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'Minimal-change hypertensive retinopathy' and 'arterial pre-hypertension', illustrated via ambulatory blood-pressure monitoring in putatively normotensive subjects

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Abstract

Purpose: To investigate the 24 h blood-pressure (BP) pattern in subjects who were found to show some incipient signs of hypertensive retinopathy but had been diagnosed as normotensives by means of casual sphygmomanometry. *Methods:* Non-invasive ambulatory BP monitoring was performed in 25 caucasian subjects (16 M, 9 F; mean age 46 $\pm$ 16 years) showing this type of retinal problem. A comparable number of controlled normotensive Caucasian subjects (15 M, 10 F; mean age: 48 $\pm$ 15 years) without funduscopic signs of hypertensive retinopathy were investigated as a reference group. A series of BP tests over time was analysed by means of conventional biometry and chronobiological methods. *Results:* The biometric estimates suggest that the investigated subjects with incipient hypertensive retinopathy, although characterized by BP values below 140/90 mmHg, show a significantly higher daily systolic BP. The increase, however, is within WHO reference limits and is not associated with the abolition of the circadian BP rhythm. *Conclusions:* The results suggest that the initial signs of hypertensive retinopathy may appear before BP elevation above WHO reference limits occurs. Because of this, it can be assumed that there is such a condition as 'minimal-change hypertensive retinopathy' associated with a haemodynamic picture of 'arterial pre-hypertension'.

Introduction

Arterial hypertension is one of the most important risk factors for damage to the cardiovascular apparatus [1–3]. Early diagnosis and therapeutic care, therefore, represent the most valid strategies for reducing morbidity and mortality in human beings. There is consistent evidence to show that the most reliable clinical tool for correctly diagnosing hypertension is the non-invasive, ambulatory (A) blood pressure (BP) monitoring (M) [4–9]. However, ABPM is not suitable for mass screening [10, 11] as candidates must be carefully selected on a cost–benefit basis. Ophthalmologists can contribute to this accurate selection by suggesting ABPM for those subjects showing funduscopic signs of hypertensive retinopathy in the absence of a manifest hypertension. In fact, there is convincing evidence for a significant correlation between the severity of hypertensive retinopathy and the presence of high BP values, when evaluated via ABPM [12–14].

Given these premises, the purpose of this study was to investigate subjects showing incomplete and incipient signs of hypertensive retinopathy whose casual sphygmomanometry results were consistently indicative of BP values within WHO reference limits. The hypothesis was formulated that these apparently normotensive subjects could be 'false normotensives' because of transient elevations in BP values during the day–night span. With this in mind, the putatively normotensive subjects (PNSs) with at least two funduscopic signs of initial hypertensive retinopathy were investigated via ABPM, taking, as a reference, truly

normotensive subjects (TNSs) ascertained to be free from hypertensive signs of organ damage.

Materials and methods

Subjects and protocol

The volunteers for this investigation were 25 Caucasian adults (16 M, 9 F; mean age: 46 ± 16 years) who had come to the Institute of Ophthalmology, University of Rome 'La Sapienza' for treatment of their visual acuity. These subjects underwent a complete ophthalmological examination, including direct and indirect ophthalmoscopy and funduscopic photography. Each of them was found to show at least two signs of incipient hypertensive retinopathy; this was confirmed by two experienced ophthalmologists and by the use of photographic iconography. The retinal signs of hypertension were as follows: changes in arteriolar diameter, course as well as axial reflexes, artero-venous crossing, artero-venous ratio. Each sign was assigned to the following scale of severity: (a) absent, (b) mild or (c) pronounced.

Importantly, none of the subjects investigated was declared to be hypertensive or to have a family history of diseases causing vascular damage. Their casual BP (sitting position) was measured on three occasions and was found to be below 140/90 mmHg on each occasion. Accordingly, these subjects were to be regarded as PNSs unless proved otherwise via ABPM.

The ABPM was performed at the Department of Clinical Sciences, University of Rome 'La Sapienza', by physicians who were not informed of the retinal status of the subjects monitored. Therefore, the research protocol was conducted as a 'double-blind study', using, as a reference, a control group of TNSs without detectable signs of hypertensive damage. The reference sample was composed of Caucasian subjects of matching age and gender (15 M, 10 F; mean age: 48 ± 15 years). All of the investigated subjects gave their informed consent to participation in the study.

The ABPM was performed via an automatic device, Model 90202, manufactured by Space Labs ICR (USA). The recorder was programmed to take sphygmomanometric readings (oscillometric technique) at 30 min intervals, via an inflatable cuff attached to the upper non-dominant arm. Monitoring was begun at 12:00 a.m. Each subject was instructed to keep a diary of the intercurrent events. Subjects experiencing excess mental, physical and sexual activity as well as unusual sleeping patterns were excluded. The other exclusion criteria were heavy smoking and heavy drinking.

Data analysis

The individual BP time series were analysed by means of an IBM microcomputer using adequate statistical software for conventional descriptive analysis and rhythmic biometry. The chronobiological approach was used because of the fact that BP shows a 'within-day' variability that physiologically reflects the periodicity of a circadian rhythm (CR) [16–22].

Conventional descriptive analysis

The individual time series were compared with WHO upper reference limits. The individual time-qualified series were all found to show systolic and diastolic values consistently below 140/90 mmHg. Because of this, the conventional biometric approach considers the 24 h BP values as raw, discrete numerical data that can be used for estimating the daily, diurnal and nocturnal mean levels, as well as the diurnal–nocturnal mean difference. The latter estimate was used to discover 'dippers' and 'non-dippers', i.e., individuals who show or do not show a decline in nocturnal BP greater than 10% of diurnal BP, as suggested by the literature [23, 24]. A statistical comparison between the conventional estimates for PNSs and TNSs was performed using the Student's 't' test for unpaired data.

Rhythmometric descriptive analysis

The chronobiometric approach was used to validate and describe the CR that characterizes nychtohaemeral BP variability. The rhythmicity was assessed by means of the Cosinor method [25–26], a method of periodic regression analysis based on the adaptation of a cosine function, with a 24 h period to the raw, discrete 'within-day' BP values. The Cosinor method allows validation of the statistical significance of the BP CR by verifying that the best-fitting oscillation is wide enough to reject the null-hypothesis of zero-amplitude at a probability level of $P < 0.05$ (Rhythm Significance Level). The Cosinor method yields these parameters of the validated CR, as follows: (1) the mesor (an acronym for Midline Estimating Statistic of Rhythm), which is the rhythm-adjusted mean; (2) the amplitude, which corresponds to the oscillatory extent from the mesor; and (3) the acrophase, which describes, in hours and minutes, the time of day at

which BP CR shows its highest elevation with respect to midnight (local time). The acrophase is expressed in negative sexagesimal degrees, which can be converted into hours and minutes (360° = 24 h; 15° = 1 h; 1° = 4 min). [The Appendix gives better definition of chronobiological terms, in accordance with the *Glossary of Chronobiology* [16].

The statistical comparison of the rhythmometric estimates was performed using Bingham's test for directional data [27].

Results

The results of the conventional biometric analysis are shown in Table 1.

The estimates demonstrate that the PNSs are characterized by a significant increase in systolic BP relative to values for TNS. Interestingly, this increase is pronounced during the day rather than the night. This means that the PNSs are not characterized by the non-dipping phenomenon, as confirmed by the estimate of the diurnal–nocturnal mean difference.

The results of the rhythmometric analysis are displayed in Table 2.

The estimates demonstrate that the PNSs are characterized by a 'within-day' BP variability, i.e., the expression of a significant CR, as for the TNSs. Importantly, the estimates indicate that the PNSs are characterized by a higher systolic BP mesor and amplitude relative to the TNSs. This significant increase, however, is not accompanied by an acrophase shift, suggesting that the BP CR is not shifted to cause the non-dipping phenomenon.

Discussion

This study has demonstrated that, in clinical practice, incipient signs of hypertensive retinopathy may be observed in subjects who are at least apparently normotensive and at zero risk for hypertensive damage to target organs. Admittedly, these subjects must be investigated via ABPM in order to eliminate the suspicion that they are 'false normotensives'.

ABPM of these subjects was performed in this study, and the suspicion of false normotension was not confirmed. In fact, subjects showing incipient signs of hypertensive retinopathy were found to show 'within-day' BP values consistently below WHO reference limits.

Conventional biometric analysis, however, demonstrated that subjects with incipient signs of hypertensive retinopathy were characterized by systolic BP values that increased significantly during the diurnal part of the day–night cycle, unlike the control subjects not showing funduscopic signs of hypertensive damage. Additionally, conventional biometric analysis clarified that these subjects were characterized by nocturnal BP values that reduced sufficiently to exclude the occurrence of the non-dipping phenomenon. On the other hand, chronobiometric analysis demonstrated that these subjects had a well-structured BP CR with a postmeridian acrophase that explained the lack of inappropriate BP elevations during the nocturnal part of the day–night cycle. Importantly, chronobiometric analysis confirmed that subjects showing incipient signs of hypertensive retinopathy were characterized by a significant increase in systolic BP mesor and amplitude, demonstrating, once again, that they should be regarded neither as true normotensives nor true hypertensives.

It must be realized that this study was performed on a limited sample. Nonetheless, its results are in keeping with the idea that initial damage to the retinal vasculature can be detected in subjects whose diurnal systolic BP values are below WHO reference limits but already significantly above the mean level associated with true normotension. For this reason, it can be assumed that a funduscopic picture exists which is characterized by 'minimal-change hypertensive retinopathy' associated with a haemodynamic tension that could be termed 'arterial pre-hypertension'.

One of the greatest difficulties encountered in this study was the definition and ordering of the initial signs of hypertensive retinopathy. In fact, the signs are non-specific (i.e., not necessarily linked to hypertension) and not easily quantifiable. Therefore, it could be said that the retinal signs were attributable to atherosclerotic lesions. However, because of the young age of the subjects investigated it is more likely that these retinal signs are indicative of hypertensive retinopathy, particularly as there were no other apparent signs of vascular damage.

The term 'arterial pre-hypertension' arises from the fact that the BP regimen is in between normotension and the hypertensive stage known as borderline hypertension. It must be reemphasised, however, that the pre-hypertensive stage is associated with arteriolar impairment. This association is of clinical relevance, and should prompt investigation, via ABPM, of the apparently normotensive subjects who show a

Table 1. Numerical analysis and statistical comparison of the 24 h values for systolic and diastolic blood pressure in 'putatively normotensive subjects' showing funduscopic signs of hypertensive retinopathy and in 'truly normotensive subjects', lacking signs of retinal abnormality

Groups	Daily mean level (mmHg)		Diurnal mean level (mmHg)		Nocturnal mean level (mmHg)		Diurnal–nocturnal mean difference (mmHg)	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
TNSs	112 ± 12	72 ± 8	119 ± 13	75 ± 9	110 ± 12	67 ± 7	10 ± 8	8 ± 7
PNSs	$123 \pm 9^*$	75 ± 7	$129 \pm 10^*$	80 ± 7	115 ± 13	68 ± 8	14 ± 11	12 ± 7

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; ± Standard Deviation; TNSs = Truly Normotensive Subjects; PNS = Putatively Normotensive Subjects with incipient signs of hypertensive retinopathy.
* $p < 0.01$ for 't' test in contrasts between PNSs and TNSs.

Table 2. Cosinor analysis and statistical comparison of the rhythmometric properties of the systolic and diastolic blood-pressure circadian rhythm in 'putatively normotensive subjects' showing funduscopic signs of hypertensive retinopathy and in 'truly normotensive subjects' lacking signs of retinal abnormality

Groups	Rhythm-level significance (P)		Mesor (mmHg)		Amplitude (mmHg)		Acrophase (degrees)	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
TNSs	<0.001	<0.001	112 ± 3	72 ± 4	8 ± 1	7 ± 1	-250 ± 59	-247 ± 59
PNSs	0.01	0.05	$124 \pm 10^*$	76 ± 8	$12 \pm 6^*$	10 ± 4	-214 ± 38	-214 ± 29

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; ± Standard Error; TNSs = Truly Normotensive Subjects; PNS = Putatively Normotensive Subjects with incipient signs of hypertensive retinopathy.
* $p < 0.01$ for Bingham's test in contrasts between PNSs and TNSs.

funduscopic picture of minimal-change hypertensive retinopathy. In fact, these subjects could be showing a haemodynamic picture which has been termed by us as 'arterial pre-hypertension'. This level of hypertensive risk is represented by a daily mean BP of $123 \pm 9/75 \pm 7$ mmHg or a diurnal mean of $129 \pm 10/80 \pm 7$ mmHg.

Appendix

Acrophase: measure of timing, namely the lag from a defined reference timepoint (the acrophase reference) of the peak time in the function approximating a rhythm.

Amplitude: measure of one half of the extent of a rhythmic change in a cycle estimated by the (sinusoidal or other) function used to approximate the rhythm, e.g., the difference between the maximum and the mesor of a best-fitting cosine.

Chronobiometric procedures: methods of statistical mathematical analysis applied to a temporal series of biological data for objectively detecting, statistically validating, biometrically estimating the occurrence and properties of cycling patterns.

Cosinor method: a method of periodic regression analysis which is used worldwide for statistically validating and biometrically estimating biorhythmic events whose periods are postulated a priori. It consists of best-fitting cosine function to experimental time data series by minimizing the sum of residuals by the least-squares method.

Cosinorgram: the optimal waveform profile fitted to a series of experimental time data series by the Cosinor method.

Diurnal: relating to biological variations or events occurring between sunrise and sunset or to events during the illuminated fraction of a near-daily schedule of alternating artificial light and darkness.

Mesor: rhythm-determined average, e.g., in the case of a single cosine approximation, it is the value midway between the highest and lowest values of the function used to approximate a rhythm.

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