sensitive, and it is questionable whether these authors determined the level of ADH itself or not. Because the ADH concentration in human plasma is very low, estimation of it has been difficult, and accordingly the research in this field has not progressed. The author used the experimental diabetes insipidus rats for bioassay of ADH⁵. These rats were about four times more sensitive to ADH than the normal rats. With this method it was possible to determine the ADH levels in human plasma. The author studied the role of ADH in chronic congestive heart failure using this method.

MATERIALS AND METHODS

1) Dehydration test.

Forty eight inpatients with chronic congestive heart failure and 15 healthy doctors, student nurses and students as controls were deprived of food and water for 13 to 16 hours prior to the withdrawing

of blood from their antecubital vein. Blood withdrawal was done between eight and nine in the morning. In most cases with chronic congestive heart failure, dietary intake of sodium chloride was fixed at 5 gm and protein 1.2 gm per kg of body weight. Plasma ADH and osmolality were determined. The circulating blood volume and the venous pressure were determined simultaneously. Urine was collected during one hour before the withdrawal of blood, and urine volume and urinary osmolality were measured. The osmolar clearance and the free water clearance were calculated.

2) Water loading test⁶.

The test was devised to investigate whether it was possible to inhibit the plasma ADH activity by lowering plasma osmolality and to induce water diuresis by ingestion of a small amount of water in congestive heart failure or not. Twelve patients with chronic congestive heart failure were examined. They were deprived of food and water overnight for 14 hours. Following a one-hour control period, the subjects were hydrated with water in a dose of 10 ml per kg body weight by mouth over a period of one hour. Before the test started an indwelling catheter was inserted. Urine during the control period and every 30 minutes after ingestion of water was collected for 4 hours. Blood was withdrawn before hydration and at the time of expected maximal diuresis after hydration. In most cases the time of expected maximal diuresis were 30 to 60 minutes after the ingestion of water ended.

Plasma ADH, plasma osmolality, urine volume

[†] The Second Department of Internal Medicine, Kansai Medical School, 1 Fumizonochô, Moriguchi City, Osaka, Japan
(Received for Publication, March 4, 1968)

and urinary osmolality were determined.

3) Effect of diuretics.

In order to study the effect of changes in the circulating blood volume on plasma ADH, furosemide was given in a dose of 40 mg to 11 cases with chronic congestive heart failure and 2 healthy normal controls. Because fluid will be lost as urine isotonicity with furosemide, plasma osmolality will not change before and after the administration of it, and consequently the influence of change in plasma osmolality on ADH secretion will be eliminated. The subjects were given 40 mg of furosemide with 50 ml of water orally after overnight dehydration (for 14 hours). Before the test started an indwelling catheter was inserted. Urine of the control period and every 30 minutes was collected for 4 to 5 hours after administration of furosemide. In most cases blood specimens were drawn before administration of furosemide and at the time of maximal diuresis. In several cases the third blood specimen was withdrawn at the end of the experiment when the urine volume had declined.

Blood was examined for ADH, osmolality, circulating blood volume, sodium and potassium. Urine volume, urinary osmolality, urinary excretion of sodium and potassium and aldosterone excretion were determined. The osmolar clearance and the free water clearance were calculated. Venous pressure was measured every hour.

4) Effect of digitalis.

Fifteen patients with chronic congestive heart failure were examined before and after digitalization with lanatoside C. The dose of lanatoside C was somewhat different case by case. Pulse rate, urine volume, body weight, venous pressure, circulating blood volume, plasma osmolality, urinary aldosterone excretion and plasma ADH etc. were determined.

ANALYTICAL METHOD

ADH was extracted from plasma with SHARE's modification⁷ of WEINSTEIN's method⁸ and later with YOSHIDA's method⁹, using about 15 to 20 ml of plasma. Bioassay was carried on the experimental diabetes insipidus rat as previously described⁵. Plasma and urine osmolality were determined cryoscopically with a Fiske osmometer, sodium and potassium were determined by flame photometry. The circulating blood volume was measured by the isotope dilution method using I^{131} -RIHSA. Urinary aldosterone was determined by the double isotope derivative method¹⁰ using C^{14} and H^3 .

RESULTS

1) Dehydration test.

Fig. 1 shows plasma ADH levels after over-

ADH & Class of Decompensation

Fig. 1

night dehydration in the control group and in patients with chronic congestive heart failure whose functional capacity was classified into 4 groups according to the classification by the New York Heart Association. In the normal controls, plasma ADH level was less than 2.1 μ U per ml of plasma. In classes 1 and 2 patients with heart failure it was normal in all cases, but in one third of classes 3 and 4 patients it was increased. There was the statistically significant difference between classes 1 and 2 group and classes 3 and 4 group ($P < 0.05$). The patients with congestive heart failure were divided into two groups, one was the group with right or right and left heart failure and the other was the group with pure left heart failure. As Fig. 2 shows, ADH level in all cases with pure left heart failure was normal but in cases with right or both side failure it was various and increased in about half of the cases.

There was no significant correlation between plasma ADH level and plasma osmolality (Fig.

Fig. 2

Fig. 3

Fig. 4

Fig. 5

3), and between plasma ADH level and the circulating blood volume¹¹ (Fig. 4) which was determined simultaneously. Because plasma ADH level was increased in half of the cases with right heart failure, the author compared the ADH level and the peripheral venous pressure which was determined simultaneously, but could not find the significant correlation

between them (Fig. 5). But there was a tendency to show increased plasma ADH level in cases with high venous pressure¹². Plasma ADH was correlated with the right ventricular end-diastolic pressure ($P < 0.01$) and the right atrial pressure ($P < 0.05$) which were determined at not distant time of ADH determination as Fig. 6 and 7 show. There was no significant correlation be-

Fig. 6

Fig. 7

tween plasma ADH level and the pulmonary capillary wedge pressure (Fig. 8)¹³.

In Fig. 9 plasma ADH levels in patients with congestive heart failure were plotted against the venous pressure and the circulating blood volume. In this figure the white circle

shows high ADH value. In all cases with venous pressure higher than 200 mmH₂O, ADH level was high except for one case. In cases whose venous pressure was between 100 mmH₂O and 200 mmH₂O plasma ADH increased in about half of them regardless of the

Fig. 8

Fig. 9

circulating blood volume. Although the venous pressure was in the normal range, plasma ADH level increased when the circulating blood

volume increased in several cases. In 2 cases where the venous pressure was normal and the circulating blood volume was relatively small,

Fig. 10

Fig. 11

plasma ADH increased moderately. In these cases there was hyponatremia probably caused by the powerful diuretics. Their plasma osmolality was low. Fig. 10 shows the clinical course of one of these cases. Body weight did not increase at the time when she had hypo-

TABLE I

Subject	Age	Sex	Diagnosis	Class	Treatment	Prehydration			Posthydration		
						ADH (μ u/ml)	Sosm (mOsm/kgH ₂ O)	Uosm (mOsm/kgH ₂ O)	ADH (μ u/ml)	Sosm (mOsm/kgH ₂ O)	Uosm (mOsm/kgH ₂ O)
1. M.T.	68	f	MSI	4	Digoxin	1.1	300	711	1.8	295	703
2. Y.T.	48	m	ASD	3	Spironolactone	1.0	289	931	<1.1	284	310
3. Y.S.	24	m	Constrictive Pericarditis	3	Lanatoside C	1.8	289	1208	1.2	288	1020
4. M.K.	24	f	MSI	3	Lanatoside C	4.2	286	320	1.7	278	101
5. "	"	"	Aur. Fibril.	3	Prednisolone	4.3	294	792	1.0	287	746
6. "	"	"	"	3	"	4.0	288	828	1.0	283	102
7. T.Y.	35	f	MS	3	+Hydrocortisone	2.8	295	962	<1.0	294	84
8. M.H.	42	f	Aur. Fibril.	3	Lanatoside C	1.0	281	586	1.2	288	596
9. M.U.	55	f	MSI+TI	3	Digoxin	0.8	286	686	1.2	282	140
10. M.K.	16	f	VSD, SBEC	2	(-)	1.5	290	930	0.6	282	849
11. K.M.	39	f	MS+ASI	2	Digoxin	0.7	281	713	<0.3	276	85
12. R.U.	43	m	MS+AI	2	(-)	0.9	291	747	<0.8	286	161
13. M.M.	27	f	MS	1	(-)	1.3	284	842	0.5	278	120
14. A.O.	19	m	Rheumatic Carditis	1	(-)	1.9	291	970	1.3	284	211

Fig. 12

natremia and also she did not have edema. This case was not likely to have a dilutional hyponatremia. But ADH level was high in spite of low plasma osmolality. ADH secretion seemed to increase in response to the decreased circulating blood volume.

2) Water loading test.

Table I shows the results of water loading test. In most cases urinary osmolality decreased markedly as the serum osmolality decreased and the free water clearance increased. At the same time plasma ADH level decreased. Fig. 11 shows changes in free water clearance after water loading. Solid line shows cases where plasma ADH decreased after water loading; on the contrary the dotted line indicates cases where plasma ADH did not decrease after that. But no significant correlation was observed between change in plasma ADH level and the degree of decrease in serum osmolality (Fig. 12). In cases where diuresis did not occur, plasma ADH decreased simultaneously with decrease in plasma osmolality in some cases, and plasma ADH did not decrease even if plasma osmolality decreased in others. In the former, there rather would be a disturbance in the renal circulation and in the latter the reason could not be clarified, but it would suggest the pres-

ence of inappropriate secretion of ADH¹⁴. In these experiments the circulating blood volume was not determined.

3) Effect of diuretics.

The author experienced two cases with hyponatremia where plasma ADH was high in spite of low plasma osmolality as mentioned above. In both cases the circulating blood volume was decreased. To study the effect of the circulating blood volume on ADH secretion, diuretics were given to the patients with chronic congestive heart failure and to the normal controls^{15, 16}. With diuretics the body fluid would decrease isotonicity.

As Fig. 13 shows, urine volume increased after administration of furosemide in normal controls. The osmolar clearance increased simultaneously with the increase in urine volume, but the free water clearance remained negative. The circulating blood volume which was 4730 ml (80.2 ml/kg) before administration of furosemide decreased significantly to 3970 ml (69.0 ml/kg) 3 hours after administration of furosemide. Plasma osmolality was 282 mOsm/kgH₂O and did not change throughout the experiment. Plasma ADH increased gradually from 0.7 μu/ml before administration to 2.6 μu/ml one and a half hours after adminis-

Fig. 13

tration of furosemide and to 5.1 $\mu\text{u/ml}$ 3 hours after. In this case, plasma ADH seemed to increase responding to the decreased circulating blood volume.

The same experiment was performed on patients with congestive heart failure.

The representative result of the effect of furosemide in patients with class 2 heart failure was shown in Fig. 14. This case was a 45-year-old woman who was suffering from the obliterative thromboarthritis. Her cardiac index was 3.71. The osmolar clearance and the free water clearance increased after administration of furosemide. Plasma ADH level was unchanged before and after administration of furosemide and it was 2.2 $\mu\text{u/ml}$. Diuresis occurred by furosemide. Urine volume of a one-hour period after administration of furosemide was about 700 ml. The circulating blood volume was 3101 ml (65.6 ml/kg) one hour

Fig. 14

after administration of furosemide which had been 3195 ml (66.5 ml/kg) before the administration. Because the change in the circulating blood volume was not significant, there seemed to occur the shift of body fluid from the extravascular space to the intravascular space. Plasma osmolality was 299 mOsm/kgH₂O and it did not change after administration of furosemide. In this case the free water clearance not only increased but became positive although there was no change in plasma ADH level. The endogenous creatinine clearance increased simultaneously with diuresis. Although it is less certain that an increase in GFR alters renal sensitivity to ADH other than through its effect on the osmolar clearance, it should be taken into consideration. Moreover, furosemide seemed to normalize the distribution of blood flow in the kidney. Blood flow increased to the outer cortical region with furosemide which had

Fig. 15

been disturbed in congestive heart failure as BARGER stated¹⁷. As the consequence of it, urine volume reaching the distal tubule increased. In one case with aortic insufficiency the free water clearance did not become positive. Plasma osmolality lowered, the circulating blood volume did not change and plasma ADH level did not change significantly after administration of furosemide.

Fig. 15 shows the case of a 55-year-old woman who was suffering from mitral insufficiency. Her cardiac index was 1.95. Her functional capacity was classified as class 3. This case voided 480 ml of urine after administration of furosemide and simultaneously the osmolar clearance and the free water clearance increased. The circulating blood volume decreased from 4619 ml (83.2 ml/kg) to 4250 ml (77.5 ml/kg) and plasma osmolality increased from 291 mOsm/kgH₂O to 294 mOsm/kgH₂O. But plasma ADH level normalized from 3.1 $\mu\text{u/ml}$ to 1.4 $\mu\text{u/ml}$. The

Fig. 16

venous pressure decreased to 87 mmH₂O which had been 158 mmH₂O. In this case the cardiac function seemed to be improved with furosemide.

Fig. 16 shows the case of a 27-year-old man who suffered from a combined valvular disease. His cardiac index was 1.03 and his functional capacity belonged to class 4. In this case furosemide increased only the osmolar clearance slightly. The free water clearance remained negative. Plasma osmolality decreased from 290 mOsm/kgH₂O to 288 mOsm/kgH₂O. The circulating blood volume decreased slightly from 5301 ml (98.2 ml/kg) to 5090 ml (95.0 ml/kg). ADH increased slightly from 2.0 $\mu\text{u/ml}$ to 2.3 $\mu\text{u/ml}$. In this case diuresis scarcely occurred but urinary secretion of aldosterone increased markedly¹⁶. This case was given the same dose of furosemide after administration of spironolactone for several days. As Fig. 17 shows, urine volume increased and the osmolar clearance increased simultaneously

Fig. 17

with furosemide at that time. The circulating blood volume normalized from 5110 ml (92.3 ml/kg) to 4300 ml (78.5 ml/kg). Plasma ADH decreased from 3.8 $\mu\text{u/ml}$ to 2.8 $\mu\text{u/ml}$ which was still above normal. Plasma osmolality was 278 mOsm/kgH₂O and unchanged before and after administration of furosemide. The venous pressure lowered and the cardiac function seemed to be improved.

4) Effect of digitalis.

Fig. 18 shows the course of a 49-year-old female patient with a combined valvular disease. She was admitted to our hospital with class 4 of heart failure. At the time of admission she complained of dyspnea and edema. Her liver was palpable about 3-finger breadth on the right midclavicular line, the venous pressure was 225 mmH₂O, her heart rate was 156 and there was 60 pulse deficit. The circulating blood volume was 3490 ml (78.4 ml/kg, 2.75 L/M²), plasma osmolality was 287 mOsm/kgH₂O. Plasma ADH was moderately increased and its level was 9.1 $\mu\text{u/ml}$. After digitalization with lanatoside C, heart rate de-

Fig. 18

TABLE II

Subject	Age	Sex	Diagnosis	Treatment	Date	Class	ADH ($\mu\text{u/ml}$)	Posm ($\text{mOsm/kgH}_2\text{O}$)	Uosm ($\text{mOsm/kgH}_2\text{O}$)
1. Y.O.	49	f	MSI+AI	(-) Lanatoside C Digoxin 0.25 mg "	Apr. 25 May 6 May 17 May 27	4 3 3 2	9.1 <1.4 3.7 <1.0	287 284 291	688 655 652 652
2. S.K.	20	m	ASI	(-) Lanatoside C Digoxin 0.5 mg "	June 14 June 17 July 18	4 3 2	1.7 1.8 0.6	293 275	735 549
3. M.K.	26	f	MSI+AF	Digoxin 0.125 mg Digoxin 0.625 mg "	July 13 Aug. 22	3 2	1.5 1.7	282 291	944 1557
4. Z.Y.	57	m	ASI+AF	(-) Lanatoside C "	Aug. 31 Sept. 2 Sept. 7	4 3 3	4.0 <2.0 4.3	319 290 293	922 1396 937
5. N.M.	51	m	AF+MI(?)	(-) Lanatoside C Digoxin 0.375 mg "	Sept. 10 Sept. 14 Oct. 12	3 2 2	<0.7 1.2 2.1	302 289 300	650 617 646
6. K.N.	24	m	MSI+AF	Lanatoside C Lanatoside C Spironolactone "	Oct. 22 Nov. 5 Nov. 18	4 4 3	4.9 3.7 6.2		
7. Z.S.	74	m	Hypertensive Heart Fail.	(-) Lanatoside C "	Dec. 2 Dec. 3 Dec. 9	4 4 4	1.3 2.2 1.7	299	775 715
8. S.N.	78	m	AF	(-) Lanatoside C "	Mar. 4 Mar. 6 Mar. 10	4 3 3	0.7 1.1 2.5	295 278 285	842 618 702
9. A.K.	59	m	Hypertensive Heart Fail.	(-) Lanatoside C "	Feb. 17 Feb. 18 Feb. 24	4 3 3	2.4 <1.5 1.0	294 291	474 493
10. S.T.	48	f	Endomyocard- fibroel.+AF	(-) Digoxin 0.5 mg "	Oct. 27 Nov. 5	3 3	2.7 2.2		779 655
11. M.H.	42	f	MSI+TI +AF	(-) Digoxin 0.5 mg "	Feb. 2 Feb. 19	4 3	4.0 1.0	295 281	1108 586

N. M. 51-y. o. m. MI

Fig. 19

Venous Pressure (mmH ₂ O)	Vital Capacity (ml)	Heart Rate (/min)	Pulse Rate (/min)	Blood Volume (ml) (ml/kg)		Plasma Volume (ml) (ml/kg)		Body wt. (kg)	Liver (fb.)	Edema	Dyspnea
225		156	96	3490	93.2	2105	56.3	44.5	3	+++	++
76	840	34	34	2920	78.1	1795	48.0	37.5	0	—	±
120		76	70	3235	86.3	2035	54.2	38.0	0	+	—
65		78	70	2600	69.6	1585	42.3	37.4	0	—	—
60	3160	102	77	5870	94.2	3570	57.2	62.7	2	—	+++
73		63	62	5700	91.3	3590	57.6	62.4	2	—	—
49	4440	52	52	5280	84.6	3520	56.4	62.7	1	—	—
89	2000	104	84	3342	69.3	2200	45.5	50.4	2	—	+
70	2420							56.5	1	—	—
144	2150	99	59	5125	96.7	2870	54.3	55.8	5	+	++
68		72	69	4070	76.2	2410	45.5	53.0	4	—	+
23	2040	63	58	3970	74.9	2295	43.3	47.5	1	—	—
76	2320	114	83	4158	88.3	2512	53.2	49.1	1.5	—	—
24	2680	52	52	3980	84.5	2472	52.4	47.2	0	—	—
	3580	63	63	4029	85.5	2692	57.1	48.6	0	—	—
202	2520	76	75					46.2	6	+	+
232	2360	85	83					46.2	4	—	—
118	2900	74	74	4641	105.5	3290	76.6	43.0	3	—	—
108		126	126	4099	78.9	2661	50.3	52.0	3	+	+
83		124	124	4100	78.9	2681	51.7		1	—	—
42		88	44	3330	64.1	2265	43.7		0	—	—
146	900	115	93	4390	118.0	2780	74.7	42.0	2	++	++
29	1020	75	71	3910	105.1	2510	67.5	40.0	0	—	+
47	1400	50	50	4320	116.1	2880	77.4	39.5	2.5	—	—
85	1130	82	82	4018	100.4	2760	68.7	43.5	0	+	+
39		67	67	3735	93.4	2569	63.9	41.7	0	+	±
36	2080	62	62	4085	102.1	2879	71.6	40.2	0	—	—
197	1720	90	90					61.6	?	++	—
		84	84					60.0	?	+	—
110	1500	90	90	5210	123.0	3122	72.4	40.2	?	++	++
30	1240	53	53					34.4	?	±	—

creased, venous pressure normalized, urine volume increased and the circulating blood volume decreased after temporary increase¹¹. This temporary increase in the circulating blood volume appeared to be due to the shift of edema fluid to the intravascular space. The plasma ADH normalized after her cardiac function improved. Later when she did not keep bed rest, her urine volume decreased and the venous pressure increased, and plasma ADH increased to 3.7 μ u/ml. And again it normalized to 1.0 μ u/ml with compensation.

In most cases with right heart failure, plasma ADH which had increased, normalized after improvement of the cardiac function with digitalization.

Fig. 19 shows the course of a 51-year-old male patient who suffered from auricular fibrillation. At first it was doubted that he had

mitral insufficiency but later it was not confirmed by the cardiac catheterization. At the time of admission his functional capacity belonged to class 3. He had tachycardia but his venous pressure was within the normal range. His liver was palpable about 2 cm on the right midclavicular line. Edema could not be found. The circulating blood volume was 4158 ml (84.7 ml/kg, 2.75 L/M²) and plasma ADH level was 0.7 μ u/ml which was within the normal range. His heart rate decreased and urine volume increased after digitalization. The circulating blood volume decreased slightly to 3980 ml (84.5 ml/kg, 2.64 L/M²) and ADH became 1.2 μ u/ml which was still within the normal range. Thus, in cases with predominant left heart failure there were no significant changes in ADH level after digitalization.

Table II summarizes the result of the experi-

ment.

DISCUSSION

The excessive retention of sodium and water in patients with chronic congestive heart failure contributes importantly to the morbid state. But the precise mechanism of sodium and water retention is still obscure. Most patients with congestive heart failure have some reduction of GFR and effective RPF. On the basis of these findings, the forward failure theory emphasizes these renal alterations resulting from reduced cardiac output as an important contributor to sodium and water retention¹⁹. On the other hand, the backward failure theory²⁰ implies that these changes are less important in genesis of edema than factors affecting directly the tubular reabsorption of sodium and water.

In cases with chronic congestive heart failure renal plasma flow is reduced more than glomerular filtration rate and therefore filtration fraction (GFR/eff. RPF) is elevated. VANDER et al.²¹ have suggested that elevated filtration fraction seen in heart failure can account for the augmented tubular reabsorption of sodium and water. But decreased filtration rate appears not to be the sole factor responsible for salt retention in congestive heart failure^{22,23}. The combination of decreased filtration rate and increased reabsorption of sodium by the proximal tubule results in a decreased delivery of solute and water to the distal tubule. At the distal tubule, sodium is reabsorbed more completely because of the diminished solute load.

Moreover, the role of aldosterone and ADH in the pathogenesis of edema was emphasized as humoral factors.

It has been postulated that increased ADH activity account for the low urine flow and blunted diuresis that are seen following a water load in patients with congestive heart failure²⁴. Although the evidence that ADH contributes significantly to the reduced urine flow in severe cardiac failure was indirect, LEAF et al.²⁴ stressed that the hyponatremia which was seen most commonly clinically in edematous patients was the consequence of severe derangement in body fluid volume and that ADH may be involved in this water retention. If excessive ADH is secreted in heart failure, stimulus to

the secretion must be other than increased body fluid osmolality, since plasma osmolality is usually low in severe congestive heart failure, especially in the case of hyponatremia. However, since ADH secretion is also influenced by some function of circulating blood volume²⁵, it might be stimulated by the altered circulation in heart failure. In this experiment, 2 cases with hyponatremia probably caused by the diuretics had decreased circulating blood volume and moderately increased plasma ADH level in spite of decreased plasma osmolality. Also, there were many cases with and without heart failure where ADH level increased as the consequence of the decreased circulating blood volume caused by forced diuresis after administration of furosemide. From these data it may be suggested that in some cases decrease in circulating blood volume has advantage over the plasma osmolality for stimulation of ADH secretion. Thus, increased ADH secretion may occur through this mechanism in some cases, and in others some still unknown factor will be responsible for inappropriate secretion of ADH²⁶.

In my experience, increased plasma ADH levels occurred in about half of the right heart failure cases and there was correlation between ADH levels in right ventricular end-diastolic pressure. These increased ADH levels in right heart failure cases normalized when the cardiac function improved with digitalization or diuretics. MAEKAWA⁶ presented a theory about these findings. According to him, the venous pressure is set at a high level by cardiac failure. An elevation in venous pressure leads to an increase in extravasation of body fluid and a decrease in venous return with an increased oncotic pressure of the venous blood. These changes in body fluid stimulate the release of ADH, which leads to hypervolemia and elevation in venous pressure, thus constituting a vicious circle.

Thus ADH may play a role in edema formation in chronic congestive heart failure. But as LEAF²⁷ and LARAGH²⁸ have stated, ADH is not essential for edema formation and some other factor causing sodium and water retention such as changes in renal circulation would appear necessary for the development of the edematous state in congestive heart failure.

SUMMARY

1) Plasma ADH level was increased in about half of right heart failure cases.

2) The significant correlation between plasma ADH level and right ventricular end-diastolic pressure or right atrial pressure was observed but there was no correlation between plasma ADH level and peripheral venous pressure.

3) With water load, plasma ADH level decreased and the free water clearance increased in most cases with not so severe congestive heart failure. Plasma osmolality decreased simultaneously. But in some cases with severe heart failure diuresis did not occur with water loading. Plasma osmolality and plasma ADH decreased in some cases, but in others, plasma ADH did not decrease in spite of decreased plasma osmolality. Changes in circulating blood volume were not determined in this experiment.

4) Plasma ADH increased with the decrease in circulating blood volume after forced diuresis with furosemide. At that time, plasma osmolality did not change significantly. If circulating blood volume did not change in consequence of shift of edema fluid into the intravascular space with furosemide, plasma ADH did not change.

5) In cases with right heart failure where plasma ADH level had been high, it normalized after improvement of the cardiac function with digitalis or diuretics.

6) Increased plasma ADH level in cases with hyponatremia after the forced diuresis appeared to occur in response to decreased circulating blood volume.

Acknowledgement

The author express her gratitude to Emeritus Prof. Dr. Maekawa, M., Prof Dr. Takayasu, M. and Prof. Dr. Shioita, T. for their kind guidance.

REFERENCES

1. ROBINSON, F.H. AND FARR, L.E.: *Ann. Int. Med.* **14**: 42, 1940.
2. BERCU, B.A., ROKAW, S.N. AND MASSIE, E.: *Circulation* **11**: 409, 1950.
3. DECHIOS, M. AND DREIFUS, L.S.: *Am. J. Med. Sc.* **222**: 538, 1951.
4. PERRY, W.F. AND FYLES, T.W.: *J. Clin. Endocrinol.* **13**: 64, 1953.
5. YAMANE, Y. AND KUNISHIGE, K.: *Jap. Circulation J.* **30**: 1381, 1966.
6. MAEKAWA, M. AND SAIMYOJI, H.: *Jap. Circulation J.* **30**: 42, 1966.
7. SHARE, L.: *Endocrinology* **69**: 925, 1961.
8. WEINSTEIN, H., BERNE, R.M. AND SACHS, H.: *Endocrinology* **66**: 712, 1960.
9. YOSHIDA, S., MOTOHASHI, K., IBAYASHI, H. AND OKINAKA, S.: *J. Lab. and Clin. Med.* **62**: 279, 1963.
10. KLIMAN, B. AND PETERSON, R.: *J. Biol. Chemist.* **235**: 1639, 1960.
11. KINOSHITA, M.: *Jap. Circulation J.* **32**: 249, 1968.
12. YAMANE, Y., KINOSHITA, M., KUBO, S., OHARA, Y., AND SAIMYOJI, H.: *Folia. Endocrinol. Jap.* **42**: 218, 1966. (abstract, in Japanese)
13. YAMANE, Y., NAGAO, Y., SHIOTA, T. AND KOBAYASHI, A.: *Folia. Endocrinol. Jap.* **43**: 1277, 1967. (abstract, in Japanese)
14. SCHWARTZ, W.B., BENNET, W., CURELOP, S. AND BARTTER, F.C.: *Am. J. Med.* **23**: 529, 1957.
15. KUBO, S., SAIMYOJI, H., YAMANE, Y., SERIU, Y., OHARA, Y., HARA, A., KINOSHITA, M., NAKAO, Y., AWAMURA, M., NISHIDA, K., KANATSU, K., NOHARA, Y. AND TAKAYASU, M.: *Jap. Circulation J.* **31**: 1954 (abstract), 1967.
16. YAMANE, Y., KINOSHITA, M., KUBO, S., NISHIDA, K., AWAMURA, M., KANATSU, K., HARA, A., SERIU, Y., NOHARA, Y., AND TAKAYASU, M.: *Folia. Endocrinol. Jap.* **43**: 303, 1967 (abstract, in Japanese)
17. BARGER, A.C.: *Ann. New York Acad. Soc.* **139**: 276, 1966.
18. KUBO, S.: *Jap. Circulation J.* (in print)
19. MERRILL, A.J.: *J. Clin. Invest.* **25**: 389, 1946.
20. DAVIS, J.O.: *Am. J. Med.* **29**: 486, 1960.
21. VANDER, A.J., MALVIN, R.J., WILDE, W.S. AND SULLIVAN, L.P.: *Am. J. Med.* **25**: 497, 1958.
22. BARGER, A.C., ROSS, R.S. AND PRICE, H.L.: *Am. J. Physiol.* **180**: 249, 1955.
23. BARGER, A.C., RUDOLPH, A.M. AND YATES, F.E.: *Am. J. Physiol.* **183**: 595, 1955.
24. LEAF, A. AND MAMBY, A.R.: *J. Clin. Invest.* **31**: 60, 1952.
25. SMITH, H.W.: *Am. J. Med.* **23**: 623, 1957.
26. BARTTER, F.C. AND SCHWARTZ, W.B.: *Am. J. Med.* **47**: 790, 1967.
27. LEAF, A. AND FRAZIER, H.S.: *Heart, Kidney and Electrolytes*. ed. by Friedberg, C.K. Grune and Stratton Co. New York p. 263, 1962.
28. LARAGH, J.H., VAN DYKE, H.B., JACOBSON, J., ADAMSONS, K. AND ENGEL, S.L.: *J. Clin. Invest.* **35**: 897, 1956.