Published in final edited form as:

Biomed Pharmacother. 2005 October ; 59(Suppl 1): S180–S187.

Plasma catecholamines: follow-up on 10-year study in health and cardiovascular disease

P. Prikryl^a, G. Cornélissen^{b,*}, K. Otsuka^c, and F. Halberg^{b,*}

^a Masaryk University, Brno, Czech Republic

^b Halberg Chronobiology Center, University of Minnesota, Mayo Mail Code 8609, 420 Delaware Street SE, Minneapolis, MN 55455, USA

^c Tokyo Women's Medical University, Tokyo, Japan

Abstract

The predictive value of blood pressure (BP), heart rate (HR), and catecholamines in terms of any subsequent development of cardiovascular disease was investigated. Systolic (S) and diastolic (D) BP, HR, epinephrine (E) and norepinephrine (NE) were measured three times a year in 1980, 1984, and 1989 on 20 clinically healthy subjects, 18 patients with 'essential hypertension', and 22 patients with angina pectoris. Of the 22 patients in the latter group, 15 died during a 2-year follow-up (1990–1991). Each individual data series was analyzed by single cosinor to assess the circannual variation. Results were summarized by population-mean cosinor for each group. Parameter tests were used to compare the circannual rhythm characteristics among the different patient groups. A circannual rhythm was invariably demonstrated on a group basis ($P < 0.05$). Differences in MESOR and/or circannual amplitude were found among the different groups. In particular, patients with angina pectoris who will die within the 2-year follow-up differ in terms of their E and NE from all other patient groups, a difference already detected at the beginning of the study, more than 10 years before they die. A similar separation is not achieved in terms of BP or HR.

Keywords

Angina pectoris; Catecholamins; Circannual; Predictive value

1. Introduction

Catecholamines are known to be circadian periodic [1–3]. Circadian rhythms in human urine peak in late morning [3] and persist during complete bedrest [2]. They are also reported to persist in soldiers subjected to physical and emotional loads without interruption for 72 h [4]. Circadian catecholamine rhythms have also been documented in several brain areas in experimental animals, including the hypothalamus and the pineal gland, as reviewed by Descovich et al. [3].

Circannual rhythms have also been reported but their pattern is less consistent among studies. Both norepinephrine (NE) and epinephrine (E) were found to peak in May in a serially-independent study of presumably healthy men and women 20–60 years of age sampled at

*Corresponding authors. Tel.: +1 612 624 6976; fax: +1 612 624 9989. E-mail address: corne001 @ umn.edu (G. Cornélissen), halbe001 @ umn.edu (F. Halberg).

Website: <http://www.msi.umn.edu/~halberg>.

different calendar dates [3]. Another study found a peak in NE in summer in presumably healthy young men, with two peaks for the urinary excretion of E [5]. In yet another study of a large group of men and women, E was reportedly increased in winter, while NE excretion did not appear to vary along the scale of the year [6]. A circannual rhythm in urinary NE was reported to peak in the winter in elderly women but not men and in children of both genders sampled longitudinally four times a year [7]. A circannual variation in plasma NE and E was also reported to peak during the winter in a longitudinal study of 10 healthy subjects sampled monthly for 13 months, showing a circannual pattern opposite to that of endothelin-1 and angiotensin II [8].

The MESOR and circadian amplitude of NE and E were also found to decrease with age [3]. This study aimed at tracking the circannual variation in catecholamines, blood pressure (BP) and heart rate (HR) in healthy subjects, hypertensive patients, and patients with angina pectoris over 10 years, and to relate the results with outcomes recorded for an additional 2 years. It constitutes a follow-up to the cluster analyses performed earlier on the same data set [9] (see also [10,11]).

2. Subjects and methods

Plasma catecholamines were determined longitudinally over the course of 10 years in clinically healthy subjects, patients with essential hypertension, and patients with angina pectoris 35–52 years of age at the start of study. Blood samples were collected from each individual three times a year in the first week of January, June, and December of 1980, 1984, and 1989, each subject contributing a total of nine samples. Venous blood was collected into polyethylene tubes with heparin after the subject laid quietly for 30 min, in the morning, in bed between 07:00 and 08:00. Catecholamines were determined using a radioenzymatic assay [12]. Systolic (S) and diastolic (D) BP were measured by auscultation using a mercury sphygmomanometer while the subject was at rest. Three consecutive measurements were taken and averaged at each timepoint. HR was assessed from the R–R intervals of a standard ECG record obtained at each visit.

The study involved 20 clinically healthy subjects, 18 patients with essential hypertension (WHO stage II) not complicated by other conditions, and 22 patients with angina pectoris, Table 1. Some of the patients with angina pectoris also had other conditions, including essential hypertension. All patients were treated as needed. During the 2-year follow-up after completion of data collection, 15 of the 22 patients with angina pectoris died. Analyses were carried out considering four groups: clinically healthy subjects, hypertensive patients, patients with angina pectoris still alive at the end of follow-up, and patients with angina pectoris who died during the 2-year follow-up.

Each individual data series (nine samples) was analyzed by single cosinor, consisting of the least squares fit of a 1 year cosine curve to the data [13,14]. Estimates were obtained for the MESOR, a chronome (time structure) adjusted mean value, the double amplitude, a measure of the extent of predictable change within a year, and the acrophase, a measure of the timing of overall high values recurring each year. The acrophase is expressed in (negative) degrees, with 360° equated to 1 year, using January 1, 1980 as reference time. Rhythm detection was determined by the zero-amplitude (no-rhythm) test [13,14]. Results were further summarized by population-mean cosinor [13,14] and compared among the four groups by parameter tests [15]. A probability below 5% was considered to represent statistical significance.

3. Results

On a group basis, a circannual rhythm could be invariably demonstrated, except for NE in patients with angina pectoris still alive at the end of follow-up that only reached borderline statistical significance, Table 2. The circannual acrophases are very similar among the four groups of patients, peaking in the spring.

Parameter tests indicate large differences in MESOR among the four groups for each variable. Of all four groups, healthy subjects have the lowest and hypertensive subjects have the highest SBP and DBP, as anticipated, Fig. 1A, B. Of interest is the finding that hypertensive patients also have a larger circannual amplitude of SBP than healthy subjects ($P = 0.041$). Whereas patients with angina pectoris have a lower MESOR of SBP and DBP than hypertensive patients ($P < 0.005$), their BP MESOR is higher than that of healthy subjects ($P < 0.001$). Moreover, patients with angina pectoris who died during follow-up also have a higher BP MESOR than patients with angina pectoris who are still alive at the end of the follow-up span (SBP: 141.1 vs. 130.1 mmHg, $P = 0.022$; DBP: 87.8 vs. 77.9 mmHg, $P = 0.045$).

Differences in HR MESOR and circannual amplitude are also found among patients groups (M: $P < 0.001$, A: $P = 0.017$). As anticipated, healthy subjects have the lowest HR MESOR, Fig. 2. Pair-wise comparisons of the HR MESOR indicate the presence of inter-group differences among all pairs, except between patients with essential hypertension and patients with angina pectoris still alive at completion of follow-up. Of interest is the difference not only in MESOR (89.3 vs. 83.3 beats/min, $P = 0.009$) but also in circannual amplitude (2.2 vs. 7.9 beats/min, $P < 0.001$) and acrophase (second half of June vs. second half of April, $P = 0.003$) between patients with angina pectoris dead or alive at completion of follow-up.

The most dramatic differences among patient groups are found for NE and E, Fig. 3A, B. Healthy subjects have the lowest MESOR of both NE ($P < 0.001$) and E ($P < 0.001$). They also have the smallest circannual amplitude of NE ($P = 0.022$) and E ($P = 0.001$). Statistically significant differences in NE and E MESOR are found for all pair-wise comparisons, except between hypertensive patients and patients with angina pectoris. The highest MESOR of both NE and E is found for patients with angina pectoris who die during the 2-year follow-up span, the MESOR difference between angina pectoris patients who die or survive being statistically significant (NE: 1.50 vs. 1.24 pmol/ml, $P = 0.012$; E: 0.33 vs. 0.17 pmol/ml, $P = 0.044$).

As seen from Fig. 3A, B, this large difference is already present, at least on a group basis, at the beginning of the record, more than 10 years before any adverse event occurred. Parameter tests performed on the data from 1980 only, 10–12 years before the occurrence of adverse events, yield results very similar to those based on all data collected over 10 years. Of interest are the findings that hypertensive patients have a circannual amplitude of SBP larger than healthy subjects ($P = 0.014$) and that differences are found between patients with angina pectoris who die or are still alive at the end of the 2-year follow-up (SBP: 140.1 vs. 130.8 mmHg, $P = 0.042$; DBP: 87.8 vs. 77.9 mmHg, $P = 0.045$; NE: 1.44 vs. 1.23 pmol/ml, $P = 0.050$; E: 0.27 vs. 0.13 pmol/ml, $P = 0.044$). Whereas no difference in the MESOR of HR is found between these two groups in 1980, a difference in circannual amplitude is already statistically significant (2.5 vs. 8.3 beats/min, $P = 0.012$).

4. Discussion

The relative predictive power of BP and catecholamines is illustrated in Fig. 4. Neil-Dwyer et al. [16] reported higher concentrations of urinary catecholamines among patients with high plasma renin activity, which they found to be statistically significantly associated with a higher incidence of morbidity and mortality in patients after a subarachnoid hemorrhage. Hamill et

al. [17] also conclude that markedly elevated concentrations of plasma NE predict outcome in patients with traumatic brain injury.

Rockman et al. [18] report markedly elevated concentrations of plasma NE in a group of patients with chronic heart failure secondary to coronary artery disease dying of low output, but only modestly elevated values in the group of survivors and the group dying suddenly. These authors did not find NE to be an important independent predictor of mortality, however, whereas plasma renin activity served that purpose in their study. Joborn et al. [19] in turn report statistically significantly higher platelet concentrations of catecholamines in non-survivors than in survivors of acute myocardial infarction during a 1-year follow-up. Initial plasma NE and E concentrations were also reportedly statistically significantly higher in patients with idiopathic dilated cardiomyopathy whose clinical condition will deteriorate as compared to similar patients who responded to medical therapy [20]. But Monge [21] reports that plasma big endothelin-1 is a better predictor of 1 year outcome than plasma NE in cardiovascular disease.

In a 7-year prospective study of 804 70-year-old men by Christensen and Schultz-Larsen [22], high plasma NE values were reportedly associated with a reduced survival rate, but high E values were reportedly associated with a better survival rate, a finding the authors attribute to the likelihood of representing a better physical working capacity. Reuben et al. [23] investigated the predictive value of high urinary catecholamine excretion for functional decline and mortality in healthy elderly people. From this 7-year prospective study on 765 high-functioning subjects, the authors conclude that high urinary catecholamine excretion likely reflects subclinical sympathetic stimulation and may serve as a marker of increased risk for functional decline and mortality. In a cohort of 136 preterm infants as well, Evans et al. [24] found that infants who died or sustained disability at 5–6 years had statistically significantly higher plasma NE concentrations on the second day of life.

A higher rate of cardiovascular and cerebrovascular events in patients with initially increased NE concentrations was reported after 1-year follow-up by Sander et al. [25] who studied 112 consecutive patients with their first brain infarction. Plasma NE also reportedly emerged as an independent predictor of fatal and non-fatal cardiovascular events in patients with end-stage renal disease in a study by Zoccali et al. [26]. In a study of 641 patients with stable angina pectoris, however, catecholamines reportedly did not differ between patients with or without events (cardiovascular death or non-fatal myocardial infarction) recorded during a median follow-up span of 40 months [27].

From a basic viewpoint, it was of interest to assess the spectral structure of each variable, pooling data from all subjects within a given group, realizing, however, the grave limitations of such an approach, stemming primarily from the large gaps between sampling in 3 seasons in 1980, 1984, and 1989, notably since a circannual variation was anticipated, validated time-microscopically, and shown to have predictive value as discussed above. The detection of a transyear with a period of about 1.3 years and an amplitude nearly equal to that of the yearly component is likely related to the presence of gaps, the two components corresponding to different interpolations during years when no data were collected. This result is mentioned only to stimulate further research, preferably based on uninterrupted longitudinal sampling, to investigate putative transyears in endocrinology and their probable adreno-cortical and adreno-medullary mechanisms. Transyears have already been described in a unique 15-year data series of breakdown products of the steroids of the gonads and the adrenal cortex, namely the daily urinary excretion of 17-ketosteroids by a clinically healthy man [28,29]. Transyears may also characterize the adrenal medulla and the sympathetic nervous system and the blood pressure via which these structures in space coordinate emotions and behavior in time at all levels of organization [30]. Components with periods of 1 year and slightly longer than 1 year may

constitute more than one 'seasonal' order. They may underlie new other-than-seasonal disorders, brought about when beats occur between these two components, a challenging new field of basic and applied investigation for students of aging and more broadly.

5. Conclusion

Most studies reviewed above relied on single determinations of catecholamines and other endpoints. Herein, all variables were determined at three different circannual stages during three cycles. It was thus possible to assess the circannual variation, even though circadians could not be determined. By partitioning the predictable yearly variation in each variable, the MESOR estimate is both more precise and more accurate than the arithmetic mean or single spotchecks. The design used herein also allowed the comparison of the circannual amplitude among the different groups. For instance, a difference in the circannual amplitude of HR was found between patients with angina pectoris who are still alive or died during the 2-year follow-up.

A set of 22 longitudinal series from patients with angina pectoris, each consisting of nine single time-qualified samples of SBP, DBP, NE and E determined in three seasons, was found to predict outcomes on a group basis 2 years after completion of the data collection. The cost of determination of catecholamines in urine vs. blood is dwarfed by the value of urine which removes a source of variability by integrating the circadian variation, admittedly a negative but sometimes a useful approach. Spotchecking the BP is cheaper. It is likely, but has yet to be proved, that in view of greater stability, catecholamine determinations on 24-h urines may serve better for a group assessment. But whether or not this assumption is correct, it seems almost certain that any use for a prediction for a given individual has no likely substitute for assessing preferably the variable's time structure or chronome as-one-goes, or as a minimum, circadian parameters of catecholamines in blood or urine, or BP.

But the skeptic may ask: Would a 7-day profile of BP and HR analyzed chronomically do much better and provide the dividend of detecting an elevated risk obscured by averaging? An elevated pulse pressure, a deficient heart rate variability, BP overswinging (CHAT, circadian hyper-amplitude-tension), and/or BP ecphasia (odd timing of the circadian BP variation), based on a chronomically interpreted 7-day profile, are abnormal dynamics associated with a large increase in cardiovascular disease risk. [31–33]. CHAT carries a risk of cerebral ischemic events and nephropathy greater than a high BP, and it is also associated with a shortened lifespan in the perspective of 28 years [34,35]. Individuals or groups are best served by self-surveillance of BP profiles interpreted chronomically with analyses available from corne001@umn.edu as are automatic monitors with an 80% reduction in cost for participants in the BIOCOS project.

This approach seems promising since even with spotchecks only, the specificity of the BP approach was only 14% lower than that based on catecholamines and the sensitivity of the BP approach was 100%, 13% better than that by catecholamines.

Acknowledgements

US Public Health Service (GM-13981; F.H.), Dr hc Dr hc Earl Bakken Fund (G.C., F.H.), University of Minnesota Supercomputing Institute (G.C., F.H.).

The help of I.J. Kopin (NIH, Bethesda, MD, USA) and R. Kvetnanský (Slovak Academy of Sciences, Slovak Republic) is gratefully acknowledged.

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EH: Essential Hypertension (WHO Stage II), AP: Angina Pectoris

Fig. 1A. Timepoint means and S.E.s of SBP.

EH: Essential Hypertension (WHO Stage II), AP: Angina Pectoris

Fig. 1B. Timepoint means and S.E.s of DBP.

Fig. 1.

Fig. 1A. Timepoint means and S.E.s of SBP.

Fig. 1B. Timepoint means and S.E.s of DBP.

Fig. 2.
Timepoint means and S.E.s of HR.

EH: Essential Hypertension (WHO Stage II), AP: Angina Pectoris

Fig. 3A. Timepoint means and S.E.s of NE.

EH: Essential Hypertension (WHO Stage II), AP: Angina Pectoris

Fig. 3B. Timepoint means and S.E.s of E.

Fig. 3.

Fig. 3A. Timepoint means and S.E.s of HE.

Fig. 3B. Timepoint means and S.E.s of E.

Fig. 4.

Average values of systolic (upper left) and diastolic (upper right) blood pressure and of norepinephrine (lower left) and epinephrine (lower right) of individual subjects. Horizontal lines represent critical values used to compute odds ratio OR and 95% confidence interval (CI), sensitivity (Se) and specificity (Sp) of separation by this criterion between patients with angina pectoris who will be still alive or have died at completion of the 2-year follow-up. Group 1 : Healthy subjects (open circles). Group 2: Patients with essential hypertension (EH) (×). Group 3: Patients with angina pectoris (AP) alive at end of follow-up (open triangles). Group 4: Patients with AP who died during follow-up (+). SBP: critical value = 130 mmHg; OR = 24.1 [95% CI: 1.04 – 559]; Se = 100%, Sp = 43%. DBP: critical value = 80 mmHg; OR = 3.75 [95% CI: 0.54 – 26.0]; Se = 60%, Sp = 71%. NE: critical value = 1.4 pmol/ml; OR = 5.00 [95% CI: 0.70 – 35.5]; Se = 67%, Sp = 71%. E: critical value = 0.15 pmol/ml; OR = 8.67 [95% CI: 1.05 – 71.6]; Se = 87%, Sp = 57%.

Table 1

Patients investigated

ID number	Diagnosis	Gender	Age (years)	Treatment
1	EH	M	42	BB
2+	AP, HLP	M	45	Ni, DP, Fi
3	Health	F	40	
4+	EH, AP, DM, HLP	M	38	BB, ACE, Ni, DP, Fi, PAD
5	Health	M	46	
6	EH	F	42	BB
7	AP	M	47	Ni
8	Health	M	36	
9+	AP, EH, DM, HLP	F	46	Ni, ACE, Fi, BB, Insulin
10	EH	M	38	BB
11	Health	F	37	
12	EH	M	47	BB, ACE
13	Health	M	40	
14+	AP, HLP	F	45	Ni, DP, Fi
15	EH	M	41	BB
16	EH	F	44	BB
17	Health	F	40	
18+	AP, HLP	M	45	Ni, DP, Fi
19	Health	M	39	
20	EH	M	46	BB
21+	AP, EH	M	47	Ni, BB, ACE, DP
22	Health	F	41	
23	EH	F	40	BB
24+	AP, HLP, DM	M	48	Ni, DP, Fi, Insulin
25	Health	M	44	
26	EH	F	38	BB
27	Health	F	37	
28+	AP, DM	F	48	Ni, DP, PAD
29	EH	M	50	BB
30+	AP, EH, HLP	M	49	Ni, DP, ACE, Fi, BB
31	Health	M	40	
32	Health	M	38	
33	Health	M	39	
34	Health	M	42	
35	Health	M	40	
36	Health	F	41	
37	Health	F	39	
38	Health	F	45	
39	Health	F	40	
40	Health	F	42	
41+	AP, HLP	M	42	Ni, DP, Fi
42	AP	F	46	Ni, DP
43	EH	M	45	BB
44	EH	M	40	BB
45	EH	M	38	BB
46	EH	M	35	BB
47	EH	M	41	BB
48	EH	F	40	BB
49	EH	F	37	BB
50	EH	F	42	BB
51+	AP, HLP	M	45	Ni, Fi, DP
52+	AP, DM	M	48	Ni, DP, PAD
53+	AP, EH	F	49	Ni, ACE, DP
54+	AP	F	50	Ni, DP
55+	AP, DM	F	47	Ni, DP, Insulin
56	AP	M	50	Ni, DP
57	AP	M	49	Ni, DP
58	AP	F	50	Ni, DP
59	AP	F	52	Ni, DP
60	AP	F	51	Ni, DP

+ Patient died during 2-year follow-up.

EH: essential hypertension, HLP: hyperliproteinaemia; AP: angina pectoris;

DM: diabetes mellitus; BB: beta blockers; Ni: nitroglycerin; DP: dipyridolium; Fi: fibrates; ACE: angiotensin-converting enzyme inhibitors; PAD: peroral antidiabetic drugs.

Table 2

Circannual rhythm characteristics

Rhythmometric summary						
	k	PR	P	MESOR $\pm$ S. E.	Amplitude (95% CI)	Acrophase (95% CI)
1	SBP:He	20	51.2	0.013	2.60 (0.01, 5.28)	-144 (-103, -235)
2	SBP:EH	18	67.9	<0.001	6.40 (5.27, 7.54)	-120 (-108, -135)
3	SBP:AP	7	62.6	<0.001	7.55 (3.25, 11.84)	-109 (-97, -146)
4	SBP:Died	15	45.3	<0.001	5.06 (1.90, 8.22)	-121 (-104, -165)
5	DBP:He	20	43.8	0.037	5.20 (0.54, 9.87)	-106 (-88, -174)
6	DBP:EH	18	59.0	<0.001	7.56 (4.97, 10.15)	-107 (-100, -119)
7	DBP:AP	7	46.4	<0.001	6.26 (1.61, 10.90)	-111 (-93, -175)
8	DBP:Died	15	43.9	<0.001	7.88 (2.13, 13.63)	-106 (-96, -147)
9	HR:He	20	43.3	0.012	3.01 (0.01, 6.49)	-118 (-97, -224)
10	HR:EH	18	55.3	<0.001	6.38 (4.75, 8.01)	-122 (-112, -137)
11	HR:AP	7	62.3	<0.001	7.95 (4.99, 10.91)	-108 (-103, -117)
12	HR:Died	15	29.1	<0.001	2.18 (1.58, 2.78)	-173 (-120, -227)
13	NE:He	20	39.6	0.012	0.037 (0.015, 0.059)	-104 (-92, -116)
14	NE:EH	18	54.3	0.002	0.053 (0.025, 0.081)	-123 (-107, -148)
15	NE:AP	7	33.3	0.087	0.058 ()	-120 ()
16	NE:Died	15	45.3	<0.001	0.120 (0.049, 0.191)	-116 (-101, -154)
17	E:He	20	29.6	<0.001	0.013 (0.007, 0.020)	-105 (-98, -118)
18	E:EH	18	38.3	<0.001	0.024 (0.010, 0.038)	-136 (-86, -157)
19	E:AP	7	22.4	0.025	0.013 (0.004, 0.022)	-140 (-76, -219)
20	E:Died	15	37.1	0.011	0.073 (0.026, 0.121)	-115 (-105, -137)

k: Number of subjects.

PR: percentage rhythm (%) - average proportion of overall variability accounted for by fitted model.

P: *P*-value from zero-amplitude (no-rhythm) test.

MESOR: midline estimating statistic of rhythm; acrophase expressed in (negative) degrees, with 360° $\equiv$ 1 year (Ref. 1 Jan 1980).

S.E.: standard error; CI: confidence interval.

SBP and DBP: systolic and diastolic blood pressure (mmHg), HR: heart rate (beats/min).

NE and E: norepinephrine and epinephrine (pmol/ml).