Blood Pressure Variations to be Considered in the Treatment of Hypertension

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Diurnal variations of the basal blood pressure in patients with essential hypertension were investigated by the indirect recording method. To estimate the reduction in blood pressure at midnight, disturbance of sleep in the patients should be considered. Relationship between neurohumoral factors and the diurnal blood pressure variations were also evaluated. 1) Variations of the casual blood pressure at the clinic visits may be stabilized beyond 15 minutes of the sitting rest. 2) During the out-patient treatment of essential hypertension with placebo for 6 weeks, 16% of the patients showed reduction in mean arterial pressure of 13 mmHg or more. 3) Significant influence of seasons on blood pressure was not apparent for 6 weeks of the placebo treatment of hypertension. But in patients under the long-term antihypertensive treatment, blood pressure in summer was maintained significantly lower than in winter. 4) Self-monitoring of blood pressure by patients at home is valuable for estimating diurnal changes of blood pressure with the antihypertensive treatment.

In order to evaluate the efficacy of the antihypertensive therapy, it is important to observe the spontaneous blood pressure variations in the individual patients and to define their own representative levels. Usually, in the hospitalized patients, basal blood pressure levels measured in the supine position under the resting conditions are used as standards, which show often remarkable reductions within several days after admission. But in the out-patients who are having the normal activities, casual blood pressure levels may be of more practical significance.

In the present investigations, several problems on the significance of blood pressure variations which are to be considered in the practical treatment of hypertensive patients have been studied.

I. Diurnal Variations of the Basal Blood Pressure

MATERIALS AND METHODS

Patients with uncomplicated essential hypertension were kept on the daily salt intake of 8 to 10 g without any antihypertensive regimen. Studies were performed more than a week after admission. Patients were kept lying at rest throughout the day except for the minimal activities as having meals, urination or defecation. In 10 patients, hourly blood pressure and heart rate recordings were made for 24 hours using an automatically inflated cuff device with digital printers (BP-203X, Nippon Colin) which could record the values of the systolic and diastolic

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Fig. 1. Hourly recordings of the basal blood pressure (closed circles) and heart rate (open bars) measured by the automatic indirect method in 10 hospitalized patients with essential hypertension.

Fig. 2. Hourly circadian recordings of blood pressure and heart rate in a 32-year-old female patient with essential hypertension. Profound reduction in blood pressure within the normotensive range was recorded during the midnight except for the value recorded when she was awake (arrow).
blood pressure in mmHg and pulse rate per minute. As to the midnight recordings, it was inquired retrospectively whether the patient was awake or sleeping when the measurement was made.

Furthermore, in order to correlate the diurnal basal blood pressure variations with some neurohumoral factors, in 7 patients with essential hypertension, 4 patients with renovascular hypertension and 8 normotensive control subjects who were kept under the above-mentioned similar basal conditions, blood pressure and heart rate were measured with a conventional sphygmomanometer at 7 a.m., 9 a.m., noon, 5 p.m. and 9 p.m., and 7 and 9 a.m. in the next morning. And at the same time, blood was drawn to measure the plasma renin activity (PRA), plasma aldosterone concentration (PAC) and plasma nor-epinephrine concentration (PNE). Urine collection was started at 9 p.m. before the day of the study and the fractional urinary excretions of electrolytes were measured between the blood samplings.

RESULTS AND DISCUSSION

Average values of blood pressure and heart rate measured hourly by the automatic indirect method in 10 hypertensive patients are shown in Fig. 1. As a whole, the blood pressure curves have two zeniths with wide variations at noon and in the evening, which may have been influenced by some physical activities associated with taking meals. Therefore, strictly speaking, the values at those times may not have corresponded with the basal conditions. Most of the patients showed reduction of blood pressure at midnight and gradual increase of blood pressure toward the early morning. In our patients, the nadir of the blood pressure curves during the midnight on an average was not so remarkable as those observed by the direct measurements with arterial catheterization. It may be due to the fact that some patients had their sleep disturbed by the inflating cuff. Actually, the levels recorded while the patient was sleeping showed lower values but when the patient was awake, the blood pressure remained high as illustrate in a case shown in Fig. 2. It is recommendable that estimation of blood pressure values measured during the midnight by the indirect cuff method should be of practical value only when the measurement is done before interrupting the patient's sleep. Direct blood pressure monitoring usually permits the unrestricted daily activities of the patients.4,5
In this sense, it represents rather the variations of casual blood pressure than those of the basal pressure of ours. This may be another reason for our smaller differences in pressure between levels during the daytime and those at the midnight.

There was no definite difference in the pattern of diurnal basal blood pressure variations between essential and renovascular hypertensive patients and normotensive subjects measured under the awake conditions as shown in Fig. 3. Diurnal variations of PRA, PAC and PNE in these 3 groups are shown in Fig. 4. As a whole, PRA and PAC show higher values in the morning and have tendencies to decline toward the evening. These 3 groups show similar patterns of such tendencies. There was no significant variation in PNE although slightly but not significantly higher values were obtained in the morning in the hypertensive groups. Fractional urinary excretions of sodium and potassium in the 3 groups are shown in Fig. 5. Sodium excretion had a peak in the urine specimen collected from the noon till 5 p.m. in either groups.

The results indicate that not only the increased sympathetic nervous activity in the morning but also the reduction of arterial pressure during the midnight may contribute to the rise of PRA in the morning in the basal conditions. It is well known that the PAC is influenced by the circadian variations of ACTH secretion. In addition, it should be considered that the variations of PRA may also be reflected on the diurnal changes in PAC.

II. Variations of the Casual Blood Pressure

1) Variations of the Casual Blood Pressure during Hospital Visits

MATERIALS AND METHODS

Patients visiting our Hypertension Clinic had an automatic blood pressure recorder cuff on their arms immediately after the arrival at the hospital and their blood pressure and heart rate were recorded at five-minute intervals while they were sitting quietly and waiting until they were called for their doctors’ inspection after 30 to 60 minutes.

RESULTS AND DISCUSSION

The changes in recorded blood pressure and heart rate are plotted in Fig. 6. There was no difference between the values recorded just before the doctors’ inspection and those measured by the doctors. After sitting rest beyond the 2 five-minute intervals, there was no significant difference between the recorded values and those measured by the doctors. Heart rate has some tendency still to continue to decrease for 35 minutes although the differences from counts by doctors are not significant beyond the third intervals.

It is suggested that 15 minutes’ sitting rest is sufficient for estimating the blood pressure level at the out-patient clinic but it may be recommendable for the patients to wait for about 30 minutes to get a stabilized heart rate.

2) Out-Patient Blood Pressure Estimations during Double-Blind “Placebo-Treated” Periods
Fig. 5. Fractional urinary excretions of sodium and potassium in patients with essential (EH) and renovascular hypertension (RVH) and in normotensive subjects (NT).

Fig. 6. Changes in blood pressure and heart rate in hypertensive out-patients from the time immediately after their arrival at the hospital, recorded by the automatic indirect method at five-minute intervals while they were sitting quietly. The bars on the left represent average values recorded just before the doctors' inspection and the bars on the right are ones measured by the doctors. Asterisks indicate the significance of difference from the doctors' measurements.

MATERIALS AND METHODS
Among the 4 multi-center double blind studies on the efficacy of antihypertensive drugs in which the effects of the tested drugs were compared with those of placebo, 183 patients with essential hypertension were collected who were treated with placebo during the "treatment
periods” for 6 to 8 weeks after the “observation periods” of 4 weeks during which time placebo was also given. Among them, 146 cases satisfied the criteria of the blood pressure levels higher than 160/90 mmHg which was estimated at the end of the observation periods and with blood pressure readings at regular hospital visits usually at two-week intervals. In each of these cases, blood pressure difference was defined as values obtained at the end of the observation periods minus values obtained at the end of the placebo-treated periods. For each value, usually an average of each two readings at the last successive visits was used.

RESULTS AND DISCUSSION

In these 146 cases, the average blood pressure at the end of the observation periods was 173/102 mmHg and that at the end of the placebo-treatment periods was 164/99 mmHg.

The degrees of differences in systolic, diastolic and mean arterial pressures are divided in 7 subgroups as shown in Fig. 7, and frequency distribution of the respective pressure is depicted on each subgroup. In systolic blood pressure, 45% of the patients showed difference within ±9 mmHg, and difference within ±19 mmHg was seen in 79% of the patients. In diastolic blood pressure, 39% of the patients showed difference within ±4 mmHg, and difference within ±9 mmHg was seen in 74% of the patients. In mean arterial pressure, 50% of the patients showed difference within ±6 mmHg, and difference within ±13 mmHg was seen in 81% of the patients.

In most of the clinical trials for evaluation of the efficacy of the antihypertensive drugs in our country, a change in mean arterial pressure within ±6 mmHg by the treatment has been classified as “no change”. According to the present collective study, only about a half of the placebo-treated patients did fall into this category. The category of slight reduction and slight elevation of mean arterial pressure in that classification has been defined as the change from ±7 to ±13 mmHg, respectively. About 20% of the placebo-treated patients may be estimated as having responses beyond this range. It has been recommended that evaluation for a patient to have effective responsiveness should be achieved when the patient shows a mean blood pressure reduction beyond 13 mmHg by any drugs after the trial period. Even with this criterion, 16% of our placebo-treated patients should be estimated as showing effective hypotensive responses at the end of the treatment periods.

3) Seasonal Changes in the Blood Pressure at the Out-Patient Clinic

MATERIALS AND METHODS

Comparison of Blood Pressure Estimations in Patients Treated with Placebo in the Warm and Cold Seasons

The above-mentioned 146 patients with essential hypertension were divided into two groups. In a group of 81 patients, the treatment periods with placebo were started from September to February when the estimations of blood pressure at the clinic for 6 weeks were made in the seasons getting cooler or colder. In another group consisting of 65 cases, the treatment periods with
placebo began from March to August when their hospital visits were in spring or summer seasons which are getting warmer or hot. In these two groups the changes in blood pressure measured at the two-week intervals for 6 weeks are compared.

Seasonal Comparison of the Blood Pressure Controls in Patients under the Long-Term Antihypertensive Treatment

In 123 patients with essential hypertension under the continued treatment with various antihypertensive drugs at our Hypertension Clinic for more than 10 years, the recorded levels of blood pressure in winter and summer seasons were compared. In every patient, all the recorded readings of the blood pressure in January and February were averaged in each year and it was defined as the patient's winter blood pressure of the year. Similarly, an average value of all the readings in July and August was taken as the patient's summer blood pressure of the year. Values thus obtained were averaged in each year as to all cases and yearly comparisons of average values between winter and summer were made from the first year of the treatment.

RESULTS AND DISCUSSION

The course curves of the average blood pressure levels at the two-week intervals for 6 weeks of the placebo-treated periods in the two groups are illustrated in Fig. 8. No significant difference was observed between the two groups. The influence of the seasons was not apparent on the course of the out-patient blood pressure readings for 6 weeks of the placebo treatment.

But in patients on the long-term antihypertensive regimen, yearly average blood pressure values recorded during winter are higher than those during summer as shown in Fig. 9. Average blood pressure before the treatment in these patients was $198 \pm 2.4 / 112 \pm 1.4 \text{ mmHg (mean } \pm \text{ SEM)}$. During the first year of the treatment, the mean values of the blood pressure fell to $161 \pm 2.0 / 96 \pm 1.1 \text{ mmHg in winter and to } 148 \pm 1.9 / 90 \pm 1.0 \text{ mmHg in summer. After 5 years of the treatment the values were } 154 \pm 1.5 / 92 \pm 0.8 \text{ mmHg in winter and } 143 \pm 1.4 / 88 \pm 0.8 \text{ mmHg in summer; and after 10 years, they were } 154 \pm 1.5 / 92 \pm 0.8 \text{ mmHg in winter and } 145 \pm 1.5 / 88 \pm 0.9 \text{ mmHg in summer. The average summer pressure was significantly lower than the winter pressure in each year after the treatment.}。“

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Fig. 9. Seasonal changes in blood pressure in 123 patients with essential hypertension who were treated for more than 10 years. Hatched bars represent averages from all the values recorded in January and February and open bars recorded in July and August yearly from the beginning of the treatment. Values are expressed as means ± SEM.

Fig. 10. Average blood pressures in winter (hatched bars) and in summer (open bars) in a female patient with essential hypertension who has been treated for 17 years. The treatment was begun when she was 45 years old. Her dosage of antihypertensive drugs is 30 mg of guanethidine, 500 mg of methyldopa and 30 mg of decaserpine daily in winter versus 20 mg, 250 mg and 20 mg, respectively, in summer.

Some epidemiological studies have indicated that casual blood pressure levels obtained in winter are somewhat higher than those in summer. Our comparative studies on changes in pressure levels in the placebo-treated hypertensive patients for 6 weeks have failed to demonstrate an apparent difference between the two groups observed in warmer and cooler seasons. However, the results from the observations on our patients under the long-term antihypertensive treatment, it is apparent that the effects of drugs are more apparent in hot seasons than in cold seasons. In
Changes in the Effects of the Antihypertensive Agent

The clinical value of self-monitoring of blood pressure by the patients at home is increasingly recognized.\textsuperscript{14-17} When the patients are instructed in learning the proper technique how to measure their own blood pressure correctly, the reliability of the readings usually could be easily checked by the simultaneous measurements by the physicians and the patients at the clinic office.

Some patients show consistently higher values at their regular clinic visits than those obtained by daily frequent measurements at home even though they have been on the long-term treatment.\textsuperscript{16} In such cases, it is recommendable that the dosage of the antihypertensive drugs should be adjusted according to the blood pressure levels obtained correctly during their ordinary home life times. On the other hand, some patients show very closely similar values measured at home with those of the office readings.\textsuperscript{15,17} In these cases, the intervals between hospital visits could be prolonged with much convenience for both the patients and the medical personnel.

Frequent self-monitoring of blood pressure at home is also valuable for estimating the diurnal blood pressure variations during a regular life especially when it is recommended that a single once-daily dose of the drug is prescribed for the simplicity of the treatment as in the case of some diuretics or beta-adrenergic blocking drugs.\textsuperscript{18}

Here we would like to present one of our experiences.

In a co-operative patient in whom the stable and very approximate readings could be obtained at home and at the clinic, daily frequent home measurements were correlated with her various life conditions between her regular hospital visits. The patient was treated with once-daily 50 mg of atenolol which resulted in an excellent and stabilized hypotensive effect, which has been maintained for two years during which time she continued self-monitoring of her blood pressure several times within a day with documentation of her daily life activities. Figure 11 illustrates an example of variations of self-measured blood pressure and pulse rate values recorded regularly at home during a four-week interval between two hospital visits on once-daily atenolol therapy, together with values measured by a doctor at the clinic. Blood pressure measured while remaining in the bed immediately after awakening is significantly higher than the levels measured during her

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ordinary home life. Transient elevation of blood pressure is observed on getting up and changing her cloths, but pressure has come down already when she takes a breakfast, and it is stabilized and gives no change after ingestion of the drug. On the other hand, heart rate increases after waking up, and continued to rise after the breakfast. And significant reduction of heart rate is observed after taking atenolol, but it gradually increases until the time before sleep. The pattern of the diurnal variations in this patient is compatible with observations made by continuous direct intra-arterial catheterization recordings in patients taking the single oral dose of atenolol.19

When the trial on the effect of a new antihypertensive drug is made on the out-patient basis, diurnal changes of the hypotensive efficacy may be more properly evaluated by the application of such a self-monitoring system.

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