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Giorgio Recordati [a,*], Alberto Zanchetti [b]

[a] *Centro Interuniversitario di Fisiologia Clinica ed Ipertensione ed Istituto di Medicina Cardiovascolare, Universita' degli Studi di Milano, Ospedale Maggiore, Italy*

[b] *Istituto Auxologico Italiano, Milano, Italy*

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[b] *Istituto Auxologico Italiano, Milano, Italy*

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Abstract

The present study was aimed at investigating whether the blood pressure-R–R interval relation obtained by ABPM may give useful information about autonomic control in the 24 h period. To this purpose ABPM was performed in 60 healthy young subjects (30 females and 30 males, mean age 21.8±1.0 years) and the collected variables were copied to a software program to convert heart rate into R–R interval values, for statistical analysis and graphic representation. The following data were calculated: 1) day and night means±SD; 2) difference and percent difference in mean night less mean day R–R interval (Δy), diastolic and systolic blood pressures (Δx) and their $\Delta y/\Delta x$ ratios; 3) intercept (a_24 h), slope (b_24 h) and r coefficient (r_24 h) of the linear regressions of 24 h R–R interval over diastolic and systolic blood pressure values.

In all subjects night, with respect to day, was characterized by R–R interval lengthening and blood pressure lowering. Despite this common pattern, day and night means and SDs, night and day differences, $\Delta y/\Delta x$ ratios, a_24 h and b_24 h were different from individual to individual, but they were characteristic and reproducible in 20 out of the 21 subjects in which ABPM was repeated twice. Subjects could thus be classified according to their $\Delta y/\Delta x$ ratios and slope (b_24 h). The 24 h blood pressure-R–R interval relation as calculated from ABPM yields individually characteristic indices of circadian sympatho-vagal reciprocity. This novel approach may be helpful in characterizing the 24 h autonomic control of several groups of patients.

Keywords: ABPM; Blood pressure-heart period relation; Autonomic space; Phase-space distribution; Phase-space trajectories; Reproducibility; Sympatho-vagal reciprocity; Proportionality ratio; Autonomic balance; Autonomic control

1. Introduction

The ambulatory blood pressure monitoring (ABPM) is a widely used, non-invasive, technique which evaluates through intermittent measurements the time course of changes in blood pressure and heart rate in a 24 h period or longer (Owens et al., 1998; Palatini et al., 2000; Clement et al., 2003; Dolan et al., 2005; O'Brien et al., 2005; Maillon et al., 2006; Pickering et al., 2006). The autonomic nervous system is the common denominator of all the cardiovascular events so far documented by the ABPM technique. As a primary cause or a reflexly engaged mechanism or as a common final effector of complex neurohumoral events the autonomic nervous system is involved in all the recorded pressor and cardiac events.

Despite this evidence and the description made several years ago that heart rate tends to vary in parallel with blood pressure (what has been interpreted as evidence of central autonomic control usually predominating over baroreceptor control) (Mancia et al., 1983), heart rate changes have rarely been investigated in detail (Palatini et al., 2000, 2006). In particular the blood pressure-heart rate relationships during 24 h have never been systematically quantified, although they appear to provide an index of autonomic activity based on two variables, rather than one.

* Corresponding author. Istituto di Medicina Cardiovascolare, Ospedale Maggiore and University of Milano, Via F.Sforza 35 20122 Milano, Italy. Tel.: +39 02 55033528; fax: +39 02 50320480.

E-mail address: giorgio.recordati@unimi.it (G. Recordati).

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To this purpose, amongst the variables recorded by ABPM, we have correlated individual blood pressure values (either diastolic or systolic) as an approximate index of the level of sympathetic outflow to the peripheral circulation with the concomitant R–R interval (also called heart period) as an approximate index of the parasympathetic activity to the heart. The reciprocal of heart rate, rather than the heart rate itself, was chosen because it is more linearly related with the underlying autonomic cardiac input and is less dependent than heart rate on baseline levels (Parker et al., 1984; Berntson et al., 1992; Quigley & Berntson, 1996).

The ensuing graphic representation is termed a phase-space in physics and cybernetics because the variable time is excluded from the study and each measurement is connected to the next by a line segment or trajectory (Asbhy, 1956; Prigogine, 1997; Kreyszig, 1988; Heylighen, 1998; Recordati, 2005).

The phase-space representation has also been used in cardiovascular physiology, for instance in describing: 1) the sigmoid, logistic curve of the baroreceptor reflex obtained by phenylephrine injection (Smyth et al., 1969; Hunt & Farquhar, 2005); 2) the regression line of the spontaneous baroreceptor reflex obtained with the sequence technique (Bertinieri et al., 1988; Parati et al., 2000), and 3) the Autonomic Space by Berntson et al. in which four major modes of autonomic control of doubly innervated organs give rise to four differently oriented vectors (Berntson et al., 1991, 1993, 1994a,b).

In the present paper we describe the phase-space distribution of the arterial blood pressure and R–R interval values obtained by ABPM in a 24 h period in 60 healthy young subjects (30 females and 30 males) who volunteered for the study.

In brief the objectives of the present study were: 1) to investigate whether with a non-invasive, intermittent technique, it is possible to unveil a blood pressure-heart period relation suggestive of the prevailing 24 h autonomic control; 2) to verify whether this relation has a measurable and reproducible trend, and 3) to provide a normal standard for this relation against which the effects of a number of different parameters, such as aging, hypertension and dysautonomia, can be compared.

Preliminary accounts of this methodology have been presented in abstract form (Recordati et al., 2005, 2006).

2. Methods

This study was performed on 65 healthy young subjects, 33 females and 32 males who volunteered for this study. All of them were students at the School of Medicine of the University of Milan, and all of them at the first experience with ABPM. Five monitorings were discarded (three females and two males): one female was under antibiotic therapy for Helicobacter Pylori, and the other two had a resting heart rate exceeding 90 bpm; one male was found hypertensive (arterial blood pressure, BP, above 140/90 mmHg) and the other did not sleep at all at night. Data were then collected from 30 female and 30 male subjects. Table 1 summarizes anthropometric data of the two groups of subjects.

Table 1
Characteristics of the study population

	F	M	P
Number	30	30	
Age (years)	21.7±0.7	21.9±1.3	NS
Weight (kg)	55.9±7.1	72.3±9.2	<0.001
Height (cm)	166.4±5.6	178.7±5.4	<0.001
BMI (kg/m^2)	20.01±1.7	22.6±2.3	<0.001
Smokers	4	7	
Clinic SBP (mmHg)	114.2±12.6	124.9±12.9	<0.01
Clinic DBP (mmHg)	71.6±8.0	82.5±9.9	<0.01
Clinic HR (bpm)	76.6±11.6	71.0±12.6	NS
ABPM measurements	87.6±3.7	87.0±3.9	NS

F=females; M=males; BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate. Quantitative values are expressed as mean±SD. ABPM measurements=mean number of valid measurements in the 24 h period. P: for comparison between the two groups (unpaired *t*-test).

2.1. Ambulatory blood pressure monitoring (ABPM)

Spacelabs 90207 devices were used to measure arterial blood pressure values from the nondominant arm during the 24 h, after validation of their readings against those of a mercury sphygmomanometer. Recording started between 11.00 a.m. and 2.00 p.m. The monitors were set to obtain BP readings at 15 min intervals during the day (07.00–23.00 h) and at 20 min intervals during the night (23.00–07.00 h). Monitorings were carried out from Monday through Friday. The subjects were asked to attend their usual daily activities, to keep still at the time of measurement and to note in a diary the time of switching off the light at night, of waking up in the morning, of main meals, and of unusual activities.

2.2. Analysis of data

After acquisition, each ABPM data set was graphically represented in the time domain (Fig. 1A), then all the data were transferred, through Excel, to an analysis and graphic program, Diadem, version 8.1 and version 9.1, National Instruments (Austin, Texas).

Each set was scanned to remove null measurements. Once in the Diadem, the interval between two consecutive heart beats (R–R interval=60000/HR in ms) was calculated and added to the data. Each measurement in a given data set was then characterized by a progressive number which identified its position with respect to the order of acquisition and by six variables measured simultaneously: time (format: hh.mm), diastolic (DBP, mmHg), mean (MBP, mmHg) and systolic (SBP, mmHg) blood pressures, heart rate (HR in bpm) and R–R interval (ms). Values of all variables were then distributed into a major set, the set of 24 h values, and with the aid of the diary records into two subsets: daytime

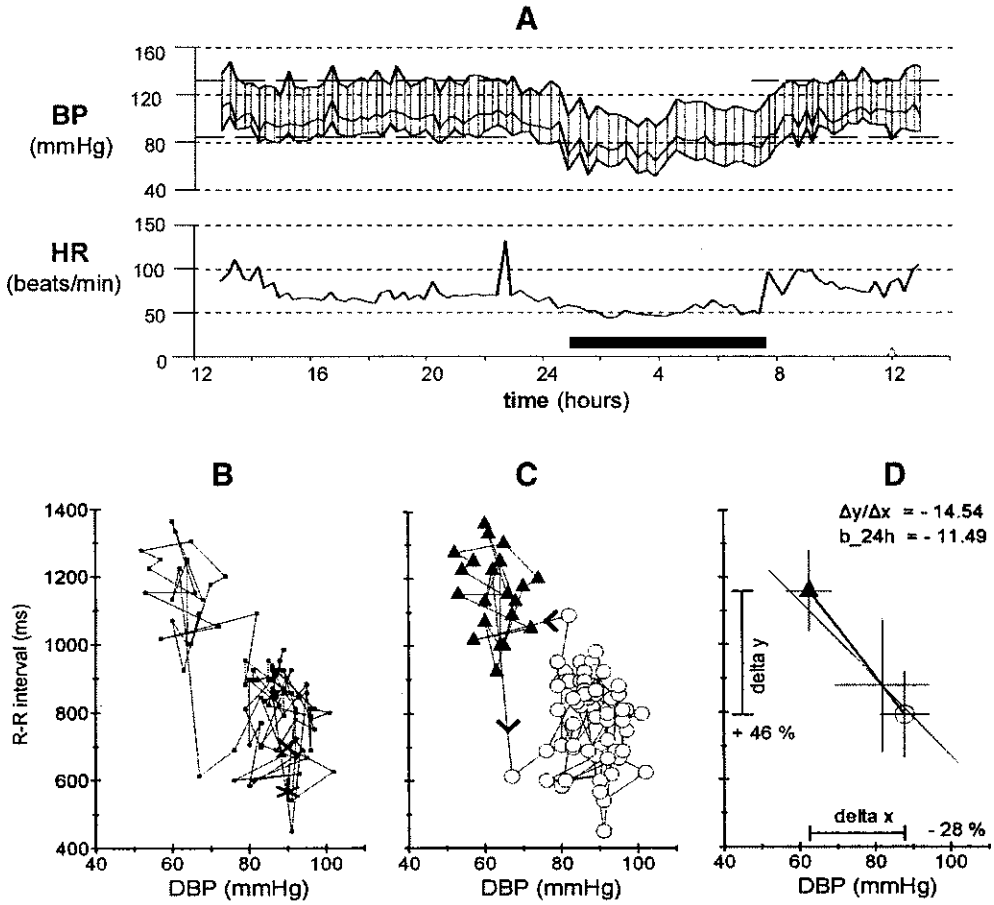

Fig. 1. Ambulatory blood pressure monitoring of a 22 years old male subject (DR, # 57), 70 kg of weight and 177 cm of height, started the 27-04-06 at 12.59 and ended after 24 h at 12.58. A: Time course of changes of SBP, MBP, DBP and HR as obtained from Spacelabs software. Each vertical line inside the blood pressure tracings indicates a measurement. B: Phase–space representation of the relation between R–R interval and DBP for the 89 measurements obtained in the 24 h period. Each measurement is connected to the previous and following one by a straight line segment, except the first and last measurements which are indicated by X and capital asterisk respectively. C: Phase–space representation of the R–R interval-DBP relation for night (black triangles) and day (white filled circles) measurements. The two arrowheads are directed towards the direction of increase in time. Note the marked separation between the two sets of measurements. D: Nighttime (black triangle) and daytime (open circle) mean values with standard deviations. The line bar marked "delta y" parallel to the ordinate axis indicates the difference between mean night and mean day R–R interval. The number near it, +46%, is the calculated percent difference over mean day R–R interval value. The line bar parallel to the abscissa axis and marked "delta x" indicates the difference between mean night and mean day DBP and the number near it, −28%, is the calculated percent difference over mean day DBP. For this subject the calculated $\Delta y/\Delta x$ ratio was − 14.54 ms mmHg^{-1}. The longest oblique line in D is the linear regression through 24 h values whose b (b_24 h), the slope of the linear regression, was − 11.49 ms mmHg^{-1}. The intersection point between the line joining the night and day means and the linear 24 h regression exactly coincides with the 24 h DBP and R–R interval means and is indicated by crossing of the 24 h standard deviations.

(from the start of the recording to the beginning of sleep and from awakening in the morning to the end of the recording) and night (from the beginning to the end of sleep). These sets were then graphically represented in the phase–space of diastolic and systolic blood pressure and R–R interval values either as line segments joining all the 24 h values to highlight trajectories (Fig. 1B) or as line segments joining open circles and closed triangles, indicating day and night values, respectively (Fig. 1C). Data points have been connected because in a geometrical representation like the phase–space, either the distance between any two points or the total trajectory's length can be measured, as an index of the variability of the blood pressure-R–R interval relation. For reasons of space and simplicity this aspect is not further discussed in this paper.

In the scheme exemplified in Fig. 1B an X sign over the first measurement marks the start of the recording and of line segments while an asterisk marks their end. In the scheme of Fig. 1C two arrowheads are drawn on the segments joining day and night sets of values to mark the direction of time.

2.3. Statistical analysis

2.3.1. Mean, SD, coefficient of variation and confidence interval

Means, standard deviations (SD), coefficients of variation (CV) and 95% confidence intervals were calculated for R–R intervals (ms), HR (bpm), DBP (mmHg), MBP (mmHg), SBP (mmHg) of the entire 24 h set and of day and night

subsets (example in Fig. 1D) , individually for each subject, and altogether in the entire cohort or two cohorts divided by gender.

2.3.2. Night–day blood pressure and R–R interval differences, and their ratios

In each individual the difference between mean diastolic and systolic blood pressures at night and during the day were measured, and indicated by Δx. Similarly the night–day difference between R–R intervals was measured and indicated by Δy. These differences are also a measure of the distances between the two sets on the abscissas and on the ordinates, respectively (Fig. 1D).

In order to explore the proportionality of changes in blood pressure and in the R–R interval, differences between night and day were also computed as percentages ((mean night–mean day)/mean day * 100) and indicated by $\%\Delta x$ and $\%\Delta y$ (Fig. 1D).

To obtain an accurate description of the reciprocal phase–space position of the day and night sets of values the ratio $\Delta y/\Delta x$ was computed to yield the slope of the segment joining day and night mean values (see example in Fig. 1D).

2.3.3. Regression through 24 h values

In each individual a linear modeling was applied to the 24 h set of data. According to the equation $y=a+bx$, the intercept "a" and the slope "b" of the regression of all 24 h R–R intervals over all 24 h diastolic and systolic blood pressures values were calculated with Diadem or the statistical program Primer on Biostatistics (Glantz, 2005), the linear regression was represented in the phase–space, and the slope of the regression was indicated by the abbreviation b_24 h at the top of the panel (Fig. 1D).

The strength and the direction of the relation between blood pressure and R–R interval values in the 24 h are expressed by the magnitude and sign of the Pearson product-moment correlation coefficient "r". The segment joining night and day means ($\Delta y/\Delta x$) and the linear regression always intersected each other at a point corresponding to the 24 h mean value (indicated in Fig. 1D by the crossing of the 24 h SD). The segment of the linear regression, being dependent on extreme values and on the variability of values around their mean, was always longer and less steep than the segment joining the means (shorter and thicker oblique line in the example of Fig. 1D).

2.3.4. Comparison between male and female groups

For comparison between male and female groups, the values of each variable, after testing for normal distribution, were compared by unpaired *Student's t test,* and significance was defined at three standard levels: $P<0.05$, $P<0.01$, $P<0.001$ (Table 1). The phase–space distribution of night and day mean values in females and males separately was measured by calculating their regression equations and by comparing their intercept and slopes (Glantz, 2005).

2.3.5. Reproducibility

To study reproducibility, a second monitoring was performed in 21 subjects (9 females and 12 males who volunteered for a repetition of ABPM) at a mean interval of 258.4±177.8 (median: 211.5, range: 20–721) days. Reproducibility was tested according to a classic method (Bland & Altman, 1986) and repeatability coefficient calculated according to standard methods (Lurbe et al., 1996; Omboni et al., 1998; Palatini et al., 1999).

3. Results

Fig. 1B and C and the top panels of Fig. 2A and B, exemplify the phase–space distribution of 24 h DBP (mm Hg) and R–R interval (ms) values in one male and two

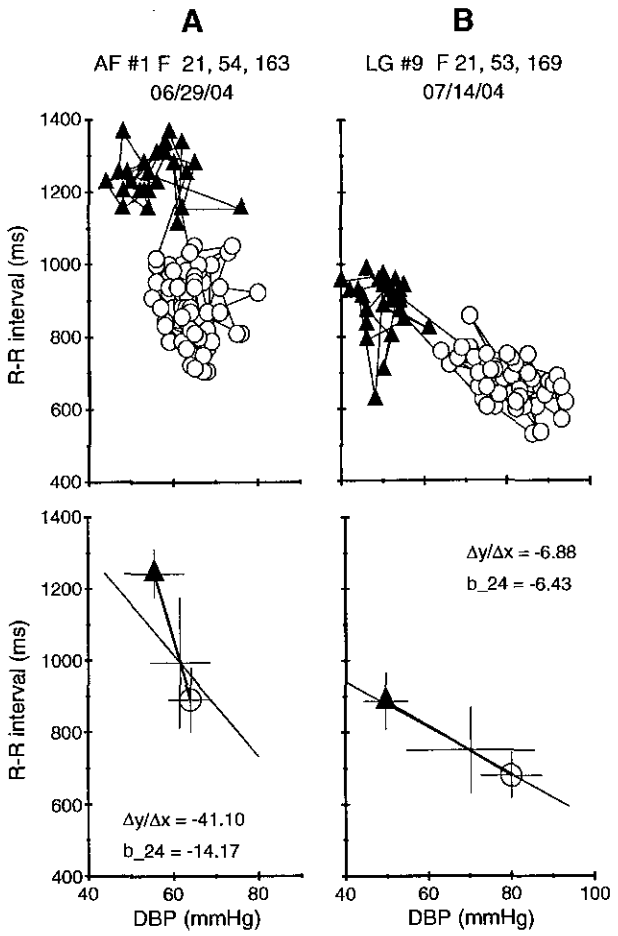

Fig. 2. Phase-space representation of ABPM of two female subjects, A and B. Letters and numbers under A and B indicate: subject's initials, progressive number of recording, gender, age in years, weight in kg, height in centimeters and date of recording. Top panels: phase–space distribution and trajectories of night and day values as in Fig. 1 C. A and B bottom panels represent the means and the standard deviations of set of values represented in top panels, the line segments joining the means and the oblique lines of 24 h values regression as in Fig. 1 D. The calculated $\Delta y/\Delta x$ ratios written inside the bottom panels indicate the slope of the line segments joining the means, while the b_24 h indicate the slope of the linear regressions through the 24 h values, both in ms $mmHg^{-1}$. Please notice the difference in the slopes of both $\Delta y/\Delta x$ ratios and 24 h linear regressions between the two subjects.

female subjects. Although the phase–space distributions of these three subjects differ one from another they also describe a common pattern. Due to the well-known physiological decrease in DBP and HR (R–R interval lengthening) during the night, the night-time set of values (filled triangles) occupies a space region above and to the left of the daytime set of values (open circles). The phase–space distribution of ABPM of all 60 healthy young subjects showed a similar pattern, with the night and day values distributed from top left to bottom right.

An attempt was made both to quantify the phase–space pattern common to all healthy normal subjects and to describe the peculiarity of each subject's phase–space distribution of ABPM values, by measuring day, night and 24 h means and standard deviations, the differences between mean night and mean day of DBP and SBP (Δx) and R–R interval (Δy), the ratio $\Delta y/\Delta x$ and the linear regression through the 24 h values.

3.1. Common pattern

3.1.1. Day, night, 24 h means and SDs

In each individual the day, night and 24 h means±SD were calculated and reported in Table 2 for all 60 subjects

Table 2
Variables mean±SD for 60 subjects

	Mean	±SD	95% CI
DBP day	74.9	8.1	73.3; 76.4
DBP night	57.0	6.4	55.8; 58.3
DBP 24 h	69.8	11.3	68.5; 71.2
SBP day	121.9	9.2	119.8; 124.0
SBP night	104.7	7.4	103.0; 106.4
SBP 24 h	117.0	11.9	115.2; 118.9
HR day	76.3	11.4	73.8; 78.8
HR night	59.3	8.0	57.4; 61.2
HR 24 h	71.5	13.3	69.3; 73.7
RR day	816.0	114.0	789.3; 842.8
RR night	1044.1	119.2	1009.9; 1078.4
RR 24 h	880.6	157.6	853.1; 908.2
Measured ratio			
$\Delta y/\Delta x$ (RR/DBP, ms mmHg^{-1})	−14.4	7.8	−16.4; −12.4
$\Delta y/\Delta x$ (RR/SBP, ms mmHg^{-1})	−15.9	11.5	−18.9; −12.9
Percent ratio			
$\%\Delta y/\%\Delta x$ (RR/DBP)	−1.3	0.6	−1.5; −1.1
$\%\Delta y/\%\Delta x$ (RR/SBP)	−2.4	1.5	−2.7; −2.0
24 h regression RR/DBP			
a (ms)	1517	257	1450; 1583
b (ms mmHg^{-1})	−9.14	2.91	−9.89; −8.39
r	−0.64	0.13	−0.67; −0.60
24 h regression RR/SBP			
a (ms)	1824	360	1731; 1917
b (ms mmHg^{-1})	−8.05	2.59	−8.72; −7.38
r	−0.59	0.14	−0.63; −0.56

DBP, SBP=diastolic and systolic blood pressures in mmHg; Δx=night−day diastolic and systolic blood pressure difference; Δy=night−day R–R interval difference; a=intercept, b=slope, r=Pearson correlation coefficient of 24 h values regressions; CI=confidence interval.

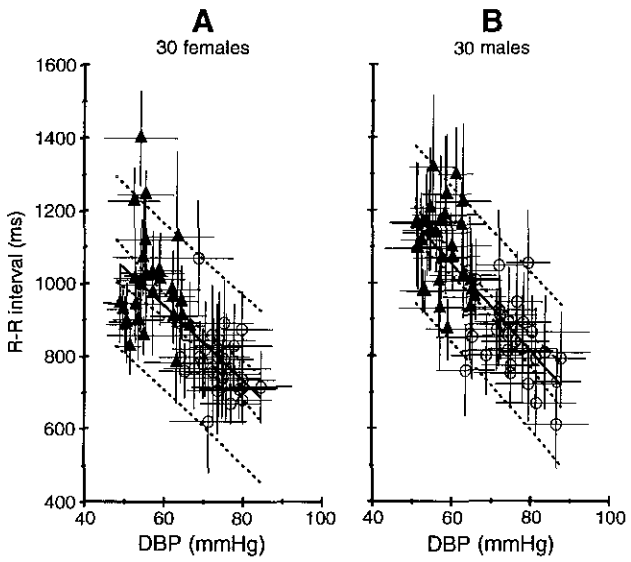

Fig. 3. Phase–space distribution of mean night (closed triangles) and mean day (open circles) values with standard deviations for the 30 females (A) and 30 males (B) subjects. The heavier oblique straight lines in the middle of the two panels are the regression lines through the mean values. The dotted lines nearest to it are the 95% confidence intervals of the regression lines while the two external dotted straight lines in each panel delimit the 95% confidence interval for a new observation.

together. The night DBP and SBP were lower and R–R intervals longer than during the day for all 60 subjects studied. Thus when represented in the phase–space in all subjects the night means occupied a space region above and to the left of the region occupied by day means both in the females' and males' groups (Fig. 3A and B).The linear regression through the night and day mean values (heavier middle oblique lines in Fig. 3A and B) was somewhat steeper for the male group but the difference between slopes did not attain the conventional level of statistical significance. The dotted external lines in Fig. 3A and B indicate the 95% CI for a new observation for the two groups of subjects.

Table 2 also shows that the 24 h SDs were always greater than the day and night SDs and the night SDs were the smallest in both groups.

3.1.2. Night–day differences

The night (x_2)–day (x_1) mean differences ($x_2-x_1=\Delta x$) were negative for DBP and SBP while they were positive for R–R interval (night less day=$y_2-y_1=\Delta y$) in all subjects. These differences, both as directly measured and when calculated as percent of the day measurements, were not significantly different statistically between males and females (unpaired Student's t test).

3.1.3. The $\Delta y/\Delta x$ ratio and the slope of the 24 h value regression

Table 2 shows that for all 60 subjects together the $\Delta y/\Delta x$ ratios (R–R interval change over DBP and SBP changes) and the slope of the linear regression of 24 h R–R intervals over

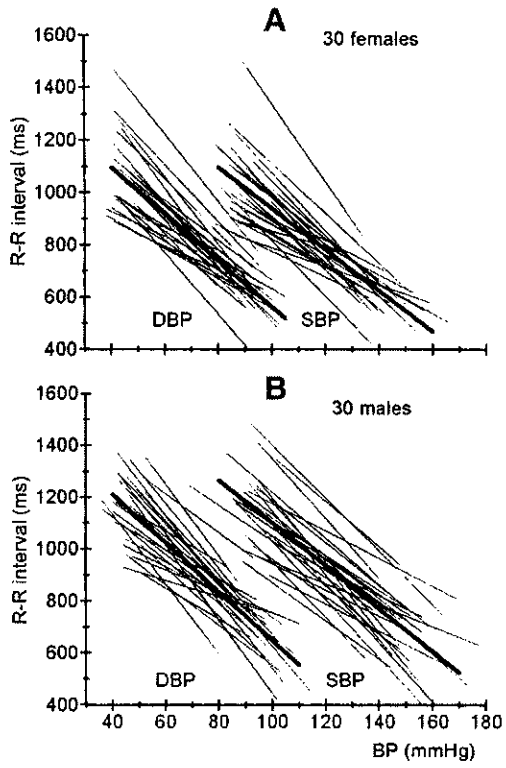

Fig. 4. 24 h linear regressions of diastolic (DBP) and systolic (SBP) blood pressures-R–R interval relations for 30 female (A) and 30 male subjects (B). The heavier lines in each of the two panels are the average regression for the group. The phase-space distribution of males SBP-R–R interval relations appear more scattered than the corresponding females' one.

24 h DBP and SBP values, *b*_24 h, were negative. When graphically represented they were thus all oriented from top left to bottom right (Figs. 1, 2, 3 and 4). In Table 2 average $\Delta y/\Delta x$ and 24 h regression slopes and the Pearson's correlation coefficient calculated on 24 h values, ranges and confidence intervals are also reported.

Pearson's correlation coefficient, r, for DBP-R–R interval relation was statistically significant at the 0.01 level in 2 subjects and at the 0.001 level in 58 subjects, indicating that DBP increments are accompanied by statistically significant R–R interval shortening, i.e. increases in HR in all subjects studied. Pearson's correlation coefficient, r, for SBP-R–R interval relation did not reach statistical significance in 1 subject, it was significant at the 0.05 level in another subject, and was significant at the 0.001 level in 58 subjects. As shown in Fig. 4B, the males' SBP-R–R interval relations appear more scattered than the corresponding DBP relations.

3.2. Individual differences

3.2.1. Day, night and 24 h means, Δx and Δy, the $\Delta y/\Delta x$ ratio and linear regression

Despite a circadian pattern common to all subjects, each individual's mean day and night blood pressures and R–R intervals, the night fall in blood pressure (Δx) and the night lengthening of R–R interval (Δy) (Fig. 3), the ratios $\Delta y/\Delta x$ and the slopes of the linear regressions through the 24 h values (Fig. 4) were different from one subject to another. In Fig. 3A, it is evident that although several females had very similar daytime DBP, for example in the range between 70 and 80 mmHg, their daytime R–R intervals could be markedly different. Similar was the case for males (Fig. 3B). A statistically significant relation was found between mean day DBP and Δx (r=0.6809, n=60, P<0.001) which indicates that the night fall in diastolic blood pressure is greater the higher is mean diastolic blood pressure during the

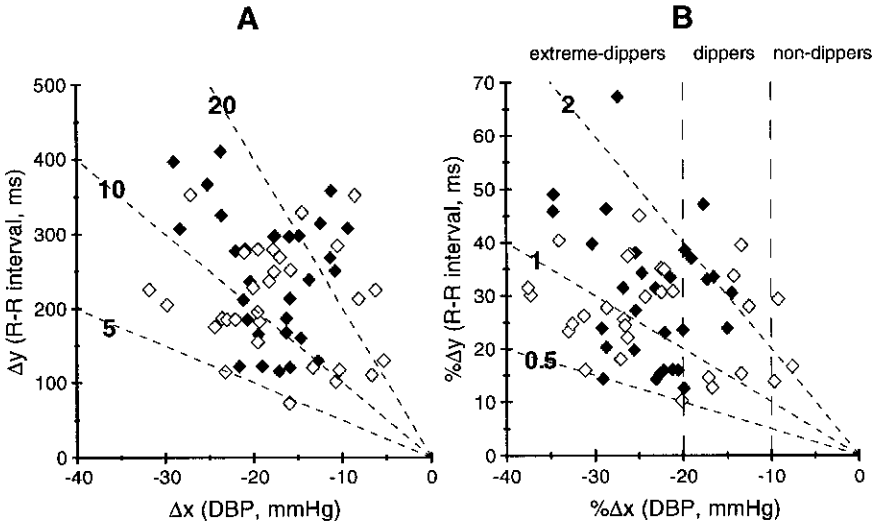

Fig. 5. A: Mean night−mean day R–R interval measured difference (Δy in ms) over mean night−mean day DBP difference (Δx in mmHg) for 30 female (filled white rhombs) and 30 male (black rhombs) subjects. The dotted oblique straight lines originating at the zero value on the abscissa have been drawn according to proportionality factors of 5, 10 and 20 ms $mmHg^{-1}$ between the two variables. B: Mean night−mean day R–R interval percent difference (%Δy in ms) over mean night−mean day DBP percent difference (%Δx in mmHg) for the same 60 subjects as in A. The dotted oblique straight lines have been drawn according to proportionality factors of 0.5. 1 and 2 ms $mmHg^{-1}$. The two vertical dotted lines have been drawn to identify subjects according to the night fall in DBP only, into the non-dipper, dipper and extreme-dippers categories.

day. Statistically non significant was the relation between mean day R–R interval and its night lengthening, Δy (r=0.0224, n=60), however. Furthermore, although the slopes of the linear regression of 24 h R–R intervals and DBP were consistently negative in all subjects, slopes could have widely different values, ranging from −14.28 to −3.14 (Table 2).

3.2.2. Subjects classification

The ratio between measured Δy and Δx values indicates the amount (in ms $mmHg^{-1}$) by which the R–R lengthens at night for a unitary decline in DBP and SBP. In Fig. 5A, which shows the relation between Δx and Δy for all subjects studied, three lines have been drawn to separate subjects with R–R interval increases for each mmHg DBP decline ranging between 0 to 5 (2 subjects), 5 to 10 (18 subjects), 10 to 20 (28 subjects) and above 20 ms (12 subjects). From Fig. 5A no differences between males and females appear. On the basis of the measured $\Delta y/\Delta x$ ratio subjects may thus be classified into different classes.

To explore proportionality of R–R interval and DBP changes, percent Δx and Δy and the % Δx/% Δy ratio were also calculated. Fig. 5B shows the relation between % Δx and % Δy changes for all subjects studied. Oblique lines indicate proportionality factors ranging between 0 and 0.5 (1 subject), 0.5 to 1 (23 subjects), 1 to 2 (27 subjects) and above 2 (9 subjects). These classes identify a proportionality factor. For example for a 25% blood pressure drop at night those subjects whose R–R lengthens by 12.5%, will be clustered around the proportionality factor line marked 0.5, subjects with a 25% R–R lengthening will be clustered around a proportionality factor of 1, while subjects with R–R lengthening around 50% will fall around the proportionality factor line marked 2. In addition of the oblique lines distributing subjects according to % $\Delta y/\Delta x$ ratios, the vertical lines in Fig. 5B separate the subjects on the basis of night DBP falls <10%, between 10 and 20%, or >20%, which correspond to the usual definition of non-dippers (3 individuals), dippers (14 individuals) and extreme dippers (43 individuals). Our subjects being young and normotensive, their large majority was made of dippers and extreme-dippers, but it is evident from Fig. 5 that, within each traditional category of "dipping", quite different ratios describing the relative bradycardia over the relative hypotension at night could be observed.

3.2.3. Reproducibility

To test reproducibility, in the 21 subjects who volunteered (12 M and 9F), the ABPM was repeated twice, the second 249.9±174.5 days after the first. In Table 3 the repeatability coefficient, twice the standard deviation of change, indicates that there was close agreement between the paired recordings for all the measured variables. As indicated by the percent repeatability coefficient, however, the reproducibility was lowest for day DBP and was lower for HR than for R–R interval measurements.

Table 3
Reproducibility of ABPM in 21 subjects

Variable	ABPM 1 means	ABPM 2 means	Change	Consistency (range)	Repeatability (%)
DBP (mmHg)					
Day	75.3	75.7	−0.5	2.6 (0.0; 11.4)	8.0 (50)
Night	55.9	57.5	−1.5	2.8 (0.0; 11.4)	7.0 (43)
24 h	69.9	70.3	−0.4	2.2 (0.1; 10.1)	6.7 (36)
SBP (mmHg)					
Day	121.6	122.0	−0.3	3.9 (0.5; 17.8)	11.1 (34)
Night	103.9	104.7	−0.7	3.4 (0.2; 13.7)	10.2 (34)
24 h	116.7	117.1	−0.4	3.5 (0.2; 16.1)	10.0 (33)
RR (ms)					
Day	811.3	805.1	6.1	58.9 (7.4; 189.4)	143.2 (44)
Night	1030.0	1040.3	−10.2	49.5 (1.5; 83.3)	132.7 (32)
24 h	869.5	871.6	−2.1	50.0 (4.3; 119.7)	117.6 (36)
Ratio $\Delta y/\Delta x$ DBP	−12.8	−13.9	1.1	3.4 (0.06; 14.8)	9.7 (36)
Ratio $\Delta y/\Delta x$ SBP	−14.6	−17.3	2.7	4.3 (0.4; 20.0)	12.8 (26)
*b*_24 h RR/DBP	−8.3	−8.9	0.6	1.9 (0.31; 6.86)	4.7 (49)
*b*_24 h RR/SBP	−7.4	−7.9	0.5	1.5 (0.20; 4.45)	3.54 (39)

Change: average difference between recordings (first minus second recording) taking into account the sign of the difference. Consistency: average difference between the recording omitting the sign of the difference, i.e., the average absolute value of the difference (range of the difference between parentheses).Repeatability coefficient: twice the standard deviation of the change. Percent coefficient: repeatability divided four time the standard deviation of the mean of the two measurements, times 100. The last four variables are in units of ms $mmHg^{-1}$.

Twenty subjects showed good reproducibility of both $\Delta y/\Delta x$ ratio and slope of 24 h RR/DBP regression. Only one subject has been found outlier for $\Delta y/\Delta x$ ratio (subject # 8) and only one for the slope of the 24 h RR/DBP regression (subject # 34). Time intervals between the two ABPM were 515 and 133 days respectively. None of the subjects was simultaneously outlier for DBP, R–R interval, $\Delta y/\Delta x$ ratio and slope of 24 h values regression.

4. Discussion

On the basis of the proposed novel methodological approach four main conclusions may be drawn from the reported results: 1) all healthy young subjects showed a common trend in the phase–space distribution of ABPM values; 2) despite this common trend each subject had his own individual phase-space distribution of ABPM values; 3) both the common circadian pattern and the individual characteristics were reproducible and 4) both are probably expression of the central reciprocity of vagal and sympathetic action and of the peripheral sympatho-vagal interactions at the target organs levels in the single subject.

4.1. The common trend

The phase–space distribution of ABPM 24 h values of all 60 subjects followed a common trend, namely the night-time set was positioned at the left and above the daytime set of values. This common trend was obviously determined by the normal circadian decline in blood pressure and lengthening of R–R interval occurring at night with respect to day which causes a shift of points to the left and upward. The set mean values also underline this common trend, daytime blood pressure being higher and R–R interval shorter than during night-time (Table 2). The reciprocal position of the two sets was also quantified by the slope of the $\Delta y/\Delta x$ ratio and by the slope of the 24 h values linear regression. In all subjects these slopes were negative and directed from top left to bottom right and the 24 h DBP-R–R interval relations were converging towards highest DBP and shortest R–R interval values (Fig. 4). Hence, with an intermittent non-invasive technique such as the ABPM it is possible to highlight the existence of a 24 h measurable trend in the relation between heart period and DBP and SBP.

The direction of the ABPM loop results from the influences of all the factors which affect cardiac and vascular function during spontaneous behaviors in a 24 h period, amongst which the most relevant ones seem the central sympathetic drive and the level of physical activity. The distance between night and day sets of values is in fact mainly determined by the centrally driven morning surge and night fall of blood pressure. During these transitional periods between two differently stable states, sleep being asymptotically stable while wakefulness being a stable oscillatory state (Recordati & Bellini, 2004), baroreflexes seem to play a secondary role since HR always parallel blood pressure changes (Carrington et al., 2003, 2005). The phase–space distribution of night and day clouds of points seems therefore to be mainly dependent on the prevalence of vagal tone and rest at night and of sympathetic tone and overt physical activity during the day, an alternation which may be described as the 24 h sympatho-vagal reciprocity (Furlan et al., 1990; Recordati, 2003).

The functional meaning of the ABPM loop may be easily appreciated if it is seen in the context of the "Autonomic Space" (Berntson et al., 1991, 1993, 1994a,b). In this context the ABPM loop is characterized by a vector directed from top left to bottom right, parallelling the effects of a centrally driven sympatho-vagal circadian alternation (the so-called vector of "reciprocity"), while the baroreceptor loop is directed from the bottom left to the top right (mimicking the vector of "coactivity") (Fig. 6). Hence the ABPM and the baroreceptor loops will be almost perpendicularly directed reflecting the different forces by which they are generated (Recordati, 2002, 2003). It is evident from our findings that during the 24 h period the pattern of centrally driven sympatho-vagal alternation predominates over the reflex pattern, as supported by previous observations of the paucity of spontaneous baroreceptor-associated patterns of blood pressure-R–R interval relations (Bertinieri et al., 1988; Parati et al., 2000).

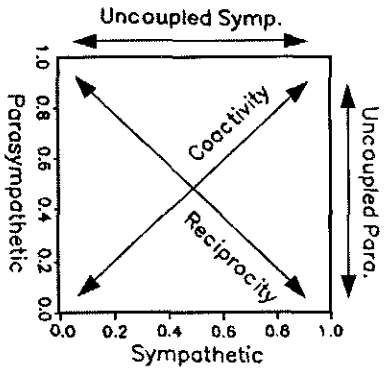

Fig. 6. Two dimensional representation of autonomic space. (Axes are expressed in proportional units of activation of the sympathetic and parasympathetic branches. The arrow extending from the left to the right axes intersections depicts the diagonal of reciprocity. The arrow extending from the back to the front axes intersections represents the diagonal of coactivity. The arrows along the axes depict uncoupled changes in the single autonomic nervous system divisions. These arrows, and vectors parallel to them, illustrate the major modes of autonomic control.) From (Berntson et al., 1993), with permission.

Our results are consistent with findings of spectral analysis of blood pressure and R–R interval variabilities derived from continuous invasive human recordings (Furlan et al., 1990). With respect to time and frequency domains the phase–space representation seems to offer a more immediate and synthetic view of 24 h circadian sympatho-vagal reciprocity, however.

4.2. Individual characteristics

The major sources of interindividual variability were the night to day distance of the two sets, Δy and Δx, the $\Delta y/\Delta x$ ratio and the overall distribution of 24 h values in space (Table 2).

As Figs. 1, 2 and 3 illustrate, the two sets were positioned at a variable distance and with different angles in different subjects. In those subjects in whom there was a clear distance between the two sets of values, like the subjects shown in Figs. 1, 2A and B, this was mainly determined by a combination of night fall and morning surge in blood pressure and heart rate. Noteworthy are the differences between the two subjects of Fig. 2. While R–R interval changes clearly prevail in Fig. 2A and the two sets of data are mainly vertically distributed, diastolic blood pressure changes prevail in Fig. 2B and the two sets are almost horizontally distributed. In the language of the Autonomic Space described above, the distribution in Fig. 2A approaches the vector of parasympathetic uncoupling, while that in Fig. 2B the vector of sympathetic uncoupling (Fig. 6). In addition to autonomic influences, many other factors may have contributed to shift the blood pressure-R–R interval relation in space, such as humoral factors, the level of physical activity during the day and the subjects' physical

fitness, the amount and quality of sleep, the time to go to bed and wakeup in the morning, data acquisition during non-REM and REM sleep, etc (Zoccoli et al., 2001).

For this reason subjects have been classified on the basis of the $\Delta y/\Delta x$ ratio both on measured and percent values (Fig. 5A and B). The proportionality ratios that we have traced in Fig. 5 illustrate the several degrees of reciprocity along which subjects with different night–day sensitivity are clustered. The steepest ratios which ensue from a prevalence of R–R interval over blood pressure changes, might indicate a preponderance of vagal over sympathetic tone, while the flattest ratios, which arise from a prevalence of blood pressure over frequency changes, might indicate a preponderance of sympathetic tone. Similar considerations may apply to interpret the different slopes of 24 h regressions which reached statistical significance at the $P<0.001$ level.

It was interesting to note that in females' the individual 24 h systolic blood pressure-R–R interval regressions were less scattered than in males' (Fig. 4). Although our findings do not provide any causal explanation, a possible contribution of estrogens to blunt cardiovascular individual differences and/or of androgens to exaggerate them is a plausible but entirely hypothetic explanation so far.

4.2.1. Reproducibility

Previous studies have shown that reproducibility of ABPM is better than that of clinic blood pressure both in children (Lurbe et al., 1996; Lurbe & Redon, 2002; Stergiou et al., 2004), adults (Musso et al., 1997) and elderly subjects (Engfeldt et al., 1994; Wendelin-Saarenhovi, 2001). We confirm these previous data and in addition we show that the reproducibility of ABPM was fairly good also for the $\Delta y/\Delta x$ ratio and for the 24 h values regression. Studying reproducibility as a percentage of repeatability (the lower the percentage of repeatability the higher the reproducibility (Table 3)) (Lurbe et al., 1996; Omboni et al., 1998; Palatini et al., 1999), the $\Delta y/\Delta x$ ratios were amongst the better reproducible variables. By taking into account all these factors, in the small population of healthy young subjects that we have studied, the phase–space representation of ABPM seems to be fairly reproducible.

4.3. Limitations

The ABPM technique has implicit methodological limitations, such as a relatively low sample rate of cardiovascular variables and lack of information about respiratory activity and the precise onset and the phases of sleep (Zoccoli et al., 2001). Hence the approach here proposed should not be viewed as a precise method for evaluating the sympatho-vagal balance of an individual, but rather as a simple descriptive index of the circadian sympatho-vagal reciprocity over the 24 h period in a clinical setting.

Although the phase-space analysis is an attractive method for condensing heart rate and arterial blood pressure changes of the 24 h period into a single plot, future work is certainly needed to verify its appropriateness for pharmacological and clinical applications.

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