Remission of Hypertension: Retrospective Observations over a Period of 20 Years

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To clarify the background and outcome of hypertensive patients who have remission of their elevated blood pressure (BP) after a course of antihypertensive drug therapy, we designed a retrospective observational study. The clinical records of 106 hypertensive men and women (BP, 164.3/104.4 mmHg) given antihypertensive drug treatment and subsequently examined every 1 to 3 mo for more than 20 yr were reviewed. The patients were divided into two groups: those who had remission (R-group) and those who did not have remission (N-group). Patients were considered in remission if no significant elevation in BP was observed for more than 1 yr after withdrawing their medication. Remissions ranging in duration from 1.6 to 21.7 yr (average duration, 6.3 yr) occurred in 19 of 106 patients (17.9%). However, antihypertensive drug treatment was eventually restarted in 17 of the 19 patients. Before treatment, comparison of the R-group and N-group revealed no differences with respect to age, body weight, BP, or serum creatinine. In contrast, the proportion of patients who lacked high-voltage deflections in their electrocardiograms (ECG) as well as that of patients whose BP was well-controlled by a single medication was significantly greater in the R-group than in the N-group (12/19 vs. 22/87, p < 0.05 and 10/19 vs. 13/87, p < 0.001, respectively). In addition, body weight in the R-group decreased significantly by the time drug therapy was withdrawn (p < 0.01). Finally, significantly more patients (14 of 19 patients) entered remission in the spring and summer (p < 0.05) than at other times of the year. We conclude that remission occurs in a subset of well-controlled hypertensive patients and may persist for several years or more. However, in the majority of patients, antihypertensive drug treatment will usually need to be restarted at some point. Patients who lack ECG high-voltage deflections and who are successfully treated with a single therapeutic agent are most likely to experience remission. Moreover, it appears that withdrawing patients from drug therapy in the spring or summer is more likely to yield a favorable outcome than at other times of the year. (Hypertens Res 1998; 21: 103-108)

Key Words: hypertension, remission, body weight, high voltage in ECG, antihypertensive therapy, seasonal variation

Withdrawal of antihypertensive drug treatment without a subsequent rise in BP was first described by Perry et al. in 1956 and has been termed “remission” (1, 2). Since that initial report, occurrences of remission have been confirmed in both retrospective (3, 4) and prospective studies (5-17). As described in recent reviews (18, 19), the prospective studies succeeded in outlining the characteristics of patients likely to be good candidates for withdrawal from antihypertensive drug therapy. However, patients participating in the prospective studies were followed up for a maximum of 5 yr, which was not sufficient to fully characterize the time-courses or outcomes of the remissions. Indeed, up to 20 yr of retrospective observations obtained from the Framingham Heart Study (3) reveal that remission is sometimes maintained for as long as 12 to 14 yr.

The present retrospective study was designed to obtain additional information about the nature of the prolonged periods of remission that occur in some hypertensive patients after having received a regimen of antihypertensive drug therapy. In addition, we aimed to identify specific characteristics consistently found in individuals who tolerate withdrawal from medication.

Patients and Methods

The present study was based on a retrospective review of the clinical records of 956 patients with uncomplicated essential hypertension who began antihypertensive drug treatment at the Institute for Adult Diseases Asahi Life Foundation hypertension clinic between 1968 and 1975. Antihypertensive drug treatment was started when average systolic BP or diastolic BP, or both, measured on two or more consecutive visits, was ≥160 mmHg or ≥95 mmHg, respectively. From the original cohort, we...
studied the 106 patients who, following diagnosis of their hypertension, were examined every 1 to 3 mo without interruption for more than 20 yr (23.08 yr on average). The other 850 patients were not included in the study group because (i) they stopped visiting the office, (ii) they dropped out after moving from the area, (iii) their visits to the clinic were too infrequent to satisfy the above criteria for the entire 20-yr period, or (iv) their hypertension was complicated by stroke, myocardial infarction, or other events that altered the course of their treatment.

The patients in the study included 59 men and 47 women; before treatment, their average age and BP were 49.3 yr and 164.3/104.4 mmHg, respectively. Once drug therapy was started, patients were carefully followed up, and excellent compliance with attendance at the hypertension clinic and with the regimen of drug therapy was maintained (20). We further divided the 106 patients into two groups: one consisting of patients whose hypertension went into remission (R-group) and another consisting of patients whose hypertension did not (N-group). Patients were considered to be in remission if after all antihypertensive medication was withdrawn no subsequent elevation of BP was observed for a period greater than 1 yr. Patients whose antihypertensive drugs were withdrawn but whose medication had to be restarted within 1 yr were included in the N-group.

In treating their patients, physicians at the hypertension clinic were requested to use as little medication as possible, provided BP was reduced to an acceptable level. Beyond that, no specific instructions for the reduction or withdrawal of antihypertensive medication were given. Once BP was well-controlled for a year or more, physicians were sometimes motivated by the clinical findings to reduce or withdraw antihypertensive drugs; thus, remission periods in this study were observed during the routine course of clinical practice. For example, if patients were experiencing symptoms of hypotension or if BP remained in the normotensive range despite poor drug compliance, doses were reduced or medications were withdrawn completely. Selecting patients for study whose hypertension went into remission during routine clinical practice differs from the method used in prospective studies.

Fig. 1. Twenty-five-year time course of systolic and diastolic blood pressures and body weight of a typical patient. This man was 41 yr of age when antihypertensive drug therapy was started. His initial blood pressures, recorded on two consecutive visits, were 160/100 and 160/102 mmHg. In 1979, the patient entered the hospital for 2 wk of exercise therapy and education regarding diet (filled bar). Open bars represent the period of drug treatment. Medications 1 and 2 were combinations of trichlormethiazide/reserpine or trichlormethiazide/hydralazine hydrochloride, and nifedipine or enalapril maleate, respectively. Open and filled circles represent the systolic and diastolic blood pressures, respectively (left-hand ordinate scale); triangles represent body weight (right-hand ordinate scale).
where antihypertensive drugs are intentionally and uniformly withdrawn on the basis of predetermined criteria. After antihypertensive medication was successfully withdrawn, patients were examined every 1 to 3 mo. Antihypertensive drug therapy was restarted if BP rose to hypertensive levels, but the decision to restart drug administration was left to the individual physicians. The demographic characteristics of the patients in the two groups were compared, and the time-courses of the changes in BP and body weight among members of the R-group were analyzed.

Numerical data are expressed as means ± SD. Continuous variables were compared by analysis of variance or by paired or unpaired Student's t-tests; categorical variables were analyzed by χ²-test.

**Results**

During antihypertensive drug therapy, hypertension went into remission in 19 of 106 patients (17.9%). The period of treatment before withdrawal of all medication varied in length, ranging from 1.3 to 17.1 yr, and the average was 7.9 yr. Patients remained in remission for 1.6 to 21.7 yr, and the average length of remission was 6.3 yr. Nevertheless, antihypertensive drug treatment was eventually restarted in 17 of the 19 patients as BP gradually returned to hypertensive levels.

The baseline characteristics of the R-group and N-group are summarized in Table 1. No significant differences were found between the two groups with respect to age, sex, body weight, body mass index, systolic and diastolic BPs, pulse rate, serum urea nitrogen levels, serum creatinine levels, and the rate of proteinuria. On the other hand, differences in ECG's were detected between the two groups. Before beginning drug treatment, a significantly (p < 0.05) larger proportion of the R-group had ECG's that lacked high-voltage deflections (SV1 + RV5 ≤ 3.5 mV, Table 1). Moreover, the proportion of patients whose hypertension was well-controlled by a single medication throughout the treatment period was significantly greater in the R-group than in the N-group (10/19 vs. 13/87, p < 0.001). Considering the data together, remission occurred in 9 of 14 patients (64.3%) who showed no high-voltage deflections in their pre-treatment ECG's and who also had BP's that were well-controlled by a single medication. Of the remaining 92 patients, only 10 (10.9%) showed similar characteristics.

Table 2 summarizes the BP, body weight, and body mass index data obtained from the R-group at the start of drug therapy, at the time medication was withdrawn, and when drug therapy was restarted. Correlated with the change in BP were body weight and body mass index, which were significantly reduced at the time medication was withdrawn, but returned to nearly pre-therapy levels when drug treatment was resumed (Table 2). Additional details are provided in Fig. 1, depicting the 25-yr time courses of systolic and diastolic BPs and body weight in a typical patient. This patient's entry into remission was associated with a relatively sudden decrease in body weight; however, the remission lasted for 14 yr.

Figure 2 graphically illustrates that prolonged periods of remission were associated with the absence of ECG high-voltage deflections as well as with the efficacy of single drug therapy. When estimating the amount of time patients spent in remission, we first analyzed the data from all 106 patients, and then separately analyzed the data from the 44 patients showing an absence of ECG high-voltage deflections and the data from the 14 patients lacking high-voltage deflections who were successfully treated with a single drug. We observed that the percentage of time patients spent in remission was 2 to 3 times greater for the group that both lacked high-voltage deflections and responded to single drug therapy than for either of the other two groups (p < 0.001).

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<th>Table 1. Baseline Characteristics of Patients According to Group</th>
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Summary of baseline values obtained from patients in the remission (R) and non-remission (N) study groups. Values are expressed as means ± SD and were recorded immediately before initiating antihypertensive drug therapy.
We also examined seasonal variations associated with patient entry into remission. Figure 3 shows that significantly more patients entered remission during the spring and summer than at other times of the year. Of the 19 patients in the R-group, 14 entered remission during the spring and summer (\( p < 0.05 \)).

**Discussion**

In this retrospective study, we confirmed the findings of earlier prospective studies showing that antihypertensive drug treatment could be withdrawn without redevelopment of hypertension in some well-controlled hypertensive patients (5-17). Moreover, we observed that remission was maintained for up to 21.7 yr, much longer than previously reported, although antihypertensive drug treatment had to be restarted in the majority of patients. Because of the extended period of remission, previous prospective studies, in which patients were followed for a maximum of 5 yr, were unable to provide precise information on the outcome of remission (5-17). To obtain more information on the long-term outcomes of patients in remission, we reviewed the clinical records of hypertensive patients who began antihypertensive drug treatment and were then carefully followed up for more than 20 yr at a single hypertension clinic. To the authors’ knowledge, this retrospective examination of hypertensive patients in remission makes use of observations gleaned over the longest time period of any
such study yet conducted.

The remissions observed in the present study occurred under circumstances that differed from those reported earlier, because eliciting remission on the basis of pre-determined criteria was not a specific goal of the physicians administering patient care. Instead, remission was noted when drug therapy was withdrawn for other reasons consistent with the patients' needs at the time. Consequently, the specific cause(s) of the remission remains uncertain. Perhaps patients who had spontaneous regression to normotension were included in the R-group; a mild form of essential hypertension has been reported to regress spontaneously (21, 22). The management committee of the Australian trial in mild hypertension reported that BP in patients with mild hypertension decreased from 158/102 to 144/91 mmHg after 3 yr without any intervention (21). Sato et al. also found that 44% of patients with mild hypertension became normotensive after 10 yr (22). We also considered the possibility that disease severity was initially overestimated in at least some patients or that the doses of their medications were too high. However, since the BP's of 17 of the 19 patients who entered remission gradually returned to hypertensive levels, thereby necessitating resumption of antihypertensive drug therapy, this seems unlikely.

The absence of ECG high-voltage deflections and the successful control of BP by a single drug proved to be powerful predictors of which patients would enter remission. These characteristics may reflect milder disease severity or shorter histories of hypertension, or both, at the time patients presented at the clinic. Nevertheless, no difference in pre-treatment BP between the R-group and N-group was observed. Physicians routinely inquired about hypertension when taking histories, but the data were not suitable for analysis because BP was not systematically measured in the general Japanese population in the 1960's.

Previous studies suggest that dietary or nutritional intervention may also increase the likelihood that patients will enter remission as well as slow the rate at which BP returns to hypertensive levels (23, 24). In a randomized trial, Stamler et al. showed that a reduction in obesity could decrease BP in patients with mild-to-moderate hypertension (23). Langford et al. also reported that weight loss and sodium restriction could help to maintain BP in the normal range when withdrawing drug therapy (24). Our observation that patient entry into remission was associated with a significant loss of body weight indirectly confirms the role of diet in determining BP. Moreover, the fact that body weight as well as body mass index returned to their initial levels when medication was restarted (Table 2) supports the idea that body weight reduction can promote remission.

Another finding of this study is the seasonal variation of entry into remission. Although there have been a number of reports on seasonal variations in BP (25–29), which show that both systolic and diastolic BP are lower in warm-hot seasons than in cool-cold seasons in both genders, ours is the first study indicating that remission is significantly more likely to occur in the spring and summer.

In conclusion, remission occurred in a subset of well controlled hypertensive patients and persisted for substantial periods of time. Patients with no high-voltage ECG deflections and those who can be successfully treated with a single antihypertensive agent are favorable candidates for remission. In addition, the best times for withdrawal of antihypertensive medication may be the spring and summer.

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References


