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Correlates of the diurnal blood pressure profile in a population study

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ABSTRACT. This study tried to identify the correlates of the diurnal blood pressure profile in a random population sample of 313 men and 317 women (age: 20-88 years). The nocturnal blood pressure fall, the cusum-derived circadian alteration magnitude and plot height and the amplitudes of the global Fourier curve and its 1st and 2nd harmonic reflect mainly the daily alteration between a high and low blood pressure span. Several of these parameters increased with a higher blood pressure level and smoking, but were inversely correlated with age and γ-glutamyltransferase (index of alcohol intake). The amplitudes of the 3rd and 4th Fourier harmonics, which mainly reflect shorter-lived blood pressure fluctuations, increased with aging. The ambulatory pressure level increased with age, body mass index, pulse rate counted by an observer (considered as an index of sympathetic reactivity), serum calcium, alcohol consumption and contraceptive pill intake, but the cusum-derived trough systolic pressure was lower in smokers than in non-smokers. In conclusion, in the population at large blood pressure variability over shorter periods of time increases with age. The variability inherent to the daily alteration of a high and low blood pressure span, decreases with aging and alcohol consumption, but rises with increasing pressure and smoking. To which extent these associations are due to certain behavioral patterns, e.g. associated with smoking or alcohol intake, remains to be elucidated.

Key words: Ambulatory blood pressure, acrophase, amplitude, blood pressure variance, cumulative sums, Fourier analysis, nocturnal pressure fall.

INTRODUCTION

Ambulatory monitoring provides the means to quantify blood pressure variability and to describe the diurnal blood pressure profile (1, 2). The methods for the parameterisation of the diurnal blood pressure profile (3) range from simple statistics, such as the mean and standard deviation of the blood pressure in single recordings to more complex and computationally intensive techniques, such as the runs test (4, 5), the parameters of the Fourier curve (5), and the so-called cusum-derived statistics (6).

Few studies (7) used more than one statistical technique to model the diurnal blood pressure profile and to study its correlates in the population at large. It was therefore the objective of this study to model the diurnal blood pressure curve by several methods and to determine the correlates of its statistical parameters. The analyses were carried out in 313 men and 317 women, who constituted a random population sample.

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METHODS

Subjects

This study is part of an ongoing population survey, in which the participants were randomly selected from the population of a geographically defined area (7, 8). The sample was stratified by gender and age in an attempt to provide equal numbers of men and women in 10 year age classes from 20 to 80 years.

The subjects included in this report were recruited starting from the last trimester of 1989 through the first semester of 1992. The sample included 1414 subjects. Subjects were excluded from further participation, when they did not live on the address listed in the population registry (N = 128, of whom 19 had died) or when they could not move about freely (N = 4). During the first year of the survey, subjects taking antihypertensive drugs, diuretics or nitrates were also excluded from participation (N = 131). Of the remaining 1151 subjects, 70% (N = 807) consented to participate and 68% (N = 786) had their ambulatory blood pressure measured. However, 68 subjects were removed from the analysis, because their ambulatory recording covered less than 20 hours, or because less than 10 readings were available for computing the day-time blood pressure mean or less than 5 for the night-time mean. In addition, 88 subjects were excluded from this analysis, because they were on treatment with blood pressure lowering drugs. The study group thus totaled 630 persons, 313 men and 317 women.

Blood pressure measurements

All participants were visited at their home, where a trained observer measured their systolic and diastolic (phase V) pressures 5 times consecutively after they had rested for 5 min in the sitting position. Pulse rate was counted over 1 min. These readings were obtained between 8:00 and 21:00 h with a standard mercury sphygmomanometer and with a cuff with an inflatable bladder length of 22 cm and with a bladder width of 12 cm. In 69 obese subjects with an arm circumference exceeding 32 cm a larger cuff (35 * 15 cm) was employed.

The nurses involved in this study were tested for the accuracy of their blood pressure measurements at three-monthly intervals. They had to record the blood pressures from a videofilm showing a falling mercury column with Korotkoff sounds (Blood Pressure Measurement, British Medical Journal, BMA House, Tavistock Square, London WC1H 9JR, UK). The nurses were considered to have passed the test, when each of their pressure readings was within 5 mmHg compared with those of experienced medical staff. Digit preference was also monitored during the study.

The ambulatory blood pressure recordings were started at the subjects' homes. Oscillometric SpaceLabs 90202 monitors (SpaceLabs Inc., Redmond, Washington, USA) (9) were programmed to obtain blood pressure readings with an interval of 20 min from 8:00 to 22:00 h, and every 45 min for the remainder of the day. In each person cuff size was similar for the conventional and ambulatory blood pressure measurements.

Analysis of the ambulatory blood pressure recordings

All ambulatory recordings were truncated so that their total duration did not exceed 24 h. The recordings were not edited, i.e. measurements were only excluded when they could not be successfully completed. Within subject means and variances of the ambulatory measurements were weighted by the time interval between consecutive readings.

In order to eliminate the transition periods between daytime activity and sleep, during which the blood pressure often changes rapidly, day-time was defined as the interval from 10:00 to 20:00 h, and night-time from midnight to 6:00 h (7, 8). The nocturnal blood pressure fall was defined as the difference between the average day- and night-time blood pressure.

A Fourier series consisting of 4 harmonics with periods of respectively 24, 12, 8 and 6 hours was fitted to each person's ambulatory readings by weighted least squares regression (5). Weighting for the time between successive blood pressure readings accounted for the inequal intervals due to the programming of the recorders and due to missed

readings. For each of the 4 harmonics and for the global Fourier curve, the amplitude and acrophase were computed. The amplitude is half the difference between each curve's minimum and maximum and the acrophase is the time lag between the maximum and midnight (reference point) (5).

Cumulative sums (cusums) and cusum-derived statistics were calculated, as described elsewhere (6). The cusum method consists of subtracting the time-weighted mean 24 h blood pressure from each individual blood pressure reading, multiplying the remainder by the duration of the preceding time interval, adding the resultant pressure-time product to the previous sum and plotting the cumulative sum against time. The cusum plot height is the difference between the maximum and minimum of the cusum plot (6). The cusum-derived crest blood pressure is the highest time-weighted blood pressure sustained for any 6 hours during 24 h, and likewise the cusum-derived trough pressure is the lowest time-weighted pressure sustained for any 6 hours (6). The cusum-derived circadian alteration magnitude is calculated by subtracting the cusum-derived trough from the crest pressure (6).

Other measurements

Serum was analysed for total calcium by complexiметric titration (10). Serum γ-glutamyltransferase (11) was measured as an index of alcohol intake. Twenty-four h urine samples were analysed for sodium, potassium and creatinine (12). A self-administered questionnaire inquired into each participant's medical history, smoking habits, and intake of medications.

Statistical analysis

Data base management and statistical analyses were performed with the SAS software (The SAS Institute Inc., Cary, North Carolina). Measurements with a skewed distribution were normalised by a logarithmic transformation before being used in regression analysis. Unless indicated, the central tendency and spread of the data were reported as the mean±standard deviation.

Statistical methods included Student's t-test and multiple linear regression analysis. Significant covariates of the parameters of the diurnal blood pressure profile were traced by a stepwise regression procedure, terminating when all regression coefficients in the model were significant at the 5% probability level. The following variables were considered as potential correlates of the diurnal blood pressure profile: age (linear and squared terms), body mass index the blood pressure level (derived from the conventional blood pressure measurements at home to have an independent estimate), pulse rate in the presence of an observer (as a proxy for sympathetic reactivity), current smoking habits (coded 0 for non-smokers and 1 for smokers), γ-glutamyltransferase as an index of alcohol intake,

Table 1 - Characteristics of the subjects.

	Men	Women
Number	313	317
Clinical measurements		
Age (years)	49 ± 14	47 ± 13
BMI (kg/m^2)	25.7 ± 3.3	25.1 ± 4.1
SBP (mmHg)	126 ± 16	121 ± 16
DBP (mmHg)	76 ± 9	74 ± 9
Pulse rate (bpm)	71 ± 10	74 ± 9
Ambulatory measurements		
24 h SBP (mmHg)	120 ± 10	115 ± 10
24 h DBP (mmHg)	72 ± 7	69 ± 7
Day-time SBP (mmHg)	127 ± 11	121 ± 10
Day-time DBP (mmHg)	78 ± 8	75 ± 7
Night-time SBP (mmHg)	109 ± 11	104 ± 11
Night-time DBP (mmHg)	63 ± 8	59 ± 7
Serum measurements		
Total calcium (mmol)	2.33 ± 0.10	2.33 ± 0.10
γ-GT (u/l)	16 ± 13	10 ± 8
24h urinary excretions		
Volume (l)	1.49 ± 0.61	1.63 ± 0.63
Sodium (mmol)	185 ± 73	151 ± 56
Potassium (mmol)	74 ± 27	64 ± 21
Creatinine (μmol)	14.0 ± 3.5	9.7 ± 2.3
Na^+/K^+ ratio	2.65 ± 1.01	2.55 ± 1.44

Values are means ± standard deviation. SBP, DBP = systolic, diastolic pressure; γ-GT = γ-glutamyltransferase.

All differences between men and women were significant ($p<0.05$) with the exception of age, serum total calcium and the urinary Na^+/K^+ ratio.

serum total calcium, the urinary sodium/potassium ratio, and in women the intake of the contraceptive pill or gonadal hormones as substitution therapy (dummy variable coded 0 in non-users and 1 in users).

RESULTS

Characteristics of the participants

The age of the 313 men and 317 women averaged 47 years and ranged from 20 to 88 years (Table 1). Systolic pressure (average of 5 measurements at home) ranged from 92 to 211 mmHg and diastolic pressure from 50 to 104 mmHg. A total of 207 persons were smokers (median: 15 cigarettes/day) and 112 reported daily intake of alcohol (median: 20 g/day). Fifty-five women took the contraceptive pill or were on hormonal substitution therapy.

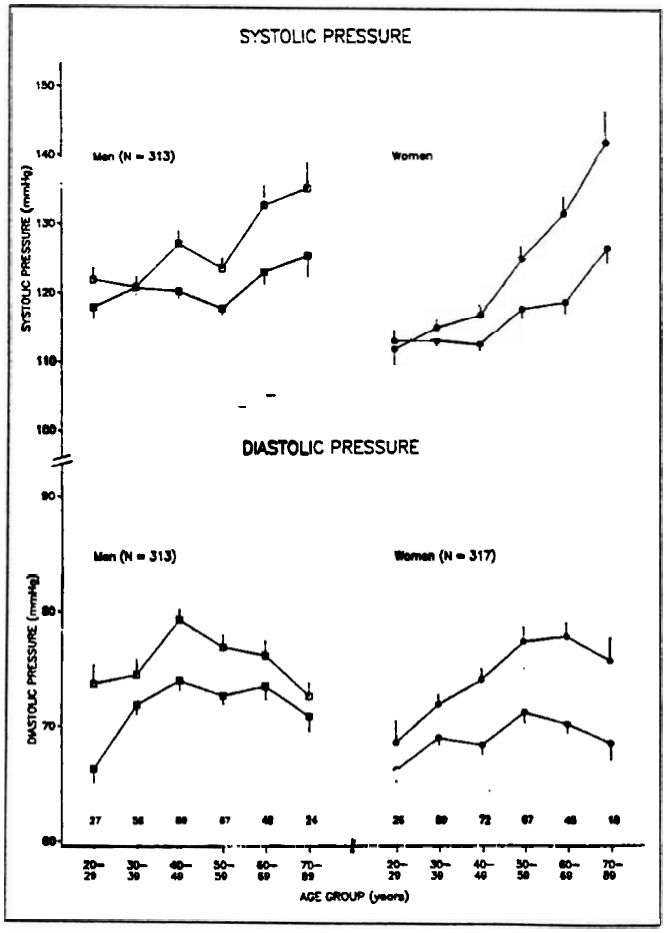

Fig. 1. The conventionally measured blood pressure (average of 5 readings by a nurse at the subjects' home, open symbols) and the 24 h ambulatory pressure (filled symbols) in 10 year age classes in men (squares) and women (circles). Values are means ± standard error. For each of the stratification groups the number of subjects is given.

The blood pressure level

Systolic and diastolic blood pressures both on conventional and ambulatory measurement

Table 2 - Parameters of the diurnal curve.

	Men		Women
Number	313		317
Variance			
Sys_v (mmHg)^2	71 ± 19		69 ± 18
Dia_v (mmHg)^2	62 ± 20		63 ± 18
Nocturnal fall			
Sys_{nf}	17.8 ± 8.7		17.3 ± 8.2
Dia_{nf}	14.7 ± 6.9		15.3 ± 6.3
Cusum parameters			
Sys_c	131 ± 11	*	126 ± 11
Dia_c	82 ± 9	*	79 ± 8
Sys_t	107 ± 10	*	103 ± 10
Dia_t	61 ± 8	*	58 ± 7
Sys_{am}	24.3 ± 8.2		23.0 ± 7.4
Dia_{am}	20.4 ± 7.1		20.5 ± 6.2
Sys_{ph} (mmHg * hr)	103 ± 36		98 ± 32
Dia_{ph} (mmHg * hr)	87 ± 32		88 ± 27
Fourier amplitudes			
Sys_a	17.0 ± 5.0		16.3 ± 4.9
Dia_a	14.4 ± 5.0		14.2 ± 4.2
Sys_1	11.3 ± 4.8		10.8 ± 5.9
Dia_1	9.6 ± 4.2		9.6 ± 4.0
Sys_2	5.8 ± 2.9		5.9 ± 4.1
Dia_2	4.8 ± 2.7		5.0 ± 3.1
Sys_3	3.8 ± 2.1		3.6 ± 2.4
Dia_3	3.4 ± 2.2		3.1 ± 2.2
Sys_4	3.6 ± 2.1		3.6 ± 2.1
Dia_4	3.3 ± 2.1		3.2 ± 2.0

Values are means ± standard deviation.

*$p<0.001$ for the difference between men and women.

Unless otherwise indicated, variables are expressed in mmHg. Sys, Dia= systolic, diastolic pressure ; Sys_v, Dia_v= within subject variance of all ambulatory readings over 24 h ; Sys_{nf}, Dia_{nf}= nocturnal fall in pressure; Sys_a, Dia_a= overall amplitude; Sys_c, Dia_c= cusum-derived crest pressure; Sys_t, Dia_t= cusum-derived trough pressure ; Sys_{am}, Dia_{am}= cusum-derived circadian alteration magnitude ; Sys_{ph}, Dia_{ph}= cusum plot height; Sys_1, Sys_2, Sys_3, Sys_4, Dia_1, Dia_2, Dia_3, Dia_4= amplitudes of the 1st through 4th harmonic.

Table 3 - Correlates of the parameters describing the diurnal blood pressure curve in 313 men.

	R^2	INT mmHg	BP mmHg	Age year	Age^2 $year^2$	BMI kg/m^2	Rate bpm	SCa mmol/l	γGT u/l	SMK 0.1
Blood pressure										
Sys_{24}	0.099	118.4	nc	-0.864	0.00920	0.79	ns	ns	ns	ns
Dia_{24}	0.161	42.3	nc	ns	ns	0.56	0.16	ns	3.57	ns
Sys_d	0.093	106.7	nc	ns	ns	0.78	ns	ns	ns	ns
Dia_d	0.126	48.5	nc	ns	ns	0.65	0.18	ns	ns	ns
Sys_{ni}	0.093	118.7	nc	−1.191	0.01252	0.63	ns	ns	ns	ns
Dia_{ni}	0.126	33.6	nc	0.082	ns	0.39	0.1ɔ	ns	4.35	ns
Sys_c	0.088	126.1	nc	−0.828	0.00888	0.89	ns	ns	ns	ns
Dia_c	0.108	53.1	nc	ns	ns	0.68	0.16	ns	ns	ns
Sys_t	0.090	110.0	nc	−0.865	0.00924	0.63	ns	ns	ns	−1.97
Dia_t	0.174	20.0	nc	0.598	−0.00510	0.38	0.15	ns	3.96	ns
Variance										
Sys_v	0.049	38.3	0.261	ns	ns	ns	ns	ns	ns	ns
Dia_v	--	--	--	--	--	--	--	--	--	--
Nocturnal fall										
Sys_{nf}	0.031	7.5	0.076	ns	ns	ns	ns	ns	ns	2.11
Dia_{nf}	0.030	16.8	ns	ns	−0.00084	ns	ns	ns	ns	ns
Cusum parameters										
Sys_{am}	0.047	11.4	0.097	ns	ns	ns	ns	ns	ns	2.10
Dia_{am}	0.031	15.3	0.089	ns	−0.00064	ns	ns	ns	ns	ns
Sys_{ph}	0.049	43.0	0.452	ns	ns	ns	ns	ns	ns	8.83
Dia_{ph}	0.032	65.5	0.457	−0.271	ns	ns	ns	ns	ns	ns
Fourier parameters										
Sys_a	0.046	23.2	0.054	ns	ns	ns	ns	−5.56	ns	ns
Dia_a	--	--	--	--	--	--	--	--	--	--
Sys_1	0.018	6.2	0.040	ns	ns	ns	ns	ns	ns	ns
Dia_1	0.022	10.7	ns	ns	−0.00043	ns	ns	ns	ns	ns
Sys_2	0.049	1.0	0.036	ns	ns	ns	ns	ns	ns	0.71
Dia_2	--	--	--	--	--	--	--	--	--	--
Sys_3	0.017	10.0	ns	ns	ns	ns	ns	−2.74	ns	ns
Dia_3	—	--	--	--	--	--	--	--	--	--
Sys_4	0.020	2.6	ns	0.021	ns	ns	ns	ns	ns	ns
Dia_4	--	--	--	--	--	--	--	--	--	--

Dependent variables. Unless otherwise indicated in this footnote, the dependent variables are expressed in mmHg. Sys, Dia=systolic, diastolic pressure; Sys_{24}, Dia_{24}=24 h ambulatory blood pressure; Sys_d, Dia_d= day-time blood pressure; Sys_{ni}, Dia_{ni}= night-time blood pressure; Sys_c, Dia_c= cusum-derived crest pressure; Sys_t, Dia_t= cusum-derived trough pressure; Sys_v, Dia_v= within subject variance of all ambulatory readings over 24 h ($mmHg^2$); Sys_{nf}, Dia_{nf}=nocturnal fall in pressure; Sys_{am}, Dia_{am}= cusum-derived circadian alteration magnitude; Sys_{ph}, Dia_{ph}=cusum plot height (mmHg * hr); Sys_a, Dia_a= overall amplitude; Sys_1, Sys_2, Sys_3, Sys_4, Dia_1, Dia_2, Dia_3, Dia_4= amplitudes of the 1st through 4th harmonic.

Regression model. INT=intercept. The following explanatory variables were considered: the level of blood pressure on conventional measurement at home (BP), age (linear and squared term), body mass index (BMI), pulse rate in the presence of an observer, serum total calcium (SCa), log. γ-glutamyltransferase (γGT), current smoking habits (SMK, coded 0 for non-smokers and 1 for smokers) and the urinary Na^+/K^+ ratio. All regression coefficients given in the table were significant ($p<0.05$). -- indicated that none of the correlations between the dependent and explanatory variables was significant. nc=not considered for entry into the regression model. ns=not significant.

were significantly higher in men than in women (Fig. 1 and Table 1). Similarly, the cusum-derived crest and trough pressures were higher ($p<0.001$) in men (Table 2).
In men (Fig. 1 and Table 3) and women (Fig. 1 and Table 4) both the 24 h and night-time systolic pressures were curvilinearly correlated with age and increased with body mass index. Age was less important as a determinant of the day-time pressure as there was only a significant correlation with systolic pressure in women.
The 24 h and night-time diastolic blood pressures of the men were positively correlated with log γ-glutamyltransferase, an index of alcohol intake, and with pulse rate counted by an observer (Table 3). In women the 24 h day-time and night-time pressures increased with pulse rate and log γ-glutamyltransferase. The 24 h and day-time systolic pressures were also 4 to 5 mmHg higher in women on oestroprogestogens as compared with the other females (Table 4).
The main determinants of the crest and trough blood pressures in men and women were age, body mass index and pulse rate. In general, these 3 factors were associated with an increase in the crest and trough blood pressure levels. In male and female smokers the trough systolic pressure was 2 to 3 mmHg lower than in non-smokers. The trough diastolic pressure in men and the trough systolic and diastolic pressures in women were positively associated with log γ-glutamyltransferase. Intake of oestroprogestogens in women was associated with a nearly 5 mmHg elevation of the crest systolic blood pressure and with a 2 to 4 mmHg increase in the trough systolic and diastolic pressures.

The diurnal blood pressure profile

With the exception of the cusum-derived crest and trough pressures, the parameters derived from the diurnal blood pressure curve were similar in men and women (Table 2). In men and women combined the acrophase of the global Fourier curve occurred at 15:33±4:45 h for systolic pressure and at 14:41±4:17 h for diastolic pressure. The correlation coefficients between the within subject variance of the 24 h blood pressure and several other measures of variability appear in Table 5.
In both men (Table 3) and women (Table 4) the main recognized determinant of the within subject variance of the 24 h blood pressure was the pressure level. The latter was assessed from the conventional blood pressure readings at home in order to obtain an estimate which was independent of the ambulatory measurements.
In both sexes (Tables 3 and 4) the nocturnal fall in systolic pressure increased with the height of pressure and was nearly 2 mmHg greater in smokers than in non-smokers. The nocturnal fall in diastolic blood pressure decreased curvilinearly with advancing age (Tables 3 and 4).
The cusum-derived circadian alteration magnitude and the cusum-derived plot height increased with higher blood pressure level (Tables 3 and 4), whereas the cusum plot height of diastolic pressure was inversely correlated with age in men and women. A negative relationship with age squared was also observed for the cusum-derived circadian alteration magnitude of diastolic pressure in men.
The cusum-derived circadian alteration magnitude and plot height of systolic pressure were greater in smoking than in non-smoking men (Table 3). Similarly, the cusum-derived circadian alteration magnitude and plot height of both systolic and diastolic pressures were greater in smoking than in non-smoking women (Table 4).
The amplitudes of the overall Fourier curve and of the 1st and 2nd harmonics tended to increase in both sexes with a higher blood pressure level on conventional measurement (Tables 3 and 4). The amplitude of the 1st harmonic of diastolic pressure was inversely correlated with age in men and women, whereas the opposite was observed for the amplitude of the 4th harmonic of systolic pressure. In men and women current smokers tended to have slightly greater amplitudes of one or more of the harmonics. In women the amplitude of the 4th harmonic of the systolic and diastolic blood pressure increased with greater body mass index.

Table 4 - Correlates of the parameters describing the diurnal blood pressure curve in 317 women.

	R^2	INT mmHg	BP mmHg	Age year	Age^2 $year^2$	BMI kg/m^2	Rate bpm	γGT u/l	SMK 0,1	Na^+/K^+	Pill 0,1
Blood pressure											
Sys_{24}	0.280	94.0	nc	–0.635	0.00873	0.56	0.13	5.93	ns	ns	4.14
Dia_{24}	0 090	50 4	nc	ns	ns	0.23	0.12	4.52	ns	ns	ns
Sys_d	0.204	88.7	nc	ns	0.00245	0.43	0.14	5.25	ns	ns	5.32
Dia_d	0 074	57.8	nc	ns	ns	0.20	0.11	3.33	ns	ns	2.55
Sys_{ni}	0.236	88.6	nc	–0.989	0.01155	0.60	0.18	6.76	ns	ns	ns
Dia_{ni}	0.119	38.0	nc	0.078	ns	ns	ns	6.75	ns	ns	ns
Sys_c	0.261	84.5	nc	ns	0.00293	0.62	0.17	5.26	ns	ns	5.29
Dia_c	0.090	58.8	nc	ns	ns	0.33	0.13	ns	ns	0.66	ns
Sys_t	0.267	82.8	nc	–0.759	0.00937	0.57	0.17	6.63	–2.91	ns	3.74
Dia_t	0.129	27.1	nc	0.587	–0.00481	ns	0.12	6.00	ns	ns	2.29
Variance											
Sys_v	0.125	19.9	0.375	ns	ns	ns	ns	ns	ns	1.55	ns
Dia_v	0.036	35.1	0.375	ns	ns	ns	ns	ns	ns	ns	ns
Nocturnal fall		-									
Sys_{nf}	0.047	13.7	0.107	ns	ns	-0.37	ns	ns	ns	ns	ns
Dia_{nf}	0.021	16.0	ns	ns	–0.00069	ns	ns	ns	ns	ns	ns
Cusum parameters											
Sys_{am}	0.093	5.8	0.136	ns	ns	ns	ns	ns	2.53	ns	ns
Dia_{am}	**0 079**	**13.1**	**0.120**	**ns**	**ns**	**ns**	**ns**	**–3.71**	**2.09**	**0.50**	**ns**
Sys_{ph}	0.070	35.7	0.488	ns	ns	ns	ns	ns	11.29	ns	ns
Dia_{ph}	0.058	61.0	0.500	–0.252	ns	ns	ns	–14.25	10.40	ns	ns
Fourier parameters											
Sys_a	0.108	3.6	0.102	ns	ns	ns	ns	ns	1.34	ns	ns
Dia_a	0-044	8.0	0.071	ns	ns	ns	ns	ns	ns	0.35	ns
Sys_1	0.023	10.2	ns	ns	ns	ns	ns	ns	1.95	ns	ns
Dia_1	0.052	7.3	0.055	–0.045	ns	ns	ns	ns	1.13	ns	ns
Sys_2	0.042	-0.5	0.054	ns	ns	ns	ns	ns	ns	ns	ns
Dia_2	0-033	0.4	0.062	ns	ns	ns	ns	ns	ns	ns	ns
Sys_3	0.051	6.6	ns	–0.173	0.00191	ns	ns	ns	0.23	ns	ns
Dia_3	– –	– –	– –	– –	– –	– –	– –	– –	– –	ns	ns
Sys_4	0.056	1.1	ns	ns	0.00024	0.08	ns	ns	ns	ns	ns
Dia_4	0.016	1.7	ns	ns	ns	0.06	ns	ns	ns	ns	ns

Dependent variables. Unless otherwise indicated in this footnote, the dependent variables are expressed in mmHg. Sys, Dia=systolic, diastolic pressure; Sys_{24}, Dia_{24}=24h ambulatory blood pressure; Sys_d, Dia_d=day-time blood pressure; Sys_{ni}, Dia_{ni}=night-time blood pressure; Sys_c, Dia_c=cusum-derived crest pressure; Sys_t, Dia_t=cusum-derived trough pressure; Sys_v, Dia_v=within subject variance of all ambulatory readings over 24 h ($mmHg^2$); Sys_{nf}, Dia_{nf}=nocturnal fall in pressure; Sys_{am}, Dia_{am}= cusum-derived circadian alteration magnitude; Sys_{ph}, Dia_{ph}=cusum plot height (mmHg * hr); Sys_a, Dia_a= overall amplitude; Sys_1, Sys_2, Sys_3, Sys_4, Dia_1, Dia_2, Dia_3, Dia_4=amplitudes of the 1st through 4th harmonic.

Regression model. INT=intercept. The following explanatory variables were considered: the level of blood pressure on conventional measurement at home (BP), age (linear and squared term), body mass index (BMI), pulse rate in the presence of an observer, serum total calcium (SCa), log. γ-glutamyltransferase (γGT), current smoking habits (SMK, coded 0 for non-smokers and 1 for smokers), the urinary Na^+/K^+ ratio and intake of oestroprogestogens (pill, coded 0 or 1). All regression coefficients given in the table were significant ($p<0.05$). – – indicates that none of the correlations between the dependent and explanatory variables was significant. nc=not considered for entry into the regression model. ns=not significant.

Table 5 - Correlation coefficients between the within subject variance of the 24 h pressure and other measures of variability.

	Sys_v	Dia_v
Nocturnal fall		
SYS_n	0.57	--
Dia_n	--	0.53
Cusum parameters		
SYS_{am}	0.77	--
Dia_{am}	--	0.77
Sys_{pn} (mmHg * hr)	0.74	--
Dia_{pn} (mmHg * hr)	--	0.74
Fourier parameters		
SYS_a	0.86	--
Dia_a	--	0.85
Sys_1	0.59	--
Dia_1	--	0.65
SYS_2	0.43	--
Dia_2	--	0.45
Sys_3	0.35	--
Dia_3	--	0.42
Sys_4	0.44	--
Dia_4	--	0.52

See Table 2 for abbreviations and units.

All correlation coefficients were significant at the 0.1% probability level (N = 630).

DISCUSSION

In this study several techniques to model the diurnal blood pressure curve in a random population sample were used and the correlates of the diurnal blood pressure profile were determined. The level of the 24 h ambulatory blood pressure was mainly influenced by the subjects' age and body mass index. The same was also true for the night-time blood pressure, which is less influenced by day-time physical activity. However, as previously reported in part of the present population (8, 13) and in a group of Irish bank workers as well (13, 14), the increase in blood pressure with age and body mass index was steeper, when in the same subjects these relations were estimated from conventional rather than from ambulatory blood pressure measurements (Fig. 1).

In the present study the ambulatory pressure was registered with a non-invasive intermittent technique. Beat-to-beat blood pressure variability could therefore not be evaluated. However, the non-invasive method made it possible to study blood pressure fluctations by means of the within subject variance of the blood pressure readings over a period of 24 h. The latter measure of variability was weighted for the time interval between successive blood pressure readings. The present observation that the variance increased with a higher pressure level is in agreement with most other studies that have looked at this association (15-18). However, in several of these studies the relationship between the height and the variability of the blood pressure was difficult to interpret, because both the dependent and independent variables were estimated from the same set of pressure readings. This problem was addressed in the present study, by defining the blood pressure level as the average of 5 conventional pressure readings by a nurse at the subjects' home and thus by estimating the pressure level independent of the variability in the ambulatory recordings.

Some parameters derived from the diurnal blood pressure profile reflect mainly the alteration between the daily periods of higher and lower blood pressure, which in general coincide with day-time activities and sleep at night, respectively. Such parameters are the nocturnal blood pressure fall, the cusum-derived circadian alteration magnitude and plot height (6) and the amplitudes of the global Fourier curve and of its 1st and 2nd harmonic (4, 5). In general, these parameters increased with the height of pressure. The greater blood pressure variability in subjects with higher pressure may account for the observed larger nocturnal blood pressure fall, or what is more likely, for a greater pressure rise over and above the basal nocturnal level in response to the physical, mental and emotional stress of daily living.

The parameters reflecting the diurnal alteration between a period of higher and lower pressure were also inversely correlated with age. Although in general older people spend more time in bed than younger subjects, they show a reduction of slow-wave, in particular

so called stage 4 sleep, increased night-time wakefulness and increased fragmentation of sleep by awake periods (19). Less striking reductions in REM (rapid eye movements) sleep and in total night-time sleep also occur with advancing age (19). The increased night-time wakefulness in older people is mirrored by increases in day-time fatigue, day-time napping and in the likelihood of falling asleep during the day (19). These age-related changes in the circadian sleep-wake rhythm probably explain why also the blood pressure differences between day and night, normally observed in younger subjects, are attenuated as a person grows older.

The 3rd and 4th harmonics in the Fourier analysis describe components in the diurnal blood pressure profile with periods of 8 and 6 h, respectively. The amplitudes of these harmonics therefore reflect mainly the shorter-lived blood pressure fluctuations through the day (4, 5). In general, the amplitudes of these harmonics tended to increase with aging. This is in keeping with previous studies, which have demonstrated that more advanced age, independent of the blood pressure level, acts to reduce the baroreflex sensitivity (16, 18). The same phenomenon probably underlies the with age increasing placebo (20) and "white coat" (13, 21) effects.

Although blood pressure is acutely raised by smoking, probably as a consequence of sympathetic stimulation (22-24), the conventionally measured blood pressure tends in population studies (25-28) to be 1 to 2 mmHg lower in smokers than in non-smokers. In keeping with these findings, in this study the cusum-derived trough systolic blood pressure was 2 to 3 mmHg lower in smokers. Consequently, the cusum-derived circadian alteration magnitude and plot height and the amplitudes of the Fourier components tended to be greater in smokers than in non-smokers. Smoking 4 cigarettes per hour at 15 min intervals, compared to one hour of non-smoking, has been shown to increase systolic pressure in normotensive smokers by 19% and diastolic pressure by 14%, while the within subject hourly standard deviations of pressure rose by 25% and 44%, respectively. Thus, smokers could be exposed to a higher sympathetic drive during a large part of their waking hours, leading to a higher level and greater variability of blood pressure during these periods and also to some degree of desensitisation of the cardiovascular system to catecholamines (30). However, in periods of smoking abstinence, such as during a physical examination in an epidemiological survey or at night during 24 h ambulatory blood pressure monitoring, the increased sympathetic tone could fade away, leaving the desensitized cardiovascular system with less sympathetic drive, which in turn could lead to a somewhat lower blood pressure.

The existence of a positive relationship between the use of alcohol and the conventionally measured blood pressure has been established by many cross-sectional and prospective epidemiological studies, although there remains some doubt on the actual slope of the relationship (31). On balance, most evidence suggests that the link between alcohol intake and the prevalence of hypertension can be uniformly demonstrated at a level of alcohol intake exceeding 5 drinks per day, and that the association is still present, when alcohol consumption varies from 3 to 5 drinks per day. However, at lower intake, up to 1 or 2 drinks per day, there is probably either no or a less important effect on blood pressure. In this study the activity of the liver enzyme γ-glutamyltransferase was used as index of alcohol intake. A positive relationship with the level of the 24 h blood pressure and the night-time blood pressure was observed in both men and women. In women the trough blood pressure was also independently and positively correlated with this index of alcohol intake. This explains why in women the cusum-derived circadian alteration magnitude and plot height tended to decrease with increasing alcohol consumption. Whether this is due to a direct effect of alcohol intake on the blood pressure variability or to differences in the behavorial patterns of drinking versus non-drinking women, e.g. less daytime and more night-time activities, remains to be established. However, the observation that acute alcohol intake stimulates

the sympathetic system and therefore can be expected to increase blood pressure variability, would plea for the latter hypothesis.

The conventionally measured blood pressure has been demonstrated to be positively correlated with serum total calcium in several surveys, more frequently in men than in women (34, 35). In this study a positive correlation was only observed with the cusum-derived trough diastolic pressure in men. A tendency of the trough pressures to be positively correlated with serum total calcium could contribute to an inverse association between serum calcium and the amplitude of the global Fourier curve, as demonstrated in this study for systolic pressure in men.

Contraceptive pill intake is known to increase the conventionally measured blood pressure on average by 5 mmHg systolic and 1 to 2 mmHg diastolic (36, 37), and to inflate the risk of overt hypertension 3 to 6 times (36). The 24 h systolic blood pressure was in this population study on average 4 mmHg raised in women on oestroprogestogens as compared with women not taking hormonal contraceptives or hormonal substitution therapy. Similarly, both the cusum-derived crest and trough systolic pressures were 2 to 3 mmHg higher in subjects on oestroprogestogens. By contrast to the level of pressure, the parameters describing the diurnal profile were not altered by the intake of birth control pills.

Physical work, mental activity and emotional stress are important determinants of blood pressure variability, but are impossible to standardize in population studies. These determinants of blood pressure variability were not accounted for in the present analysis. This may explain why in multiple regression only a small fraction of the total variance of the diurnal blood pressure profile was explained. The application of the Fourier technique to intermittent blood pressure recordings also carries a risk of excessive smoothing. The progressive decrease of the amplitudes from the 1st to the 4th harmonic might to some extent represent an example of aliasing error, although it is true that slower fluctuations are generally wider than faster ones.

In spite of these obvious limitations, the present study demonstrated that in the population at large blood pressure variability over shorter periods of time tends to increase with age. The variability which goes with the daily alteration between a high and a low blood pressure span, diminishes with advancing age and alcohol consumption, but rises with increasing pressure and smoking. To which extent these associations are attributable to behavioral patterns associated with for instance aging, smoking or alcohol intake, rather than to a direct influence of these factors on the cardiovascular system and its regulation, remains to be established.

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