(2) A Clinical Study of the "Water-Electrolyte Regulation Mechanism" in Chronic Congestive Heart Failure with Emphasis on Renin and Catecholamine

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In our laboratory, a series of clinical investigations on the endocrine factors in chronic congestive heart failure (CHF) has been conducted with special attention to the regulation mechanism.¹⁻¹⁰⁾

Urinary aldosterone excretion was often high in patients with right- and both-sided heart failure, and showed a positive correlation with the degree of edema. In cases successfully treated with bed rest and/or digitalis, aldosterone was reduced to and remained within normal limits. In cases requiring continued use of diuretics in addition to rest and digitalis, aldosterone was reduced temporarily but then rose again. In the latter cases, CHF persisted and aldosterone played a physiological role in maintaining homeostasis in response to the continuous loss of sodium and water induced by forced diuresis.

Urinary excretion of catecholamines (CA), especially norepinephrine (NE) increased progressively as the functional class (N. Y. H. A.) proceeded. In cases treated successfully with rest and/or digitalis, the increased NE returned to normal. In cases resistant to treatment, the high excretion rate of NE persisted. When an adrenolytic drug was administered in cases of hypertensive heart failure, the CHF was aggravated. These results suggest that the sympatho-adrenomedullary system contributes to the support of the circulatory function in CHF.

In response to water-loading (10 ml/kg by mouth), the plasma ADH concentration was reduced in 12 of the 15 tests, and water diuresis occurred in 20 out of 27 tests. In one patient, plasma ADH was determined repeatedly and showed a positive correlation with serum osmolality, and in the 27 tests, there was a significant positive correlation between peripheral venous pressure and serum osmolality. These results suggest that an elevation in venous pressure causes an increase in extravasation of body fluid and a decrease in venous return with an increased osmotic pressure of venous blood, and that these changes in body fluids may stimulate the secretion of ADH. Even in CHF, ADH seems to act homeostatically together with aldosterone in adjusting the blood volume to maintain the venous pressure and hence the circulatory function.

The authors treated two patients with severe CHF, in whom hyponatremia,

hyposmolality and marked hypovolemia were induced by continuous administration of potent diuretics, and the secretion of ADH increased while that of aldosterone did not. It was thought that it was crucial for existence under these circumstances to maintain the circulating blood volume rather than the osmolality.

The present study was, therefore, undertaken to investigate the effects of furosemide-induced acute isotonic diuresis on the humoral factors in relation to plasma volume (PV) changes in CHF.

Subjects and Methods

Twenty-eight tests were performed on 5 normal volunteers and 21 inpatients with CHF. After 14 hours of deprivation of water and food, furosemide (40 mg) was given by mouth with 50-100 ml of water. Blood samples were drawn from the antecubital vein. Plasma renin activity (PRA) was determined at 15, 30, 60, 120, 180 and 240 minutes and PV, at 1, 2 and 4 hours, after furosemide ingestion. Plasma ADH was determined at the time of expected maximum diuresis. The analytical methods used were: PRA by radioimmunoassay of angiotensin I using ^{125}I in cases 1-8, and by Pickens' method in cases 9-14; urinary CA by Euler-Lishajko's method; urinary aldosterone by Kliman-Peterson's double isotope derivative assay; plasma ADH by bioassay (Yamane-Kunishige's method); and PV by ^{131}I -RIHSA.

Results and Discussion

The main results are shown in Table I. In cases without edema, the PV decreased and epinephrine (E), PRA, aldosterone and ADH increased, in response to the profuse diuresis. In edematous patients, despite a comparable diuresis, the PV did not decrease and the secretion of those hormones was not stimulated. In edematous patients, any deficiency in the PV induced by diuretics can be replenished from the expanded interstitial fluid depot, so that only small changes, if any, occur in the PV and no appreciable increases occur in ADH, aldosterone, CA or PRA. This replenishment is more difficult in subjects without edema, and a significant PV depletion occurs, which stimulates the secretion of the humoral factors. During the acute furosemide test, there were no appreciable changes in serum sodium or potassium levels. Thus it is probable that under the test conditions, a decrease in PV is the adequate stimulus for the regulation mechanism, rather than the loss of sodium itself, the loss of extracellular fluid or changes in serum osmolality, sodium or potassium concentrations. There are several reports that point to the primary role of PV in the effects of potent diuretics on PRA and aldosterone.⁸⁻¹⁵⁾

It is accepted that CA stimulates the release of ADH, and that vasopressin and vasotocin suppress the release of renin. CA and renin stimulate the secretion of each other. Thus it is probable that renin acts as a mediator among those factors that constitute the regulation mechanism. So far there have been no clinical reports

TABLE I THE RESPONSE OF URINE VOLUME, PLASMA VOLUME, PLASMA RENIN ACTIVITY, EPINEPHRINE, NOREPINEPHRINE, ALDOSTERONE AND ANTIDIURETIC HORMONE TO ORAL ADMINISTRATION OF FUROSEMIDE(40mg)

CASE	UV	PV	PRA	E	NE	CASE	UV	PV	PRA	E	NE	ALDO	ADH	CASE	UV	PV	ALDO	ADH
	m/30min	l/m ²	ng/ml hr	ng/min	ng/min		m/30min	l/m ²	ng/ml hr	ng/min	ng/min	μg/hr	μu/ml		m/30min	l/m ²	μg/hr	μu/ml
1. 58, m, I H D, M I Pheochromocytoma	0 99/120 1.88 I 35 234 1.86 II 215 172 III 166 118 1.71 IV 122 119 1.79	1.88 1.84 1.28 1.58 0.85 1.42 0.97	1.59 1.84 1.28 1.58 0.85 1.42 0.97	253 143 140 3285 2953 137 2946 153 228 2459 2757	253 216 3055	3329	9. 58, f. M S	0 49/131 1.55 0.4 I 115 470 II 330 180 1.33 1.55 III 515 20 IV 23 17 1.40	1.55 0.4 13.2 27.5 15.0 27.5 6.6 1.4 28.3 31.3 2.6 0.9 45.1 46.6	4.4 60.1 13.0 39.0 23.5 28.3 31.3	40.6 60.1 13.0 39.0 23.5 28.3 31.3	0.92 4.68 0.23	17. 42, f. M S I, A I	0 69/30 1.89 I 55 231 1.78 II 362 283 1.80 III 225 117 1.73	1.89 1.78 1.80 1.73	1.67 1.73	<1.3 1.7	
2. 28, f. A S D, M I	0 21/155 1.30 I 22 305 II 96 80 1.33 III 74 105 1.27 IV 60 40 1.22	1.30 2.80 3.19 9.43 9.63 17.5 12.7	2.25 2.80 3.19 9.43 9.63 17.5 12.7	7.8 11.3 14.4 134.3 95.7 38.7 42.0 86.9 107.4 19.6 26.4 109.8 126.7 30.6 27.2 104.6 89.5	7.8 95.7 107.4 126.7 89.5	3329	10. 38, m. M S, P, H T	0 54/120 1.96 0.82 I 82 290 II 258 177 1.86 0.21 III 117 113 IV 112 85 1.75	0.82 1.92 1.18 1.86 0.21 10.9 13.4 13.0 13.2	9.1 13.6 6.6 13.1 7.3 37.8 53.4 41.0 41.9 29.6 33.6	36.2 49.5 40.2 37.8 53.4 41.0 41.9 29.6 33.6	2.01 4.06 1.78	18. 45, f. Hypertension Arterio-sclerosis	0 55/40 1.61 I 170 528 1.57 II 310 220 1.67 III 132 1.31 2.75	1.61 1.57 1.67 2.75	0.62 2.2 2.2		
3. 53, f. Angina pectoris	0 138/115 1.80 I 317 585 1.56 II 314 176 1.71 III 82 34 IV 62 1.43	1.80 0.21 1.10 2.02 1.74 1.77 1.66	1.80 0.21 1.10 2.02 1.74 1.77 1.66	5.6 20.6 25.2 19.4 6.0 19.9 21.4 8.8 16.6 18.7 18.0 23.9 17.2 10.9 25.2	7.9 6.0 16.6 17.2 25.2	3329	11. 55, f. M S, P, H T	0 89/118 1.95 0.12 I 46 255 1.76 0.16 II 325 330 III 232 137 1.68 IV 90 80 1.57	0.12 1.76 0.16 0.12 1.68 1.57	8.4 19.9 31.4 16.3 13.2 15.6 15.8 14.2 18.9	127.8 111.6 139.0 106.5 90.9 96.9 90.9 97.6 89.5	0.34 5.28 2.66	19. 62, m. A I	0 307/130 2.01 I 42 122 II 275 337 2.02 III 271 164 IV 200 95 1.91	2.01 1.57 2.02 1.73 1.91	1.0 2.2 2.2		
4. 66, f. M S, A S	0 243/150 1.88 I 337 545 1.73 II 400 302 1.53 III 173 125 IV 113 79 0.31	1.88 0.21 0.28 0.35 0.46 0.58 0.31	1.88 0.21 0.28 0.35 0.46 0.58 0.31	6.9 11.2 9.0 35.4 34.4 10.0 7.1 42.7 44.5 11.4 14.0 58.1 62.5 11.1 5.9 64.8 74.2	27.3 34.4 44.5 62.5 74.2	3329	12. 42, f. M S	0 90/90 1.19 0.23 I 21 180 1.16 0.33 II 209 114 1.13 0.33 III 73 42 IV 35 26 1.13	0.23 0.33 0.33 15.0 11.5 9.8	4.1 9.6 13.4 11.3 5.9 15.0 55.7 46.7	57.2 51.6 56.6 62.2 49.9 57.6 55.7 46.7	0.58	20. 55, f. M I	0 43/120 1.86 I 6 87 II 390 431 1.77 III 437 354 1.73 IV 147 200 1.73	1.86 1.77 1.73 1.73	0.60 4.94 7.64	3.1 1.4	
5. 20, f. A I	0 56/128 1.66 I 63 480 1.44 II 473 263 1.44 III 139 85 IV 33 22 1.46	1.66 0.97 1.08 1.85 1.43 1.37 4.20	1.66 0.97 1.08 1.85 1.43 1.37 4.20	2.6 17.1 8.5 59.4 64.1 18.9 20.8 23.7 42.5 14.3 15.2 72.8 72.7 10.9 51.6	39.1 64.1 42.5 72.7 51.6	3329	13. 61, m. Pericardial effusion	0 40/120 2.02 0.17 I 35 230 2.03 0.17 II 305 230 2.10 0.09 III 185 165 IV 105 85 2.13	0.17 0.17 0.09 0.09 2.13	12.5 8.0 286.2 250.5 9.9 13.4 180.3 118.2 8.0 13.1 205.2 266.4 16.8 15.7 260.7 280.2	283.1 250.5 118.2 266.4 280.2	6.38 2.01 2.01	21. 27, m. M S I, A I	0 30/140 2.70 I 35 91 II 141 105 III 51 36 1.98 IV 95 3.09	2.70 1.98 1.98 3.09	1.16 10.5 6.07	2.0 2.3	
6. 58, m. I H D, M I Pheochromocytoma	0 68/135 1.77 I 75 207 1.79 II 179 200 1.66 III 94 80 IV 61 55 1.74	1.77 12.0 13.8 14.8 24.5 25.2 28.7	1.77 12.0 13.8 14.8 24.5 25.2 28.7	14.3 17.1 8.5 59.4 64.1 18.9 20.8 23.7 42.5 14.3 15.2 72.8 72.7 10.9 51.6	14.3 42.5 72.7 51.6	3329	14. 44, m. Constrictive pericarditis	0 60/120 2.03 0.50 I 20 84 2.03 2.50 II 207 213 III 189 148 2.06 1.85 IV 134 105	0.50 2.50 2.06 1.85	6.0 13.6 10.1 114.6 77.7 7.3 5.7 71.7 66.2 13.2 13.0 88.8 82.2 13.1 12.5 88.5 68.9	100.8 114.6 77.7 71.7 66.2 88.8 82.2 88.5 68.9	0.93 1.25 1.01	22. 36, m. M S, A I T I	0 45/180 1.51 I 32 143 II 391 252 III 186 105 IV 132	1.51 1.51 3.61 2.20	0.21 5.5 2.20	<2.2	
7. 70, f. A S D	0 42/120 1.73 I 21 147 1.71 II 238 215 1.77 III 181 161 IV 129 109 1.73	1.73 0.29 0.39 0.37 0.41 0.39	1.73 0.29 0.39 0.37 0.41 0.39	6.2 11.2 114.5 73.5 6.1 8.5 59.4 64.1 6.5 11.5 61.7 85.3 4.7 8.3 67.9 96.5	96.4 73.5 64.1 85.3 96.5	3329	15. 19, m. Control	0 120/155 1.75 I 80 377 II 472 231 III 116 76 1.37 IV 35 25	1.75 1.75 1.37 1.37	0.99 3.12 3.52 3.97	2.06 5.30 3.97 3.36 5.1	0.7 2.6 5.1	23. 27, m. M S I, A I	0 43/120 1.95 I 13 153 II 245 187 1.60 III 125 85 IV 76 62 1.68	1.95 1.60 1.60 1.68	3.8 2.8		
8. 39, m. Constrictive pericarditis	0 43/124 2.47 I 12 25 II 48 372 2.19 III 270 242 2.35 IV 218 134 2.16	2.47 1.48 1.68 2.19 2.35 2.16	2.47 1.48 1.68 2.19 2.35 2.16	12.1 10.8 8.4 193.7 94.8 5.9 5.0 94.8 103.4 9.1 6.6 122.4 135.8 10.3 147.6	94.8 103.4 135.8 147.6	3329	16. 21, m. Control	0 93/137 1.74 I 337 590 II 568 274 1.48 III 97 103 IV 97 103	1.74 1.48 1.48 1.41	0.26 1.44 1.15 7.86 4.16 1.92 1.20 6.48 6.05 6.08 3.52 9.70 5.86 3.13 2.24 6.74 8.34	7.18 4.16 6.05 8.34	2.1 4.7	24. 30, m. Eisenmenger complex	0 19/125 1.51 I 66 61 1.28 II 41 58 1.13 III 81	1.51 1.28 1.13	5.3 3.3		
25. 60, m. M S I A S I	0 30/51 1.80 I 490 384 1.58 II 255 155 1.44 III 44/15	1.80 1.58 1.44	1.80 1.58 1.44	1.80 1.58 1.44	1.80 1.58 1.44	3329	25. 60, m. M S I A S I	0 30/51 1.80 I 490 384 1.58 II 255 155 1.44 III 44/15	1.80 1.58 1.44	1.80 1.58 1.44	1.80 1.58 1.44	1.80 1.58 1.44	1.80 1.58 1.44	1.80 1.58 1.44	1.80 1.58 1.44	1.80 1.58 1.44	1.80 1.58 1.44	
26. 29, f. Control	0 48/30 2.10 I 22 96 II 45 33 III 376 228 1.66 IV 274 158 1.69	2.10 2.18 1.66 1.69	2.10 2.18 1.66 1.69	2.10 2.18 1.66 1.69	2.10 2.18 1.66 1.69	3329	26. 29, f. Control	0 48/30 2.10 I 22 96 II 45 33 III 376 228 1.66 IV 274 158 1.69	2.10 2.18 1.66 1.69	2.10 2.18 1.66 1.69	2.10 2.18 1.66 1.69	2.10 2.18 1.66 1.69	2.10 2.18 1.66 1.69	2.10 2.18 1.66 1.69	2.10 2.18 1.66 1.69	2.10 2.18 1.66 1.69	2.10 2.18 1.66 1.69	
27. 18, f. Control	0 24/120 1.47 I 13 13 1.51 II 10 13 III 16 22 IV 366 299 0.99	1.47 1.51 0.57 2.01	1.47 1.51 0.57 2.01	1.47 1.51 0.57 2.01	1.47 1.51 0.57 2.01	3329	27. 18, f. Control	0 24/120 1.47 I 13 13 1.51 II 10 13 III 16 22 IV 366 299 0.99	1.47 1.51 0.57 2.01	1.47 1.51 0.57 2.01	1.47 1.51 0.57 2.01	1.47 1.51 0.57 2.01	1.47 1.51 0.57 2.01	1.47 1.51 0.57 2.01	1.47 1.51 0.57 2.01	1.47 1.51 0.57 2.01	1.47 1.51 0.57 2.01	
28. 55, f. Control	0 100/128 1.61 I 79 634 1.31 II 294 200 III 115 42 1.12	1.61 1.31 1.12	1.61 1.31 1.12	1.61 1.31 1.12	1.61 1.31 1.12	3329	28. 55, f. Control	0 100/128 1.61 I 79 634 1.31 II 294 200 III 115 42 1.12	1.61 1.31 1.12	1.61 1.31 1.12	1.61 1.31 1.12	1.61 1.31 1.12	1.61 1.31 1.12	1.61 1.31 1.12	1.61 1.31 1.12	1.61 1.31 1.12	1.61 1.31 1.12	

UV: urine volume, P: circulating plasma volume, PRA: plasma renin activity, E: urinary epinephrine, NE: urinary norepinephrine, ALDO: urinary aldosterone, ADH: plasma antidiuretic hormone, O: control period, I: 0 - 1 hr period after Furoreside, II: 1 - 2 hr period, III: 2 - 4 hr period, IV: 4 - 5 hr period, MS: mitral stenosis, AS: aortic stenosis, PH: pulmonary hypertension, HT: systemic hypertension, A: aortic stenosis, AI: aortic insufficiency, AS: aortic stenosis-insufficiency, PH: pulmonary hypertension, TI: tricuspid insufficiency, ASD: atrial septal defect and IHD: ischemic heart disease.

* n: 64

UV: urine volume, PV: circulating plasma volume, PRA: plasma renin activity, E: urinary epinephrine, NE: urinary norepinephrine, ALDO: urinary aldosterone, ADH: plasma antidiuretic hormone, O: control period, I: 0 - 1 hr period after furosemide, II: 1 - 2 hr period, III: 2 - 3 hr period, IV: 3 - 4 hr period, V: 4 - 5 hr period, MS: mitral insufficiency, MSI: mitral stenosis, AS: aortic stenosis, AI: aortic insufficiency, ASI: aortic stenosis-insufficiency, PH: pulmonary hypertension, TI: tricuspid insufficiency, ASD: atrial septal defect and IHD: ischemic heart disease.

* HT: 64 mmHg

of detailed combined evaluations of the responses of E, NE and PRA to furosemide. Although E and PRA changed together in 9 out of 13 cases and the increase of E appeared to precede that of PRA, the sequence of events is not clear. No clear-out relationship was seen between E and aldosterone, or PRA and aldosterone. Our previous investigations and the present study show that the increase in urinary NE is remarkable in CHF, while E changes markedly in response to furosemide-induced acute diuresis. The explanation for this must await further investigations.

The possibility is proposed that the renin-angiotensin system stimulates the secretion of aldosterone on one occasion, and the release of ADH on another, although the selecting or switching mechanism is not known.

Conclusion

In chronic congestive heart failure, aldosterone and ADH act physiologically to maintain the adequate circulating blood volume through the regulation of sodium and water, respectively. Catecholamines act to regulate the cardiovascular tone to maintain proper circulation. Renin seems to act as a mediator among the factors, not only in the renin-angiotensin-aldosterone system, but also in the renin-angiotensin-ADH system, as well as by interaction with catecholamines.

Acknowledgment

We wish to pay tribute to the memory of the late Professor Emeritus M. Maekawa, who introduced us to this field of study. We thank Prof. S. Hayase and M. Miyahara, chairmen, for giving us the opportunity to join the symposium, and gratefully acknowledge the co-operation of our colleagues in Kyoto University, especially Drs. Y. Ohara, S. Kubo and K. Bito.

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