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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Pathophysiological significance of catecholamine in cardiac disease provides a challenging problem of investigation. It is still suggestive up to present that CANNON et al.¹⁾ reported in 1926 that the dogs which lost physiological response to physical and mental stresses after a complete sympathectomy with an adrenalectomy had survived with the normal life function in the laboratory showed no demonstrable abnormalities in the cardiovascular system. RAAB postulated that increased adrenosympathetic activity has an unfavorable effect^{5)~9)} on the myocardium, because of increased myocardial consumption of oxygen, enhanced peripheral vascular resistance, reduced energy efficiency of the myocardium, ischemic state²⁾³⁾ of the myocardium intimal thickening and lipid deposition⁴⁾ of the arterial wall. He believes that those with increased adrenosympathetic activity will become victims of the ischemic heart disease without a visible vascular damage. On the other hand, SARNOFF and BRAUNWALD and his colleagues postulated that myocardial catecholamine plays an important role in controlling myocardial contraction by the central nervous system both in normal heart^{10)~11)} and in failing heart¹²⁾¹³⁾. This report will deal with the clinical aspects of catecholamine in patients with cardiac failure together with some evidences obtained in the experimentally

produced cardiac failure in rabbits.

1) URINARY EXCRETION OF CATECHOLAMINE IN PATIENTS WITH CARDIAC FAILURE :

Daily urinary excretion of adrenaline, noradrenaline, acid catechol and Dopamine are shown in Table I. Amount of active catechols, namely, adrenaline and noradrenaline were found to be getting increased according to the severity of cardiac failure, reaching to the maximum at Grade III¹⁴⁾ and diminishing in Grade IV¹⁵⁾, though well over the normal limit. Noticeable differences could hardly be found in urinary excretion of the active catechols between the patients with valvular disease and hypertension: a consistent pattern is given by plotting the urinary excretion level against the functional classification of the cardiac failure. This pattern could be traced too, by progression and regression of the clinical conditions, namely, urinary level rose when the conditions turned from Grade II to Grade III, and fell when they shifted from Grade III to Grade IV, or vice versa.

2) URINARY EXCRETION OF CATECHOLAMINE DURING THE PERIOD OF RAPID DIGITALIZATION :

Male, 60 years of age, M. S. I. Grade IV. Urinary level of catecholamine was rather low before starting digitalization. Lanatoside C, 0.4mg three times every six hours resulted in

TABLE I URINARY LEVEL OF EXCRETION OF CATECHOLS IN NORMAL SUBJECTS AND PATIENTS WITH CARDIAC FAILURE DUE TO VALVULAR DISEASES

Catechols γ /day	Adrenaline	Noradrenaline	Acid Catechols	Dopamine
Normal Subjects (30 cases)	5.2 ± 1.7 (0.21)	20.1 ± 4.8 (0.79)	245 ± 46.0	34.1 ± 4.8
Cardiac Failure Grade I (5 cases)	4.2 (0.18)	19.6 (0.82)	274	43.0
Cardiac Failure Grade II (81 cases)	9.2 ± 1.7 (0.20)	36.7 ± 10.3 (0.80)	298 ± 111.5	46.1 ± 15.5
Cardiac Failure Grade III (67 cases)	19.7 ± 4.4 (0.24)	62.2 ± 15.6 (0.76)	604 ± 140.6	64.8 ± 16.3
Cardiac Failure Grade IV (25 cases)	7.5 ± 1.0 (0.17)	37.3 ± 9.4 (0.83)	284 ± 90.3	44.1 ± 15.5

Note: Figures in parentheses mean $\frac{\text{Adrenaline or Noradrenaline}}{\text{Adrenaline} + \text{Noradrenaline}}$

marked improvement of the clinical conditions. Urinary excretion of adrenaline was definitely increased but that of noradrenaline a little. Female 34 years of age M. S. Grade II. With digitalization, neither marked hemodynamic change nor increased urinary catecholamine could be seen. Male 41 years of age, M. S. I. Grade IV had minimal urinary excretion of catecholamine. Both adrenaline and noradrenaline were increased temporarily by rapid digitalization, during which these continued to decrease. Five days later he died.

Ratio of adrenaline to noradrenaline¹⁶⁾ in urine was found to be increased when digitalis exerts the beneficial effect but it decreased or unchanged when ineffective. Speaking of the diurnal variation of urinary excretion of catecholamine, it was reduced gradually with or without an initial increase in Grade II and Grade III, and Grade IV respectively when the clinical conditions got better with digitalis. On the contrary, little change¹⁷⁾¹⁸⁾³³⁾ was shown, though a transient increase was occasionally seen, when it was refractory to digitalis.

If urinary level of catecholamine is considered to represent an index of the hormonal secretion, it is apparent that cardiac failure is invariably accompanied by increased secretion of catecholamine. So, it is justifiable to say that the sympathoadrenal activity is accelerated in cardiac failure. The pattern of urinary catecholamine seen in the course of the treatment with digitalis seems not to indicate that increased secretion of catecholamine has only the serious effect on the pathological hemodynamic of cardiac failure, but that it takes place in regulating internal milieu by the positive inotropic effect on the failing heart. Since myocardial catecholamine of the normal subject consists mainly of norepinephrine, it naturally plays an important role, but adrenaline should never be ignored¹⁹⁾, because of increase in the ratio of adrenaline to noradrenaline in urine found in the patients successfully controlled with digitalis.

3) INFLUENCE OF RESERPINE ON CARDIAC FAILURE :

Decline of the urinary level of catecholamine at Grade IV as well as the minimal

changes of it in patients refractory to digitalis would be considered either the cause or the effect of deterioration of cardiac function. So, the influence of reserpine on cardiac failure is worth making observation. As shown in Fig. 1, a man 35 years of age with mitral insufficiency in Grade III has indicated marked increase in urinary excretion of catecholamine which has been reduced with lowering the hemodynamic function during the period of one week of reserpine treatment. The laboratory findings are presented in Fig. 2, in eight patients of various severity treated with reserpine, indicating the pathophysiological significance of myocardial and circulation catecholamine in cardiac failure. Further, it is apparently reasonable to think that the reduced sympathoadrenal activity is attributable to deterioration of cardiac function. It is worth noting the reports that treatment with reserpine occasionally gave rise to ankle edema²⁰⁾²¹⁾ or myocardial damage²²⁾ and that the sympathoadrenal activity is inevitable²³⁾ for regulating hemodynamic in cardiac failure.

4) URINARY AND MYOCARDIAL CATECHOLAMINE IN THE RABBITS WITH EXPERIMENTALLY PRODUCED AORTIC OBSTRUCTION²⁷⁾ :

Urinary excretion of catecholamine, both in adrenaline and noradrenaline, were found to be rapidly increased, reaching the maximum in 2 to 3 days and reduced in 4 to 6 days to the normal level or a little higher than normal after obstructing the aorta by introducing the vinyl catheter with a tiny piece of laminaria at its tip in the vicinity to the aortic valve. Adrenaline was found to be disproportionately increased to noradrenaline. Those increments were proved to be significant to those found with the sham operation. (Fig. 3). In the rabbits treated with reserpine 0.1mg per kg per day for increase in urinary excretion of catecholamine was found to minimal or absent even after the aortic obstruction which was invariably accompanied by pulmonary edema as in the non-reserpinised. Few of the reserpinised animals survived (Fig. 4).

Myocardial content of catecholamine was measured with the entire heart of the rabbit, being 1.37 to 1.51 $\mu\text{g/gm}$ in 4 normal and 0.38 $\mu\text{g/gm}$ 8 to 10 days after of reserpinisa-

Fig. 1. Diurnal changes of urinary excretion of active catechols and clinical course while the treatment with reserpine

Fig. 2. Summarized illustration of clinical features of the cardiac patients treated with Reserpine

Fig. 3 Urinary excretion of adrenaline and noradrenaline in rabbits after the aortic obstruction
 — animal with failing heart
 animal subjected to the sham operation without cardiac failure

Fig. 4. Urinary excretion of adrenaline and noradrenaline in reserpinized rabbits after the aortic obstruction

tion. Myocardial content of catecholamine was increased to 2.35 to 4.40 $\mu\text{g}/\text{gm}$ in three rabbits three days after the aortic obstruction and reduced to 0.68 to 1.08 $\mu\text{g}/\text{gm}$ in other three on 14th to 20th operation day^{28,29}. The results obtained were coincident with the clinical data in Table I.

5) CATECHOLAMINE IN ACUTE FAILURE :

Urinary excretion of catecholamine has been found to be increased in acute myocardial in-

farction⁴⁾³⁰⁾³¹⁾ and during the anginal attack³²⁾. Catecholamine, especially noradrenaline, has been a choice of drug for the cardiogenic shock due to myocardial infarction and more effective than digitalis and angiotensin. An attempt has been made to observe myocardial contractility and blood pressure after injection of catecholamine to the rabbits with myocardial infarction produced by ligating the anterior descending branch of the coronary artery. Blood pressure and myocardial contractility have been shown to be reduced by the coronary arterial obstruction, and restored by the intravenous injection of catecholamine 3 μg per kg, unless obstruction was made completely. Positive inotropic effect of catecholamine, namely, induced increase in myocardial contractility, has been remarkably reduced by pressure on the thoracic inferior vena cava, apparently supported by venous return³⁶⁾³⁷⁾ (Fig. 5). In spite of the clinical experience that cardiac glucoside has less beneficial effect on the cardiogenic shock, Lanatoside C caused increase in myocardial contractility, though not remarkable, in the rabbits with the coronary obstruction.

Effects of noradrenaline on acute cardiac

Fig. 5. Myocardial contractility of the left ventricle and arterial blood pressure after the intravenous administration of noradrenalin ($3\mu\text{g}/\text{kg}$) to the rabbit with intact coronary artery (upper in the left column), with incomplete (middle) and with complete obstruction (lower) of the left descending artery. Effect of inferior vena cava occlusion on myocardial contractility of the left ventricle and arterial blood pressure after the intravenous administration of adrenaline $5\mu\text{g}/\text{kg}$ (right column).

failure involve positive inotropic action on the one hand while it increased venous return on the other. The beneficial response of the heart with coronary obstruction to Lanatoside C may be increased catecholamine in the myocardium and circulating plasma of acute myocardial infarction as well as by increased urinary catecholamine in chronic cardiac failure sensitive to digitalis. It is interesting to note that the action of ouabain is dependent on release of catecholamine¹⁵⁾ and the inotropic action of glucoside is no way modified²⁴⁾.

CONCLUSION

Analytical studies have been carried out on urinary excretion of catecholamine in the cardiacs and its myocardial content in the rabbits with aortic obstruction, showing that increased secretion of the pressure hormone is invariably accompanied by cardiac failure. Some comments have been made on pathophysiological significance of catecholamine in cardiac failure.

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5. Water and Electrolyte Metabolism in Congestive Heart Failure†

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Several aspects of water and electrolyte metabolism in congestive heart failure are reviewed experimentally.

1. TOTAL BODY EXCHANGEABLE Na

It was already established that in patients with congestive heart failure, the body water content per unit body weight is increased in comparison with the non-edematous patients. This increase is suspected to be due to the accumulation of light molecules in the body. It is now confirmed that the total body exchangeable Na per unit body weight is also increased in this situation.

2. URINARY WATER EXCRETION AND OSMOLAR DILUTION AFTER ORAL WATER LOAD IN PATIENTS WITH HEART FAILURE

In supine patients, sometimes, water excretion and urinary dilution were not so marked as in non-cardiac controls who would not develop edema. Pitressin injection, immediately after the establishment of maximal diuresis, sometimes failed to achieve such maximal concentration level as seen in control patients. The effect of Pitressin was not prolonged in cardiac patients. It is inferred that in patients with heart failure there are sometimes a drop in

diluting ability as well as a suppression in Pitressin response. In one patient, serum osmolality also remained lowered even after the water diuresis had subsided.

In ambulant patients, these defects were more pronounced and sometimes became apparent in whom no such disturbances were observed during supine position. These results support the view that rest is of cardinal importance for the maintenance of water balance in cardiac patients.

3. EFFECT OF ELEVATED RENAL VENOUS PRESSURE ON RENAL BLOOD FLOW AND URINE VOLUME IN THE RABBIT KIDNEY

Renal venous pressure was elevated by partially clamping the renal vein. Urine volume was augmented by saline or mannitol infusion throughout the experiment.

In cases of constant arterial pressure perfusion, below renal venous pressure of 10 mmHg, i. e., within the range of effective autoregulation of renal blood flow, urine volume remained also constant. Beyond 20mmHg of the renal venous pressure, renal blood flow declined and urine volume paralleled it.

In cases of constant blood flow experiments,

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