Characteristics of circadian rhythm in patients with intracerebral hemorrhage before death

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ABSTRACT

الأهداف: التحقق من خصائص الإيقاع السيركادي الذي يحدث في فترة الأربع وعشرين ساعة لدى حالات النزيف الدماغي الداخلي قبل حدوث الوفاة.

الطريقة: أُجريت هذه الدراسة الاسترجاعية في قسم جراحة الأعصاب بالمستشفى الثاني التابع لكلية غوانغدوغ الصحية، زانج يانغ، غوانغدوغ، الصين، وقد استمرت خلال الفترة من سبتمبر 2002م إلى فبراير 2009م. شملت الدراسة 122 حالة وفاة بعد إصابتها بنزيف داخل الدماغ، ولقد قمنا بقياس ضغط الدم ومعدل نبض القلب كل نصف ساعة خلال 72 ساعة قبل الوفاة. وتم تقسيم البيانات الخاصة بضغط الدم ومعدل القلب قبل والوفاة إلى 3 فترات زمنية وهي: الفترة أ (48–72 ساعة قبل الوفاة)، والفترة ب (24–48 ساعة قبل الوفاة)، والفترة ج (24 ساعة قبل الوفاة). وحُللت البيانات الخاصة بهذه الفترات باستخدام طريقة كوسينور وذلك من أجل تحديد ما إذا كان الإيقاع السيركادي حاضراً أو غائباً. وعلى أساس ذلك قُسمت الحالات المشاركة بعد تحليل كوسينور إلى حالات غائبة وحاضرة. وقد تم التنبؤ بسير المرض وتشخيصه في كلي المجموعتين وتحليلهما بواسطة اختبار تي، ومربع كاي.

النتائج: أشارت نتائج الدراسة إلى عدم وجود اختلاف بين المجموعتين وذلك بعد تحليل العوامل المؤثرة على التنبؤ بسير المرض، كما لم يكن هناك اختلافاً واضحاً بين الفترات الثلاثة وذلك بعد مقارنة نتائج التقدير المتوسط للإيقاع السيركادي. ولكن اتضح بعد مقارنة نطاق الإيقاع السيركادي للفترات الثلاثة بأن نطاق الفترة ج قد كان أقصر من الفترتين أ وب (p<0.001). كما كانت نسبة الحالات في المجموعة الغائبة والحاضرة مختلفة اختلافاً واضحاً من الناحية الإحصائية خلال الفترات الثلاثة (p<0.001).

خاتمة: أثبتت الدراسة بأنه يمكن اعتبار الإيقاع السيركادي عاملاً مستقلاً من شأنه التنبؤ بحدوث الوفاة بين المرضى المصابين بالنزيف الدماغي الداخلي.

Objective: To investigate characteristics of circadian rhythm in intracerebral hemorrhage before death.

Methods: This retrospective study was carried out from September 2002 to February 2009. One hundred and twenty-two dead cases with intracerebral hemorrhage (ICH) were collected. The study was carried out in the Department of Neurosurgery in The Second Affiliated Hospital of Guangdong Medical College, Zhanjiang, Guangdong, China. Blood pressure (BP) and heart rate (HR) were recorded every half-hour during the 72 hours before death. Data of BP and HR before deaths were divided into 3 time periods, namely, period A (72-48 hours to death), period B (48-24 hours to death), and period C (24 hours to death). Data from the 3 periods were analyzed using the Cosinor method to determine whether circadian rhythm was present or absent. The cases were divided into a present and absent group after Cosinor analysis. Prognostic factors in the 2 groups were analyzed by Student's t-test and Pearson's chi-squared test.

Results: Significant differences in prognostic factors between the 2 groups were not found. When circadian midline-estimating statistic of rhythms over the 3 periods were compared, there were no significant differences. However, when circadian amplitudes over the 3 periods were compared, the amplitudes during period C were significantly lower than period A or B (p<0.001). The percentage of cases in the absent and present groups was significantly different (p<0.001) over the 3 periods.

Conclusion: As an independent factor, circadian variation could predict death in patients with ICH.

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Intracerebral hemorrhage (ICH) is a major public health problem with an annual incidence of 10-30 per 100,000 population.[1] Around one third of patients with ICH have a fatal outcome.[2] How to predict the situation before death in ICH is very important to clinical treatment. Since ambulatory blood pressure (BP) monitoring (ABPM) was introduced in the clinic,[3] it has been shown in several studies[4-8] to predict mortality in different patient populations. Jiang et al[9] suggested that the availability of ambulatory BP monitors has facilitated the assessment of BP variability that cannot be determined from single casual measurements taken in the physician's office. Guan et al[10] also indicted that ABPM can give more information on circadian BP characteristics, which are a stronger predictor of hypertension-related organ damage, including brain damage, than single office measurements. Furthermore, the study has proclaimed that older women with weak circadian activity rhythms have higher mortality risk, and regulating circadian activity rhythms will improve health outcomes in older adults.[11] Although the association between circadian rhythms and illness is fairly strong, evidence from studies focusing on circadian variation in ICH before death is limited. According to the above reports, it could be seen that circadian variation of cardiovascular function, such as BP and heart rate (HR), has a relationship with cardiovascular events, including ICH. We presumed that characteristics of circadian rhythm of BP and HR before death could predict death in ICH. Therefore, the aim of the present study was to investigate characteristics of circadian rhythm of systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR before death in ICH.

Methods. This is a retrospective study for which Ethical Approval was obtained from the Ethics Committee of The Second People's Hospital. A total of 122 dead ICH cases admitted to the Department of Neurosurgery in The Second Affiliated Hospital of Guangdong Medical College, Zhanjiang, Guangdong, China from September 2002 to February 2009 were collected. The following inclusion criteria were used to select cases in the present study: (1) All cases were first ICH. (2) The location of the hematoma was at the left or right basal ganglia. (3) The BP and HR were continuously recorded every 30 minutes for 72 hours before death by multifunctional monitoring equipment. (4) All cases had neurological symptoms, signs, and CT scan with a definite diagnosis of ICH. We excluded others with hemorrhages resulting from cerebral trauma, rupture of arteriovenous malformation, ruptured aneurysm with spontaneous subarachnoid hemorrhage, tumor bleeding, or bleeding diathesis. The multifunctional monitoring equipment was applied with a Mindray PM-90005 device (Mindray Medical International Co., Ltd., Shengzhen, China).

Each series of data of BP and HR in the 72 hours before death was divided into 3 periods, namely, period A (72-48 hours to death), period B (48-24 hours to death), and period C (24 hours to death). The data of BP and HR in periods A, B, and C were analyzed by the single Cosinor method.[12,13] The characteristics of the cosine equation were as follows: $Y(t)=M+A\cos(\omega t+\phi)$. Estimates of parameters are thus obtained for each variable and each patient separately: (1) the mid line-estimating statistic of rhythm (M: MESOR), a rhythm-adjusted mean; (2) the amplitude (A), a measure of the predictable extent of change within one cycle (the double amplitude is the fitted curve peak-trough difference); (3) the acrophase (ϕ), a measure of the timing of overall high values within one cycle, by reference to local midnight.[14] The residual differences between the observed and fitted values are independent, uncorrelated, and normally distributed according to the assumptions of the single Cosinor method. To check whether these assumptions could be validated, regression diagnostic tests were applied. These tests check for independence of residuals as well as for lack of fit, normality of residuals, and homogeneity of variance. The limit of statistical significance was set at P less than 0.05. If the characteristics of series data of BP and HR fit the cosine curves perfectly ($p<0.05$), presence of circadian rhythm would be defined. Otherwise, circadian rhythm would be defined as absent ($p>0.05$). According to the results of the analyzed circadian rhythm during period A, period B, and period C, all cases were divided into 2 groups: circadian presence group (presence group) and circadian absence group (absence group). Prognostic factors that would influence circadian rhythm and outcome were collected and analyzed as follow: (1) Age at admission; (2) Gender; (3) Body mass index; (4) Operative treatment; (5) Current/past smokers; (6) Current/past drinkers; (7) Diabetes mellitus; (8) Previous cardiovascular disease; (9) Serum total cholesterol; (10) Inosine; (11) Urea; (12) Hematoma volume, and (13) Rupture into ventricles. Hematoma volume was calculated by CT scan according to the ABC/2 method,[15] in which A is the greatest diameter on the largest hemorrhage slice, B is the diameter perpendicular to A, and C is the approximate number of axial slices with hemorrhage multiplied by the slice thickness.

Statistical analysis was performed by the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 12.0. Values were expressed as means±SD or percentages. Means were compared by the Student's t-test, or one-way ANOVA test. The percentage was calculated in the presence and absence group by Pearson's

Chi-square test. The limit of statistical significance was set at P less than 0.05. Confidence interval (CI) was set at 95%.

Results. A total of 122 cases had ICH (71 men and 51 women). Age was 67.6±10.7 years, and hematoma volume was 50.5±11.9 ml. Sixty-seven patients (54.9%) had left, and 55 patients (45.1%) had right basal ganglia hemorrhage. A Glasgow Coma Scale (GCS)[16] of 13-15 was considered grade 1; 7-12 considered grade 2; and 3-8 considered grade 3. Fifty-nine patients (48.4%) had initial grade one consciousness, 46 (37.7%) had grade 2, and 17 (13.9%) had grade 3. After analysis of circadian rhythm during periods A, B, and C, the prognostic factors between the absence and presence groups for SBP, DBP, and HR are summarized in **Tables 1-3**. In the present study, prognostic factors that would influence circadian rhythm and outcome were age, gender, BMI, operative treatment, current/past smokers, current/past drinkers, diabetes mellitus, previous cardiovascular disease, serum total cholesterol, inosine, urea, hematoma volume, and rupture into ventricles. All the prognostic factors in the 2 groups were analyzed by the Student's t-test, or one-way ANOVA test. As can be seen from **Tables 1-3**, no significant differences of factors between the 2 groups were found. There were also no statistically significant differences found on comparison of circadian MESOR of SBP, DBP, and HR during the 3 periods

Table 1 - Clinical characteristics between the absence and presence group in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) during period A (N=122).

Characteristics	SBP			DBP			HR		
	Absence (n=32)	Presence (n=90)	*P*-value	Absence (n=28)	Presence (n=94)	*P*-value	Absence (n=36)	Presence (n=86)	*P*-value
Age,‡ years	67.6±4.8	65.6±6.4	0.244*	68.3±4.8	64.6±4.3	0.173*	69.1±5.0	67.4±2.5	0.552*
Gender, n (%)			0.958†			0.454†			0.673†
Male	18 (57.5)	51 (56.6)		16 (56.6)	50 (55.3)		19 (52.4)	51 (54.2)	
Female	14 (42.5)	39 (43.4)		12 (43.4)	44 (44.7)		17 (47.6)	35 (45.8)	
Body mass index,‡ kg/m^2	27.8±3.2	28±2.8	0.513*	26.8±2.4	27.7±1.8	0.213*	27.4±2.1	27.6±2.6	0.460*
Operative treatment, %	70.6	63.4	0.732†	71.4	68.2	0.512†	78.3	77.5	0.901†
Current/past smokers, %	39.8	44.5	0.615†	38.2	42.1	0.730†	32.2	40.1	0.055†
Current/past drinkers, %	32.4	29.8	0.804†	28.3	30.1	0.231†	27.2	29.1	0.605†
Diabetes mellitus, %	27.3	30.3	0.546†	19.8	20.5	0.946†	21.1	26.1	0.058†
Previous cardiovascular disease, %	45.6	52.3	0.142†	54.4	52.3	0.704†	38.7	40.53	0.217†
Serum total cholesterol,‡ mmol/L	6.94±1.1	7.34±1.2	0.171*	7.61±0.8	7.34±1.2	0.232*	7.56±0.7	7.37±1.1	0.577*
Inosine,‡ µmol/L	94.7±15.2	101.5±28.1	0.087*	92.5±11.0	93.4±9.2	0.684*	95.4±12.6	94.5±14.2	0.875*
Urea,‡ mmol/L	5.6±1.1	5.2±1.8	0.230*	5.2±0.9	5.5±1.3	0.155*	5.0±1.7	5.1±1.8	0.158*
Hematoma volume,‡ ml	51.5±14.2	48.6±12.3	0.645*	49.3±8.3	45.4±10.0	0.103*	48.7±15.2	48.3±11.3	0.825*
Rupture into ventricles, %	48.1	52.3	0.062*	52.1	47.8	0.062*	47.8	46.3	0.770*

*Independent-samples Student's t-test, †Pearson's chi-square test, ‡mean±SD

Table 2 - Clinical characteristics between the absence and presence group in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) during period B (N=122).

Characteristics	SBP			DBP			HR		
	Absence (n=31)	Presence (n=91)	*P*-value	Absence (n=30)	Presence (n=92)	*P*-value	Absence (n=33)	Presence (n=89)	*P*-value
Age,‡ years	61.3±2.7	64.6±6.7	0.324*	63.2±2.4	68.8±2.3	0.671*	68.2±7.2	70.4±2.5	0.254*
Gender, n (%)			0.058†			0.935†			0.174†
Male	17 (55.1)	51 (58.3)		16 (52.4)	46 (51.3)		18 (54.2)	50 (56.3)	
Female	14 (45.9)	40 (41.7)		14 (47.6)	46 (48.7)		15 (45.8)	39 (43.7)	
Body mass index,‡ kg/m^2	26.2±3.1	27±1.8	0.552*	26.8±3.3	26.7±1.3	0.803*	28.2±3.1	28.2±1.2	0.642*
Operative treatment, %	80.6	73.4	0.132†	74.4	78.2	0.673†	68.4	71.3	0.345†
Current/past smokers, %	40.3	42.3	0.466†	37.4	43.3	0.130†	34.3	33.1	0.633†
Current/past drinkers, %	33.6	32.8	0.564†	29.9	30.1	0.938†	24.5	24.1	0.853†
Diabetes mellitus, %	30.3	28.1	0.631†	20.5	22.4	0.136†	22.4	25.4	0.565†
Previous cardiovascular disease, %	44.3	54.2	0.124†	51.2	52.1	0.854†	39.2	42.3	0.127†
Serum total cholesterol,‡ mmol/L	7.13±1.3	7.94±2.3	0.125*	7.32±1.8	7.04±1.4	0.535*	7.01±1.7	7.88±2.1	0.074*
Inosine,‡ µmol/L	95.3±8.2	91.5±12.1	0.537*	93.3±11.0	93.2±9.4	0.745*	93.2±11.3	94.4±11.1	0.425*
Urea,‡ mmol/L	5.2±0.1	5.1±0.8	0.055*	5.5±0.3	5.1±1.1	0.147*	5.5±0.7	5.2±1.0	0.358*
Hematoma volume,‡ ml	52.2±12.1	50.6±11.1	0.113*	49.1±4.1	47.2±11.1	0.213*	51.7±11.2	50.1±9.3	0.746*
Rupture into ventricles, %	43.2	47.2	0.210*	43.2	46.2	0.259*	42.1	44.1	0.103*

*Independent-samples Student's t-test, †Pearson's chi-square test, ‡mean±SD

Table 3 - Clinical characteristics between the absence and presence group in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) during period C (N=122).

Characteristics	SBP			DBP			HR		
	Absence (n=85)	Presence (n=37)	*P*-value	Absence (n=100)	Presence (n=29)	*P*-value	Absence (n=72)	Presence (n=50)	*P*-value
Age,‡ years	63.1±2.2	61.1±4.5	0.587*	67.2±4.6	65.8±6.1	0.450*	64.1±2.7	68.4±5.5	0.468*
Gender, n (%)			0.243†			0.095†			0.802†
Male	45 (52.5)	20 (54.3)		54 (51.4)	11 (48.2)		37 (51.6)	26 (52.1)	
Female	40 (47.5)	17 (45.7)		46 (48.6)	11 (51.8)		35 (48.4)	24 (47.9)	
Body mass index,‡ kg/m^2	26.2±4.5	26±2.1	0.150*	27.1±2.1	26.5±4.3	0.803*	27.2±2.1	26.3±2.3	0.842*
Operative treatment, %	73.7	75.3	0.802†	73.1	74.5	0.831†	71.5	72.9	0.514†
Current/past smokers, %	51.3	48.5	0.066†	35.4	32.3	0.824†	35.1	38.6	0.101†
Current/past drinkers, %	28.1	31.2	0.202†	32.1	33.2	0.254†	26.4	21.5	0.100†
Diabetes mellitus, %	32.1	30.2	0.512†	28.5	21.3	0.106†	28.5	27.5	0.640†
Previous cardiovascular disease, %	49.3	50.4	0.841†	43.5	47.5	0.562†	31.1	40.5	0.205†
Serum total cholesterol,‡ mmol/L	7.15±0.9	7.50±1.2	0.311*	7.50±1.5	7.42±1.9	0.564*	7.55±1.5	7.84±1.8	0.566*
Inosine,‡ µmol/L	91.1±4.4	99.1±10.2	0.107*	96.4±15.4	98.0±6.5	0.501*	90.1±10.1	93.1±12.4	0.112*
Urea,‡ mmol/L	5.5±0.3	5.8±0.4	0.104*	5.2±1.0	5.6±0.7	0.546*	5.0±0.7	5.2±0.9	0.140*
Hematoma volume,‡ ml	50.1±11.2	51.4±10.4	0.814*	49.5±4.1	48.4±12.5	0.562*	52.0±12.1	51.4±10.3	0.725*
Rupture into ventricles, %	40.21	41.1	0.818*	46.1	48.2	0.411*	43.2	43.2	0.250*

*Independent-samples Student's t-test, †Pearson's chi-square test, ‡mean±SD

Table 4 - Circadian amplitude, mid line-estimating statistic of rhythm (MESOR), and percentage of absence and presence of circadian rhythms in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) during periods A, B, and C.

Index	MESOR	Amplitude	Percentage (%)	
			Absence	Presence
SBP* (mm Hg)				
Period A	132.57±11.87	6.81±1.80	26.22	73.78
Period B	134.80±12.91	5.33±1.08	25.41	47.59
Period C	136.32±12.60	1.22±0.23	69.67	30.33
P-value (95% CI)	0.171† (110.14-158.98)	1.26E-32† (0.89-7.48)	χ^2=64.96, *p*=3.44E-28‡	
DBP* (mmHg)				
Period A	74.22±5.43	4.33±1.08	22.95	77.05
Period B	74.64±5.33	3.12±0.98	24.59	75.41
Period C	75.89±5.65	0.75±0.11	81.97	18.03
P-value (95% CI)	0.135† (64.21-85.30)	3.78E-24† (0.42-5.33)	χ^2=112.35, *p*=6.71E-19‡	
HR* (beats/min)				
Period A	75.67±6.20	6.89±1.34	29.51	70.49
Period B	75.84±6.02	7.24±1.48	27.05	72.95
Period C	78.55±5.37	2.01±0.43	59.02	40.98
P-value (95% CI)	0.109† (68.25-84.56)	9.43E-21† (1.84-8.02)	χ^2=32.60, *p*=8.66E-14‡	

*Independent-samples Student's t-test, †Pearson's chi-square test, ‡mean±SD

(**Table 4 & Figure 1a**). However, on comparison of circadian amplitudes of SBP, DBP, and HR during the 3 periods, the amplitudes of SBP, DBP, and HR during period C were significantly lower than periods A and B (**Table 4 & Figure 1b**). The percentage of cases between the absence and presence groups in SBP, DBP, and HR were also significantly different by statistical analysis of chi-square test during periods A, B, and C (**Table 4 & Figure 1c**). The number of cases in the circadian absence group during period C was significantly greater than the other 2 periods. Three best-fit cosine curves were drawn by best-fit cosine function equations of SBP, DBP, and HR during periods A, B, and C. The characteristics of curves were that MESOR of SB, DBP, and HR during period A, B, and C were not significant difference, but amplitudes during periods A and B were higher than period C (**Figure 2**). Best-fit SBP during period A for Y=132.57+6.81*COS(2π/24*t-270/360*2π); Best-fit DBP during period A for Y=74.22+4.33*COS(2π/24*t-270/360*2π); Best-fit Hr during period A for Y=75.67+6.89*COS(2π/24*t-270/360*2π). Best-fit SBP during period B for Y =134.80+5.33*COS(2π/24*t-270/360*2π); Best-fit DBP during period B for Y=74.64+3.12*COS(2π/24*t-270/360*2π); Best-fit Hr during period B for Y =75.84+7.24*COS(2π/24*t-270/360*2π). Best-fit SBP during period C for Y

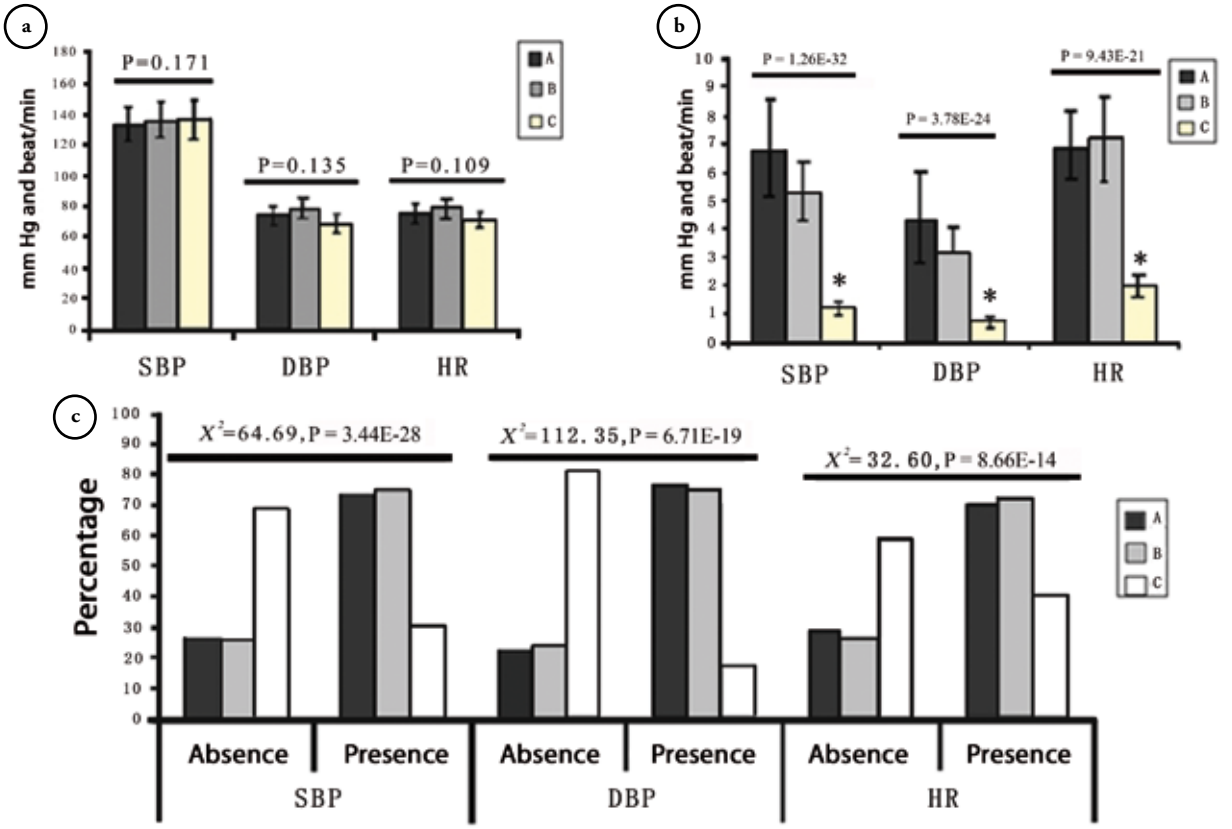

Figure 1 - Comparison of **a**) circadian midline estimating statistic of rhythm (MESOR) of blood pressure (BP) and heart rate (HR), **b**) amplitude of BP and HR, and **c**) percentage between absence and presence groups, during periods A, B, and C. *p<0.001

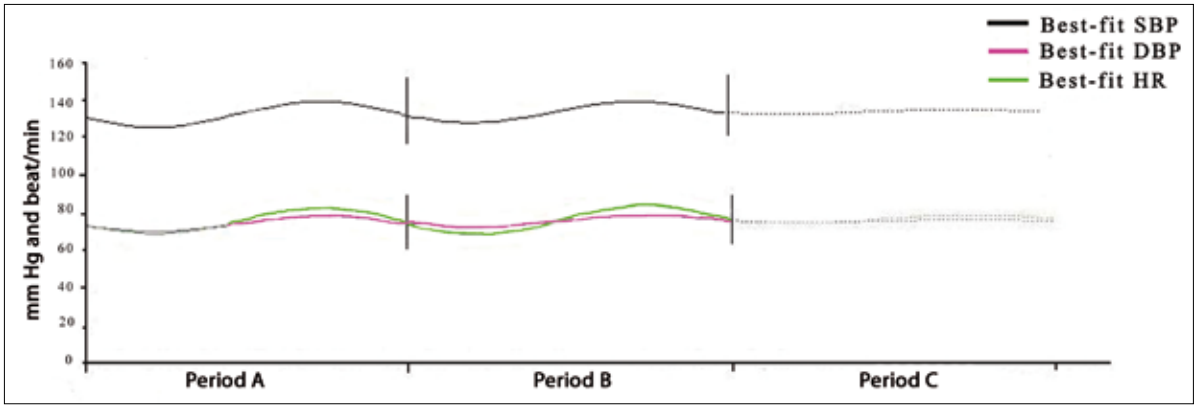

Figure 2 - Comparison of the 3 best fit cosine curves of blood pressure and heart rate during periods A, B, and C. Solid curves during period A, B stood for presence of circadian rhythm, whereas dotted curves during period C represent absence of circadian rhythm.

=136.32+1.22*COS(2π/24*t-270/360*2π); Best-fit DBP during period C for Y =75.89+0.75*COS(2π/24*t -270/360*2π); Best-fit Hr during period C for Y=78.55+2.01*COS(2π/24*t-270/360*2π).

Discussion. In this study, we divided patients into absence and presence groups after analysis of circadian rhythms by the single Cosinor method. The results showed that the amplitudes during period C were significantly lower than period A or B, and the percentage of cases in the absent and present groups was significantly different.

Hence, although the MESOR of BP and HR were not significantly changed, the majority of circadian

rhythms were absent in the 24-hours before death. As an independent factor, circadian variation could predict poor outcome in patients with ICH.

Most organisms on earth, as well as humans, have biological rhythms, including circadian rhythms. The biorhythm is the time structure within us as a product of adaptation to cycles in the nature.[17,18] Life originally integrates itself into the cycles of an anthropogenically unpolluted environment, while biological rhythms are still being modified by individual lifestyle, illness, subjective mood, and depression.[19] The location of the central circadian clock has been proven as the suprachiasmatic nucleus (SCN) in animals, even humans. The central circadian clock was observed to not only modulate the circadian rhythm, but it is also involved in some diseases when its normal function is lost. According to results of this study, when the SCN was disturbed by the ICH, the circadian rhythm of the cardiovascular system would disappear. The conclusions of Dauphinot[21] show that dysfunction of the autonomic nervous system precedes an insufficient decrease in nocturnal BP independent of hypertension status, which is similar to the results of our study. Hence, early variation of circadian rhythm could reflect the degree of injury in the ICH brain, and dysfunction of the autonomic nervous system. Much accumulating evidence[22-28] suggests that circadian rhythm is associated with poorer outcome in the patients who lack normal nocturnal BP fall (non-dippers). Tranah et al[11] analyzed data of 10,366 cases and showed that circadian activity rhythm abnormalities are prognostic of greater risk of mortality in older community-dwelling women. Another study reported that type 2 diabetes patients with non-dipping of night blood pressure were at higher risk of death as compared with dippers, independent of known cardiovascular risk factors.[29] In addition, previous studies indicate that a loss of circadian variation in atrioventricular conduction and QT intervals were associated with an increased risk of cardiac death.[30,31] As far as our analyses of circadian rhythm are concerned, we infer that circadian variation is associated with risk of ICH death, which is similar to previous reports. Nevertheless, we considered 3 different aspects in comparison with previous literature. Firstly, the circadian rhythms were analyzed by Cosinor in the present study, which can express circadian characteristics preferably by parameters of cosine function: amplitude, MESOR, and acrophase. Furthermore, circadian variation always predicted outcome in patients with various chronic diseases in previous studies. In contrast, our results imply that circadian variation can predict fatal decompensation before death in patients with ICH, which could be in favor of clinical emergent treatment. Lastly, the index of circadian rhythm that we analyzed is not only SBP and DBP but also included HR. No matter what index we choose, the same results are obtained, hence providing more evidence in support of our study findings.

In summary, the circadian amplitudes of SBP, DBP, and HR were lower in the 24-hours before death in ICH patients. Most of the circadian rhythms were also absent 24-hours before death in the ICH patients. Our results suggest that circadian variation, as an independent factor, could predict death in patients with ICH. We believe that it is very important to analyze circadian rhythms after ICH, which may be useful in predicting preclinical fatal decompensation and identifying opportunities for therapeutic intervention. Of course, our study has limitations that could be improved in future studies. The small sample size was one limitation. If our findings could be replicated in a larger cohort, this would suggest that 24-hour ambulatory BP/HR monitoring and analysis of circadian rhythm should be routine in patients with ICH. In addition, we hope the new Cosinor software, which can analyze biorhythms quickly and accurately, will become available in the clinical setting.

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