JOURNAL OF CARDIOVASCULAR DIAGNOSIS AND PROCEDURES
Volume 13, Number 4, 1996
Mary Ann Liebert, Inc.

Analysis of 24-H Noninvasive Ambulatory Blood Pressure Profiles by a Third-Degree Polynomial Approach

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ABSTRACT

Extensive experience of the circadian variation of blood pressure (BP) has been reported. But some problems exist concerning the correct and satisfactory evaluation of 24-h BP profiles. A well-known approach is the Halberg's "cosinor" method. But it could be considered inadequate for blood pressure recordings because it is based on a rigid model that does not practically fit empirical data. We suggest an approach based on a cubic function as a suitable method for such an analysis. Our investigation studied the behavior of 24-h blood pressure by a model where the function *f*(*t*) is a third-degree polynomial. We recruited 52 untreated patients affected by essential hypertension. Ambulatory BP recordings were made using a portable noninvasive system. Data were analyzed by a computerized procedure for both estimating parameters of the cubic-polynomial model and obtaining conventional and function-derived parameters. Eleven of 52 hypertensives showed no common rhythm: 8 patients had no statistically significant rhythm and 3 had a reversed rhythm. The 8 of 11 hypertensives who had no statistically significant rhythms were also "nondippers" according to the criteria of Verdecchia et al.[8] The remaining 41 patients were matched and compared to 41 normotensive subjects. In general, function-derived parameters stressed differences between the two groups more than the conventional ones. We suggested an analysis of 24-h BP data based on a cubic function model. We verified that such a methodology is feasible. At the moment, it seems a useful approach for clinical investigation.

INTRODUCTION

Extensive experience of the circadian variation of blood pressure (BP) has been reported.[1–4] But some problems exist about the correct and satisfactory evaluation of 24-h BP profiles. A useful approach could be to evaluate the circadian blood pressure profiles rather than make a merely arithmetic analysis that uses simple calculation based on averages and standard deviations. A well-known approach is the Halberg's "cosinor" method.[5] It could be considered inadequate for blood pressure recordings because it is based on a rigid model that does not practically fit empirical data.[6] Therefore, an alternative approach is required. Fundamentally, the analysis of 24-h noninvasive ambulatory BP profiles is difficult for two reasons. First, data are spaced irregularly in time; second, the signal itself is unstable for accidental fluctuations not linked to cir-

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cadian pressure rhythm. We suggest an approach based on a cubic function as a suitable method for such an analysis. This approach avoids the rigid assumptions of any fixed parametric model for the circadian rhythm, and especially allows asymmetric profiles. The method produces curves that closely follow the general trend of the profile. For this reason we suggest an analysis of 24-h BP profiles based on a model where the function $f(t)$ is a third-degree polynomial: $f(t) = a + bx + cx^2 + dx^3$ and represents the circadian best fit of crude data on a 24-h time interval. We used an algorithm based on the multiple linear regression analysis.

Our investigation aimed at studying the behavior of 24-h BP by the above-mentioned approach. We intended to verify the capacity of this method to both recognize and strongly represent the biphasic daily rhythm of BP as well as the possibility of obtaining useful parameters for clinical and/or research purposes.

METHODS

Subject selection

We recruited 52 untreated patients (26 women and 26 men), aged between 33 and 61 years (average age ± 1 SD: 46.3 ± 11.7) affected by essential hypertension stage 1 and 2, according to JNC V criteria[7] and with BP measured on three visits at 1-week intervals.

We had excluded all subjects with a history and/or clinical findings of both overt cardiac and extracardiac diseases. Moreover, all the patients were selected after having excluded a condition of secondary hypertension by a routinary laboratory and instrumental assessment.

At each visit the same clinician took three readings of BP and heart rate (HR). The average of the last set of readings was used for clinic measurements. Diastolic BP refers to Korotkoff V phase. The 24-h BP data of each patient were analyzed with the approach based on cubic function. Then, only the patients with a significant rhythm, with the maximum peak of the related-function during the day, were selected and compared to normotensive subjects. Each hypertensive patient was matched with a normotensive subject for gender, age, body mass index, and family history of hypertension (on the basis of individual responses to a questionnaire on family medical history). All were in sinus rhythm. All the subjects were informed of the purpose of the study and gave their consent.

Ambulatory blood pressure monitoring (ABPM)

Ambulatory blood pressure recordings were made using a portable, fully automatic, noninvasive system (TM 2420, A & D Instruments), connectable through the serial interface (RS232) to a personal computer. In our laboratory automatic BP recordings showed a correlation of $r = 0.96$ (slope of the regression line = 0.98) with both systolic BP and diastolic BP measured in the same arm using a mercury sphygmomanometer. The battery-powered monitor (weight 0.300 kg) was carried by the subjects on a belt and it was attached to a conventional cuff wrapped and taped around the upper arm. The brachial artery was palpated and the microphone positioned over the artery under the cuff. The cuff was automatically inflated by a pump in the monitor at predetermined intervals. The device uses an auscultatory method, the microphone picking up phases I and V of Korotkoff sounds. Ambulatory blood pressure was recorded during everyday routines, excluding physical and working activity and stress-related conditions. The unit was set to take BP and HR readings every 10 min in the daytime (7.00 to 23.00 h) and every 15 min at night (23.00 to 7.00 h). This approach has been well tolerated by many patients who were recruited. Only two hypertensive patients were excluded, since the frequent recording of BP during the night interfered with their sleep. Systolic readings greater than 290 or less than 40 mm Hg and diastolic readings greater than 150 or less than 12 mm Hg were automatically discarded. Then, individual BP readings were automatically deleted if they were not included between the 2.5 and the 97.5 percentiles of the distribution of all the readings. Recordings were included in this study only if at least 80% of the maximal number of 128 readings during the 24-h period passed the deletion criteria.

Data analysis

Values are reported as mean ± standard deviation. A two-tailed unpaired t test was performed to detect difference in means and $p < 0.05$ indicated a significant difference between the two groups. The average

BP and HR, as well as standard deviation, were calculated from the 24-h recordings and day and night ones. A computerized procedure, based on the multiple linear regression analysis, was performed to estimate parameters of the cubic-polynomial model. We used R^2 as a measure of the goodness of fit of the cubic polynomial model. Analysis of variance was performed on regression. Statistics for the equation and single independent variables were obtained. A p value < 0.05 was assumed as a statistically significant index for the presence of circadian rhythm.

We also computed the following parameters on BP and HR functions by a computerized procedure: value and time at maximum peak, value and time at minimum peak, value and time at flex point, slope of the tangent at the flex point, mean integral.

RESULTS

Eleven of 52 hypertensives showed no common rhythm: 8 patients had no statistically significant rhythm (consequently with flattened daily fluctuations) and 3 had a reversed rhythm (that is, a biphasic and significant daily rhythm, but with the maximum peak of the function during the night). The 8 of 11 hypertensives who had no statistically significant rhythms were also "nondippers" according to the criteria of Verdecchia et al.[8] On the contrary, the remaining 3 patients who had a blunted nocturnal fall in blood pressure according to our method were barely "dippers" according to the arithmetic calculus. The remaining 41 patients (average age ± SD: 44.4 ± 12.1 years) were matched and compared to 41 normotensive subjects (average age ± SD: 44.6 ± 11.9 years). The behavior of hourly mean systolic and diastolic BP and HR of normotensives and hypertensives is shown in Figure 1. As regards clinic and other conventional BP

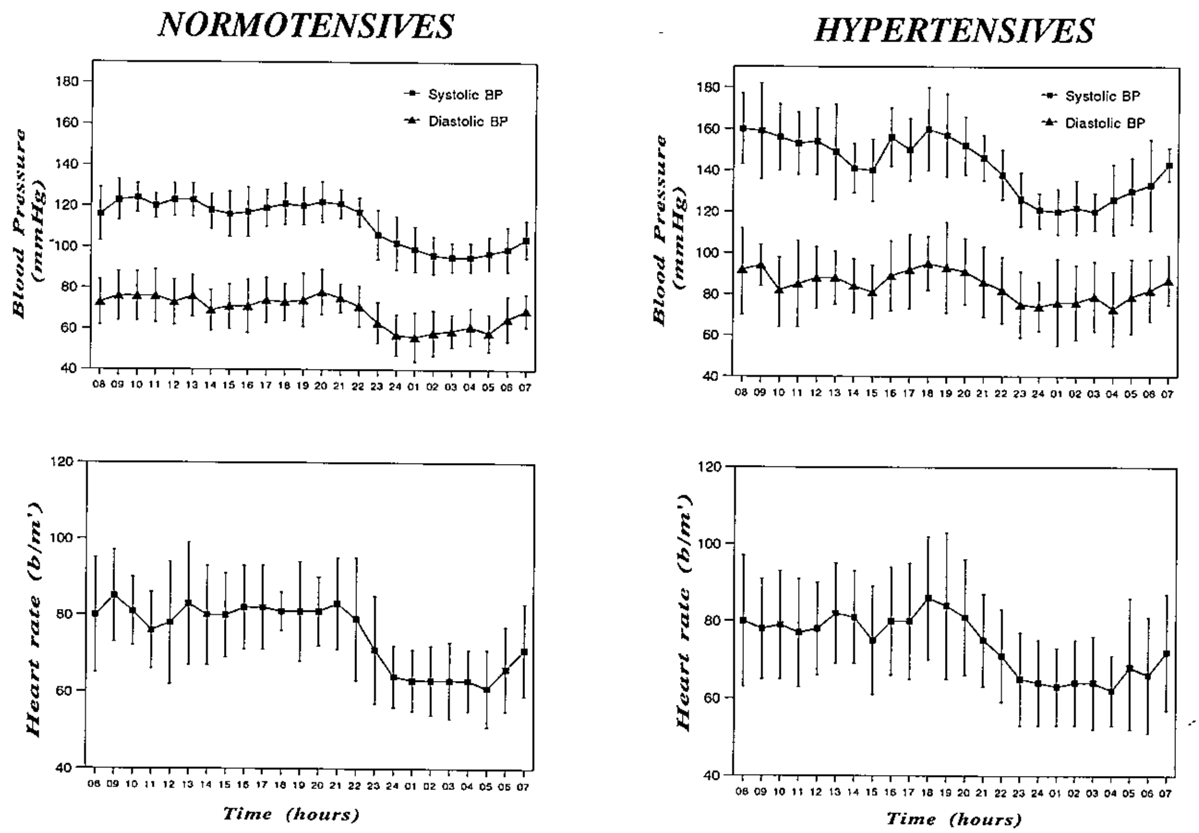

FIG. 1. Hourly mean systolic and diastolic blood pressures (BP), and hourly mean heart rate throughout 24 h in both 41 normotensive subjects and 41 untreated hypertensive patients.

TABLE 1. SYSTOLIC BP PARAMETERS: NORMOTENSIVE SUBJECTS IN COMPARISON WITH HYPERTENSIVE PATIENTS[a]

	Normotensives	*Hypertensives*	p<
Clinic BP (mm Hg)	121 ± 5	156 ± 20	0.0001
ABPM parameters (mm Hg)			
24 h BP	114 ± 5	144 ± 9	0.001
Daytime BP	119 ± 6	153 ± 10	0.001
Nighttime BP	99 ± 7	124 ± 10	0.001
Function-derived parameters			
BP at max peak (mm Hg)	125 ± 7	169 ± 19	0.001
BP at min peak (mm Hg)	101 ± 6	138 ± 22	0.001
BP at flex point (mm Hg)	113 ± 5	152 ± 21	0.001
Time at max peak (h)	13.77 ± 1.34	13.70 ± 2.23	N.S.
Time at min peak (h)	3.94 ± 1.61	2.70 ± 1.27	0.001
Time at flex point (h)	20.86 ± 1.24	20.21 ± 1.45	0.04
Slope of the tangent at flex point	−2.56 ± 1.17	−3.80 ± 0.97	0.001
Mean integral (mm Hg)	113 ± 5	154 ± 20	0.001
R^2 (%)	38 ± 10	23 ± 15	0.001

[a]BP, blood pressure; ABPM, ambulatory blood pressure monitoring; max, maximum; min, minimum; N.S., not significant.

data we found obvious differences between the two groups (Tables 1 and 2). Parameters obtained from the function recognized these differences too (Tables 1 and 2). In general, function-derived parameters stressed differences between the two groups more than the conventional ones. As regards HR we found no difference between the two groups (Table 3).

TABLE 2. DIASTOLIC BP PARAMETERS: NORMOTENSIVE SUBJECTS IN COMPARISON WITH HYPERTENSIVE PATIENTS[a]

	Normotensives	*Hypertensives*	p<
Clinic BP (mm Hg)	77 ± 11	91 ± 17	0.001
ABPM parameters (mm Hg)			
24 h BP	70 ± 10	85 ± 14	0.001
Daytime BP	74 ± 10	89 ± 14	0.001
Nighttime BP	60 ± 8	77 ± 15	0.001
Function-derived parameters			
BP at max peak (mm Hg)	77 ± 9	102 ± 20	0.001
BP at min peak (mm Hg)	61 ± 8	88 ± 21	0.001
BP at flex point (mm Hg)	69 ± 9	93 ± 20	0.001
Time at max peak (h)	13.44 ± 1.66	15.66 ± 3.51	0.001
Time at min peak (h)	3.13 ± 1.30	3.51 ± 3.94	N.S.
Time at flex point (h)	20.28 ± 1.41	22.70 ± 3.79	0.001
Slope of the tangent at flex point	−1.70 ± 0.49	−1.86 ± 0.87	N.S.
Mean integral (mm Hg)	69 ± 8	94 ± 21	0.001
R^2 (%)	24 ± 7	20 ± 10	0.04

[a]BP, blood pressure; ABPM, ambulatory blood pressure monitoring; max, maximum; min, minimum; N.S., not significant.

TABLE 3. HR PARAMETERS: NORMOTENSIVE SUBJECTS IN COMPARISON WITH HYPERTENSIVE PATIENTS[a]

	Normotensives	*Hypertensives*	p<
Clinic HR (b/m)	82 ± 12	80 ± 13	N.S.
ABPM parameters (b/m)			
24 h HR	77 ± 9	76 ± 10	N.S.
Daytime HR	81 ± 9	79 ± 11	N.S.
Nighttime HR	65 ± 9	65 ± 11	N.S.
Function-derived parameters			
HR at max peak (b/m)	85 ± 8	88 ± 28	N.S.
HR at min peak (b/m)	67 ± 9	67 ± 20	N.S.
HR at flex point (b/m)	75 ± 8	79 ± 24	N.S.
Time at max peak (h)	14.69 ± 1.13	14.40 ± 1.69	N.S.
Time at min peak (h)	4.45 ± 1.96	3.83 ± 1.66	N.S.
Time at flex point (h)	21.17 ± 1.42	20.90 ± 1.68	N.S.
Slope of the tangent at flex point	−1.98 ± 0.79	−2.22 ± 1.83	N.S.
Mean integral (b/m)	76 ± 7	78 ± 23	N.S.
R^2 (%)	30 ± 11	27 ± 10	N.S.

[a]HR, heart rate; ABPM, ambulatory blood pressure monitoring; max, maximum; min, minimum; N.S., not significant; b/m, beats per minute.

DISCUSSION

Our investigation points out the possibility of analyzing 24-h ABPM data by an approach based on a cubic function model. First, we think that this method is capable of recognizing a blunted nocturnal fall in blood pressure in an objective way compared to a merely arithmetic method. Indeed, it does not need either any time interval to define day and night or any arbitrary cut-off point to evaluate the nocturnal fall in blood pressure.

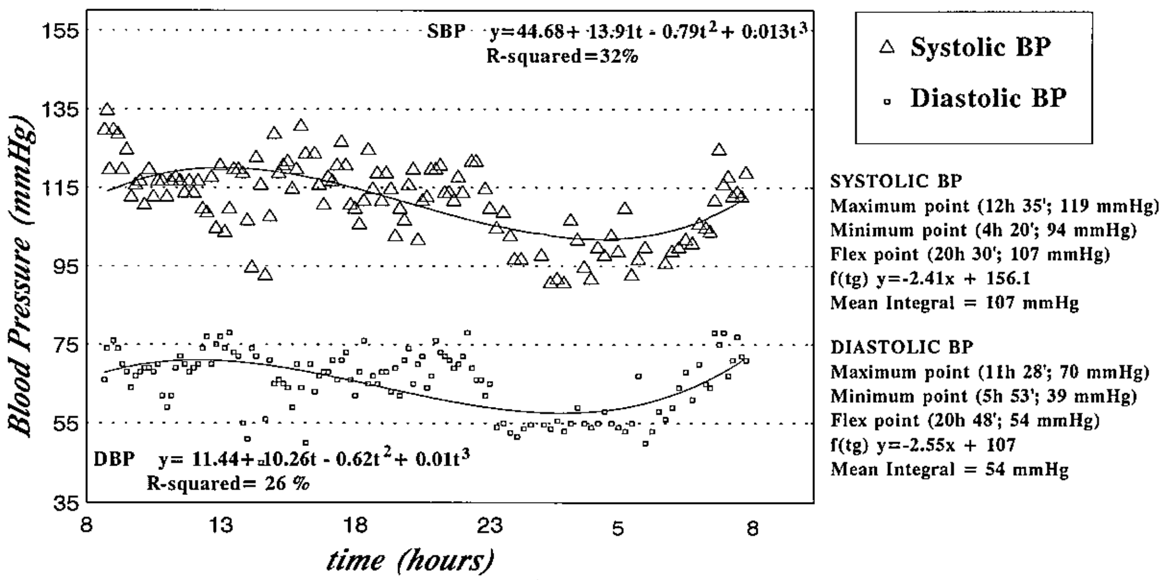

FIG. 2. Example of postprocessing data: L.G., man, 38 years old, normotensive.

On the other hand, this method has shown the capacity to well characterize the daily BP behavior in subjects with a physiological nocturnal fall in blood pressure. Moreover, differences between normotensive and hypertensive subjects are stressed. It seems that the model is able to filter the 24-h BP data to obtain only the rhythm-related data. So, such a methodology seems to provide for removal of the stochastic variability of data, giving the investigator a purified BP daily profile. Thus, it seems feasible to obtain parameters from the rhythm profile and not merely from crude data. All that represents, without doubt, an advantage because, using this method, BP variations not related to the rhythm would be generally bypassed. Another important advantage is represented by the possibility of detecting and quantifying the rhythm. Moreover, when the rhythm exists one can mathematically know if it is reversed. An example of postprocessing data is shown in Figure 2. We think the obtained functions are representative of daily BP behaviors.

In conclusion, we wanted to verify the feasibility of such a methodology. At the moment, it seems a useful approach for clinical investigation. However, this report represents only an initial effort that needs further investigation.

ACKNOWLEDGMENT

We thank Anna Parroco, researcher of the Institute of Applied Statistics, University of Palermo, for her assistance with statistical analysis.

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Received January 4, 1996; Accepted May 13, 1996

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