Ann. Ist. Super. Sanità, vol. 29, n. 4 (1993), pp. 693-704

Chronobiologic assessment of antihypertensive therapy

Kohji TAMURA, Isao KOHNO, Ikuo TSURUTA, Hiroshi IJIRI and Takamichi NAKAMURA

Second Department of Medicine, Yamanashi Medical College, Yamanashi, Japan

Summary. - This paper is an example of the clinical application of chronobiologic methods to the diagnosis of the major killers of modern societies, i.e., hypertension. Passing from the description of the methodology to clinical examples, the article provides convincing evidence of the importance of the chronodiagnostic approach to ambulatory blood pressure monitoring not only for a more accurate diagnosis, but also for a more appropriate therapy.

Key words: blood pressure, chronobiology, circadian rhythm, hypertension, monitoring.

Riassunto *(Valutazione cronobiologica della terapia antipertensiva)*. - Questo articolo è un esempio tecnico dell'applicazione dei metodi cronobiologici alla diagnosi di uno dei maggiori killer della moderna società, l'ipertensione. Passando dalla descrizione della metodologia agli esempi clinici l'articolo fornisce la prova della importanza dell'approccio cronodiagnostico al monitoraggio della pressione arteriosa per una più accurata diagnosi e terapia.

Parole chiave: pressione arteriosa, cronobiologia, ritmi circadiani, ipertensione, monitoraggio.

Introduction

The recent development of ambulatory blood pressure monitoring (ABPM) and associated software has enabled us to assess the long-term variability of blood pressure in patients with hypertension [1]. Although ABPM may not be necessary for the diagnosis and management of most patients with hypertension, this technique has proved useful in the performance of clinical trials to assess antihypertensive agent efficacy [1-6]. In order to apply the information obtained by ABPM to clinical practice, several crucial questions have to be answered. How should the pressure data be collected by ABPM and what kind of data analysis provides the best indication of hypertension? What is the reference range of the time-associated variability of ambulatory blood pressure? What are the diagnostic criteria for hypertension based on ABPM? What parameters are associated with an increased cardiovascular risk? What kind of transformation of the ambulatory blood pressure profile by antihypertensive agents is really associated with a reduction of the morbidity and mortality due to hypertension? Unfortunately, there exists no standardized method of assessment and limited epidemiologic data related to ABPM [1]. Therefore, many basic points about this method remain to be clarified before it can be accepted as a routine clinical technique.

This article discusses the following issues: 1) the circadian characteristics of blood pressure in essential hypertension, 2) the circadian characteristics of the pharmacodynamics of antihypertensive agents and 3) the proper selection and timely administrations of antihypertensive agents.

Circadian characteristics of blood pressure in essential hypertension

Data collection and analysis

There is no standardized method for the analysis of time-associated data and many approaches have been proposed for the assessment of hypertension as shown in Table 1.

Both non-parametric and parametric methods have been used. In order to decide which blood pressure parameter is the most useful, it is necessary to make a more detailed evaluation of its clinical significance.

We have used the ambulatory blood pressure monitoring device developed by Nippon Colin (Japan). Blood pressure and heart rate were monitored every 30 min for 48 h under ordinary living conditions (Fig. 1). For the analysis of systolic blood pressure, two different approaches were taken in our studies as illustrated by a representative case (Fig. 1 and Table 1).

Non-parametric estimation. - The absolute magnitude of systolic blood pressure: by regarding the circadian variability of systolic pressure as aperiodic in nature, the standard statistical method of the time-blocked mean was applied. The mean systolic pressure for the 24 h period was 184 mmHg, that the night time span period was 174 mmHg, and that of the daytime period was 189 mmHg. Naturally, these three values, have a different clinical significance. *The relative magnitude of the systolic blood pressure*: in order to quantitate the magnitude of deviations from the age – and sex – matched reference range a pressure time index was derived.

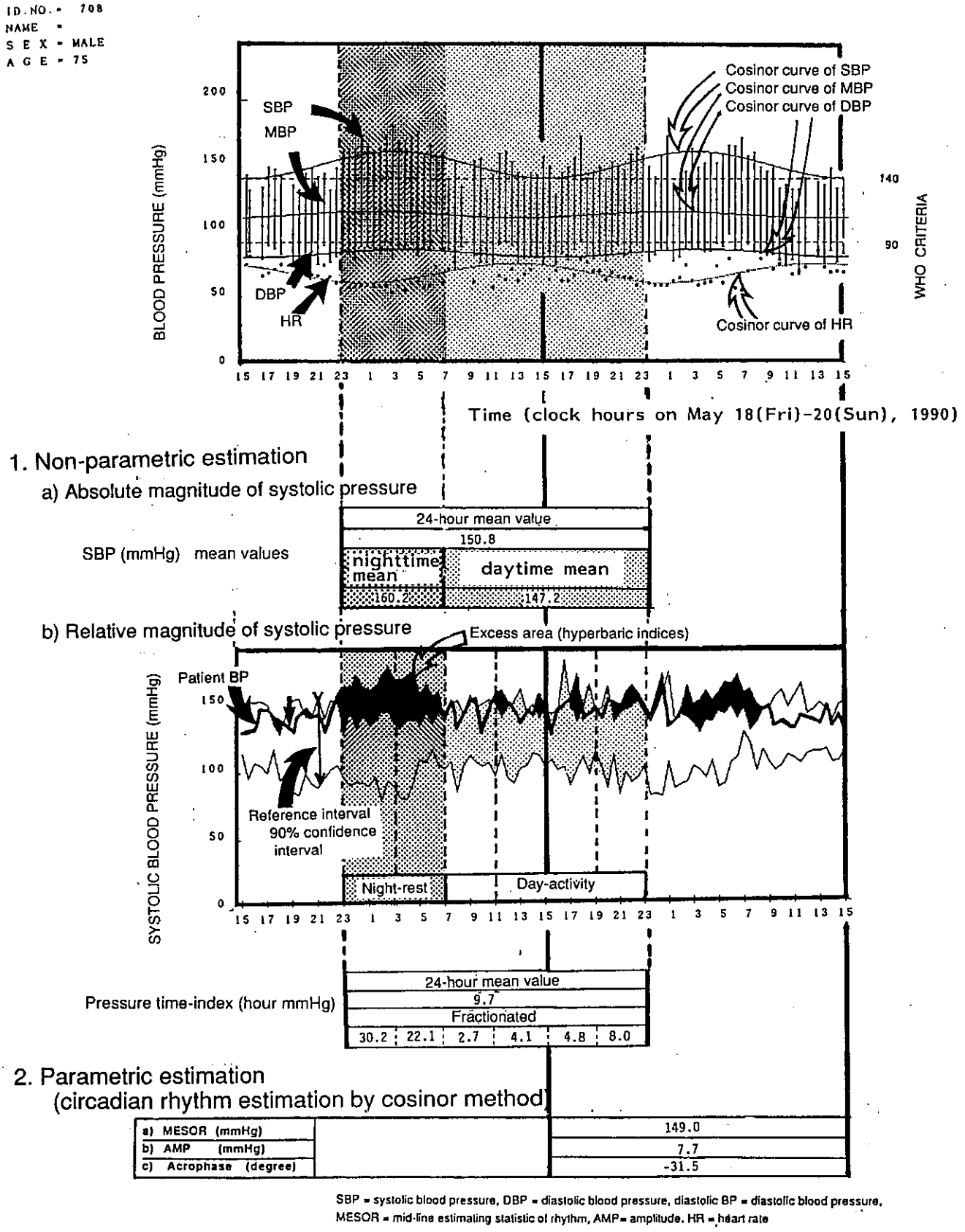


Fig. 1. - Estimation of systolic blood pressure by the non-parametric and parametric approaches. SBP = systolic blood pressure, HR = heart rate, MESOR = mid-line estimating statistic of rhythm, AMP = circadian amplitude.

This reference range was obtained from the ambulatory measurements taken at 15 min intervals over 48 h in 415 healthy normotensive volunteers who were selected non-randomly and openly. The formation of each confidence interval was based on age (5-year increments) and gender. The use of these confidence intervals as a reference for the circadian variation of blood pressure and heart rate has been advocated in our laboratory [1]. The magnitude of the pressure-time index as an hourly mean value integrated throughout the 24 h period was 41 mmHg times hour. This is shown as the black area above the 90% confidence interval. In order to estimate the magnitude of the time-associated blood pressure excess in the various time fractions (time-fractionated pressure time index), the indices for 4 h periods were also computed (Fig. 1).

Parametric estimation (Fig. 1) - In order to assess the periodic nature and circadian rhythm of systolic blood pressure and heart rate variability, the detection of the rhythm and the quantitative estimation of its characteristics must be performed. Several methods have been proposed as procedures for rhythm estimation (Table 1), and the cosinor method is one of them [15, 16]. This method is well documented in the literature and suitable software for this method is open already. There are many reports based on this method in the field of chronobiology [14-16]. However, this approach clearly represents the oversimplification of the complicated time trends of pressure with both short and long periods. Therefore, it should be remembered that this approach is only valid under the certain assumptions. However, various parameters of the circadian rhythm, such as the rhythm-adjusted mean (MESOR), the circadian amplitude and its acrophase, calculated by the cosinor method are useful for detecting alterations of the total circadian rhythm of blood pressure in hypertension. The MESOR was quite similar to the 24 h mean value in our study, since the blood pressure and heart rate were determined throughout a 48 h period at regular intervals. The circadian amplitude was calculated as half of the difference between the highest and lowest points in the circadian rhythm defined by the cosinor model. This value provides an overall estimate of the amplitude of circadian change in the parameters outlined above. Lastly, the acrophase was derived as the time of the highest point in the circadian rhythm obtained from cosinor analysis. This was the estimated time span required to reach the crest of the circadian rhythm, and was therefore expressed as a time lag from midnight until the peak blood pressure.

Table 1. Assessments of hypertension (diagnosis) and the time course of antihypertensive therapeutic efficacy reported in the literature

Assessment of hypertension (diagnosis)

1) *Non-parametric approach* [1]

- *A)* Absolute magnitude of blood pressure
  - *a)* Mean values whole-day mean value (24 h mean) [7] staircase of time-block values (i.e., q. 2-4 h) night time resting and/or day time activity spans [8, 9] 24 h SD or CV
  - *b)* Computation of area under the pressure curve [9, 10] (threshold value)
- *B)* Estimation of spread of blood pressure variability histogram of blood pressure trough-to-peak ratio of blood pressure spectral blood pressure powers within 0.003-0.35 Hz
- *C)* Outlying from reference value [2, 11] (hyperbaric and hypobaric indices) averaged, hourly time-fractionated

2) *Parametric approach*

- *A)* Pattern of blood pressure change [12, 13]
- *B)* Fourier analysis of blood pressure harmonics by the cosinor method [14-16]

Assessment of time course of antihypertensive therapeutic efficacy [2] (To estimate the differences between pre-treatment and post-treatment values or to estimate the placebo effect)

1) *Non-parametric approach*

- *A)* Level of blood pressure differences
- *B)* Blood pressure spread variability differences
- *C)* Hyperbaric and hypobaric index difference

2) *Parametric approach*

- *A)* Pattern difference
- *B)* Cosinor parameter difference

Morning increment of blood pressure

The morning increment of blood pressure has been recognized as a characteristic variation of blood pressure in essential hypertension.

Recent epidemiologic studies [15, 16] have shown that major cardiovascular events such as acute myocardial infarction, cerebrovascular accidents, and sudden death tend to occur in the morning. Therefore, it has been proposed that a morning rise of blood pressure and heart rate may act as a trigger mechanism for such events [17].

The morning pressure variation in reference individuals with "normotensive" blood pressure has been assessed [18]. In young individuals, blood pressure is predominantely higher in males than in females throughout the 24 h period. Both genders show an abrupt increase of blood pressure after waking up. In the elderly, the amplitude of this morning increment is less pronounced as compared with that in the young.

In patients with essential hypertension, the morning rise of pressure in the night-dipper type [19] was more prominent than that seen in the reference individuals (Fig. 2).

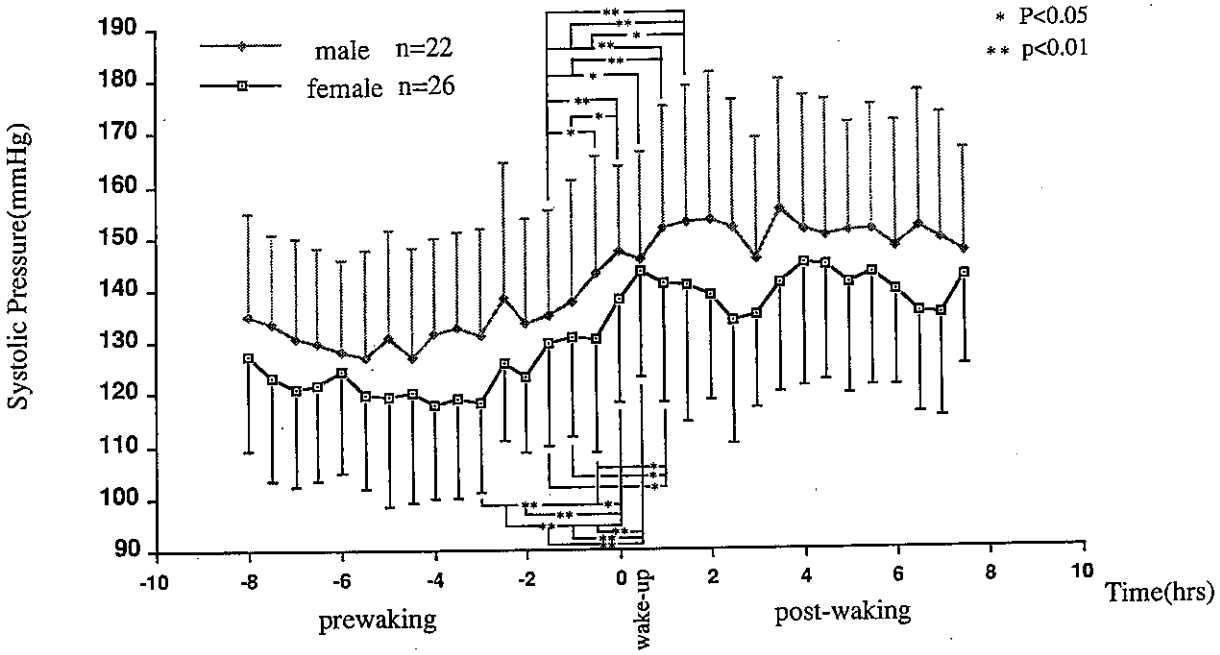


Fig. 2. - Morning increment of systolic blood pressure in hypertensives aged from 50 to 59 years. The zero reference time was taken as the waking time based on diary records.

This increment of blood pressure in the morning should be recognized as part of the characteristic circadian variability of pressure in hypertension.

Night "dipper" vs "non-dipper" patterns of blood pressure

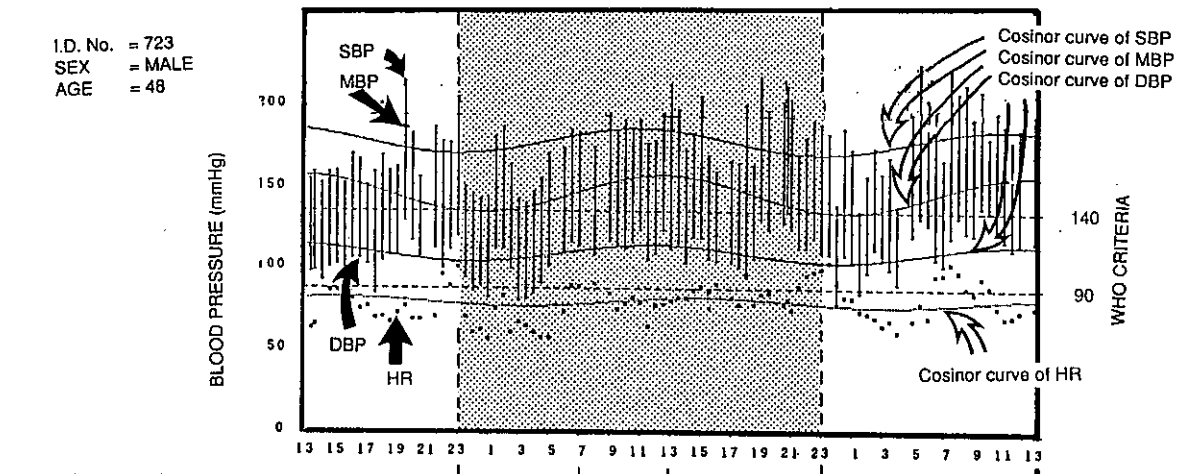
Other clinical implications obtained from ABPM studies are related to blood pressure variation during the night time. Blood pressure during the daytime is normally higher than during the night span (night "dipper" pattern). However, it has been recognized that the blood pressure during the night may not be lower than during the day (night "nondipper" pattern) in patients with autonomic failure, the elderly, and patients with renal parenchymal hypertension [19]. The clinical significance of this night "non-dipper" pattern is not yet fully known. However, it has been suggested that these individuals may have a higher risk of cardiovascular complications [19]. Therefore, it is necessary to determine the prognostic and therapeutic implications of this finding.

A representative night "non-dipper" individual is shown in Fig. 3. The systolic blood pressure was higher during the night time (160 mmHg) than during the daytime (147 mmHg). In order to assess the approximate time lag from midnight until the peak pressure, the circadian acrophase was calculated by the cosinor method (Fig. 4). In young hypertensives, the circadian acrophase was similar to that in the young reference subjects. However, in elderly hypertensives the circadian acrophase was distributed more widely than that of elderly reference subjects. Moreover, in the reference group the circadian acrophase was distributed more widely during the night in the elderly subjects when compared with the young reference individuals [20].

Circadian characteristics of antihypertensive agents

In order to select the proper agents to match the variations of blood pressure in an individual patient, the circadian characteristics of the antihypertensive agents also need to be clarified. Therefore, the following question should be answered: "Do all antihypertensive agents have the same effect on the circadian variation of blood pressure in essential hypertension?". The data on this subject are still incomplete, even though many studies have been performed [2, 4, 21-23].

Several attempts have been made to assess the time course effects of antihypertensive therapy (Table 1), including both non-parametric and parametric approaches. Based on our methods for evaluating the efficacy of these agents, the following results were obtained. An open and non-randomized study was designed to evaluate the circadian characteristics of various antihypertensive agents. Each class of antihypertensive agents had its own characteristic effects on the circadian variability of blood pressure (Figs 5 and 6) [2, 24]. Eight different antihypertensive agents were given to eight groups of patients with essential hypertension selected from among those attending our

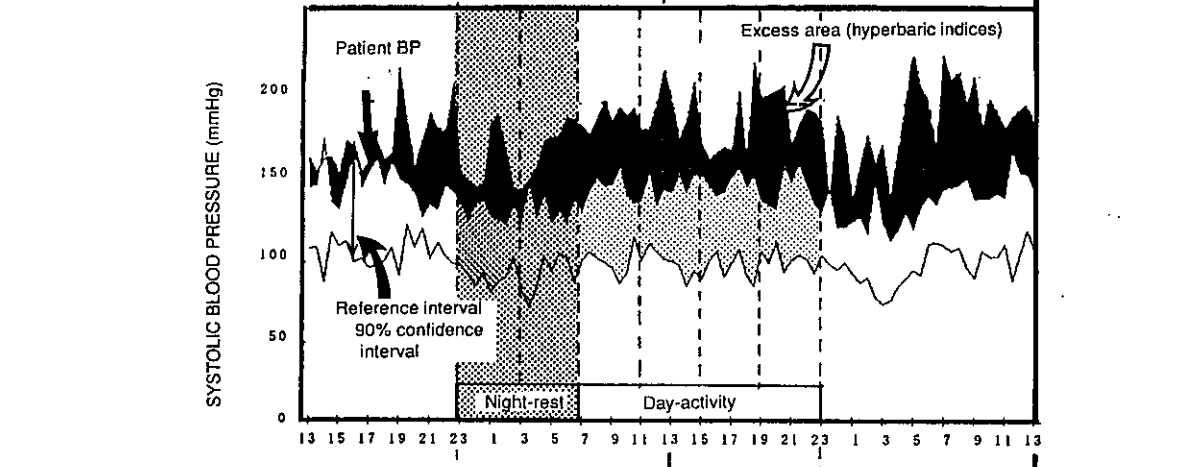


1. Non-parametric estimation

a) Absolute magnitude of systolic pressure

SBP (mmHg) mean values	24-hour mean value	
	184.1	
	nighttime mean	daytime mean
	174.4	189.5

b) Relative magnitude of systolic pressure



Pressure time-index (hour mmHg)	24-hour mean value					
	41.6					
	Fractionated					
	0.0	3.5	9.1	24.6	6.4	0.4

2. Parametric estimation
(circadian rhythm estimation by the cosinor method)

a) MESOR (mmHg)	184.2
b) AMP (mmHg)	7.9
c) Acrophase (degree)	-164.7

. SBP = systolic blood pressure, DBP = diastolic blood pressure, diastolic BP = diastolic blood pressure,

Fig. 3. - A representative case of night "non-dipper" type hypertension in systolic blood pressure. The black areas indicate the area of the pressure-time index that exceeds the reference range.

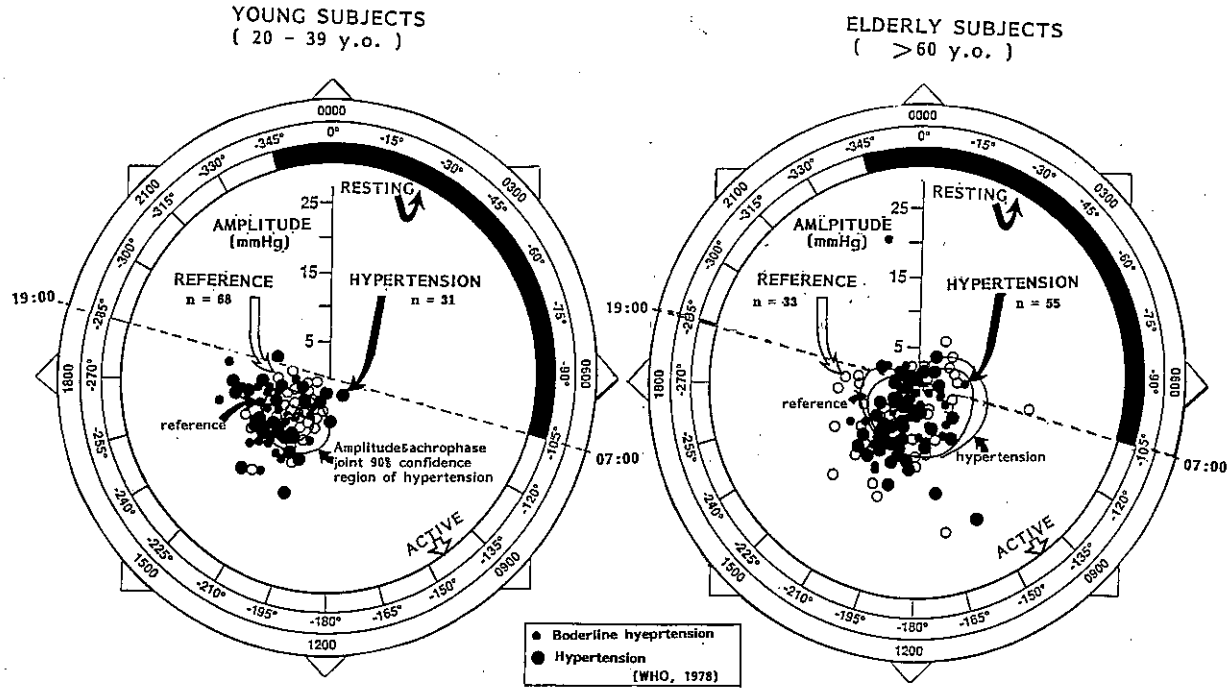


Fig. 4. - A polargraphic representation of the distribution of the circadian amplitude and acrophase joint in a 24-h period. Reference individuals and hypertensive subjects (with borderline hypertension and hypertension according to the WHO criteria) are compared. The left panel shows the data for the young age group and the right panel shows data for the elderly group.

outpatient clinic. All the patients had mild to moderate hypertension, based on the casual blood pressure and the WHO hypertension criteria. All agents were given empirically according to the recommended dosages and times of administration. Nicardipine hydrochloride-retard (40 mg) was given bis in die for one week; captopril (12.5 - 25 mg, ter in die) was given for three weeks; captopril-retard (18.75 - 37.5 mg, b.i.d.) was given for 6 weeks; metoprolol (40 mg, t.i.d.) was given for 4 weeks; nilvaldipine (calcium antagonist a newly developed by Fujisawa Pharmaceutical Co., Japan) was given for 2 weeks; diltiazem (30 - 60 mg, t.i.d.) was given for 4 weeks; bunazosin (1 mg, t.i.d.) was given for 4 weeks; and nipradilol (3 - 6 mg, b.i.d., selective beta-blocker newly developed by Kowa Pharmaceutical Co., Japan) was given for 4 weeks.

Timely and treatment of hypertension

Since it has been clarified that both the blood pressure of hypertensives and the efficacy of antihypertensive agents have circadian characteristics, these two should be matched to improve the control of hypertension. Thus, to perform individualized therapy of hypertension, antihypertensive agents should be prescribed according to the specific characteristics of the 24 h variation of blood pressure and heart rate. Administration timed according to the cycle of blood pressure is desirable not only to enhance the pharmacologic effect but also to reduce undesirable side effects. This concept has been called chronotherapy [25]. Furthermore, chronotherapy may reduce the total daily dosage of drugs and so provide cost and quality of life benefits. All 8 agents were significantly effective in lowering the 24 h mean systolic and diastolic pressures. The efficacy in reducing blood pressure and heart rate during the daytime period was similar that for the 24 h mean values. However, the effects on the mean nocturnal heart rate differed, with nicardipine significantly increasing the heart rate during this period when compared with the other agents (Fig. 5). The normalizing effects on blood pressure and heart rate as a pressure-time index were also assessed (Fig. 6.). The systolic blood pressure index was significantly decreased by all the agents, but neither captopril nor its retard form decreased the diastolic pressure index. Nicardipine retard alone significantly increased the heart rate index.

Assessment of the circadian rhythm showed that the circadian amplitude was minimized after treatment with these agents. The circadian acrophase showed no significant change.

The clinical implications of this study lie in the clear differences of the effects of these agents on the blood pressure. Such differences should be taken into consideration when selecting antihypertensive agents for long-term therapy, and antihypertensive

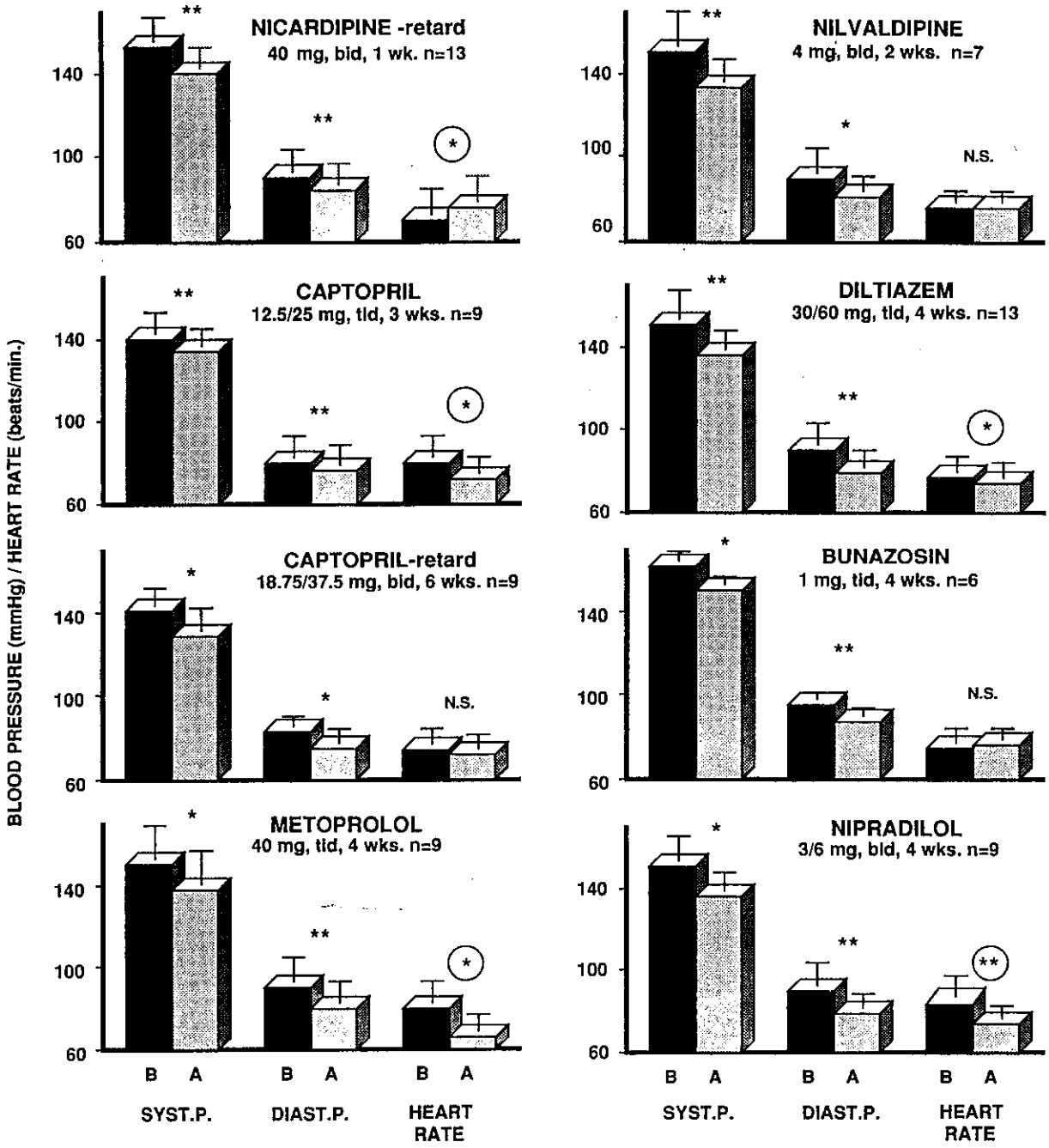


Fig. 5. - The effects of various antihypertensive agents on the mean blood pressure and heart rate during the night time in patients with essential hypertension.
B = before treatment, A = after treatment, DIAST. P. = diastolic blood pressure, $^{*}p < 0.05$, $^{**}p < 0.01$, N.S. = not significant.

therapy should be individualized by this type of approach [2].

In the case shown in Fig. 7, the systolic pressure-time index (indicated as the black area) was 14 h times mmHg. Namely, the blood pressure was mostly excessive throughout the 24 h period when compared with the reference range. Furthermore, the fractionated pressure-time index (4 h intervals) range from 7 to 28 4 h times mmHg. This patient was especially hypertensive from 08:00 to 12:00 and from 20:00 to 04:00. Nicardipine hydrochloride (20 mg t.i.d.) was administered for two weeks. As shown in the lower panel, the pressure time index was minimized from 14 to 2 h times mmHg. The fractionated pressure time index was also minimized in every time block.

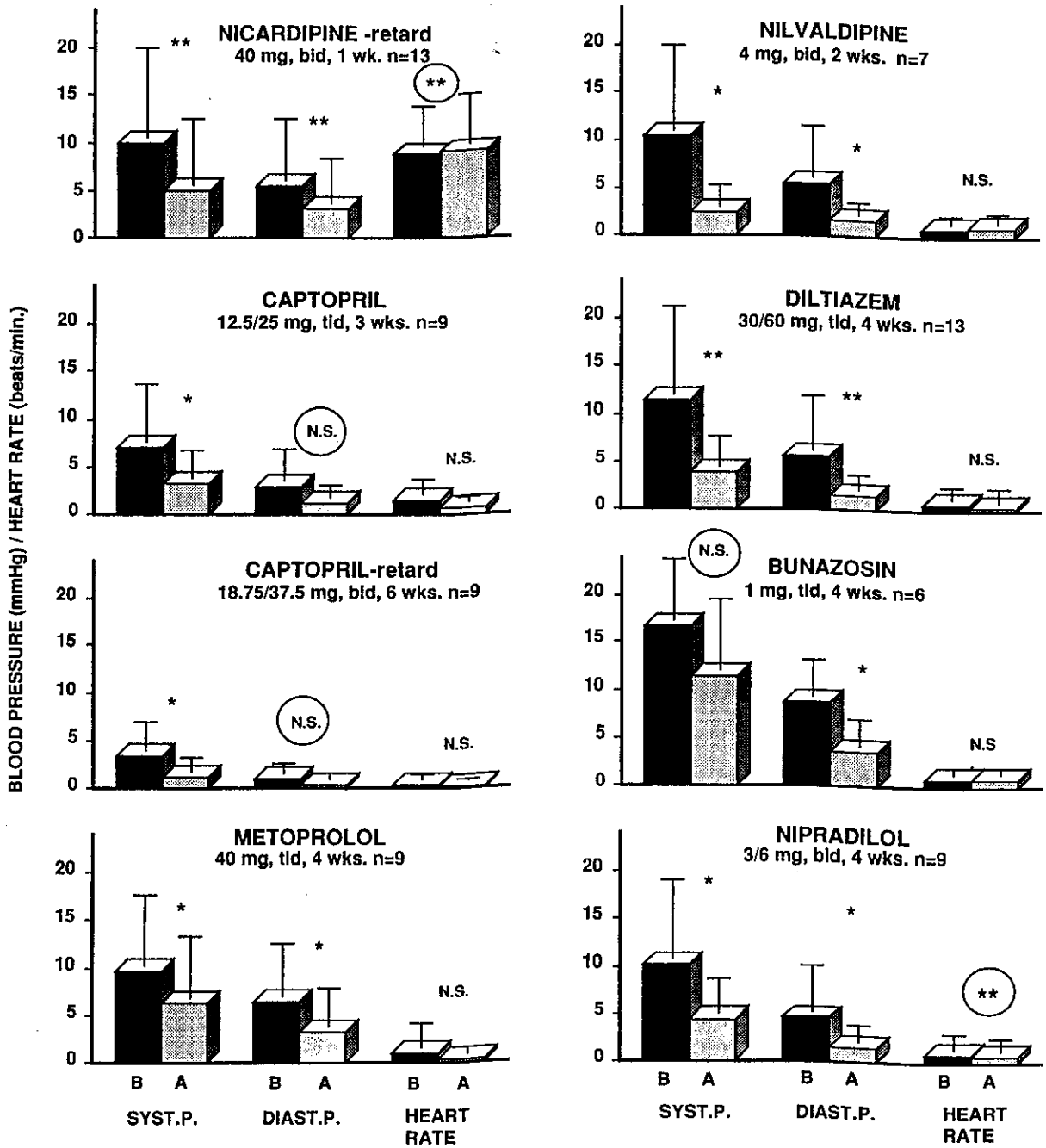


Fig. 6. - The effects of various antihypertensive agents on the pressure-time index in patients with essential hypertension.

B = before treatment, A = after treatment, DIAST. P. = diastolic blood pressure, $^{*}p < 0.05$, $^{**}p < 0.01$, N.S. = not significant.

Furthermore, the difference of the time-fractionated pressure-time index of the systolic blood pressure was calculated. Nicardipine lowered the systolic pressure at the time spans that showed higher values before treatment. Thus, with this approach the appropriate timing of dosing and the efficacy of a specific antihypertensive agent could be assessed.

Renal parenchymal hypertension is of the night "non-dipper" type [26]. In this patient with chronic glomerulonephritis, the excess of blood pressure compared with the reference range was mainly recognized during the night time. The hourly magnitudes of the excess was 15 mmHg times h for systolic blood pressure and 9 mmHg times h for diastolic pressure. Paying special attention to the

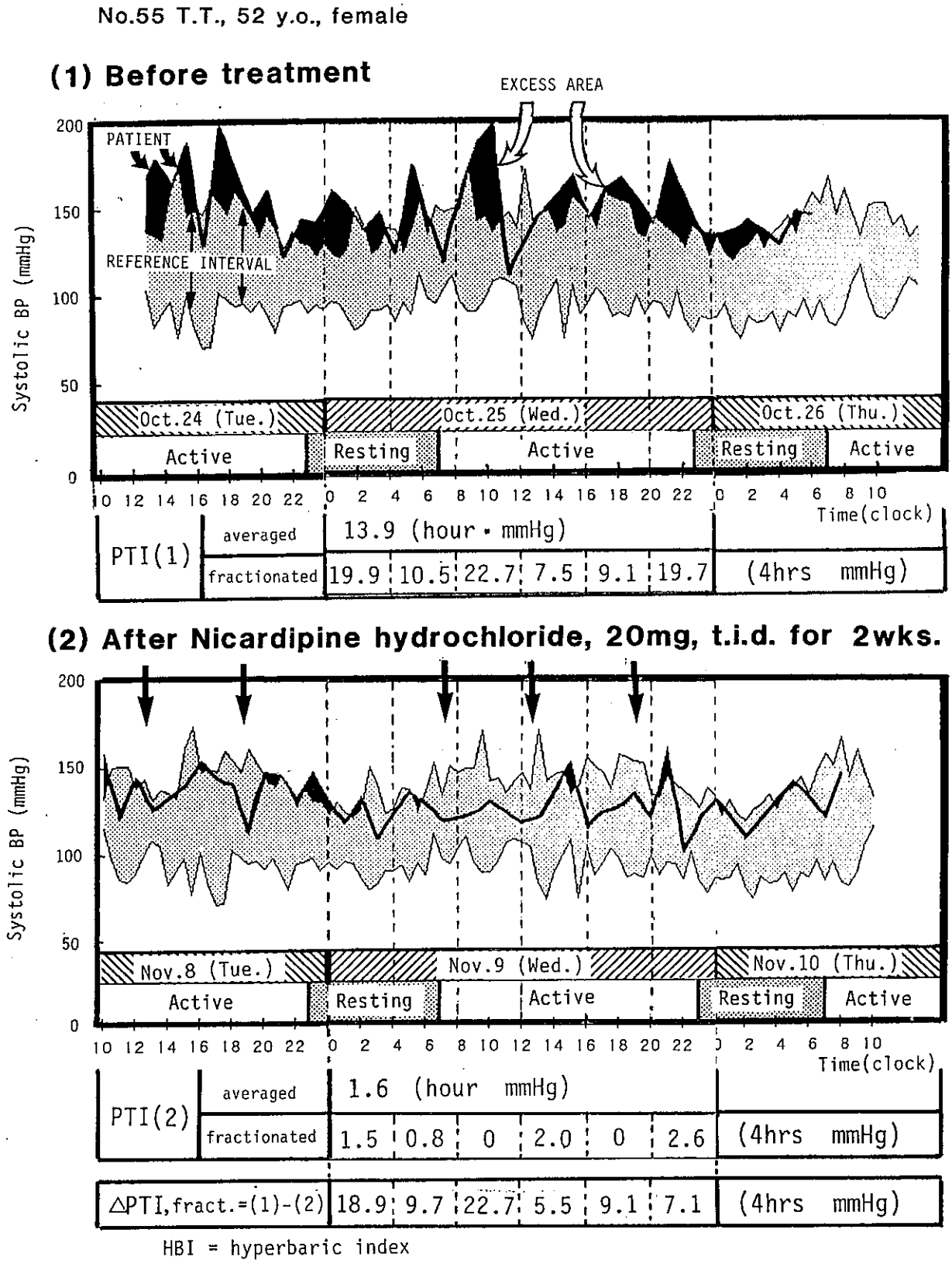


Fig. 7. - Evaluation of timed medication in the treatment of hypertension.
PTI = pressure time index.

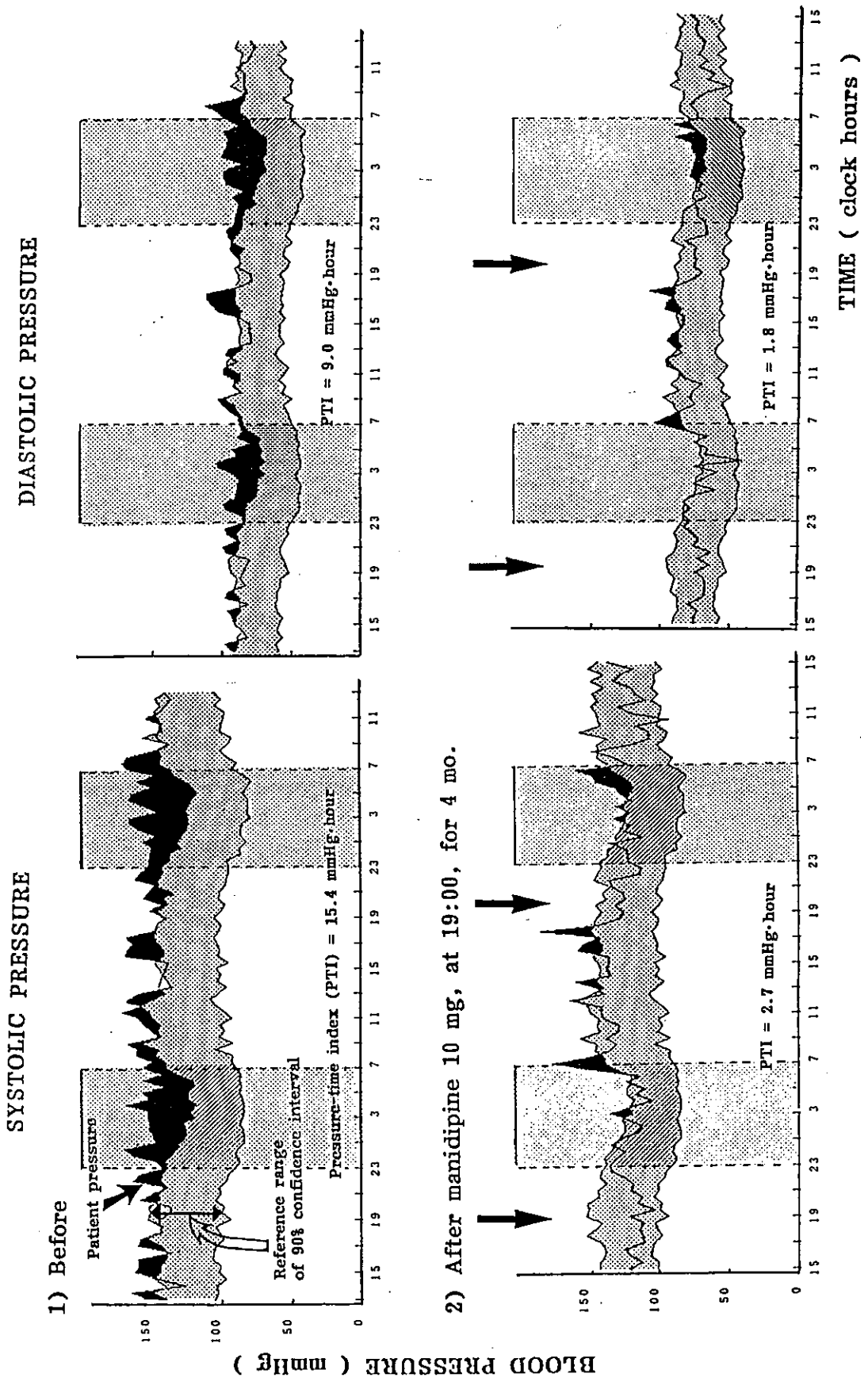


Fig. 8. Efficacy of timed medication for night "non-dipper" type hypertension in a patient with chronic glomerulonephritis.

non-dipper nature of the hypertension, manidipine (a calcium antagonist newly developed by Sankyo Pharmaceutical Co., Japan) was administered once daily at 19:00 for 4 months. This agent is a long-acting calcium antagonist. Both the systolic and the diastolic pressure were normalized by this approach, especialiy during the nighttime. Therefore, antihypertensive therapy was successful in controlling this characteristic disorder of the circadian blood pressure profile.

Conclusions

In hypertension, the blood pressure still shows a circadian rhythm. Antihypertensive agents also have circadian characteristics in regard to their efficacy. Therefore, timely therapy of hypertension should be performed by matching these two circadian variations.

Submitted on invitation.
Accepted on 18 February 1993.

REFERENCES

1. *National high blood pressure education program working group report on blood pressure monitoring.* U.S. Department of Health and Human Services Publics Health Service, National Institutes of Health, U.S.A., 1990.

2. TAMURA, K. 1991. Chronobiologic evaluation of drug efficacy in hypertension. *Chronobiol. Int.* **8**: 511-525.

3. CHEUNG, D.G., GASSTER, J.L. & WEBER, M.A. 1989. Assessing duration of antihypertensive effects with whole-day blood pressure monitoring. *Arch. Int. Med.* **149**: 2021-2025.

4. CONWAY, J. & COATS, A. 1989. Value of ambulatory blood pressure monitoring in clinical pharmacology. *J. Hypertens.* **7** (Suppl. 3): S29-S32.

5. O'BRIEN, E., COX, J.P. & O'MALLEY, K. 1989. Ambulatory blood pressure measurement in the evaluation of blood pressure lowering drugs. *J. Hypertens.* 7: 243-247.

6. PICKERING, T.G., HARSHIFIELD, G.A., DEVEREUX, R.B. & LARAGH, J.H. 1985. What is the role of ambulatory blood pressure monitoring in the management of hypertensive patients? *Hypertension* **7**: 171-177.

7. MILLAR-CRAIG, M.W., BISHOP, C.N. & RAFTERY, E.B. 1978. Circadian variation of blood-pressure. *Lancet* **1**: 795-797.

8. CLARK, L.A., DENBY, L., PREGIBON, D. *et al.* 1987. A quantitative analysis of the effects of activity and time of day on the diurnal variations of blood pressure. *J. Chronic Dis.* **40**: 671-681.

9. WHITE, W.B., DEY, H.M. & SCHULMAN, P. 1989. Assessment of daily blood pressure load as a determinant of cardiac function in patients with mild to moderate hypertension. *Am. Heart J.* **118**: 782-795.

10. ZACHARIAH, P.K., SHEPS, S.G., ILSTRUP, D.M. *et al.* 1988. Blood pressure load-A better determinant of hypertension. *Mayo Clin. Proc.* **63**: 1085-1091.

11. CUGINI, P., LEONE, L., DI PALMA, L. *et al.* 1990. Construction of reference standards for blood pressure 24-hour patterns. *Statistician* **39**: 285-299.

12. MANCIA, G. 1990. Blood pressure variability: mechanisms and clinical significance. *J. Cardiovasc. Pharmacol.* **16** (Suppl. 6): S1-S6.

13. PALATINI, P., MARTINA, S., PENZO, M., MORMINO, P., BUSINARO, R., DEL TORRE, M., ANACLERIO, M., GUZZARDI, G. & PESSINA, A.C. 1990. How can we establish normal whole-day blood pressure levels? *J. Ambulatory Monitoring* **3**: 129-137.

14. HALBERG, F., DAYERS, J.I.S., CORNELISSEN, G. & WEBER, M.A. 1984. Cardiovascular reference data base for recognizing circadian mesor and amplitude hypertension in apparently healthy men. *Chronobiologia* **11**: 175-298.

15. BINGHAM, C., ARBOGAST, B. CORNELISSEN, G., LEE, J.K. & HALBERG, F. 1982. Inferential statistical methods for estimating and comparing cosinor parameters. *Chronobiologia* **9**: 397.

16. MONK, T.H. & FORT, A. 1983. "Cosina" a cosine curve fitting program suitable for small computers. *Int. J. Chronobiol.* **8**: 193-224.

17. MULLER, J.E., STONE, P.H., TURI, Z.G., RUTHERFORD, J.D. *et al.* 1985. Circadian variation in the frequency of onset of acute myocardial infarction. *N. Engl. J. Med.* **313**: 1315-1322.

18. SMOLENSKY, M.H. & D'ALONZO, G.E. 1988. Biologic rhythms and medicine. *Am. J. Med.* **85** (Suppl. 1B): 34-46.

19. HONMA, H., KOHNO, I., TSURUTA, I., KOMAYA, T., NAKAMURA, T. & TAMURA, K. 1992. *Morning rise of blood pressure and heart rate as a possible trigger mechamism of cardiovascular events.* The American Society of Hypertension (Seventh Scientific Meeting) May. 1992. New York.

20. TSURUTA, I., ISHII, H., MUKAIYAMA, S., KOMAYA, T. & TAMURA, K. 1991. Circadian variabilities for ambulatory blood pressure in 437 "normals". *Am J. Hypertens.* **4** (Part 2) 100A.

21. O'BRIEN, E., SHERIDAN, J. & O'MALLEY, K. 1988. Dippers and non-Dippers. *Lancet.* **1**: 397.

22. CUGINI, P., KAWASAKI, T., LEONE, G., DIPALMA, L., LETIZIA, C. & SCAVO, D. 1987. Discrimination and spectral resolution of ultradian and circadian periodicities

for 24-hour blood pressure patterns of sodium manipulation in normotensive humans. *Jpn Circ. J.* **51**: 1296-1304.

23. LACOURCIERE, Y. 1988. Analysis of well-being and 24 h blood pressure recording in a comparative study between indapamide and captopril. *Am. J. Med.* **84**: 47.

24. NEUTEL, J.M., SCHNAPER, H., CHEUNG, D.G., GRAETTINGER, W.G. & WEBER, M.A. 1990. Antihypertensive effects of β-blockers administered once daily: 24 h measurements. *Am. Heart. J.* **120**: 166-171.

25. RAFTERY, E.B., MANN, S., BALASUBRAMANIAN, V. *et al.* 1982. Once-daily pindolol in hypertension: an ambulatory assessment. *Am. Heart. J.* **104**: 417.

26. SMITH, V.E., TAMRES, L.K., MULDOON, M.F., WILLIAMS, D.M., DING, Y., MANUCK, S.B. & JACOB, R.G. 1991. Neither awake nor sleep blood pressures better predict target-organ effect. *J. Cardiovascular Phamacol.* **17** (Suppl. 2): S125-S128.

27. HALBERG, F., CARANDENTE, F., CORNELISSEN, G. & KATINAS, G.S. 1977. Glossary of chronobiology. *Chronobiologia* **4** (Suppl. 1): 189.

28. PORTALUPPI, F., MONTANARI, L., MASSARI, M., CHIARA, V.D. & CAPANNA, M. 1991. Loss of nocturnal decline of blood pressure in hypertension due to chronic renal failure. *Am. J. Hypertens.* **4**: 20-26.