The Role of Catecholamines in Circulatory Regulation on the Chronic Congestive Heart Failure

Clinical Study of the Urinary Catecholamine Excretion in the Patients with Chronic Congestive Heart Failure

HIROSHI YASUI

Since the discovery of pressor action of epinephrine, there offered innumerable investigations concerning its physiological significance on cardiovascular system. On the other hand, norepinephrine was synthesized by Strolz in 1904. However, biological significance of norepinephrine remained to be indefinite, though there observed some differences between epinephrine and norepinephrine concerning their pharmacodynamic actions; pressor action, cardiac effect, metabolic effect, etc. Later, the differences between the effects produced by sympathetic stimulation and those by exogenous administration of epinephrine were gradually ascertained. Especially, since von Euler established the fact that norepinephrine is the substance released from the sympathetic nerve endings and the neurohormone acting to the effectors of various tissues innervated by sympathetic nerve, there offered remarkable advances in the investigation of catecholamine concerning their pathophysiological significance on cardiovascular disorders, accompanied by the progress in the quantitative determination of catecholamine. Recently, studies on norepinephrine in cardiovascular diseases have been advanced relating to the activity of sympathetic nervous system.

It is now clear that myocardial contractility is considerably augmented by increase in the sympathetic influence upon the heart, and that the effects of stimulating the cardiac sympathetic nerves on the myocardium closely resemble those resulting from the injection of norepinephrine. These observations suggest a fundamental role of cardiac sympathetic nerves in regulating the activity of the heart. Nowadays, however, despite the well known cardiovascular actions of catecholamines, significance of their role in the cardiovascular diseases remains contentious. From the observations that the metabolic characteristics in the human failing heart closely resemble those elicited by toxic catecholamine action on the myocardium, Raab indicated that epinephrine and norepinephrine play a pathogenetic role to cardiovascular disorders. On the other hand, from the observations displaying the augmented discharge of adrenergic neurohormones into the circulation on the patients with congestive heart failure, Braunwald et al. indicated the activity of sympathetic nervous system is augmented in the congestive heart failure and that thus augmented sympathetic activity plays an important supporting role in cardiovascular regulation.

At present, there are still some discrepancies upon the reports about the excretion levels of catecholamines in the patients with congestive heart failure. Then, in the present study, in order to determine the excretion pattern of the urinary catecholamines and to make sure of the role of the catecholamines in the patients with congestive heart failure, 24-hour urinary

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* An outline of this study was reported at the XXVII General Assembly of the Japanese Circulation Society, 1963 (Osaka), and was reported by Prof. M. Maekawa at the XVI General Assembly of the Japan Medical Congress, 1963 (Osaka) and 61st General Assembly of Japanese Society of Internal Medicine, 1964 (Kyoto).

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catecholamines were determined in hospitalized patients with congestive heart failure of various origin. The present study includes the statistical observations between the urinary catecholamines and several clinical manifestations presented in congestive heart failure, and the time-course observations on 15 patients.

**Materials and Method**

One hundred hospitalized patients with chronic congestive heart failure, 65 men and 35 women, aged from 14 to 78, were studied. The underlying cardiac diseases of these patients are shown in Table I. In the beginning, the relations of 24-hour urinary catecholamines, norepinephrine and epinephrine, to the severity of heart failure, venous pressure, vital capacity, renal plasma flow and glomerular filtration rate were investigated in these patients. The severity of heart failure was determined according to the functional classification of New York Heart Association; 12 patients were in class I, 47 in class II, 23 in class III and 18 in class IV. Among 88 patients ranged from class II to IV, 26 had left-sided failure and the remainder had both-sided failure.

Then the time-course changes in 24-hour urinary catecholamines were studied in 15 patients, summarized in Table II, with special reference to venous pressure, vital capacity, and urine volume. In addition to these determinations, serum sodium, serum potassium and excretion level of sodium in 24-hour urine were also measured. Throughout the course of investigation, all patients were placed on a constant daily sodium intake, and their daily intake of water was prescribed for various levels according to the severity of each case. After the control period of certain duration (3 to 4 days), in almost all cases lanatoside-C was administered intravenously in the first place, which was followed by the replacement of oral digoxine. Diuretics, including thiazides and spironolactone, were also administered. In 2 patients, reserpine and guanethidine were used as antiadrenergic drug.

For the determination of urinary norepinephrine and epinephrine, the trihydroxyindole (THI) method of von Euler and Lishajko was employed with some modifications. In the present study, hydrolyzed form (free and conjugated form) of catecholamines was determined in all patients and, in some patients, nonhydrolyzed form (free form) was also determined together with hydrolyzed form. Norepinephrine and epinephrine values obtained from normal persons were as follows; hydrolyzed form, norepinephrine 50.9 microgram per day with s.e. 3.90 and epinephrine 8.95 with s.e. 1.31; non-hydrolyzed form, norepinephrine 20.3 with s.e. 2.52

**Table I** Classification on Underlying Cardiac Diseases

<table>
<thead>
<tr>
<th>Classification</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Valvular Disease</td>
<td>62</td>
</tr>
<tr>
<td>(Includ. Mitral Stenosis)</td>
<td>33</td>
</tr>
<tr>
<td>2. Myocardial Heart Disease</td>
<td>8</td>
</tr>
<tr>
<td>3. Hypertensive Heart Disease</td>
<td>14</td>
</tr>
<tr>
<td>4. Congenital Heart Disease</td>
<td>16</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100 Cases</td>
</tr>
</tbody>
</table>

**Table II** 15 Cases on Detailed Investigation

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Cardiac Diagnosis</th>
<th>Side of Failure</th>
<th>Class of Heart Fail.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T. Y.</td>
<td>60</td>
<td>M</td>
<td>Coronary Heart Disease</td>
<td>R &amp; L</td>
<td>IV</td>
</tr>
<tr>
<td>2</td>
<td>T. I.</td>
<td>34</td>
<td>M</td>
<td>Atypical Tetral. of Fallot</td>
<td>R &amp; L</td>
<td>IV</td>
</tr>
<tr>
<td>3</td>
<td>I. A.</td>
<td>18</td>
<td>F</td>
<td>Aortic Insufficiency</td>
<td>R &amp; L</td>
<td>III</td>
</tr>
<tr>
<td>4</td>
<td>I. T.</td>
<td>54</td>
<td>F</td>
<td>Mitral Insufficiency</td>
<td>R &amp; L</td>
<td>IV</td>
</tr>
<tr>
<td>5</td>
<td>M. Y.</td>
<td>43</td>
<td>M</td>
<td>Mitral Stenosis &amp; Insuff.</td>
<td>R &amp; L</td>
<td>III</td>
</tr>
<tr>
<td>6</td>
<td>F. M.</td>
<td>42</td>
<td>F</td>
<td>Hypertensive Heart Disease</td>
<td>R &amp; L</td>
<td>III</td>
</tr>
<tr>
<td>7</td>
<td>N. K.</td>
<td>20</td>
<td>F</td>
<td>Mitral Stenosis</td>
<td>R &amp; L</td>
<td>III</td>
</tr>
<tr>
<td>8</td>
<td>Y. T.</td>
<td>65</td>
<td>M</td>
<td>Aortic Insufficiency</td>
<td>L</td>
<td>II</td>
</tr>
<tr>
<td>9</td>
<td>E. Y.</td>
<td>23</td>
<td>F</td>
<td>Mitral Insufficiency</td>
<td>R &amp; L</td>
<td>III</td>
</tr>
<tr>
<td>10</td>
<td>H. M.</td>
<td>36</td>
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<tr>
<td>11</td>
<td>G. K.</td>
<td>23</td>
<td>M</td>
<td>Mitral Stenosis</td>
<td>L</td>
<td>III</td>
</tr>
<tr>
<td>12</td>
<td>M. Y.</td>
<td>28</td>
<td>M</td>
<td>Ao-L-RV Syndrome*</td>
<td>R &amp; L</td>
<td>IV</td>
</tr>
<tr>
<td>13</td>
<td>T. I.</td>
<td>31</td>
<td>M</td>
<td>Atrial Septal Defect</td>
<td>R &amp; L</td>
<td>IV</td>
</tr>
<tr>
<td>14</td>
<td>T. S.</td>
<td>58</td>
<td>M</td>
<td>Hypertensive Heart Disease</td>
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<tr>
<td>15</td>
<td>N. O.</td>
<td>45</td>
<td>F</td>
<td>Mitral Stenosis</td>
<td>R &amp; L</td>
<td>III</td>
</tr>
</tbody>
</table>

* Aorto-left-Ventricle to Right-Ventricular Shunting Syndrome

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and epinephrine 4.46 with s.e. 0.87, respectively.¹⁰

RESULTS

1. Norepinephrine and Epinephrine Excretion in 24-hour Urine and Severity of Heart Failure.

The values of hydrolyzed form of norepinephrine and epinephrine in 24-hour urine of the 100 cases are shown in Fig. 1 and 2, according to the classification of heart failure. Norepinephrine values were within normal limit with one exception in class I and were found to increase progressively on the severity of heart failure. The mean value of urinary norepinephrine was 45.1 mcg in class I, 81.5 in class II, 159.9 in class III and 257.9 in class IV. There was no case showing the urinary norepinephrine value within the normal limit in class III and IV. Urinary excretion of epinephrine in the same condition showed the similar result. The similar result was obtained on the non-hydrolyzed form of catecholamines determined in 28 patients together with hydrolyzed form (Fig. 3). The above mentioned relationship of catecholamine to the severity of heart failure was on the same pattern in any cardiac decompensation regardless its underlying diseases. It was demonstrated by the time-course determination of catecholamines that urinary excretion of catecholamine gradually reduced with improvement of heart failure (Fig. 4). On the other hand, the result obtained in 5 cases laud on bed rest only showed that the urinary excretion of catecholamine progressively increased as the patient’s condition turned to worse than ever (Fig. 5).

2. Venous Pressure and Norepinephrine Excretion

* All values in this paper signify those of hydrolyzed form of catecholamines, when no explanatory note.

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Venous pressure was adopted as a possible quantitative sign of congestive heart failure, especially that of right-sided failure. With excretion of the points applicable to the left-sided failure, the elevation of venous pressure level corresponded to an increase in urinary norepinephrine to some extent as shown in Fig. 6.

3. Vital Capacity and Norepinephrine Excretion

The relation of urinary norepinephrine to vital capacity is shown in Fig. 7. The absolute value determined with spirometer on each case could not be the suitable presentation of the pulmonary function because the bodily structure and duration of heart failure could affect the vital capacity on individual patient. For this reason, 2 methods were applied to the presentation of vital capacity. The first method: the value measured with spirometer was put in a percentage to the standard vital capacity. The second method: the maximum vital capacity.

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Fig. 4. Case 1. T. Y., 60 y. o. male. Coronary heart disease. Heart failure of class IV with both-sided failure. This patient was treated with bed rest and digitalis only.

**Changes in Urinary Norepinephrine on Aggravation of Heart Failure**

Observed in 5 Cases, Laid on Bed Rest only

Fig. 5. Increasing alterations of the urinary norepinephrine in 5 cases laid on bed rest only. These patients were observed without medicament treatment.

Fig. 6. The relation of the urinary norepinephrine to the level of venous pressure determined in 90 patients.

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**Correlation Between Urinary Norepinephrine & Venous Pressure**

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**Correlation Between Urinary Norepinephrine & Vital Capacity**

Fig. 7. The relation of the urinary norepinephrine to the vital capacity. In the left of the figure, each value of vital capacity measured is present on the decreased rate to the standard vital capacity decided in each patient. In the right half, each value indicates the decreased rate to the maximum vital capacity measured in each patient.
was employed instead of standard vital capacity. This maximum vital capacity was the maximum one among the values which were obtained during the period when the patient's symptoms had already released. As shown in Fig. 7, the decrease of vital capacity corresponds to the elevation of the urinary norepinephrine, though this relation is better in the right half of the figure than in the left one.

4. Renal Clearance and Urinary Norepinephrine

The values of renal plasma flow (RPF) and glomerular filtration rate (GFR) were plotted against the urinary norepinephrine values (Fig. 8). As shown, the decrease in GFR did not result in a decreased norepinephrine excretion. On the contrary, a high level of norepinephrine corresponds to the decreased level of GFR. The observation on the RPF and urinary norepinephrine indicates that the urinary norepinephrine level was increased when the decrease of RPF showed advance, and especially, increased level of urinary norepinephrine was high in the case of RPF less than 50 per cent of normal limit.

5. Changes in Norepinephrine in the Course of Treatment

A) Time-course change in urinary norepinephrine on the improvement of congestive heart failure: Fig. 4 (case 1) shows one of the examples representing daily changes of norepinephrine and some clinical manifestations. This case showed orthopnoic dyspnea and besides generalized edema and ascites on admission. Norepinephrine and epinephrine level in 24-hour urine before the digitalisation was 332 and 56 mcg respectively. After the digitalis therapy by intravenous administration of lanatoside-C sodium diuresis gradually occurred from the third day. Afterwards, the decrease of venous pressure and body weight was followed by increasing vital capacity. With improvement of

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**Fig. 8.** The relation of the urinary norepinephrine to glomerular filtration rate and renal plasma flow.
the patient's condition, urinary norepinephrine was decreased gradually and was within the limit of normal range. And fairly good correlations between the values of 24-hour urinary norepinephrine and venous pressure or vital capacity were recognized during the course of the disease (Fig. 9).

B) Change in norepinephrine excretion on the initial phase of digitalisation: Eleven cases were treated with intravenous administration of lanatoside-C as the first choice. The results observed are summarized in Table III. Each value of norepinephrine (24-hour urinary excretion), venous pressure and vital capacity was obtained before digitalisation, on the day when the saturation of digitalis was achieved and from the third to the 5th day after the saturation of digitalis, respectively. As a matter of convenience, 11 patients were divided into 3 groups according to the clinical effect induced by digitalisation: in the first group digitalisation resulted in a significant improvement of heart failure, in the second group moderate effect was observed and in the third almost no improvement was seen by digitalisation only (Fig. 10). In 7 of the total cases, the rise in urinary norepinephrine was observed on the day when the saturation of digitalis was achieved. In the same condition, the transient rise in venous pressure was observed in 3 of 10

Fig. 9. The relation between the urinary norepinephrine and venous pressure or vital capacity in the course of heart failure. Case 1. T. Y. 60 y. o. man, with coronary heart disease and class IV heart failure. The clinical courses of this patient was demonstrated in Fig. 4.

Fig. 10. The changes in norepinephrine excretion in the course of digitalisation. “A”: the control period. “B”: on the day the saturation of digitalis was achieved. “C”: from 3rd to 5th day after the saturation of digitalis.

Table III  Changes in 24-Hr. Urinary Norepinephrine and Other Clinical Data in the Course of Digitalisation
Intravenous Administration of Lanatoside-C

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Control Period</th>
<th>On the day, Digitalis saturated</th>
<th>Period of Maintenance Dosage</th>
<th>Clinical Effect</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>NE</td>
<td>VP</td>
<td>VC</td>
<td>NE</td>
</tr>
<tr>
<td>1</td>
<td>332</td>
<td>255</td>
<td>600</td>
<td>305</td>
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<tr>
<td>2</td>
<td>216</td>
<td>240</td>
<td>2100</td>
<td>188</td>
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<td>3</td>
<td>101</td>
<td>165</td>
<td>1930</td>
<td>142</td>
</tr>
<tr>
<td>4</td>
<td>140</td>
<td>200</td>
<td>980</td>
<td>106</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>201</td>
<td>1550</td>
<td>178</td>
</tr>
<tr>
<td>6</td>
<td>184</td>
<td>160</td>
<td>2200</td>
<td>129</td>
</tr>
<tr>
<td>7</td>
<td>110</td>
<td>153</td>
<td>2100</td>
<td>121</td>
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<td>11</td>
<td>109</td>
<td>220</td>
<td>1400</td>
<td>114</td>
</tr>
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</table>

* The values in this period were obtained between the 3rd and 5th day after the beginning of maintenance administration of digitalis.
† NE: Norepinephrine, VP: Venous Pressure, VC: Vital Capacity

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cases in which venous pressure was measured. Three cases which did not show a temporary rise in urinary norepinephrine had higher values during the control period. The above mentioned findings were observed on 3 groups.

C) Changes in urinary norepinephrine on 2 cases in the course of diuretic therapy added to digitalisation: In case 3 (Fig. 11), intravenous administration of lanatoside-C resulted in almost no improvement of heart failure, and urinary norepinephrine level did not decrease. Through the addition of spironolactone to digitalis, the decompensation was moderately subsided and urinary norepinephrine level gradually decreased, but the heart failure was again aggravated by the discontinuation of this diuretic therapy. The second administration of spironolactone failed to improve this condition and urinary norepinephrine level again increased more and more. On this occasion, it is interesting fact that the norepinephrine value was elevated to higher level than in the control period. Later, the administration of trichlormethiazide was not able to bring a satisfactory result and led the urinary norepinephrine level to the transient rise. Thus in this case, all clinical manifestations of congestive heart failure were not stable and could not be improved with the above stated therapy, and similarly the urinary excretion of norepinephrine was also unstable and remained in fairly high level, in general.

In Fig. 12, the case 7 is illustrated. With digitalisation, the heart failure was not improved completely, and urinary norepinephrine remained its high level, nearly 150 mcg. The intermittent administration of trichlormethiazide added to digitalis brought about wide variation on excretion of norepinephrine, that is, the urinary norepinephrine during the diuretic therapy tended to decrease remarkably compared to that of the previous stage. This decrease in the urinary norepinephrine was followed by its considerable rise after the discontinuation of the drug. And after the several repetition of this diuretic therapy, finally, the urinary norepinephrine level gradually settled down within the normal limit as the progressive improvement of heart failure. In this case, the urinary norepinephrine level had been pre-

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Figure 11. Case 3, I.A., 18 y.o. girl. Aortic insufficiency. Both-sided heart failure of class III. This patient was treated with digitalis and additional administration of trichlormethiazide (TCMT) and spironolactone.
sent unstable and high until the cardiac decompensation was subsided.

D) Changes in urinary norepinephrine on 3 cases representing refractory heart failure: In Fig. 13 (case 2), class IV heart failure, after the several days of control period, the intravenous

**N. K. 20 y. F. Decompensation III, Mitral Stenosis**

Lanatoside C i.v.

<table>
<thead>
<tr>
<th>TCMT</th>
</tr>
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<tbody>
<tr>
<td>500</td>
</tr>
<tr>
<td>200</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>50</td>
</tr>
</tbody>
</table>

Fig. 12. Case 7. N. K. 20 y.o. woman. Mitral stenosis with auricular fibrillation. Both-sided failure of class III. This patient was treated with digitalis and intermittent administration of trichlormethiazide (TCMT) added to the digitalis therapy.

**T. I. 34 y. M.**

Digitalis

Spironolactone

3000 | VP
2000 | VP

300 | VC
200 | VC

<table>
<thead>
<tr>
<th>MCG</th>
<th>NE</th>
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<tbody>
<tr>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>3.5</td>
<td></td>
</tr>
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<td>1.4</td>
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<tr>
<td>1.3</td>
<td></td>
</tr>
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<td>0.6</td>
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<table>
<thead>
<tr>
<th>Sens</th>
<th>Na</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 13. Case 2. T. I. 34 y.o. man. Atypical tetralogy of Fallot and class IV heart failure. This patient was treated with digitalis and diuretics, trichlormethiazide (TCMT) and spironolactone, but these therapy failed to subside the decompensation. A refractory case.

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administration of lanatoside-C was not effective, therefore spironolactone, and later trichlormethiazide, were administered in addition to the digitalis. In spite of these treatments, venous pressure remained over 250 mmHg and no efficacious increase of vital capacity was recognized. Though fairly good natriuresis was obtained by this diuretic therapy given during the period between the tenth and the thirtieth day, there occurred no sufficient decrease in urinary norepinephrine followed by rebound phenomenon after the withdrawal of the diuretics. In this period, the urinary norepinephrine level was usually elevated more than in the control period. The second diuretic therapy starting on about the thirtieth day caused again the considerable natriuresis accompanied with certain decrease of urinary norepinephrine and with almost no improvement of heart failure. Then the intractable hyponatraemia was found in this period. During this hyponatraemic period, the urinary excretion of norepinephrine increased always progressively to the level of 294 mcg. Finally, the patient died soon after his norepinephrine excretion tended to decrease.

The next case (case 12) had been on the state of decompensation in class III or IV and had been treated with repeated diuretic therapy for several years before admission. As shown in Fig. 14, digoxine was administered throughout the entire course of the disease, and clinical symptoms were managed with diuretic therapy. During the period when the electrolytes balance was kept within normal limits, the diuretic treatment resulted in an increase of the urinary sodium excretion with a concomitant definite decrease in the urinary norepinephrine. But, except a decrease of body weight, no significant improvement of the heart failure was recognized; this case also refractory to the treatment and, in this case too, temporary diuresis caused by diuretics was followed by lesser urine volume and more rise in urinary norepinephrine. Once an intractable hyponatraemia occurred, the diuretic therapy almost lost its efficiency, and as a development of this condition, urinary excretion of norepinephrine increased progressively and finally reached the value of 402 mcg per day. And, similarly to the former case, as more advanced the heart failure, urinary norepinephrine level tended to fall soon before death.

The third case is demonstrated in Fig. 15.

Fig. 14. Case 12. M. Y. 28 y. o. man. Ao-L-RV syndrome. Heart failure IV, refractory one. This patient was treated with spironolactone and intermittent use of trichlormethiazide (TCMT) in addition to the digitalisation.

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(case 13). On admission, the arrhythmia was suggestive of digitalis intoxication, so the diure-

**Fig. 15.** Case 13. T. I. 31 y.o. man. Atrial septal defect and class IV decompensation of both-sided failure. On admission, he was suggestive of digitalis intoxication, so he was treated chiefly diuretics. A refractory case.

**Fig. 16.** Case 14. T. S. 58 y.o. man. Hypertensive heart failure of class III, both-sided failure. On this case, antiadrenergic drug, guanethidine, was initially administered and then diuretic drug, trichlormethiazide, and digitalis were administered.

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tics were chiefly employed for the treatment. Though the diuretic therapy brought about the temporary improvement, urinary norepinephrine level was rather augmentative during the therapy, even with its definite decrease during the period of temporary remission. In the mean time, the diuretic therapy was gradually deprived of its effect, then the general condition was beyond the control and the patient was finally died.

6. The Administration of Antiadrenergic Drugs to the Patients with Congestive Heart Failure

The case 14 (Fig. 16) was diagnosed as hypertensive heart failure of class III on admission. The administration of guanethidine, given initially 20 mg later 30 mg daily, resulted in an intensification of the signs and symptoms of congestive heart failure. The venous pressure increased from 140 to 190 mmHg. The vital capacity fell to 700 ml. No fall of arterial blood pressure was observed in spite of this antihypertensive therapy, and on the contrary, even a slight increase in arterial blood pressure was noticed. The additional administration of trichlormethiazide to guanethidine treatment did not improve completely the decompensation but definitely. Digitalis administration by intravenous lanatoside-C for the first time released almost completely the signs and symptoms of heart failure. On guanethidine treatment, urinary norepinephrine was gradually decreased to low level following the initial phase releasing the norepinephrine, and the patient's condition became worse as the urinary norepinephrine level decreased. In case 15 (Fig. 17) the matter of the concerned was similar, i.e. heart failure was also deteriorated with the reserpine medication. In this case too, the diuretic therapy added to reserpine medication merely resulted in a temporary improvement of heart failure but definite, and thus aggravated heart failure was released with the digitalisation.

DISCUSSION

It is still under controversy whether the urinary excretion level of catecholamine is possible to be an indicator for the circulating catecholamine and then, that of the secretion level of this neurohormone. Catecholamine is metabolized almost completely prior to its secretion in the urine and a small amount of infused

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Fig. 17. Case 15. N. O. 45 t.o. woman. Mitral stenosis and class II heart failure. Reserpine 0.3 mg daily was administered for initial use. Then dihydrochlorothiazide (DCT) was employed for the therapy. Digitalis was added to reserpine medication.

_N. O. 45 y. F._

<table>
<thead>
<tr>
<th>Hosp. day</th>
<th>Urinary Norepinephrine</th>
<th>Urine Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>2000 mcg</td>
<td>1000</td>
</tr>
<tr>
<td>20</td>
<td>5000 mcg</td>
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<tr>
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<td>3000 mcg</td>
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<td>2000 mcg</td>
<td>2000</td>
</tr>
<tr>
<td>50</td>
<td>1000 mcg</td>
<td>1000</td>
</tr>
</tbody>
</table>

_DCT | Venous Pressure | Digitalis |

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catecholamine was found in the urine. Afterwards, it may be seen critical to consider that catecholamine is excreted paralleled to its secretion, because the urinary output of catecholamine is small compared to its total secretion. But, von Euler indicated that the fairly constant ratio is kept between the infused catecholamine and its recovery in the urine. On the other hand, when the release of norepinephrine was increased by the injection of tyramine, a greater quantity of the released norepinephrine appeared unchanged in coronary venous bed. This observation suggests that the enzymatic processes by which norepinephrine is inactivated may be limited. Therefore, it may be considered that the urinary catecholamine level for a given period of time may reflect its secretion level for the same period to a greater part, even though catecholamine may not be excreted exactly paralleled to its endogenous secretion. In the present study, the urinary excretion level of catecholamine increases progressively corresponding to the severity of heart failure in both hydrolyzed and nonhydrolyzed form and is independent on the various underlying disease which causes the congestive heart failure as concerned. These result may permit to conclude that the alteration in the urinary catecholamine corresponds to that in the internal circumstances which are commonly manifested in the congestive heart failure. There are discrepancies on the result in this respect. Pekkarinen et al. reported a slight average increase of epinephrine excretion in the patients with heart failure, especially in those with medium insufficiency, and smallest excretion of epinephrine in those with severe insufficiency. Upon norepinephrine excretion, they found almost no abnormal value. Tomomatsu et al. described that the values of both urinary epinephrine and norepinephrine were progressively increased from class I to III and decreased in class IV but higher than normal range. On the other hand, Reab and Gigee were unable to detect abnormal catecholamine excretion in heart failure.

It is troublesome matter to assume the origin of thus augmented urinary catecholamines. The catecholamines excretion, especially norepinephrine excretion, was increased by muscle works. Braunwald et al. reported, in the patients with heart failure, the augmentation of plasma norepinephrine during the physical exercise, and no consistent change occurred on plasma epinephrine in the same condition. Frankenhausen et al. indicated that exaggerated psychic tension readily increased the urinary level of epinephrine particularly. In the human urine, the percentage of norepinephrine is considerably greater than that of epinephrine, though, in the human adrenal medulla, epinephrine concentration is several times of norepinephrine. Now, it is well established that norepinephrine is the neurohormone released from sympathetic nerve endings and is the neurotransmitter in sympathetic nervous system which is widely distributed in all over the body. Besides, the increased activity of sympathetic nervous system is reflected by the augmentation of the urinary excretion of norepinephrine. Therefore, it is very reasonable to assume that a significantly large portion of urinary norepinephrine is deprived from the sympathetic nervous system. The present result on the urinary excretion of norepinephrine may imply that the extreme acceleration of sympathetic nervous system, including, of course, that of the heart and vascular tissues, may occur in the patients with congestive heart failure and this acceleration is progressively augmented corresponding to the severity of heart failure, from class I to IV.

It is the most important factor to set the venous pressure level that the failing cardiac chamber can not handle its venous return. Wool et al. indicated that the peripheral veins of patients with congestive heart failure were constricted as compared with those of noncardiac patients. The importance of venous tone in circulating regulation is gaining increasing recognition and there are some observations concerning the reflex control and neurohumoral regulation of systemic venous bed in heart failure. Now, it is considered that reflex mediated through the sympathetic nervous system are also important factor together with backward congestion to set the venous pressure level. The present result that the elevation of venous pressure corresponds to the increase of the urinary norepinephrine might also be a re-
flection of the presence of neurohumoral regulation on venous system in heart failure. It is well known that the reduced renal hemodynamics is recognized in heart failure. Since the mean central arterial pressure is not appreciable changed by heart failure, the decreased renal blood flow indicates an increased renal vascular resistance. For the explanation of an increased vascular resistance, Barger et al. suggest the contribution of sympathetic-adrenal stimulation, and Blake and Maxwell suggest increased renal venous pressure as a manifestation of the generalized increase of venous pressure. In the present study, the urinary norepinephrine level increased as a decrease of renal plasma flow, and there was no indication which was suggestive of the significant disturbance for the catecholamine excretion in spite of marked decrease in glomerular filtration rate. These results may suggest that the intensified sympathetic-adrenal stimulation which occurred to a greater extent in the advanced congestive heart failure is one of the important factor in reduction in the renal hemodynamics through vasoconstriction possibly of vaso efference.

Digitalis, acting directly to the failing heart itself, has a direct beneficial effect on reduced myocardial contractility. In case 1 (Fig. 4) digitalisation was successful to the improvement of the failing heart. In this case, the urinary catecholamine level gradually decreased along with the improvement of heart failure and finally settled within the normal limit when the heart failure was subsided. As Maekawa proposed, the diuresis due to digitalisation is a completely "physiologic" or "natural" diuresis but not "enforced" one and an improvement of congestive heart failure by digitalisation is primarily based on improvement of failing heart muscle itself. This result observed in case 1, may be interpreted to mean that the change in the activity of sympathetic nervous system corresponds to the gradual decrease in the severity of the heart failure, and it may be natural that there exists significantly good correlation between the urinary norepinephrine and venous pressure or vital capacity in this case.

There are some difficulties in making it clear the significance about the temporary rise in the urinary norepinephrine observed during the initial phase of digitalisation. The similar result was obtained by Tomomatsu et al. on the urinary epinephrine. The existence of increased activity of sympathetic nervous system in heart failure was already discussed in this paper. In mammals, the heart, in general, contains a high concentration of norepinephrine secondary to adrenal medulla and the spleen, and epinephrine concentration is less than 10 per cent of norepinephrine. On the other hand, there are no agreement upon the catecholamine content in the failing human heart.

However, it may be probably assumed that the depletion of myocardial norepinephrine stores due to enhanced activity of sympathetic nervous system in heart failure may contribute to the reduced norepinephrine concentration of the myocardium, and that the catecholamine content in failing human heart may show various according to the given conditions. Cesson-Fossion observed the administration of ouabain diminished the norepinephrine content in the myocardium. The importance of catecholamines in the myocardial contractility was indicated. Bing et al. provided that spontaneous failure occurring in the experimental heart-lung preparation was likely due to the result of diminished catecholamine in that tissue. Now, it is uncertain whether myocardial catecholamine stores influence the effect of digitalis glycoside. According to Caireri et al., the action of ouabain was related to catecholamine released from the myocardium. On the contrary, Yelnosky et al. indicated that the increase in myocardial contractile force due to ouabain was not dependent to the release of catecholamine from the tissue. From the present observation it is impossible to decide how myocardial norepinephrine relate to the action of the digitalis glycoside in failing heart and it may be unjustifiable to consider that the rise in the urinary norepinephrine is originated from the released norepinephrine from the heart even though there are considerable amount of norepinephrine present in the heart. However, as discussed, sympathetic nervous system, hence secreted norepinephrine, can not be independent to the improvement of failing myocardium by digitalisation. The indication that the tem-
porary rise in venous pressure observed in 3 cases, may probably due to the concomitant augmented activity of sympathetic nervous system. Then, the present result may suggest that increased activity of sympathetic nervous system may attribute to result in a good e
d digitalis to the failing myocardium, and that this temporary rise in the urinary norepinephrine may be attributable to the participation of the generalized enhancement of sympathetic nervous system especially in the heart and vascular tissues to gain the improvement of heart failure.

In most cases with heart failure, it is usually necessary to employ diuretic treatment in addition to the digitalisation. As MäeKawa proposed, the diuresis by diuretics is not "physiologic diuresis" but "enforced diuresis". Namely, in the treatment of heart failure, the diuretic therapy is not true causal treatment but symptomatic one in wide sense, since the diuretics do not act primarily to the failing heart but act to the unbalanced body fluid produced by heart failure. As observed, the urinary norepinephrine level tends to decrease during the administration of diuretics when this therapy is efficient to heart failure. In the case 3, the first administration of spironolactone resulted in a fairly good diuresis and a marked decrease in the urinary norepinephrine. This may be due to the improvement of heart failure. And then, the second diuretic therapy failed to bring diuresis and the urinary norepinephrine level progressively increased more and more. On the other hand, the observation in the case 7 may suggest that the urinary norepinephrine increased, after its transient decrease, against the alteration in sodium-water balance caused by intermittent thiazide therapy, until the adaptation to thus altered condition occurred. As observed, the "enforced diuresis" generally may result in a rise in the urinary norepinephrine level to greater extent when this therapy is not successful for the improvement of the heart failure. This conclusion may be supported by the observation indicated in 3 refractory cases (case 2, 12 and 13). It is widely accepted that the sympathetic tone is altered by mobilisation of sodium. Then, it is likely to be considered that, when the alteration of body fluid, caused by diuretic therapy, acts contrary to the physiologic process, thus induced discord, through sodium metabolism, rebounds to sympathetic nervous system as a stress to produce more increase in the activity of this system.

It was a characteristic feature of the refractory stage of congestive heart failure that the urinary catecholamine level was usually augmented markedly regardless of the temporary remission of the disease. As stated above, the observation in 3 refractory cases indicates that the diuretic therapy did not play a fundamental role to remove the true cause of the heart failure. The more enhanced urinary norepinephrine level with the occurrence of intractable hyponatremia may also imply the maximum limit of activity kept in exhausted sympathetic nervous system. The tendency of decreasing the urinary norepinephrine level during several days before the death, may be interpreted to mean that the sympathetic nervous system which is one of the most important system to maintain the cardiovascular regulation, finally fell into insufficiency on this stage.

In heart failure, not only sympatho-adrenal system but also other endocrine system such as aldosterone and glucocorticoids etc. always properly contribute to the regulation of the condition. Since the response of sympatho-adrenal system may be influenced by a character of the given stimuli and a degree of participation of other regulation system than sympatho-adrenal system, accordingly, it seems quite natural that catecholamines do not necessarily react and contribute to each condition induced by congestive heart failure always in a uniform manner. Besides, from above observations, it would seem reasonable to assume that sympathetic nervous system plays an important supportive role in circulating regulation of patient to congestive heart failure, rather than a pathogenetic role.

In order to make sure this supportive role of sympathetic nervous system, antiadrenergic drugs were given to 2 cardiac patients. From the results obtained, it is evident that the antiadrenergic drug is capable of aggravating the heart failure. Braunwald and Gaffney recognized that intensification of congestive heart
failure during the guanethidine administration tended to occur on the patients with more advanced decompensation. It is well known fact that guanethidine and reserpine are capable of lowering the norepinephrine content of various tissues. In the case 14, the aggravation of heart failure corresponded to the gradual decrease in the urinary norepinephrine. These antiadrenergic drugs produce a decrease in myocardial contractility and markedly depress the cardiovascular reflex response. On the other hand, it is now quite acceptable that the myocardial contractile force can be stimulated by increasing the number of impulses through the sympathetic nerve. Braunwald et al. indicated the augmentation of plasma norepinephrine level by physical exercise in patients with congestive heart failure exceeding values observed in the normal subjects. In consideration of above mentioned publications, it is quite reasonable to suggest that the aggravation of the heart failure produced by administration of antiadrenergic drugs may be due to the loss of adrenergic support to myocardial function. Therefore, through the observations in the present study, it may be concluded with certainty that the sympathetic nervous system plays an important compensatory role in the circulatory adjustment of patient to congestive heart failure.

**Summary**

In order to determine the excretion pattern of urinary catecholamines and ensure the role of the catecholamines in the chronic congestive heart failure, 24-hour urinary catecholamines were determined by THI-method on 100 patients with chronic congestive heart failure caused by various underlying diseases. 1) The level of urinary catecholamines, especially that of norepinephrine, in both hydrolyzed and non-hydrolyzed form, were found to be increased progressively corresponding to the aggravation of severity of heart failure. This result suggests the extreme acceleration of sympathetic nervous system in congestive heart failure. 2) The observation that the elevation of venous pressure corresponded to an increase in urinary norepinephrine may be a reflection of the presence of neurohumoral regulation of venous pressure. 3) Correlation between the urinary norepinephrine value and decrease rate of vital capacity were observed. 4) There was fairly close correlation between the urinary norepinephrine value and renal plasma flow. This result suggests the contribution of sympatho-adrenal stimulation to the reduced renal hemodynamics in the heart failure.

Fifteen patients were laid on time-course study. 5) The urinary norepinephrine level decreased gradually corresponding to the decrease in severity of heart failure. 6) The temporary rise in the urinary norepinephrine level was generally observed in the initial phase of digitalisation. It may be reasonable to assume that the augmented sympathetic nervous system may play a certain role, preferably supportive, to gain the effect of digitalis glycoside on the failing myocardium. 7) Five cases, including 3 with refractory heart failure, were treated with diuretics in addition to the digitalisation. The results obtained may indicate that the "enforced diuresis" by the diuretics, unlike "natural" or "physiologic diuresis" by digitalisation, may produce the augmented sympathetic nervous system until the occurrence of adaptation response to the conditions brought about by the "enforced diuresis" and that repeated performance of the "enforced diuresis" finally led the heart failure to refractory, and the patient to death when the reinforcement of the augmented sympathetic nervous system is deprived by its exhaustion. 8) Moreover, the indication that intensification of the heart failure was observed in the 2 cases laid on the administration of antiadrenergic drugs, may imply the adrenergic support to myocardial function regulating the heart failure. In conclusion, these results may be interpreted to mean with certainty that the sympathetic nervous system plays an important compensatory role in the circulatory regulation of patient to congestive heart failure.

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