Variability of Arterial Blood Pressure and Classification of Essential Hypertension by Multivariate Statistical Analysis

OSAMU TOCHIKUBO, M.D., SATOSHI UMEMURA, M.D.
KAZUMASA NODA, M.D., AND YOSHIHIRO KANEKO, M.D.

The subjects included in the present study were 141 hospitalized patients with essential hypertension (EH) and 45 patients with EH complicated with apoplexy and myocardial infarction. Of the former, 15 underwent a 24-hour measurement of direct arterial pressure under unrestricted conditions, and 45 were examined for functioning of the carotid sinus reflex. (1) Even among the hospitalized patients with EH, blood pressure (BP) showed large diurnal variations. Falls and spontaneous fluctuations in BP were observed at a time during nocturnal sleep. The lowest BP (the “dole” pressure) observed at that time remained almost unchanged throughout the night (S.D. ≤ 6 mmHg) for each patient. Since casual BP varies considerably during a day, other laboratory findings should also be taken into account for evaluation prior to initiating antihypertensive treatment. (2) The 186 patients with EH were classified by multivariate statistical analyses of laboratory findings into 4 clusters (types). Then, a new severity index was made in order to evaluate atherosclerotic and hypertensive changes in each patient. (3) A newly devised carotid sinus stimulator was used to enhance the distensibility of the carotid sinus. A decrease in systolic blood pressure (ΔSBP) was observed after stimulation although differences in ΔSBP were found between the 4 clusters. There was a positive correlation between ΔSBP and the elastic modulus of the common carotid artery (r = 0.55, P < 0.01). (4) Each cluster was characterized by differences in plasma renin activity and cardiovascular abnormalities. This classification is considered to be useful for the antihypertensive treatment.

The prevention of cardiovascular complications is the cardinal aim for treatment of cases diagnosed as having hypertension. At present, the most important criterion for the diagnosis and treatment of this disease is casual blood pressure determined indirectly. Blood pressure, however, varies greatly with the environment, and with emotional and physical activity.1,2 Moreover, there is no clear-cut demarcation between “normal” and “hypertensive” blood pressure levels.3 It has, therefore, been difficult to work out a program of treatment based on casual blood pressure alone.

In the present study, diurnal changes in blood pressure were examined in patients with essential hypertension (EH). Furthermore, to establish the

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Key Words:
Variability of blood pressure
“Dole” pressure during sleep
Function of carotid sinus reflex
Distensibility of arterial wall
Severity index

The Second Department of Internal Medicine, Yokohama City University, School of Medicine, Yokohama, Japan

Address for reprints: Osamu Tochikubo, M.D., The Second Department of Internal Medicine, Yokohama City University, School of Medicine, 4-57 Urafune-cho, Minami-ku, Yokohama 232, Japan

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TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Number (Male:Female)</th>
<th>Age (Mean ± S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential hypertensives with complications</td>
<td>45 (30:15)</td>
<td>58.0 ± 10.7</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13 (9:4)</td>
<td>58.0 ± 8.6</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>11 (8:3)</td>
<td>48.0 ± 11.6</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>21 (13:8)</td>
<td>62.8 ± 7.6</td>
</tr>
<tr>
<td>Essential hypertensives without vascular complications</td>
<td>141 (81:60)</td>
<td>48.3 ± 12.4</td>
</tr>
<tr>
<td>Direct pressure measurement</td>
<td>15 (10:5)</td>
<td>42.0 ± 13.1</td>
</tr>
<tr>
<td>Carotid sinus pulse-pressure stimulation</td>
<td>46 (28:18)</td>
<td>51.0 ± 15.0 yr</td>
</tr>
</tbody>
</table>

Fig.1. The telemeter apparatus used for recording of arterial pressure under the almost unrestricted condition.
1. pressure transducer
2. transmitter or data recorder
3. infusion pump
4. receiver
5. monitor scope
6. A-D converter
7. digital display
8. recorder
9. tape data recorder and microcomputer

classification of EH, and to map out guidelines for its treatment a multivariate statistical analysis was performed on taking account of spontaneous fall in blood pressure which followed hospitalization and the result of laboratory examinations, including plasma renin activity and arterial elasticity. Then, a possible relationship between the type of EH with several parameters, such as a function of the carotid sinus reflex and the occurrence of cardiovascular complications was studied. In addition, how best to use a microcomputer in antihypertensive therapy will be discussed.

MATERIALS AND METHODS

Patients classified by multivariate statistical analyses were selected from those admitted to Yokohama City University Hospital. They included 45 EH patients with complications (of whom 13 with myocardial infarction, 21 with cerebral infarction and 11 with cerebral hemorrhage), and 141 EH patients without any of the above-mentioned complications. Fifteen patients from the latter group had their blood pressure measured by continuous direct arterial pressure for a 24-hour period under unrestricted conditions, and 46 patients underwent examinations for carotid sinus function (i.e., the carotid sinus pulse-pressure stimulation). Table I shows the sex and average age of all the patients studied. Secondary hypertension was excluded through a routine screening test. All studies were performed with the consent of the patients.

Continuous recording of direct arterial pressure under unrestricted conditions

A continuous recording of direct arterial pressure was performed for a 24-hour period under almost unrestricted conditions. Blood pressure was measured through a teflon cannula

inserted percutaneously into the left brachial artery. The pressure transducer used was a Statham P37. The patient carried a micro-infusion pump (Oxford Mark II perfusion unit) to prevent blood coagulation and a miniaturized data recorder or a transmitter for the telemeter. The wave form of a received signal was submitted to a peak-holding to detect the peak (systole), and bottom (diastole) of each pressure pulse, and the systolic and diastolic blood pressures were expressed in digits and recorded simultaneously at a velocity of 20 mm a minute. When necessary, ECG, EEG and EOG (electro-oculogram) were recorded by monitoring with a telemeter. The miniaturized data recorder was a product of Gloria Enterprise Co., Ltd. The telemeter apparatus adopted was a modification of the 271 Model, manufactured by San-ei Instrument Co.,
common carotid artery was measured by an ultrasonic echo-phase-traking apparatus in the manner already reported. After measurement, the diameter of the common carotid artery on each side (D) and changes in diameter (ΔD) caused by arterial pulse pressure (ΔP) were determined. The pressure distension ratio (PD) was determined for the elastic modulus by the following formula: PD = ΔP/(ΔD/D × 100) mmHg/%. The average PD was then calculated from the results obtained on the carotid arteries on each side. Pulsatility of the common carotid artery was expressed by the pulsatile index (PI) which is expressed in the following formula: PI = ΔD/D × 100% (Fig. 2). The pulse pressure was measured indirectly with an automatic sphygmomanometer previously reported.

Method of classification of EH (Fig. 3)

The 141 patients with untreated EH without a history of myocardial infarction or apoplexy were divided into three groups; “fixed”, “labile”, and “intermediate”. The patients in the fixed group still had blood pressure exceeding 160/90 mmHg for one week after the initial hospitalization in spite of the restriction of sodium chloride content in the diet to 7 g a day. In patients in the labile group, systolic and diastolic blood pressure had decreased at least 30 and 15 mmHg respectively, within one week after hospitalization, and blood pressure dropped to below 160/90 mmHg during the first week.
Fig. 7. A typical 24-hour BP pattern (case 14 in Fig. 9). The values of BP were sampled at 10-second intervals and calculated mean values and 2SD of BP for every 2 minute.

Patients whose blood pressure did not show any of the above changes after admission were classified as the intermediate group and were excluded from the cluster analysis (Fig. 3).

The fixed and labile groups were subjected to cluster analyses by the centroid method using a digital computer (FACOM-230) and were classified from the dendrogram computed, and their types were predicted through a discriminant function (D₄) calculated by discriminant analyses. A factor analysis was then performed to identify them. The following variables were used for those analyses: age, casual blood pressure (systolic and diastolic BP) at the time of admission to the hospital, plasma renin activity (PRA) determined by the RIA method, ocular funduscopic abnormality, cardio-thoracic ratio (CTR), the configuration of the aortic arch on the chest X-ray (AO), electrocardiographic evidence of left ventricular hypertrophy (LVH) (SV₁ + RV₅), ST-T ischemic changes, left ventricular wall thickness (LVWT) in the diastole determined by an ultrasonic echocardiography (UCG), PD, PI, and the serum creatinine level.

Retinal abnormalities related to the hyper-
Fig. 9. Diurnal variability (4 S.D.) of blood pressure in each patient. The values of BP were sampled at one-minute intervals throughout a day and 4 S.D. were calculated. The average of diurnal variability (4 S.D.) obtained from the 15 patients was 69 mmHg in systolic BP and 50 mmHg in diastolic BP.

### Table II Average of Mean and S.D. of BP During Sleep and Waking States

<table>
<thead>
<tr>
<th></th>
<th>Mean Systolic</th>
<th>Mean Diastolic</th>
<th>Standard Deviation Systolic</th>
<th>Standard Deviation Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting</td>
<td>165.2 ± 28.8</td>
<td>100.9 ± 20.0</td>
<td>17.0 ± 5.6</td>
<td>12.1 ± 5.3</td>
</tr>
<tr>
<td>Lying</td>
<td>167.9 ± 24.6</td>
<td>102.8 ± 16.0</td>
<td>12.8 ± 5.2</td>
<td>9.8 ± 5.3</td>
</tr>
<tr>
<td>Sleeping</td>
<td>158.9 ± 26.7</td>
<td>95.6 ± 17.3</td>
<td>11.8 ± 3.6</td>
<td>9.8 ± 4.0</td>
</tr>
<tr>
<td>“Hill” BP</td>
<td>148.1 ± 30.9</td>
<td>90.3 ± 20.7</td>
<td>11.7 ± 5.2</td>
<td>8.3 ± 4.3</td>
</tr>
<tr>
<td>“Dale” BP</td>
<td>171.6 ± 37.8</td>
<td>104.8 ± 23.3</td>
<td>9.4 ± 3.7</td>
<td>6.8 ± 2.2</td>
</tr>
<tr>
<td>24 hours</td>
<td>145.5 ± 33.1</td>
<td>86.8 ± 19.2</td>
<td>6.1 ± 2.5</td>
<td>4.5 ± 2.0</td>
</tr>
</tbody>
</table>

Mean ± S.D. mmHg

Figures shown above were obtained in the following manner.
1) Blood pressure was measured in 15 patients at one-minute intervals for 24 hours. The values thus obtained were classified by state and position.
2) The mean and standard deviation (M ± S.D.) of blood pressure during various states and positions were calculated for each patient.
3) The M ± S.D. were further calculated for the mean values and the S.D. values obtained from the 15 patients. (The “Hill” BP is the peak BP and the “Dale” BP is the bottom BP of a fluctuation of BP in the spontaneously fluctuating period during sleep).

Tension were graded from 0 to 4 according to the criteria of Keith-Wagner (KW). The aortic arch (AO) was classified into four grades, 0 to 3. Grade 0 was free from abnormal findings. Grade 1 showed whether a projection, an elongation, or a dilatation of the AO. Grade 2 exhibited 2 of these changes. Grade 3 was affected distinctly by calcification of the arterial wall. LVH (SV₁ + RV₅) represented the sum of amplitude of the S wave in the lead V₁ and the R wave in the lead V₅ of the 12-lead electrocardiogram. Ischemic ST-T changes in the ECG were graded into four, 0 to 3. Grade 0 was within the normal limits. In grade 1, the ST segment showed a slight depres-

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Carotid sinus stimulation

Of the 115 patients who had been classified into 4 clusters, 45 were subjected to the estimation of the function of the carotid sinus reflex. They were subjected to a measurement through a newly devised apparatus, pulse-pressure (P-P) stimulator of the carotid sinus. It consisted of two capsules equipped with rubber bags, which were 5 cm in diameter (Fig. 4) and were connected to the P-P stimulator system (Fig. 5). Being triggered by a time signal given by the electrocardiogram and plethysmogram of the carotid artery, a negative pressure was imposed on the capsules when the carotid sinus became distended, followed by a reduction in air volume in the capsules. When the carotid sinus contracted, a positive pressure was imposed on the capsules to enhance the distension of the carotid sinus. The internal pressure of the capsules was controlled alternately over a range of ±90 mmHg. The capsules were attached to the skin at sites corresponding to each side of the carotid sinus while the patient who consented to the study was lying down and rested in a recumbent position. After the patient had rested for more than 20 min, heart rate and blood pressure were measured indirectly through an automatic apparatus for 10 min. This apparatus made it possible to measure heart rate and blood pressure at one-minute intervals. Then the patient stimulated with the P-P stimulator for 5 min, and heart rate and blood pressure were measured as described above. Those procedures were performed twice, and the average fall in the systolic blood pressure through the 2 trials (Δ SBP) was calculated (Fig. 6).

Fig. 10. Average change in BP during various daily activities of 15 patients. The maximum BP during the activity was compared with the average BP of the preceding 5 min. (N = number of observations)

Fig. 11. An example of continuous recording of BP during sleep in a 39-year-old female (Case 5 in Fig. 9). There are observed two different periods; marked, spontaneous fluctuations in pressure occurred during one period, and stable pressure during the other.

Application of a microcomputer

The microcomputer used to classify EH patients by discriminant function and to select the treatment of hypertensives was the Mark II microcomputer manufactured by Sord Computer System, Inc.

RESULTS

Diurnal Changes in the Blood Pressure of Hospitalized Patients with EH

As shown in Fig. 7, the blood pressure of a patient with EH changed remarkably according to the degree of activity in daily life and decreased during sleep. The casual blood pressure measured at 1 hr intervals during the waking period varied all over the scatter diagram of direct BP during the waking period (Fig. 8). The average blood pressure measured directly for 24 hr was lower than that of casual blood pressure readings obtained indirectly. If a statistical standard deviation (S.D.) is adopted, the range of 4 S.D. of the systolic and diastolic pressures (SBP and DBP) is almost included in this ellipse of the scatter diagram of BP during a day. The range of 4 S.D., as expressed by the mean for 15 patients, was 69, S.D. ± 24 mmHg, and 50, S.D. ± 21 mmHg, for the SBP and DBP, respectively (Fig. 9). The average blood pressure in a sitting position, which is the condition for the measurement of casual blood pressure, was higher than the

that in a sitting position in the 15 patients was 8.7, S.D. ± 12.9 (SBP)/6.2 ± 8.0 mmHg (DBP). The average blood pressure in a lying position during the waking period was almost analogous to that of the whole day. The mean difference between the former and the latter of the 15 patients was -0.3 ± 5.0/1.0 ± 6.0 mmHg. In the hospitalized patients, the average blood pressure in a lying position during the waking period was closer to that for whole day than to that in a sitting position. The average of S.D. for the 15 patients was 12.8 (SBP)/9.8 (DBP) and 11.8/9.8 mmHg in the blood pressure in sitting and lying positions, respectively (Table II). As shown in Fig. 10, blood pressure changed markedly according to change in daily activity.

Changes in Blood Pressures during Sleep

Blood pressure during the nocturnal sleep was lowered by 17.1 ± 11.7 (SBP)/11.9 ± 7.2 (DBP) mmHg on the average compared with that during the waking period (Table II). Two distinct periods were differentiated in the sleep period. One of them was a BP stable period when blood pressure was relatively stable. The other was a BP spontaneously fluctuating (SP) period, when blood pressure fluctuated suddenly, spontane-
TABLE III  CORRELATION BETWEEN THE TYPES PREDICTED BY A DISCRIMINANT FUNCTION D₄ AND CLUSTERS BY A CLUSTER ANALYSIS

<table>
<thead>
<tr>
<th>Predicted type</th>
<th>Discriminant analysis</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cluster F</td>
<td>F = 24, E = 0, H = 2, M = 0</td>
<td>26</td>
</tr>
<tr>
<td>E</td>
<td>1, 20, 2, 0</td>
<td>23</td>
</tr>
<tr>
<td>H</td>
<td>3, 6, 39, 1</td>
<td>49</td>
</tr>
<tr>
<td>M</td>
<td>0, 0, 1, 16</td>
<td>17</td>
</tr>
<tr>
<td>Intermediate Group</td>
<td></td>
<td>8, 9, 9, 0</td>
</tr>
</tbody>
</table>

TABLE IV  SUMMARY OF DATA IN EACH CLUSTER

<table>
<thead>
<tr>
<th>Cluster</th>
<th>F</th>
<th>E</th>
<th>H</th>
<th>M</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>26</td>
<td>23</td>
<td>49</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>38 ± 11</td>
<td>61 ± 9</td>
<td>48 ± 9</td>
<td>44 ± 8</td>
<td>yr</td>
</tr>
<tr>
<td>SBP</td>
<td>175 ± 22</td>
<td>182 ± 16</td>
<td>190 ± 19</td>
<td>204 ± 17</td>
<td>mmHg</td>
</tr>
<tr>
<td>DBP</td>
<td>107 ± 12</td>
<td>102 ± 11</td>
<td>115 ± 15</td>
<td>125 ± 16</td>
<td>mmHg</td>
</tr>
<tr>
<td>Optic fundus</td>
<td>1.0 ± 0.5</td>
<td>1.8 ± 0.6</td>
<td>1.8 ± 0.5</td>
<td>3.2 ± 0.5</td>
<td>KW classification</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.0 ± 0.8</td>
<td>1.2 ± 1.3</td>
<td>1.3 ± 0.6</td>
<td>4.8 ± 3.0</td>
<td>mg/dl</td>
</tr>
<tr>
<td>ECG</td>
<td>ST-T changes</td>
<td>0.3 ± 0.5</td>
<td>1.2 ± 0.8</td>
<td>1.3 ± 0.7</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>LVH (SV₁ + RV₂)</td>
<td>3.4 ± 0.7</td>
<td>3.6 ± 0.7</td>
<td>4.7 ± 1.3</td>
<td>5.3 ± 1.2</td>
<td>mV</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>CTR</td>
<td>46 ± 3</td>
<td>52 ± 3</td>
<td>53 ± 5</td>
<td>54 ± 5</td>
</tr>
<tr>
<td>AO</td>
<td>0.2 ± 0.6</td>
<td>1.8 ± 0.6</td>
<td>1.1 ± 0.7</td>
<td>1.1 ± 0.7</td>
<td>arbitrary grade</td>
</tr>
<tr>
<td>UCG</td>
<td>LVWp</td>
<td>1.1 ± 0.2</td>
<td>1.2 ± 0.3</td>
<td>1.5 ± 0.4</td>
<td>1.7 ± 0.4</td>
</tr>
</tbody>
</table>
| Elastic Modulus | 9 ± 4 | 19 ± 4 | 14 ± 4 | 21 ± 5 | mmHg/│
| Pulsatile Index | 6.6 ± 2.0 | 4.1 ± 1.2 | 5.4 ± 2.0 | 3.5 ± 10 | %    |
| PRA      | 2.4 ± 1.7 | 0.6 ± 0.4 | 1.6 ± 1.5 | 4.4 ± 2.7 | ng/ml/hr |

*Mean ± S.D.*

(SBP = systolic BP, DBP = diastolic BP, LVH = left ventricular hypertrophy represented SV₁ + RV₂ of the ECG, CTR = cardio-thoracic ratio AO = configuration of the aortic arch, LVWp = left ventricular wall thickness in the diastole, Elastic Modulus = PD of the common carotid artery, Pulsatile Index = PI of the common carotid artery, PRA = plasma renin activity)

ously, independently, or in a rhythmic fashion (Fig. 11). This spontaneous fluctuation of BP was observed at frequency of tens to hundreds in one night. The average absolute fluctuation was 25 (SBP)/16 (DBP) mmHg and the greatest fluctuation exceeded 100 mmHg. When fluctuations appeared repeatedly in a rhythmic fashion, the duration of each fluctuation was approximately 20 to 120 sec. It should be noted that peak blood pressure ("hill" pressure) in the SF period revealed a relatively large change, and that lower blood pressure (tentatively called "dale" pressure) in this period hardly changed, remaining at almost the same level during the night (Fig. 11).

Examples of the "dale" pressure are shown in Fig. 12. Those pressure appeared in the SF period which occurred between two BP stable periods. When blood pressure increased ("uphill") and then decreased, creating a fluctuations the velocity of the increase was a little higher than that of the decrease, and the "dale" pressure appeared at the beginning of the "uphill". Blood pressure at the beginning of "uphill" must be almost the same as next "dale" pressure. If an increase in blood pressure begins during a decrease, at a level comparable to another peak, it may be impossible to call the "dale" pressure.

The "dale" pressure reading was the smallest in a day, showing no significant fluctuations (Fig. 13). The average standard deviation of "dale" pressure in the night was small and 6.1 (SBP)/4.5 (DBP) mmHg (Table II). There was a high correlation between "dale" pressure and the average blood pressure for the whole day: r = 0.89 (SBP), r = 0.80 (DBP) (Fig. 14). In clinical practice, blood pressure has been measured in a sitting or lying position. The value obtained by this routine method fluctuates wide in a day and has low statistical reliability. Therefore, it must be emphasized that additional criteria are crucial for the determination of an appropriate therapy for each patient.

Classification of Pathophysiological Changes by Multivariate Statistical Analyses

A dendrograph was obtained by the cluster analysis on the basis of clinical data for 49 patients who had been classified into the labile group. They were further divided into 2 clusters, with a negative correlation (r = -0.75) to each other (Fig. 15). These two clusters were tentatively called E cluster (elastic type) and F cluster (functional or mild type), respectively. Of the 49 patients, 23 belonged to the E cluster and 26 to the F cluster. Similarly, 66 patients in the fixed group were divided into 4 clusters. One was called M cluster (malignant type), and the other was called H cluster (hypertrophic type) including 3 subclusters, H1, H2, and H3. Seventeen patients belonged to the former and 49 to the latter (Fig. 15).

To discriminate among the 4 clusters, i.e., E, F, H and M, the discriminant function, D4, was prepared from all the input variables excluding LVWT in UCG and PRA. It was proved that this method made it possible to discriminate between

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**Fig. 16.** The height of each bar represents the average of BP before and after the hospitalization in each cluster (mean ± S.E.).

**Fig. 17.** Ages and clinical data for patients in each cluster. (statistically significant difference * p < 0.05, ** p < 0.01 compared to other clusters)

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the clusters in an average of about 88% of the patients examined. It was clear from the close correlation observed between the number of patients of the individual types when classified by this function $D_4$ and that in the individual clusters when classified by the dendrograph (Table III). Patients in the intermediate group were divided equally into three types, E, F and H. The results indicate that the discriminant function $D_4$ can predict with a relatively high degree of accuracy the 4 clusters which would be classified by the cluster analysis. Similarly, the discriminant function $D_2$ utilizing only 5 variables was calculated as $D_2 = 0.118 \times DBP + 0.684 \times KW + 0.144 \times CTR + 0.373 \times LVH - 0.041 \times PD$ for the prediction of 2 groups, fixed and labile. Of the 49 patients in the labile group, 48 ($D_2 \leq 0.23$ in these patients) were predicted to be in the labile group. Of the 66 patients in the fixed group, 64 were predicted to be in the fixed group ($D_2 > 0.23$ in these patients).

As summarized in Table IV, and Figs. 16 and 17, patients in cluster F were younger and affected by rather mild cardiovascular disturbances compared with those of other clusters. They were free from any abnormalities in the elastic modulus PD ($9 \pm 4$ mmHg%) and PI, as compared with those in other clusters. They had a higher PRA ($2.4 \pm 1.7$ ng/m/hr) than those of cluster E from the same labile group. Therefore, they were affected by a mild hypertension, belonging to stage I of the WHO classification.

Patients in cluster E were older than those in any other groups. In them, a calcification of the aortic arch was frequently observed in spite of a slight increase in the diastolic blood pressure, few changes in the optic fundi, and a mild hypertrophy of the heart. Patients of cluster E showed disturbances in the PD ($19 \pm 4$ mmHg%) and PI, and smaller values for PRA ($0.6 \pm 0.4$ ng/ml/hr) than those of any other clusters ($P < 0.01$).

Cluster H was characterized by so-called fixed hypertension, or sustained hypertension. In patients of this group, the heart was hypertrophic, the PD was disturbed slightly, and hypertension was moderate or severe. These changes seemed to correspond to those in stage II or III of the WHO classification. Cluster H contained subcluster H1 which resembled cluster F, and also subcluster H3 which resembled cluster M (Fig. 15).

Patients in cluster M exhibited renal disturbances and hypertensive retinopathy in addition to changes characteristic of cluster H. They showed larger PRA values ($4.4 \pm 2.7$ ng/ml/hr) than patients in any other clusters. Most patients in cluster M were suffering from severe or malignant hypertension.

In our previous studies, a principal component analysis was carried out on the results of laboratory examinations which were performed on 60 persons with normal blood pressure, 86 patients with EH, and 13 patients with elderly systolic hypertension. The results are summarized in Fig. 18. Where the hypertensive factor (H-change) is presented on the abscissa, and the atherosclerotic or elastic factor (S-change) on the ordinate. On the basis of correlation coefficients among the principal components examined, clinical criteria and an easy method for the estimation of H-change or S-change in hypertensive patients were elaborated as shown in Table V. These were applied to 115 patients who had been classified by a cluster analysis. The method was as follow; 1) the score, 1 to 4, was obtained on the basis of clinical criteria determined for BP, KW-classification, serum creatinine, cardiac hypertrophy (LVH, CTR, and LVPW), ST-T change, aortic change (AO or PD) and age, 2) the scores were multiplied by each H- or S-weighting value, which was in proportion to the correlation coefficient of the H-factor or S-factor, and 3) they were added together to obtain the total score of H- or S-change for each
TABLE V SEVERITY INDEX FOR HYPERTENSION

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>XH×XS</th>
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</thead>
<tbody>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>1</td>
<td>~149</td>
<td>150~174</td>
<td>175~199</td>
<td>200~</td>
<td>0</td>
</tr>
<tr>
<td>Diastolic</td>
<td>2</td>
<td>~89</td>
<td>90~104</td>
<td>105~119</td>
<td>120~</td>
<td>9</td>
</tr>
<tr>
<td>Fundi Grade (KW-Classification)</td>
<td></td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>II</td>
<td>III×IV</td>
</tr>
<tr>
<td>Renal Serum creatinine (mg/dl)</td>
<td>4</td>
<td>~1.2</td>
<td>1.3~2.0</td>
<td>2.1~3.0</td>
<td>3.1~</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTR %</td>
<td>5</td>
<td>~49</td>
<td>50~54</td>
<td>55~59</td>
<td>60~</td>
<td>8</td>
</tr>
<tr>
<td>LVH (SV1+RV5mV)</td>
<td>6</td>
<td>~3.4</td>
<td>3.5~4.4</td>
<td>4.5~5.4</td>
<td>5.5~</td>
<td>0</td>
</tr>
<tr>
<td>LV PW (mm)</td>
<td>7</td>
<td>~1.09</td>
<td>1.1~1.39</td>
<td>1.40~1.59</td>
<td>1.6~</td>
<td>0</td>
</tr>
<tr>
<td>Ischemic change in left ventricular leads</td>
<td>8</td>
<td>Within normal limit</td>
<td>ST ↓ (~ 0.1 mV) or T/R &lt; 10%</td>
<td>ST ↓↓ (0.1 mV~) &amp; inverted T</td>
<td>ST ↓↓↓ (0.1 mV~) &amp; inverted T coronary T etc.</td>
<td>3</td>
</tr>
<tr>
<td>Aortic Configuration of the aortic arch AO</td>
<td>9</td>
<td>Normal</td>
<td>Elongation or dilatation</td>
<td>Elongation &amp; dilatation</td>
<td>Calcification</td>
<td>0</td>
</tr>
<tr>
<td>Elastic modulus of the carotid (mmHg/%) PD</td>
<td>10</td>
<td>~9.0</td>
<td>9.1~13.0</td>
<td>13.1~17.0</td>
<td>17.1~</td>
<td>3</td>
</tr>
<tr>
<td>Age (yrs old)</td>
<td>11</td>
<td>~34</td>
<td>35~44</td>
<td>45~59</td>
<td>60~</td>
<td>0</td>
</tr>
</tbody>
</table>

Hypertensive (H) Change = Σ (Score of Criteria) × (H-Weighting value)
Atherosclerotic (S) Change = Σ (Score of Criteria) × (S-Weighting value)

H- and S-change are given as the sum of scores of all criteria multiplied by respective weight values.
Cardiac hypertrophy receives an average score of No.5 and No.6 or No.5, No.6 and No.7.
* When Elastic Modulus (PD) is not measured, score of AO is multiplied by 3 and 17 to obtain H- and S-change respectively for score of the aortic criteria. (For abbreviations see Table IV)

The results were plotted two-dimensionally (Fig. 19). The ellipses in the figure represent the ranges in which more than 90% of the patients of the corresponding clusters classified by cluster analysis were included. The cluster of a new outpatient can be estimated by applying the figure to a patient to see to which ellipse the patient belongs. It was noticed that both H- and S-changes were mild in the patients in cluster F, and S-changes were severer than H-changes in the patients in cluster E. Furthermore, both H- and S-changes were moderate in those in cluster H. In the patients in cluster M, H-changes were much severer than those in other clusters. Therefore, the classification of patients into clusters could be evaluated through the use of 2 factors, H- and S-changes.

Function of Carotid Sinus Reflex (Fig. 20)
The carotid sinus was stimulated from the outside of the skin with the P-P stimulator in 46
smallest value was 6.5 ± 3.9 mmHg, which was obtained in the 12 patients from cluster F in the same labile group (P < 0.01). The average decrease in systolic blood pressure was 12.6 ± 6.4 mmHg in the 15 patients from cluster H and 15.6 ± 1.9 mmHg in the 6 patients from cluster M.

There was a positive correlation between the PD of the common carotid artery and ΔSBP (r = 0.55; p < 0.01). Accordingly, in the labile group, the patients in cluster E had a disturbed PD of this artery owing to a reduced distensibility of the arterial wall. In the patients in cluster E blood pressure decreased when the distensibility of the carotid sinus was enhanced from outside. It appeared that the function of the carotid sinus reflex in the patients of cluster E might have been disturbed by a decrease in the distensibility of this sinus.

Classification of Types of EH and Cardiovascular Complications (Fig. 21)

Patients who were suffering from hypertension complicated with cardiovascular disorders were classified into disease types by the discriminant function D4. The most predominant complication among E type patients was cerebral infarction (16/21 patients), and myocardial infarction (7/13 patients) also was rather predominant. The predominant complication in H type
myocardial infarction N=13

Fig. 21. Typing of patients with vascular complications by the discriminant function D₄ (x²; compared with control numbers of patients E = 23, F = 26, H = 49 and M = 47).

DISCUSSION

Variation in Blood Pressure

It is widely accepted that the high level of casual blood pressure is closely related to an increased risk of the development of certain cardiovascular disease. But it has been recognized for many years that blood pressure is a continuous physiological variable which cannot be determined by a simple measurement at a given sampling point. It is known that casual measurement of blood pressure in the outpatient clinic gives higher values than the 24 hr average. Some studies have suggested that blood pressure is highest in the morning shortly after waking and then falls progressively throughout the day. Blood pressure reaches a nadir at 3:00 and begins to rise again at 5:00 to reach the highest level at 9:00. This circadian variation in blood pressure was not associated with physical activity. On the other hand, arterial pressure is thought to be closely correlated to physical activity and the depth of sleep. Nevertheless, it is well known that blood pressure always falls, often profoundly, during sleep.

Blood pressure varies from beat to beat, from

patients was cerebral hemorrhage (7/11 patients), although this was insignificant when compared between the patients with cerebral hemorrhage and those who served as controls. Patients in cluster M had significant renal or heart failure complications.
Further Examination for Secondary Hypertension

Fig. 23. A method of using the microcomputer for the management and therapy of hypertension. A type of EH is predicted by discriminant function Dk and an estimation for the effect of anti-hypertensive drugs may be predicted in the future by discriminant function Dn.

minute to minute, with physical as well as emotional activity. When one considers that the heart beats 110,000 times in each 24 hr period, thus generating 110,000 systolic and diastolic pressures, it is clear that a meaningful definition of blood pressure must be the average of all values13. The correlation between the overall severity of hypertensive complications and the average blood pressure obtained with a portable recorder worn during the patients' normal daily activity was significantly higher than the correlation between the severity of illness and the casual blood pressure8. In another study the 5- and 8-year mortalities from hypertensive complications are reported to relate closely to basal blood pressure, which supposedly excluded transient fluctuations.

If there is one blood pressure value for a patient which can be statistically reproduced under a given condition of measurements, that value may be regarded as a representative blood pressure value of the patient. It is observed that in the present investigation, blood pressure measured when the subject was seated varied greatly. When hospitalized patients are regarded as a population, blood pressure measured in a lying position was closer to the average for the day. But, casual blood pressure measured in such a position varies considerably during a day. It is presumed that "dale" pressure of the spontaneously fluctuating (SF) period during sleep may be one of the lowest blood pressure values in the course of a day. At this time, blood pressure also showed minimal variations. This state of fluctuation of blood pressure during sleep has already been reported1.10 Long before desynchronized sleep (REM stage) was recognized, MacWilliam42 observed a sudden increase in arterial pressure during periods of sleep which he defined at the time as "disturbed" because of many dreams and nightmares. The indentification of REM stage of sleep and the introduction of polygraphic recording methods have made it possible to follow with greater accuracy the evolution of hemodynamic changes during sleep. Variations or spontaneous fluctuation of arterial pressure during a certain stage of sleep observed by EEG might be present both in stage 240,44 and in the REM stage2,20,38,40,44. In stage 2, in some subjects, these variations became periodic from time to time, identifiable with the arterial pressure oscillations described by Sigmund Mayer40,41. In the REM stage an increase in arterial pressure was more pronounced but not necessarily in relation to variations of arteriolar tone or of heart rate40. Pressure was slightly higher, but not to a significant degree, in REM stage than in stage 240. In animals, variations or oscillations of blood pressure have been observed in the REM stage24,25,43 (called phasic change24).

We recorded EEG, direct arterial pressure, and heart rate simultaneously in 3 patients during sleep. The SF period seemed to correspond to the periods when a sleeping EEG pattern was recorded, and corresponded especially closely with the intervals of REM sleep (Fig. 13). Sometimes changes in heart rate were noticed in the ascending stage of blood pressure (Fig. 22), and they were seen sometimes in periods other than that of REM stage. Accordingly, the SF period might seem to correspond with the intervals of stage 2 and the REM stage. From the results of another measurement over a 24 hr period performed on a patient after 1 week, it was confirmed that the value of "dale" pressure in the SF stage was almost the same as those measured before. If a vascular unloading technique26 is available, it will be possible to measure systolic and diastolic blood pressures at each heart beat.
indirectly, and to measure blood pressure continuously and readily during sleep. Therefore, this "doble" pressure may serve in the future as a statistical representative blood pressure value for the respective individual.

**Classification of EH**

At present, an indirect casual blood pressure is used as a clinical basis for the diagnosis and treatment of hypertension, since it is readily measurable in spite of its lack of reliability from a statistical viewpoint. However, application of the antihypertensive therapy should not be established solely on the basis of casual blood pressure. It is necessary to make a standard or criteria for the treatment by combining casual blood pressure with the results of some other clinical examinations. There are many indices for the classification of severity of hypertension that have been used conventionally. These are classifications of Keith-Wagner, Carcoran et al., Duncan et al., Sokolow et al., and Roland, the severity index of V-A and the stages of WHO. In every index, the severity of hypertension is expressed one-dimensionally, and it is mixed up with the severity of atherosclerosis accompanying hypertension. None of these many indices, however, takes into account the possibility of a spontaneous fall in blood pressure or the PRA which is, at present, considered to be of therapeutical significance. In every heretofore existing index, the classification itself has been established on a stochastically ambiguous basis. The classification which we propose here was devised to supplement these defects of conventional indices of classification, and in the future, prospective follow-up studies are required to refine its value.

Recently, cerebral infarction and myocardial infarction have become prevalent in Japan. They have frequently followed hypertension and there is strong evidence to suggest that they are related to the occurrence of atherosclerosis. The prognosis is not always good in some cases of hypertension under treatment, and there is still some doubt about the value of antihypertensive therapy in reducing the incidence of myocardial infarction in hypertensive patients. As already reported, PD of the carotid artery is 7.5 ± 2.5 mmHg%, on the average, in normotensive subjects, or less than 10 mmHg% in more than 90% of these subjects. However, it was over 15 mmHg% in many patients with cerebral or myocardial infarction. In patients with cluster E, hypertensive changes were moderate, but PD was increased intensely (19 ± 4 mmHg%). These patients were presumed to have been suffering from a dysfunction of the carotid sinus in the control of blood pressure in response to decrease in the distensibility of the arterial wall. These disturbances are considered to have influence on the occurrence of cerebral and myocardial infarction. Therefore, patients with hypertension of cluster E or E type must be treated carefully, taking the above factors into consideration.

When patients with F type hypertension due to discriminant function D kept under conditions of moderate physical or emotional quietness, and given a modest dietary salt restriction, it is possible that blood pressure will be lowered spontaneously. The same would be true for the patients with E type hypertension. Since there is the possibility that hypotension will carry with it the risk of inducing a cerebral or myocardial infarction, one must exercise extreme caution in the use of hypotensive drugs for the E type patients. The application of antihypertensive drugs has been indicated absolutely for patients with hypertension of H and M clusters or types.

The treatment program seems to differ according to the type of hypertension. The classification of hypertension into types requires a complicated calculation, for which the use of a computer is recommended. There is another advantage for using a computer, that is an optimum prescription consisting of a combination of suitable kinds of drugs can be provided by taking many contraindications and the severity of organ complications of the patient into consideration. In addition, because of experiments now under way, it may be possible in the future to feed back the practical effect of antihypertensive drugs into the computer, for example, to change the coefficient Ani of the discriminant function for the effectiveness of drugs, and to let the computer itself determine the selection of drugs as shown in Fig. 23. Antihypertensive treatment has sometimes resulted in fatalities. To ensure safety, it is assumed necessary that antihypertensive therapy is conducted under a dual control system; i.e., the judgment of the physician and computer control as an auxiliary means.

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