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3. Antidiuretic Hormone in Congestive Heart Failure[†]

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The role of ADH in the pathogenesis of congestive heart failure has been quite obscure. This was mainly due to the fact that no reliable method for the determination of ADH was established. Recently, the method of bioassay was revised and made applicable to clinical use by Drs. Y. YAMANE and K. KUNISHIGE of this laboratory. In addition, a reliable osmometer became available for the measurement of serum and urinary osmolality. The purpose of this study was to clarify the role of ADH in congestive heart failure, employing these methods.

The present study consists of three parts: (1) Plasma ADH level, serum osmolality and the pertinent clinical data in congestive heart failure, and correlations between two of them. (2) A water loading test was devised to study whether it was possible to inhibit the plasma ADH activity and to evoke a water diuresis by ingesting a small dose (10 ml per kilogram) of water by mouth, in congestive heart failure. Since it was essential to obtain a sustained profuse diuresis with a sufficient depression in endogenous ADH activity, for the study of the function of osmoreceptor to release ADH or the study of the sensitivity of the target organ to ADH. (3) The effect of cortisol on the response to an acute water loading was studied, because it has long been known that cortisol augmented water diuresis under certain circumstances. The mechanism of this action has been the subject of animated controversy. The authors intended to study the action of ADH in

relation to other hormones, especially to cortisol.

SUBJECTS AND METHODS

Subjects examined were fifteen inpatients with heart disease who are listed in Table I. They were placed on diets containing fixed quantities of sodium chloride and protein (in most cases five grams of sodium chloride and 1.2 grams per kilogram of ideal body weight of protein).

An acute water loading test was performed after overnight (more than 14 hours) deprivation of water and food. Following a one-hour-control period, the subjects were hydrated with warm water in doses of 10 ml per kilogram body weight by mouth, over a period of one hour, being given one twelfth of the total volume at every five minutes. Before the test an indwelling catheter was inserted. Urine of the control period and every thirty minutes' urine was collected for 4 hours after the period of hydration was begun. Five blood specimens were drawn, before hydration and every one hour thereafter. Urine and blood were examined for osmolality, sodium, potassium, creatinine and urea; the osmolal clearance and the free water clearance were calculated. Plasma ADH levels were determined before hydration and at the time of expected maximal diuresis after hydration, which was in most cases 30 minutes after the ingestion of water was ended.

The effect of cortisol on the response to an acute water loading was examined by comparing the responses under conditions with and without cortisol administration. On the fourth or fifth day after the oral cortisol administration in doses of 30 mg a day was started, the water loading test was performed in the same manner, but this time 30 mg of cortisol (physiological daily requirement) was given by mouth three to four hours before the water was taken.

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TABLE I SUBJECTS AND RESULTS OF THE ACUTE WATER LOADING TEST (10 ML PER KILOGRAM ORALLY).

Exp. No.	Sub-jects	Age Sex	Diagnosis	Class	Stadium	Treatment	Condition	Prehydration				Posthydration				VP
								Diet	Serum	Urine	ADH	Serum	Urine	ADH	4hr-Urine /Load	
								NaCl g/day	Prot. mosm/kgH ₂ O	mosm/kgH ₂ O	μ U/ml plasma	mosm/kgH ₂ O	μ U/ml plasma	%	mmH ₂ O	
1	CK*	53 ♀	MS	IV	crescendo	Lanatoside C 0.3-0.2mg Aminophylline		5 60	281	500		272	569			
2	"			IV	"	"	Cortisol 30mg p.o.	" "	282	541	2.3	284	85		76.3	94
3	MT	68 ♀	MSI	IV	crescendo	Digoxin 0.25mg		5 —	300	711	1.1	295	703	1.8	26.7	64
4	"			IV	"	"	Cortisol 30mg	" —	302	685		291	673		33.0	88
5	MK	24 ♀	Comb. Vato. Disease SBEC Rheumatic	III	decrecendo	Prednisolone 5mg Lanatoside C 0.2mg		5 50	286	320	4.2	278	101	1.7	66.7	146
6	"			II	plateau	"		" "	294	792	4.3	287	746	1.0	12.2	112
7	"			III	"	"	Cortisol 30mg	" "	288	828	4.0	283	102	1.0	57.1	65
8	MH	40 ♀	MIS+TI	III	plateau	Digoxin 0.25mg		5 60	281	589	1.0	288	587	1.2	29.9	22
9	YS	24 ♂	Constr. Pleuro-Pericarditis	I	crescendo	(—)		3 —	280	920		278	121		72.6	
10	"			II	"	Lanatoside C 0.4mg Digoxin 0.5-0.375mg		" —	289	1208	1.8	288	1020	1.2	12.5	160
11	MU	55 ♀	MS	III	crescendo	Triamterene 300mg Prednisolone 12.5mg (intraarticular.)		5 60	286	686	0.8	282	140	1.2	126.6	85
12	"			II	"	Do	Cortisol 30mg	" "	293	855		289	523		29.3	72
13	ST	48 ♀	Endomyocardial Fibrosis	III	decrecendo	(—)		restrict.	293	779	2.7	285	81		73.2	197
14	"			II	"	Digoxin 0.5mg		" —	288	655		283	76		110.7	165
15	YT	48 ♂	ASD	II	plateau	Digoxin 0.5mg		5 60	289	931	1.0	284	310	<1.1	45.2	128
16	TY	35 ♀	MS	II	decrecendo	(—)		5 70	288	813		285	66		145.6	82
17	"			II	crescendo	(—)		" "	295	962	2.8	294	84	<1.0	91.1	103
18	"			II	plateau	(—)	Postcommissurotomy (premenstr.)	" 65	282	824	+	278	60	<0.7	58.3	70
19	KM	39 ♀	MS AS with AI Rheumatic	II	plateau	Digoxin 0.375mg	At 3 months' gestation	5 50	281	713	0.7	276	85	<0.3	110.6	45
20	"			II	"	"	Cortisol 30mg	" "	282	853		279	88		142.2	66
21	EK	49 ♀	MIS, Patent Ductus Botalli	II	plateau	Digoxin 0.375mg	Prednisolone 10mg	8 60	286	624		286	98		195.4	60
22	"			I	"	"	(—)	" "	286	645		284	138		74.3	75
23	RU	43 ♂	MS, Auricular Fibrillation Slight AI	II	decrecendo	Aleviatin 0.3 Mysolin 0.7 Luminal 0.06		5 75	291	747	0.9	286	161	<0.8	138.8	78
24	"		Chr. Rheum. Carditis Epilepsy	I	plateau	"	Cortisol 30mg	" "	289	657		286	142		131.0	48
25	MK	16 ♀	?VSD SBEC	II	plateau	Finalin G 1.5 X. scopol. 0.06	(premenstr.)	5 60	290	930	1.5	282	849	0.6	11.7	115
26	"			I	"	"	Cortisol 30mg	" "	292	1003	8.1	289	131	<0.3	66.8	114
27	AM	27 ♀	MS	I	decrecendo	Luminal 0.06	(premenstr.)	5 65	284	842	1.3	278	120	<0.5	67.9	35
28	"			I	plateau	"	Cortisol 30mg	" "	287	863	0.6	282	106	+	100.9	38
29	AO	19 ♂	Rheumatic Carditis Wenckebach Rhythm	I	plateau	(—)		5 75	291	970	1.9	284	211	+	44.9	53

* 15ml/kg body weight

ANALYTICAL METHODS

The osmolality of serum and urine was determined cryoscopically with a FISKE osmometer. Sodium and potassium were determined by flame photometry with a Baird flame photometer. Urea was determined by diacetyl monoxime method (FEARON's reaction), and creatinine was determined by FOLIN-WU method (JAFÉ's reaction).

Plasma ADH was extracted by SHARE's modification of WEINSTEIN's method and the bioassay was done according to a modified method of DICKER on male rats of Wistar strain, which had been made diabetes insipidus, destroying stereotactically the infundibular stem of hypothalamus by electrolysis.

Urinary aldosterone was determined by the modified MATTOX's method. Seventeen-hydroxycorticosteroids in urine were determined by the method of REDDY, JENKINS and THORN-PORTER and SILBERL.

RESULTS AND DISCUSSION

I PLASMA ADH LEVEL, SERUM OSMOLALITY AND THE PERTINENT CLINICAL DATA

Serum osmolality after over 14 hours' deprivation of water was within the normal limits, as shown in Table I.

Plasma ADH level studied in this series under the above-mentioned condition was not high. High levels were observed, however, under certain circumstances (Table I).

Fig. 1-a shows the correlation between the serum osmolality and the plasma ADH level. There seems to be correlation between them, however, it is not statistically significant ($r=0.4852$, $n=12$, $0.1 < p$).

Fig. 1-b shows the correlation between them in the course of a patient, 24 year-old female,

Fig. 1-a. Correlation between the serum osmolality and the plasma ADH level ($r=0.485$, $n=12$, $0.1 < p$).

with combined valvular disease, subacute bacterial endocarditis, and class IV to III decompensation. The correlation was statistically significant ($r=0.935$, $n=5$, $0.01 < p < 0.05$).

Fig. 1-b. Correlation between the serum osmolality and the plasma ADH level in the course of a patient ($r=0.935$, $n=5$, $0.01 < p < 0.05$).

No readily discernible correlation was observed between the plasma ADH level and the severity of congestive heart failure classified according to the criteria of New York Heart Association.

As a trial, the stadium of decompensation was classified into three groups from the clinical course, i. e., stadium of decrescendo, plateau, and crescendo decompensation. No difference in the plasma ADH level was observed among the three groups.

A statistically significant correlation was observed between the venous pressure and the serum osmolality ($r=0.71$, $n=27$, $p < 0.001$, including the data obtained in patients under the treatment with glucocorticoids, but $r=0.406$, $n=17$, $0.1 < p$, when the data obtained in patients under the glucocorticoid treatment were excluded) (Fig. 2-a).

There was a correlation between the venous pressure and the plasma ADH level after over 14 hours' deprivation of water ($r=0.571$, $n=12$, $0.05 < p < 0.1$) (Fig. 2-b).

But no correlation was observed between the pulmonary vital capacity and the plasma ADH level.

No correlation was observed between the daily urinary excretion of aldosterone and the

Fig. 2-a. Correlation between the venous pressure and the serum osmolality ($r=0.71$, $n=27$, $p<0.001$, including the data obtained in patients under the treatment with glucocorticoids, but $r=0.406$, $n=17$, $0.1<p$, when the data obtained in patients under the glucocorticoid treatment were excluded).
 ●: without glucocorticoid
 ×: under the glucocorticoid treatment

plasma ADH level.

No correlation was observed between the daily urinary excretion of 17-hydroxycorticosteroids and the plasma ADH level ($r=-0.22$, $n=12$, $0.1<p$). However, a statistically significant correlation was seen between them, when data obtained in patients under the glucocorticoid treatment were included ($r=-0.520$, $n=16$, $0.01<p<0.05$).

Assuming that 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, the above-mentioned observation that the plasma ADH level correlated to the venous pressure but not significantly to the grade of decompensation, may suggest that the release of ADH depends rather on the change in the cir-

Fig. 2-b. Correlation between the venous pressure and the plasma ADH level after over 14 hours' deprivation of water ($r=0.571$, $n=12$, $0.05<p<0.1$, excluding the data obtained in patients under the glucocorticoid treatment, but $r=0.218$, $n=18$, $0.1<p$, when the data obtained in patients under the glucocorticoid treatment were included).

culating blood volume than on the expansion of the total extracellular fluid volume.

II. RESPONSE TO AN ACUTE WATER LOADING

The results of the water loading test are summarized in Fig. 3.

Urinary osmolality decreased markedly as the serum osmolality decreased, and then they began to recover simultaneously. The serum osmolality did not recover up to the prehydration level in all cases with only one exception, while the urinary osmolality recovered to the prehydration level in many cases. No satisfactory explanation has yet been given for this fact, although it seems to be natural that the serum osmolality does not recover to the prehydration level in only three hours after hydration.

In most cases the serum osmolality and the plasma ADH level changed simultaneously in

the same direction in response to water loading. But no consistent correlation was obtained between the degree of decrease in serum osmolality and that in plasma ADH.

The percentage of fractional urine volume to the water load ($V/\text{Load } \%$) and the free water clearance changed simultaneously. The peaks of the two were reached in the same period, i. e., in most cases in the fourth period which is the first 30 minutes after the period of hydration was ended.

Urinary excretion of osmolar substances ($U\mu \text{ osm/min}$) had the peak in many cases in the third period or in the fourth. It is of interest that the peak of osmolar substance precedes the peak of water excretion.

Urinary excretion of creatinine, osmolar substances, urea, sodium and potassium was increased in the third and the fourth periods. The discrepancy between the urinary excretion of solutes and water is not explained clearly, but may perhaps be presumed as the result of the time lag between the secretion inhibition and action inhibition of ADH, i. e., ADH may have some latent period in losing its action.

Taking the ratio of the four-hour urine to the water load ($\Sigma V/\text{Load}$) as an index of diuresis, its correlation with pertinent factors were examined.

It had no correlation with the serum osmolality in the prehydration period.

It was more than 100 per cent in all of the four cases with the plasma ADH less than $0.9 \mu\text{U/ml}$ plasma in the prehydration period.

It had no correlation with the daily urinary excretion of aldosterone or 17-hydroxycorticosteroids.

On the other hand, it had a statistically significant correlation with the ratio of urinary sodium to potassium in the prehydration period ($r=0.713, n=18, p<0.001$). While no correlation was observed between the ratio of urinary sodium to potassium in the prehydration period and the daily urinary excretion of aldosterone.

There was no correlation between the ratio of four-hour urine to the water load, and the venous pressure and cardiothoracic ratio, respectively.

Examples of the water loading test are shown

in Fig. 4.

III. THE EFFECT OF CORTISOL ON THE RESPONSE TO WATER LOADING

The authors stated previously as follows: In patients with posthypophysectomy syndrome and with posttraumatic diabetes insipidus, cortisol augmented the diuretic response to an acute water loading. Namely, cortisol increased the urine volume and the free water clearance under conditions in which the plasma ADH activity was inhibited.

The same effect of cortisol was also seen in patients with congestive heart failure in the present study. The effect of 30 mg of oral cortisol on the response to acute water loading are summarized in Fig. 5. Each datum indicates the maximal value which was obtained in one of the eight 30-minutes' specimens in the course of four hours' experiment. As shown in Fig. 5, the ratio of four-hour urine to water load was augmented in seven cases out of nine. The maximal data of urine flow, free water clearance, osmolar clearance, and urea excretion were also augmented in experiments with cortisol in almost all cases. The data of sodium, potassium and creatinine clearances, however, showed no consistent tendency. The increase in urine flow seems mainly due to the increase in the free water clearance.

As to the mechanism of the water diuretic action of cortisol, two alternative explanations exist. DINGMAN et al. contend that cortisol inhibits the release of ADH. KLEEMAN et al. suggest that cortisol is essential to allow maximal impermeability to water to develop in the diluting segments of the nephron, in the absence of ADH. KLEEMAN's suggestion is favorable for the explanation of the above-mentioned observations. Even in a case of diabetes insipidus in whom ADH is presumably absent, cortisol augmented the urine flow and the free water clearance. And cortisol promotes water diuresis only in the absence of ADH, i. e., only when the water is ingested in other patients than diabetes insipidus.

As to the effect of cortisol on the plasma ADH level, only two determinations are now available, in one case the plasma ADH level was markedly elevated and in the other it was

Fig. 3. Results of the acute water loading test.

Fig. 4. Results of the water loading test in a patient under different conditions. Fig. 4-a shows the results of a test performed when the cardiac failure was almost compensated, while Fig. 4-b shows the results of a test performed ten days later when the cardiac failure was moderately severe.

Fig. 5. Effect of cortisol (30 mg) on the response to an acute water loading (10 ml per kilogram).

moderately depressed.

SUMMARY AND CONCLUSION

In the present series of patients, no consistent correlations were observed between the plasma ADH level and the severity of congestive heart failure or the stadium of decompensation. However, a positive correlation was observed between the plasma ADH level and the venous pressure. A positive correlation was also observed between the serum osmolality and the venous pressure. There seemed to be a positive correlation between the plasma ADH level and the serum osmolality, and this correlation was remarkable in the course of a patient.

The plasma ADH activity after over 14 hours' deprivation of water was usually within the normal limit in patients with congestive heart failure examined in the present study. High levels were observed, however, under certain conditions. There were no consistent data which indicated the impaired osmoreceptor function.

The serum osmolality after water deprivation was within normal limits and the decrease in serum osmolality after hydration was accompanied by an inhibition of plasma ADH activity in most cases. Although there was no hyponatremic case in this series, it might be presumed that in some cases of hyponatremia, except for the cases in which the homeostasis mechanism is extremely exhausted, the regulation to maintain the circulating blood volume predominates over the regulation of osmolality.

The venous pressure is set at a higher level by cardiac decompensation. 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. Even in this case the ADH seems to act homeostatically together with mineral corticoids in adjusting to the high venous pressure set by cardiac failure.

In conclusion, the ADH system seems to play a role in homeostasis of the body fluid in congestive heart failure. The mode of action seems to be a physiological one even in cases with congestive heart failure in the present study. And the action of the ADH is thought to have something to do not only with mineralocorticoids but also with cortisol.

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4. Cardiac Failure and Catecholamine†

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