Non-Invansive Automatic 24-H Monitoring of Blood Pressure In Clinical Physiology And Internal Medicine

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KAN BASINCININ KLİNİK FİZYOLOJİ VE İÇ HASTALIKLARINDA 24 SAATLİK NON-İNVASİV OTOMATİK KONTROLÜ

ÖZET

Kan basıncının (Tansiyon) 24 saat içinde gösterdiği günlük değişim (varyasyon) değerleri, onun kro no biyolojik ölçümünün (monitoring) bir klinik zorunluluk olduğunu ortaya koymaktadır.

Bu araştırmada, kan basıncının (BP) 24 saatlik ölçüm miktarları kronobiyolojik yönden değerlendirilmiştir.

Sağlıklı kimselerdeki bazı sonuçlar, klasik fizyolojinin 24 saatlik bulguları ile tutarlılık gösterirken, bazıları da kan, basıncının circadian bir ritim gösterdiği ve bu ritmin sentral sinir sisteminin bir yerinde bir yönetim loküsü bulunduğuna işaret etmektedir. Bu bakımdan, teorik olarak, hipertansiyon özel formlarının (ters ya da desinkronize) tanıda göz önüne alınması gerekmektedir.

Bir kısım antihipertansiv tedaviler, tansiyonda bir desinkronizasyon yaptığı (ritim bozduğu) için, klinik farmakoloji, 24 saatlik kan basıncına göre düzenlenerek tedavi geliştirilebilir. Böylece kan basıncında meydana gelebilecek ritim bozuklukları, ilaç dozlarının kronobiyolojik olarak düzenlenmesi ile ortadan kaldırılabilir.

Ayrıca tansiyon vital bir parametre olarak kaoul edilince, klinik prognoz da geliştirilebilir. Tansiyonun genel dağılım tablosundaki değişikliklerden, mortalitenin cerebral apopleksi ya da intoksikasyona bağlı olduğu da tahmin edilebilir.

I. INTRODUCTION

The 24-h monitoring of blood pressure (BP) is going to disclose further fashionating aspects of medicine. Really, the impact of this methodology with healthy and sick man is going to open new frontiers involving both the basic and clinical problematics of medical science.

The content of this report would be an illustrative example of the medical optimization which can be reached by adopting the temporal approach to BP. The presentation gives emphasis to the contribution of our research group clarifying that new goals can be obtained by analizing the 24-h BP values as a numerical distribution (modal domain) as well as a chronologic sequence (temporal domain). Therefore, conventional statistics and chronobiologic methods are not opposed but highly integrated.

Data presented herein are the result of a non-invasive BP recording. Several techniques have been used, i.e., 1. the tensopsy by medical and paramedical staff; 2. the automatic recording by quasi-

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portable devices manufactured by Nippon Colin (Komaki, Japan, model BP 203 X), and Invivo Research Laboratories (Tulsa, Oklahoma, USA, model Omega 1000). A 24/48-h test of BP was used with measurements at 15-60 min interval.

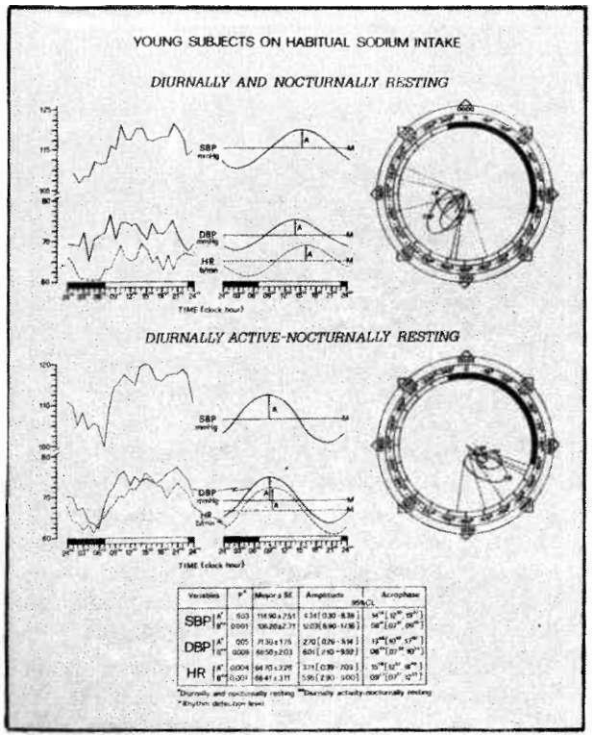
H. 24-H MONITORING AND CLINICAL PHYSIOLOGY

A large part of our knowledge in traditional physiology of human cardiovascular apparatus has been derived by studies exploring the effects of motor-rest schedule on hemodynamic parameters.

The 24-h BP patterns have been, thus, investigated in clinically healthy subjects changing their scheme of motor-rest activity.

Figure 1 displays the BP circadian chronograms concerning young subjects studied in a diurnal and nocturnal rest as well as in a routine of diurnal activity and nocturnal resting.

Profiles denote that subjects active by day and recumbent by night are characterized by peculiar parameters in the BP circadian rhythm (CR). The comparison with the recumbent posture reveals a decrease in mesor, an increase in amplitude, an advance in acrophase.



Figurc-1. Effects of motor-rest schedule on the 24-h patterns of systolic (SBP) and diastolic (DBF) blood pressure and heart rate (HR) in clinically healthy young subjects.

The present results indicate that the 24-h BP patterns in diurnally active and nocturnally recumbent subjects are characterized by a readjustment involving all the rhythmometric parameters. Such a phenomenology leads to postulate that the adaptability of BP to motor activity implies the involvement of biological clock(s).

Figure 2 illustrates the effects of the change in motor-rest activity in clinically healthy orderly subjects.

The diurnal activity in old people is associated with a decrease in mesor and amplitude and a delay in acrophase for the BP CR.

The pressor adaptability to standing posture is, thus, peculiar in aged subjects suggesting a less capacity of pacemaker (s) to give variability and tone to the BP CR. This is a further sign of clinospectometry in biological oscillating functions typical of senescence.

Experimental evidences are convincing that central nervous structures play a deterministic role in chronoorganizing the circadian fluctuation of BP.

The BP CR has been, thus, investigated in a group of patients hospitalized in the emergency

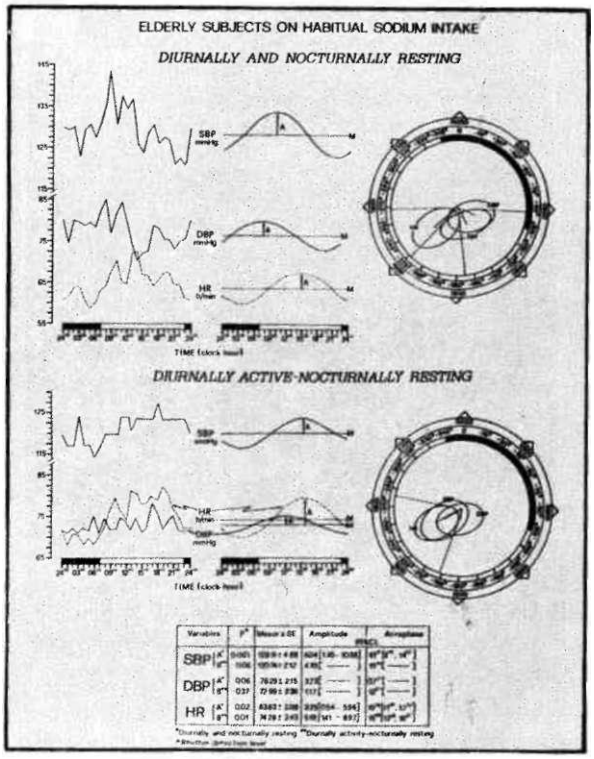


Figure-2. Effects of motor-rest schedule on the 24-h patterns of systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) in clinically healthy elderly subjects.

department for a comatous state (stage II-IH) due to cerebral apoplexia or voluptuary overdose of sedatives.

Figure 3 shows the BP circadian curves recorded.

Cosinor analysis was able to reject the null hypothesis, amplitude = 0, at a significant level of probability less than 5% in few patients (17%). The occurrence of the BP CR has been observed only in patients in coma for more than four days.

Such findings reinforce the importance of the central nervous areas linked with the alertness state as structures containing the biological clock(s) for BP. It is also stressed the Halberg's hypothesis (1) that weak oseiUator(s) may enter in the chronobiologic control of cardiovascular functions.

Physically, the pressure in arterial circulation is determined by cardiac output and peripheral vascular resistance.

The role of heart rate (HR) in determining the BP CR has been, thus, investigated in subjects wholly dependent on a cardiac pacemaker with a fixed frequency.

Figure 4 displays the BP circadian chronograms of this study.

The occurrence of a CR for BP is clear.

The finding suggests that the presence of the HR CR is not fundamental for the BP cyclicity. On this ground, one can hypothesize that the cyclic variability of BP may be realized via periodic changes in peripheral vascular resistance.

The most important controller of vascular contractility is the sympathetic nervous system.

Its importance as a donor of rhythm to the 24-h BP patterns has been, thus, investigated in hypertensive patients under treatment with posologically fixed doses of propranolol (40 mg, orally, every 6 hours, at 03.00; 09.00; 15.00; 21.00).

Figure 5 shows the cosinor-derived polar plot pertinent to this study.

With the posology and the beta-blocking agent adopted, the test of sinusoidality was unable to find a statistically predictable cyclicity with a period roughing from 12 to 24 hours in the 24-h BP patterns. The finding leads to suggest that the sympathetic nervous system is involved in the rhythmic control of BP, via its beta-adrenoceptors.

Several biochemical factors are active on vascular tone, and effective on circulatory volume.

Among these agents there are both renin and aldosterone.

Their potential role as determinants of BP CR is, however, unknown.

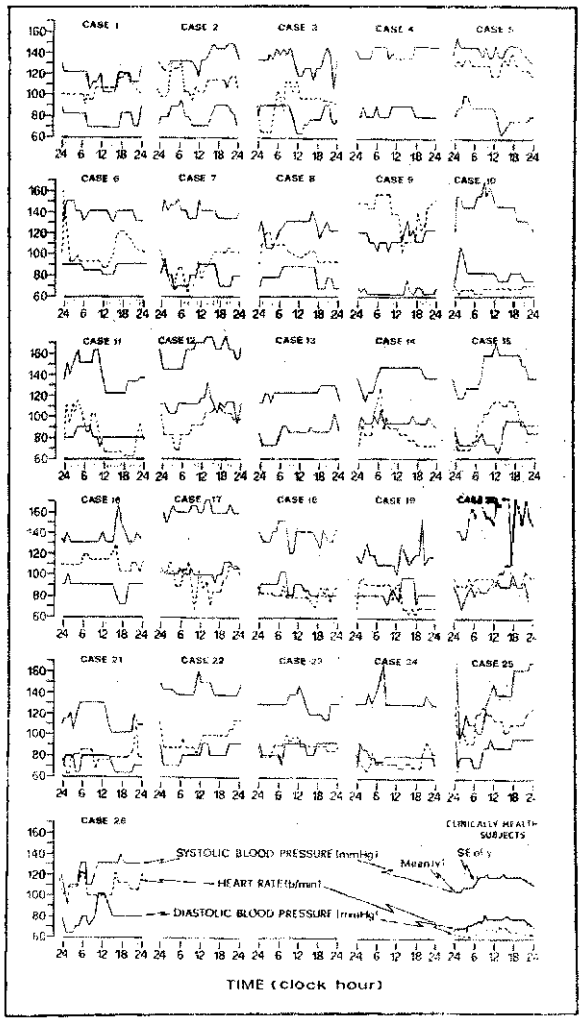


Figure-3. 24-h patterns of blood pressure and heart rate in a group of patients in coma (stage II or III) due to cerebral hemorrhagia or acute intoxication by sedatives or domestic gaseous mixture.

Figure 6 displays the results of a study devoted to investigate the relationship of renin and aldosterone with the 24-h BP patterns.

Best fitting cosine curves and 95% confidence ellipses clarify that there is a consistent latency of time between the acrophases pertinent to the circadian fluctuation of biochemical and hemodynamic variables.

Because of this asynchronism, one could presume that renin and aldosterone are not the immediate causes for the circadian crest of BP.

To confirm this hypothesis, the 24-h patterns of renin, aldosterone and BP have been investigated in hypertensive patients under treatment with Captopril, an angiotensin converting enzyme inhibitor, which is responsible for a blockade of the renin and aldosterone-actions.

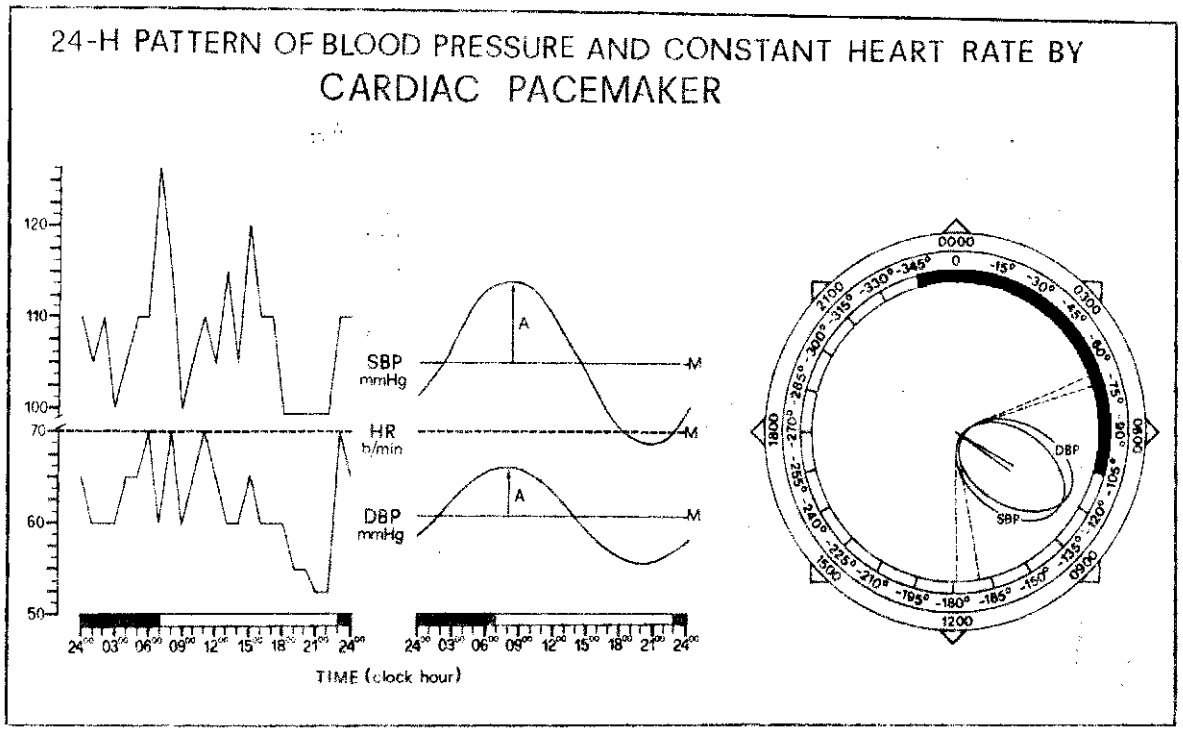


Figure-4. Occurrence of a circadian rhythm for systolic (SEP) and diastolic (DBP) blood pressure in a condition of temporally amodulated heart rate due to the cardiac dependence on a pacemaker with a fixed frequency.

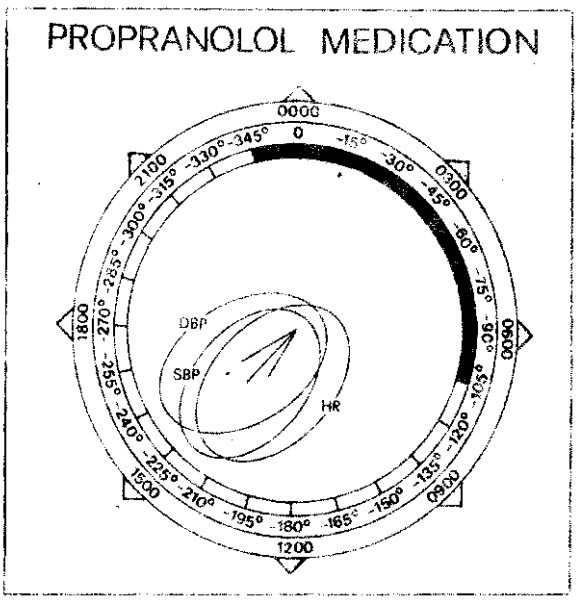


Figure-5. Polar plot of cosinor-derived rhythmometry on the 24-h patterns of systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) in mesor-hypentensives treateed with propranolol in a homeostatic pasology of 40 mg, per as, every 6 hours starting at 03.00.

Figure 7 illustrates the nyehtohemeral curves re-ordered in this research.

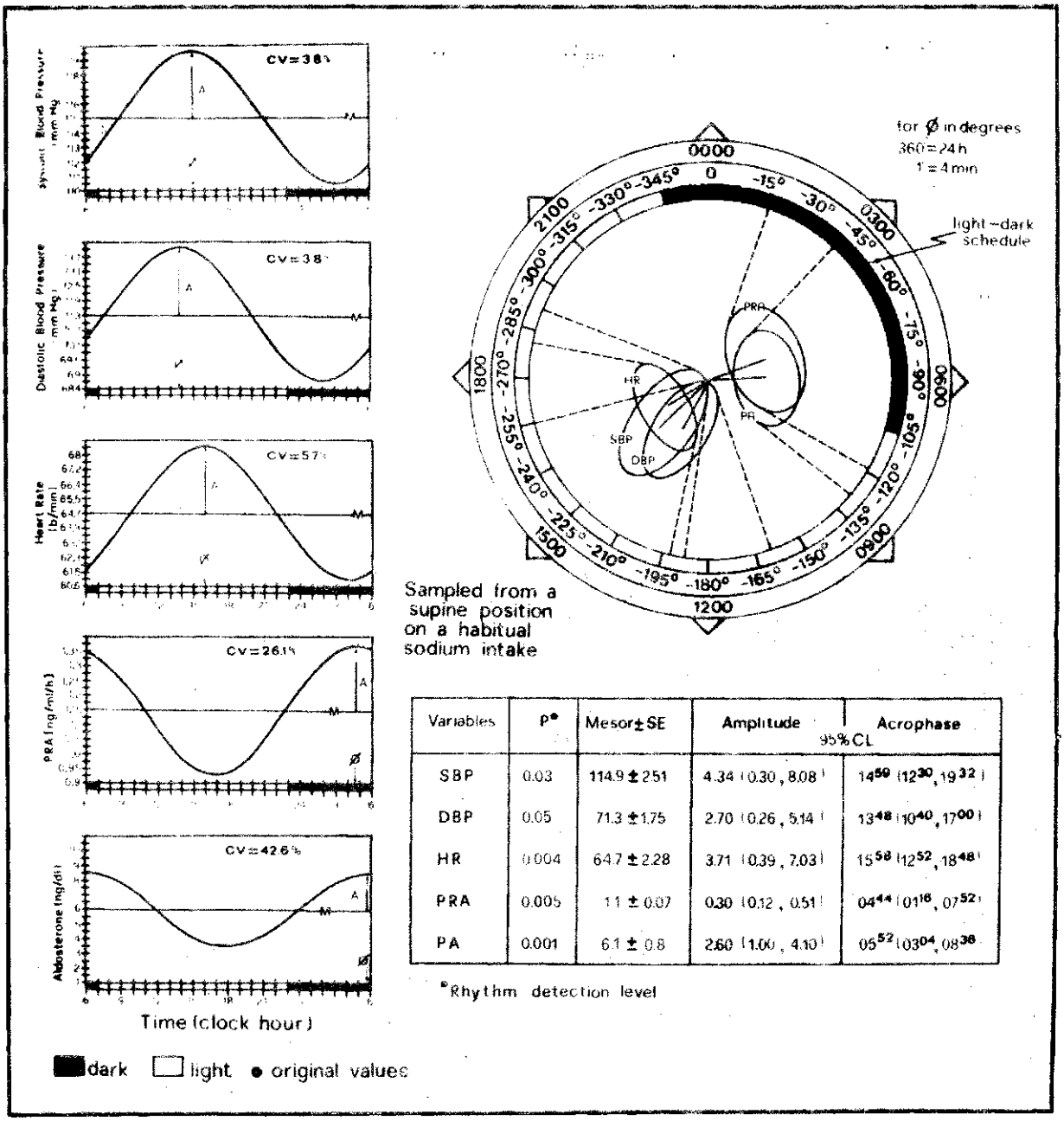
It is evident the persistence of the BP CR even though the circadian periodicity of renin and aldosterone has disappeared.

The finding is a convincing evidence for a negligible role of renin and aldosterone as donors of rhythm to the 24-h BP patterns.

III. 24-H BP MONITORING AND INTERNAL MEDICINE

Chronobiologically, arterial hypertension may exist as amplitude-hypertension or as mesor-hypertension (2). In both the hemodynamic conditions the BP CR maintains the acrophase quite unchanged in its timing. Furthermore, the temporal localization of acrophase is consistently comparable with the crest of BP recorded in normótensive subjects. High BP may, however, occur in odd hours (3). Basically, this phenomenon may result in a heterophasism with a possible reversion or desynchronization for the BP CR. Forms of reverse hypertension or desynchronized hypertension may be, thus, postulated (Figure 8).

The effort of our research group was to document the clinical conditions characterized by such



Variables	P*	Mesor±SE	Amplitude 95% CL	Acrophase 95% CL
SBP	0.03	114.9 ± 2.51	4.34 (0.30, 8.08)	14^{59} (12^{30}, 19^{32})
DBP	0.05	71.3 ± 1.75	2.70 (0.26, 5.14)	13^{48} (10^{40}, 17^{00})
HR	0.004	64.7 ± 2.28	3.71 (0.39, 7.03)	15^{58} (12^{52}, 18^{48})
PRA	0.005	1.1 ± 0.07	0.30 (0.12, 0.51)	04^{44} (01^{16}, 07^{52})
PA	0.001	6.1 ± 0.8	2.60 (1.00, 4.10)	05^{52} (03^{04}, 08^{38})

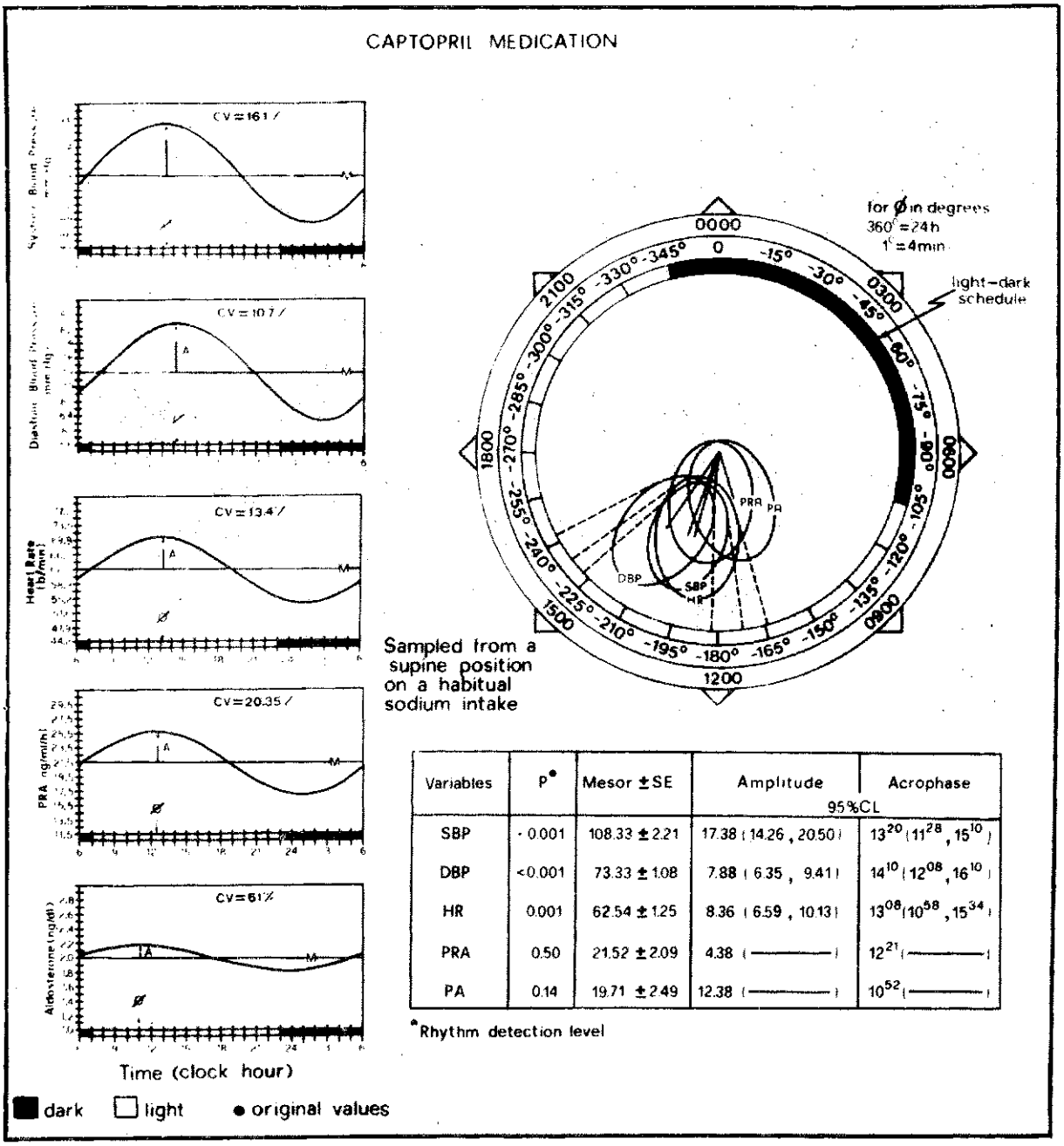
*Rhythm detection level

Figure-6. Temporal interrelationships between Orcadian rhytthms of plasma renin activity (PRA), aldosterone (PA), systolic (SBP) and diastolic (DBP) blood pressure, and heart rate (HR) in clinically healthy subjects.

unusual types of hypertension keeping mind to the fact that a reverse or desynchronized form of high blood pressure could be diagnostic per se.

Figure 9 depletes the BP acrophasogram for hypertension states investigated.

No form with a reversion or desynchronization of both the systolic and diastolic component of BP has been encountered. The most common finding was the internal desynchronization characterized by the disappearance of CR for one component of BP, mostly the diastolic one. Such a phenomenon is clearly detectable in some patients with Cushing's syndrome, Conn's syndrome and pheochromocytoma. Accordingly, one can suggest that the 24-h BP monitoring may be used as a diagnostic tool for identifying such endocrinological types of hypertension.



Variables	P*	Mesor ± SE	Amplitude (95%CL)	Acrophase (95%CL)
SBP	< 0.001	108.33 ± 2.21	17.38 (14.26 , 20.50)	13^{20} (11^{28} , 15^{10})
DBP	<0.001	73.33 ± 1.08	7.88 (6.35 , 9.41)	14^{10} (12^{08} , 16^{10})
HR	0.001	62.54 ± 1.25	8.36 (6.59 , 10.13)	13^{08} (10^{58} , 15^{34})
PRA	0.50	21.52 ± 2.09	4.38 (———)	12^{21} (———)
PA	0.14	19.71 ± 2.49	12.38 (———)	10^{52} (———)

*Rhythm detection level

Figure-7. Occurrence of circadian rhythm for systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) in the presence of a Captopril-induced abolition of the circadian rhythmicity for plasma renin activity (PRA) and aldosterone (PA).

IV. 24-H BP MONITORING AND CLINICAL PHARMACOLOGY

The control of therapeutic effects for most antihypertensive drugs has been, and is, made by means of casual measurement of BP. Protocols approaching such a pharmacotherapeutic problem under a chronobiological point of view are scanty (4-8). Furthermore, the impact of medicine with the 24-h BP monitoring essentially denotes a traditional schematism dictated by the conventional biometry (9-20).

The inferential biometry, alias rhythmometry (21-23), should be, thus, innovative for clinical pharmacology.

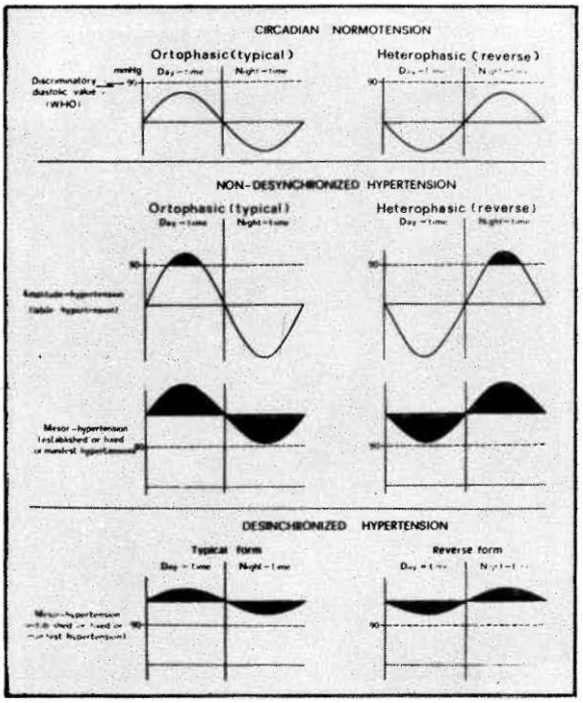


Figure-8. New types of arterial hypertension can be postulated by assuming that the 24-h patterns of blood pressure may be characterized by an antiphasic or desynchronized circadian rhythmicity.

On this ground, our laboratory found of particular interest to inferentially investigate the circadian rhythmometry of **BP** in hypertensives Under treatment with a classical homeostatic nosology of antihypertensive drugs.

Figure 10 is the polar plot of cosinor-derived rhythmometry pertinent to such a study.

The planimetry of **95%** confidence ellipses clearly indicate that some homeostatic therapies may be associated with the abolition of **BP** CR.*

Accordingly, the traditional schemes of antihypertensive treatment can be chronobiologically classified as non-desynchronizing or desynchronizing (Table -1).

A chronotherapeutic protocol is, thus, highly recommended for the latter category of antihypertensive drugs.

V. 24-H BP MONITORING AND CLINICAL PROGNOSIS

The temporal recording of hemodynamic parameters has been recently used for predictive purposes **(24, 25)** considering that **BP** and HR are vital parameters.

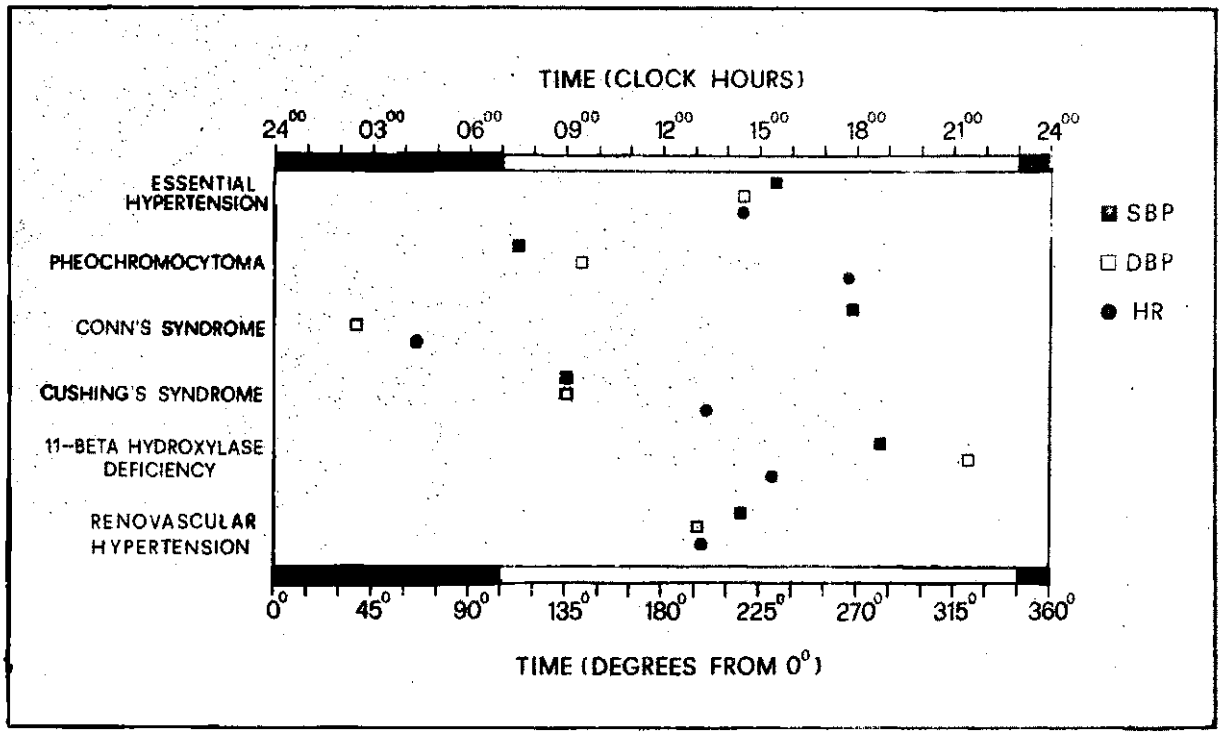


Figure-9. Acrophasogram for systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) in some secondary forms of arterial hypertension.

(*) Zero-amplitude assumption has been not rejected by fitting a cosine function with a period changing from 20 to 28 hours.

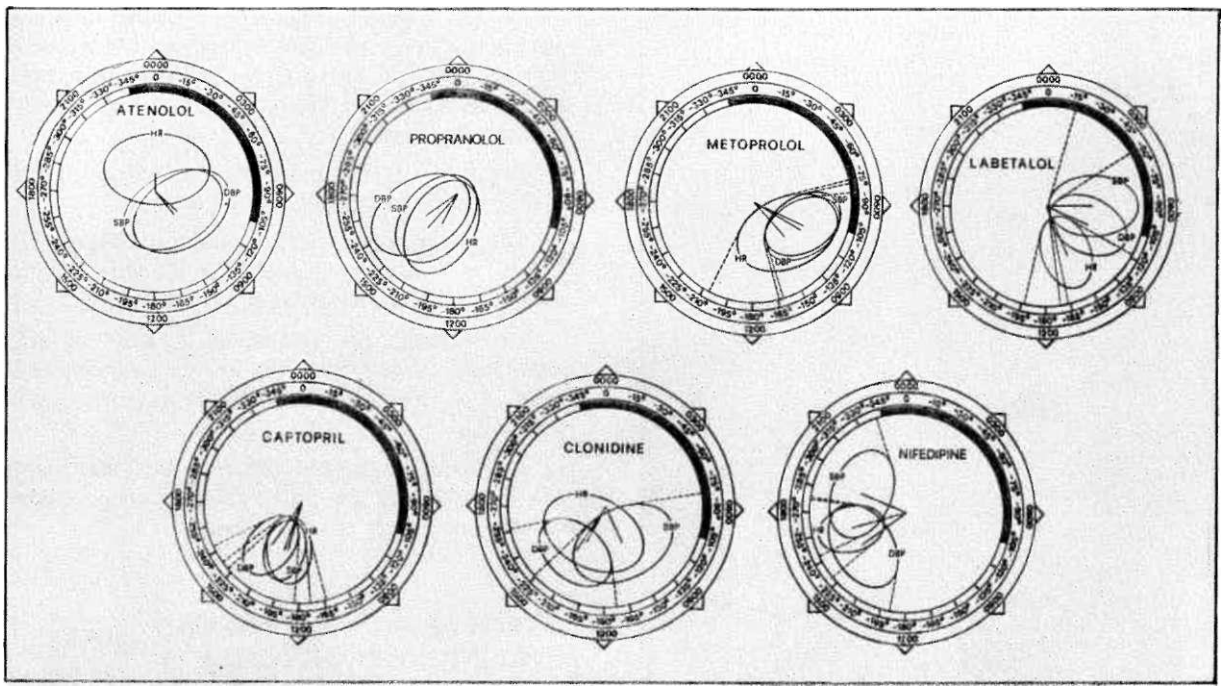


Figure-10. Effects on the circadian rhythm of systolic (SBP) and diastolic (DBP) blood pressure by some antihypertensive drugs administered according to the homeostatic posology classically recommended.

Table - 1

Antihypertensive Drugs Experimented to Cause Or Not the Desynchronization For the Blood Pressure Circadian Rhythm At the Posology Recommended By the Conventional Pharmacology

A) Non-desynchronizing agents	B) Desynchronizing agents
— Labetalol	— Propranolol
— Metoprolol	— Atenolol
— Prazosin	
— Clonidine	
— Nifedipine	

Our research group experimented time-qualified BP values as a prognostic classifier for patients in coma for cerebral hemorrhagia or depression due to intoxication by sedatives or domestic combustible gaseous mixture respectively ingested or inhaled for suicidal purpose.

Figure 11 tridimentionally shows the bivariate distribution of systolic and diastolic BP non-invasively recorded over the 24-h span in two groups of comatous patients who died or survived. The graphic pertinent to a group of clinically healthy subjects is additionally included.

By inspection it is visible that the gaussian diagrams are consistently different.

The bivariate discriminant analysis found the groups significantly discriminable (F value = 106; $p < 0.001$). Their mortality is discriminated by a discriminant value of 15.1.

The univariate reference intervals for the systolic and diastolic distribution has been plotted on a bi-dimensional diagram (Figure 12).

Such a planegraph can be used for predicting the mortality of a specific patient by plotting the coordinates of its systolic and diastolic median BP calculated by a 24-h monitoring. Expectancy of life is favorable or not depending on the area where the coordinates fall.

VI. CONCLUSIONS

The studies of our laboratory have been mentioned with the aim of indicating that the chrono-biological approach to the 24-h BP monitoring is now in a clinical stage after the basic and propaedeutic phase of standardization and semantics.

Studies presented herein would be just an illustrative, although limited, example that progress is being made which may provide new insight into medicine.

The optimization of medicine is global involving both basic and clinical problematics.

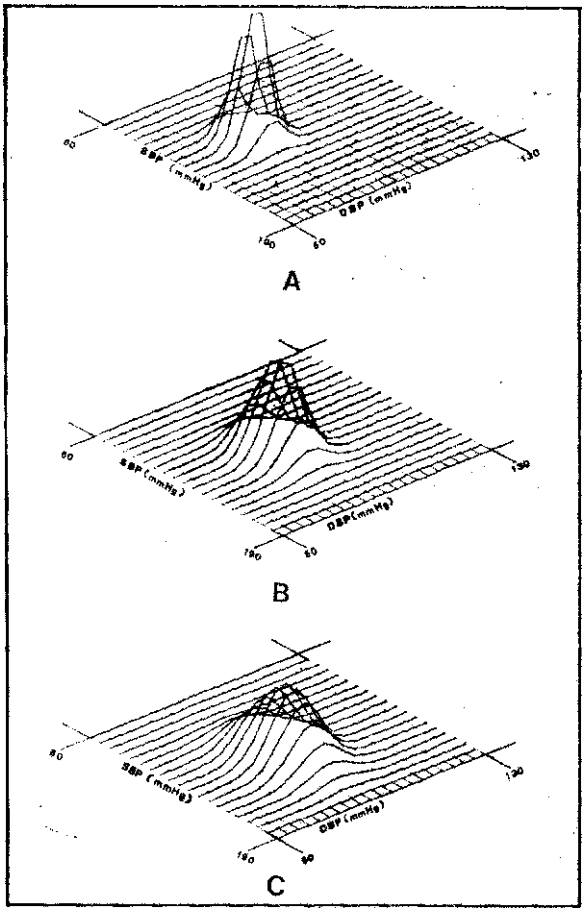


Figure-11. Bivariate gaussian distribution for systolic (SBP) and diastolic (DBP) blood pressure monitored over the 24-h span in clinically healthy subjects (A) and in severely brain-damaged patients in coma died (B) or survived (C).

On a human physiological ground, the investigation of cardiovascular functions along the scale of time makes the traditional concepts to need a dramatic revision or complementation.

On a clinical ground, new diagnostic, prognostic and therapeutic criteria can be acquired.

The auspiece is a further aggregation of technology to medicine via the Chronobiotechnology and Chronobiological Engineering.

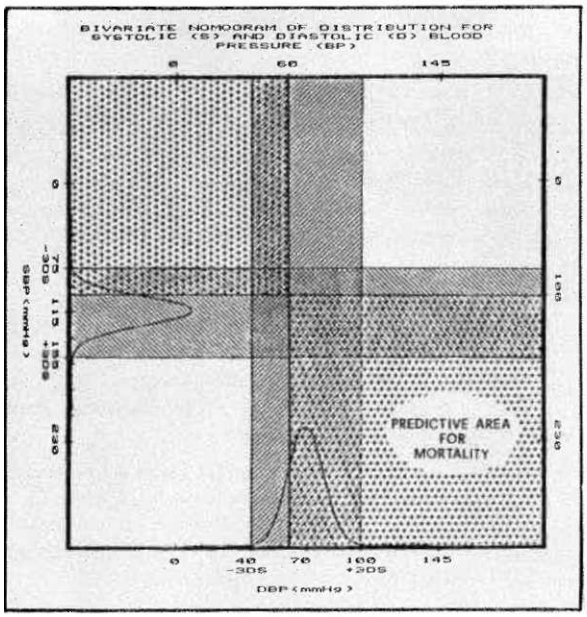


Figure-12. Planegraph for predicting mortality due to severe brain-damage by plotting the coordinates for systolic (SBP) and diastolic (DBP) modal pressure.

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