

CIRCADIAN RHYTHM OF BLOOD PRESSURE AND HEART RATE IN UNCOMPLICATED HEALTHY HUMAN PREGNANCY

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A b s t r a c t

Blood pressure (BP) and heart rate (HR) were automatically monitored for 48 hours at 15-min intervals in 31 hospitalized pregnant women at low risk for BP disorder. Each of the recorded 56 data series for systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and heart rate (HR) was chronobiologically assessed. A rhythm-adjusted mean (MESOR), 24-hour and harmonic amplitudes, 24-hour and harmonic acrophases were grouped by trimester of pregnancy and further subjected to analysis of variance. The repeatedly reported well-established lowering of BP MESOR was not detected in this particular sample, while, as anticipated, the HR MESOR increased statistically significantly in the course of pregnancy. Ultradian components, with a period from 1 to 12 hours and an amplitude higher than that of the 24-hour component, were found in 25% of the SAP data series recorded during the second and third trimesters. Such ultradian components were detected in only one of the 36 simultaneously recorded HR series. Analysis of the individual variability in the statistical endpoints, based on 9 women contributing records in each trimester of pregnancy, revealed in the course of pregnancy greater variability in circadian amplitude and acrophase than in the individual BP MESOR. Healthy pregnancy differentially affects the BP and HR chronomes. The reproducible individual BP MESOR, obtained by 48-hour monitoring at 15-min intervals in hospitalized pregnant women, may be useful in early diagnosis of gestational hypertension, but for detection of circadian hyper-amplitude-tension (CHAT), longer than 48-hour monitoring is needed.

Key words

circadian rhythm, ultradian component, internal ultradian desynchronization, chronobiological assessment

Abbreviations:

MESOR midline-estimating statistic of rhythm, 2A - double amplitude (measure of predictable change within a cycle), CHAT - circadian hyperamplitude tension of blood pressure

INTRODUCTION

Recurrent variations in blood pressure (BP) and heart rate (HR), with a period longer than that of the cardiac cycle (26), have been documented in data series

spanning 24 hours or longer (15). Such records typically show higher BP and HR values during the day and lower ones during the night. For example, the difference between the highest and lowest values for systolic arterial BP (SAP) usually amounts to 40-60 mm Hg (6, 14, 16). Chronobiologically in terms of inferential statistics, BP and HR data series can be assessed by one of several parametric approaches (there are also complementary nonparametric ones) (6, 12). One such approach considers a time series as the sum total of several components with different periods and amplitudes (6). Due to its usually larger amplitude in comparison with the other components, related probably to its documented genetic anchor, the 24-hour rhythmic component makes the dominant contribution to the variability of BP and HR profiles in healthy adults (6, 16). The contributions of harmonics are viewed without specification of which, in a set of components, is a rhythm in its own right, rather than serving to quantify the waveform of the circadian rhythm.

From a cardiovascular point of view, a clinically healthy pregnancy is a paradoxical state wherein the BP MESOR does not increase, despite the accumulating retention of salt and water, and the associated increase in cardiac output and plasma volume (4). Moreover, BP in pregnancy is statistically significantly lower than in a non-pregnant state (2, 7, 8). The coordination of BP in pregnancy may hence involve a currently unknown mechanism, that overrides the expected BP increase in response to volume expansion (11).

A chronobiological assessment of ambulatorily monitored BP and HR in pregnancy has already provided ranges for the physiological 24-hour variations in each trimester (2, 7, 8, 14, 25). However, most of the studies so far are directed at the possible use of early alterations in the 24-hour BP rhythm as harbingers of cardiovascular complications in pregnancy. Thus, a correlation between the risk for gestational hypertension (based on the medical history) and the rhythm-adjusted mean (MESOR), the circadian amplitude of the BP rhythm, and an inversion of the BP profile in pregnant women with preeclampsia-eclampsia are reported (14, 20, 21). The limitation of much of the work thus far is the open problem of the optimal length and density of BP and HR monitoring, that ensures an individual reproducibility of BP and HR variations. Analysis of serial 24-hour BP records shows a large intra-individual day-to-day variability, that limits the applicability of 24-hour profiles (13).

Relatively little attention is paid to the interrelations of the rhythmic variations in BP and HR during a clinically healthy pregnancy. In this context we studied the rhythmic structure of BP and HR during pregnancy in hospitalized women at a low risk for BP disorder. Here we report that the chronobiological assessment of 48-hour BP and HR data series revealed a differential effect of pregnancy on BP and HR rhythmicity. In addition, this approach provided a reproducible individual BP MESOR in the course of a clinically healthy pregnancy, that may be useful in

the early diagnosis of gestational hypertension, but is no substitute for day-to-day surveillance by self-measurement, until continuously monitoring automatic devices become available at a generally affordable cost.

MATERIAL AND METHODS

Subjects

Thirty-one pregnant women from 19 to 41 years of age (28 ± 5.6 years; mean \pm SE) were hospitalized for at least 3 days before BP and HR monitoring at the Institute of Obstetrics and Gynecology in Sofia. Answers to a BP and HR risk questionnaire (7), with a score range from 0 to 6, and informed consent were obtained in each case. Only results from women at low risk for hypertension (score < 2) are reported. The women did not receive medication before and during the study. The routine hospital schedule included breakfast around 08:00, lunch around 13:00, dinner around 19:00 and sleep/rest from 22:00 to 07:00.

Protocol

SAP, DAP and HR were measured oscillometrically during 48 hours at 15-min intervals by an ambulatory blood pressure monitor (ABPM-630, Colin Electronics, Komaki, Japan). The instruments were calibrated against a mercury sphygmomanometer before each recording session. Data collection was interrupted only for taking a shower. Some of the women contributed 2 or 3 records during different trimesters of their pregnancy. As a result, 56 data series with simultaneous records of SAP, DAP and HR were available for analysis.

Data analysis

An initial linear analysis involved the single cosinor fit of a 24-hour cosine curve. The endpoints thus derived from 3 independent groups of subjects ($n=11$ for each trimester) in comparison with the data from 9 women, who were studied in each trimester of pregnancy, resulted in highly comparable results. Thereafter, the MESOR, 24-amplitude and acrophase of all SAP, DAP and HR data series were grouped by trimester of pregnancy and subjected to a one-way analysis of variance (1-way ANOVA).

The 48-hour data series were also subjected to linear-nonlinear rhythmometry (12) in order to obtain estimates for the rhythm-adjusted mean (MESOR) and for the period of the best-fitting curve (BFP), and at this period and its harmonics, for the amplitude and acrophase (measures of the extent and timing of predictable change within a cycle, respectively). The anticipated circadian rhythm was statistically validated when the zero amplitude (no-rhythm) assumption was rejected at a probability level of 5% or less.

RESULTS

A. Pregnancy differentially affects ultradian BP and HR rhythmicity

The chronobiologic assessment of BP and HR is illustrated in *Fig. 1* for one pregnant woman (DGK) monitored during trimester II during her 19th gestational week. The original data are shown as a function of time on the left, with results summarized on the right. The relatively large variability in the data is noteworthy.

A statistically significant 24-hour rhythm of SAP, DAP and HR was found in all data series, except for the SAP and DAP data series of one pregnant woman in the third trimester of pregnancy. The 24-hour group endpoints for each trimester of pregnancy are given in *Table 1*.

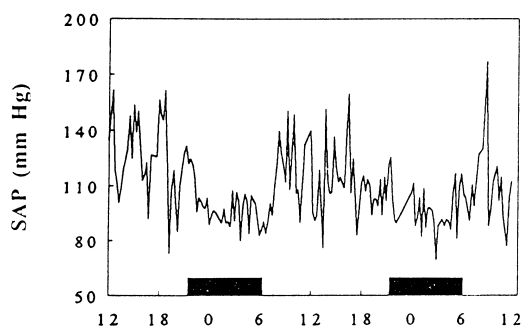
Chronobiological endpoints for systolic (S) and diastolic (D) arterial pressure (AP) and heart rate (HR) in the course of healthy uncomplicated pregnancy

All results are given as Mean \pm SE; MESOR and 24-hour amplitude for SAP and DAP are shown in mm Hg whereas those for HR are shown as beats per minute.

The MESOR values for BP and HR were differentially affected in the course of pregnancy. In this study, no changes in BP are found along the course of pregnancy, while the MESOR of HR is increased significantly ($P<0.002$). No statistically significant changes in the group 24-hour amplitude or relative amplitude (double amplitude/MESOR ratio; %) were detected in the course of pregnancy in the present study (*Table 1*).

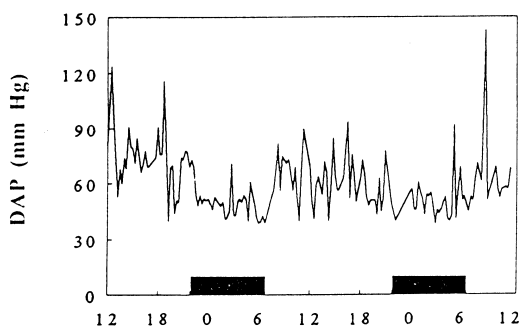
48

DGK (14 gw)



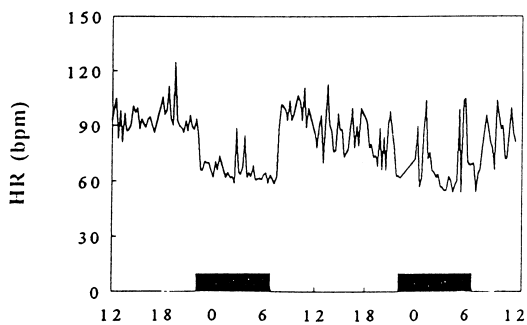
SAP

BF Period: 24 h
MESOR: 109.2 mm Hg
Amplitude: 13.8 mm Hg
Acrophase: 14:48 h



DAP

BF Period: 24 h
MESOR: 60.1 mm Hg
Amplitude: 11.0 mm Hg
Acrophase: 14:44 h



HR

BF Period: 24 h
MESOR: 81.0 bpm
Amplitude: 13.5 bpm
Acrophase: 14:56 h

TIME OF DAY (hours)

Fig. 1.

Chronobiologic assessment of 48-hour data series of systolic (S) and diastolic (D) arterial pressure (AP) and heart rate (HR) simultaneously monitored at 15-min intervals in a pregnant woman (DGK) during the second trimester of pregnancy (14th gestational week). The original data are shown to the left. Note the relatively large variability in the data series. The chronobiologic endpoint summary for each record is given to the right.

B. Large variability of circadian amplitude in the course of pregnancy

Fig. 2 shows the intra-individual variability of the major endpoints in the linear chronobiological analysis of the circadian BP and HR rhythms for 9 women, studied during each trimester of pregnancy. The individual SAP and DAP MESORs showed relatively smaller changes. The largest change in a given individual was less than 20%. The HR MESOR increased steadily in each case. The changes in the individual 24-hour amplitudes and acrophases were large. In extreme cases, the 24-hour amplitude was doubled or diminished by 75% in the second or third trimester as compared to the first. The acrophases also varied by up to 3 hours (*Fig. 2*). A further scrutiny of Figure 2 reveals an apparently greater disparity in the patterns of HR vs. those of SAP or DAP.

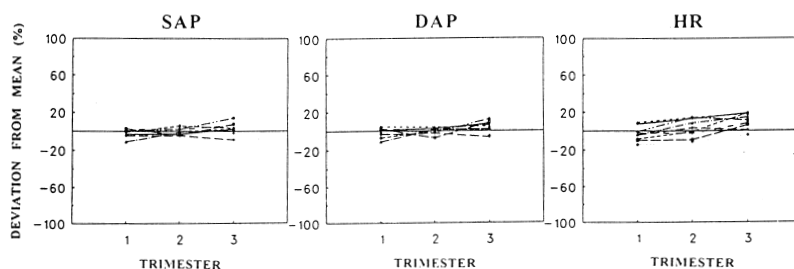
DISCUSSION

Two contradictory views exist regarding the generation and maintenance of BP and HR rhythmicity. One view considers the recurrent day-night variations as a mere consequence of the activity-rest cycle. Studies in monkeys are interpreted as suggesting a special „regulatory“ mechanism for BP constancy in the presence of marked circadian rhythms of blood and urinary hormones or metabolites (22). In addition, the 24-hour rhythm of BP reportedly adjusts its acrophase immediately after transmeridian flights, in contrast to other circadian rhythms (1). The double amplitude/MESOR ratio for BP, averaging about 20% (*Table 1*), cannot be viewed as a strong demonstration for the efficient homeostatic „feedback control“ of BP (11). Based on these considerations, the data series obtained by automatic monitoring are frequently analyzed only as daytime, nighttime and 24-hour means.

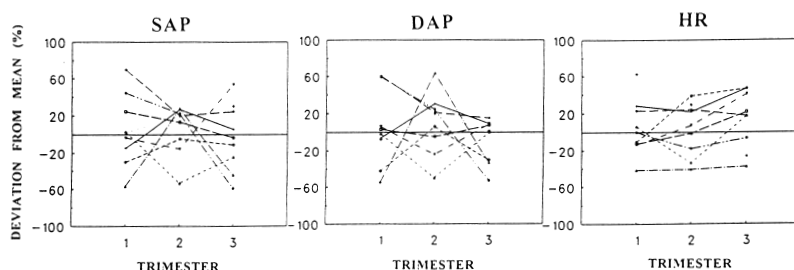
The chronobiologic view holds that endogenous mechanisms play an important role in the generation and maintenance of BP and HR rhythms with different frequencies (6). Multiple findings support this notion (18). First, it has long been claimed on the basis of population averages that human BP varies by only a few mm Hg, whereas on an intra-individual basis, it varies by over 50 mm Hg. Second, chronobiologically, even the original data used to document an immediate shift in timing after transmeridian flights reveal that the shift is rapid but not immediate. The phase adjustment after jet lag is fast but not complete one day after arrival. Third, the BP response to exercise is circadian stage-dependent. Fourth, the 24-hour BP rhythm persists in recumbency and even in a comatose patient. Finally, the 24-hour BP rhythm can be inverted under conditions of normal rest-activity cycle and/or can free-run (17).

Irrespective of these findings, the chronobiological assessment of data series collected under normal (synchronized) conditions and without special effort to avoid or diminish the effects of external factors such as posture, meals, physical activity, etc., is justified by outcomes. The superiority of the chronobiologic

A. MESOR



B. AMPLITUDE



C. ACROPHASE

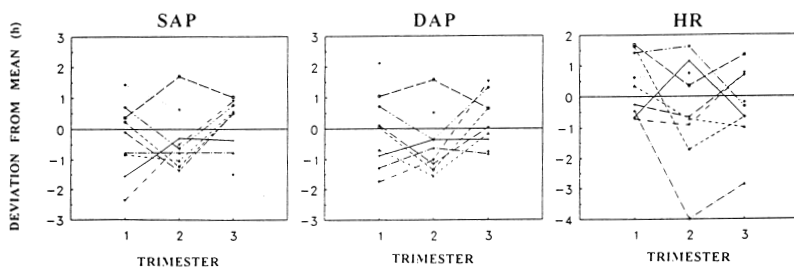


Fig. 2.

Individual variability in chronobiologically-derived endpoints in the course of pregnancy. Systolic (S) and diastolic (D) arterial pressure (AP) and heart rate (HR) data series of 9 pregnant women were monitored in each trimester of pregnancy. The extent and direction of the individual relative change in MESOR (panel A) and 24-hour amplitude (panel B) was calculated relatively to the respective group mean value from all data series ($n=27$) ((individual value/mean group value - 1) \times 100) and plotted for each trimester. The change in individual 24-hour acrophase (panel C) is given as a difference (delay/advance) from the mean group acrophase (in hours).

Note the relatively small variability of individual MESORs in comparison with 24-hour amplitudes. The patterns of individual change in the 24-hour amplitude and acrophase, derived from SAP and DAP data series were very similar but different from that of the simultaneously recorded HR (compare the first two graphs in panel B and panel C between them and then to the third graph, illustrating the individual 24-hour amplitude and acrophase changes in HR).

assessment of data series obtained under usual conditions of life in comparison with analyses based on the mean values alone is illustrated by the demonstration of statistically significant changes in the cardiovascular variables in situations when the traditional approach is not informative (5, 15).

A major finding in this study, qualifying all others insofar as individuals are concerned, is that the chronobiologically-derived endpoints for BP and HR require more than a 48-hour record. On a group basis, we extend the prior knowledge that BP and HR can show different rhythmic behavior. We here add to such findings that in the frequency domain (as well as in the phase domain), BP and HR can be differentially affected, i.e., in the course of a MESOR-normotensive pregnancy. The group HR variations retained their predominant circadian rhythm in the face of the increase in the HR MESOR. In contrast, ultradian components dominated 25% of the SAP records during the second and third trimester of pregnancy (*Table 1*). This difference in the BP and HR MESOR coordination is in agreement with observations in Minneapolis (Minnesota), where non-hospitalized pregnant women were monitored with the same instruments at 1-hour intervals for 48 hours (7, 14). In Minnesota, however, the MESOR of BP was found to be decreased during the second trimester of pregnancy (7).

Taken together, these observations support the notion that the 24-hour variations in BP and HR are under different physiological coordination and are synchronized in usual daily life by a relatively weak mechanism. Several other lines of evidence are in agreement with this view. Thus, studies „from womb to tomb“ reveal that the prominent 24-hour component of HR rhythmicity persists from newborns to centenarians (6). In contrast, the BP variations show a predominant infradian component (with a period of 7 or 3.5 days) in early extrauterine life. This component is replaced by a 24-hour variation later in life, whereas ultradian changes (with frequencies higher than 1 cycle per day) become more prominent with aging (6, 19). In contrast to the inverted or greatly reduced 24-hour BP rhythm, HR variations retain their usual 24-hour rhythm in patients with Cushing's syndrome or in patients treated with corticosteroids (20, 23). Whether the increased cortisol concentrations in pregnancy and the observed ultradian components with the persisting 24-hour rhythm of cortisol secretion (10, 24) are related to the observed BP ultradian components remains to be elucidated. The changes in BP and HR rhythmicity, described in the present study, along with the evidence for an altered sleep pattern in the advanced stages of healthy pregnancy (3), raise the possibility that the hormonal changes during gestation could affect the central mechanisms implicated in the internal synchronization of BP and HR rhythmicity.

An important methodological task for the application of a chronobiologic assessment of BP and HR in individual cases is to define the optimal length and frequency of measurements in order to obtain reliable statistical endpoints. As already mentioned, statistically significant differences in MESOR and 24-hour

amplitude are found when individual BP records from separate 24-hour data series are compared (13). Our study showed a good individual reproducibility of the BP MESOR when 3 individual 48-hour records obtained in each trimester of pregnancy were compared (Fig. 2). However, the BP MESOR seems to be dependent on the overall activity level during the monitoring span. Thus, the reported group BP MESOR for each trimester in this study is significantly lower than that found in Minneapolis where the pregnant women were monitored with the same instrumentation but were not hospitalized (7, 14). Furthermore, the group BP MESOR derived on the basis of 48-hour records obtained with a stationary monitor (restricting the pregnant woman to the hospital room) was significantly lower in each trimester than the BP MESOR found with ambulatory monitoring in the same hospital unit in this study (comparison not shown). Although no differences were found for the circadian period of BP and HR of women studied with an ambulatory or room-restricted monitor, the 95% confidence interval for the circadian period was statistically significantly wider for the stationary monitoring.

Therefore, care should be taken to standardize the conditions and instrumentation for monitoring. Nevertheless, 48-hour ambulatory monitoring at 15-min intervals in hospitalized women provides an individual MESOR reproducibility and may be a useful protocol for further clinical studies. In contrast, a relatively large individual variability was found for the 24-hour acrophase and amplitude. The phase variability is not surprising in the light of the approximately 1-hour variability noted in the individual circadian phase of body temperature and urinary 6-OH-melatonin of volunteers under conditions of constant routine (9). Therefore, whether individual phase or amplitude changes obtained from 48-hour data series may be of clinical importance and appearance of further cardiovascular risk remains to be elucidated (27).

In summary, our data indicate that the rhythmic variations in BP and HR are differentially affected during a healthy uncomplicated pregnancy. In addition, BP MESORs derived on the basis of 48-hour records in hospitalized women could be a useful tool in the early diagnosis of BP disorders in pregnancy.

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CIRKADIÁNNÍ RYTMUS KREVNIHO TLAKU A SRDEČNÍ FREKVENCE V PRŮBĚHU FYZIOLOGICKÉHO TĚHOTENSTVÍ

S o u h r n

Krevní tlak a srdeční frekvence byly automaticky monitorovány po dobu 48 hodin v patnáctiminutových intervalech u 31 hospitalizovaných těhotných žen s malým rizikem poruch krevního tlaku. Údaje ze serie 56 měření systolického a diastolického krevního tlaku a srdeční frekvence byly chronobiologicky zhodnoceny. MESOR (přibližně střední hodnota), amplituda

a akrofáze cirkadiánního rytmu byly seskupeny podle trimestru těhotenství a dále podrobeny analýze variance. Opakovaně uváděné snížení MESORu krevního tlaku nebylo v tomto vzorku těhotných zjištěno, přičemž se podle předpokladu MESOR srdeční frekvence zvýšil v průběhu těhotenství statisticky významně. Ultradiánní složky s periodou od 1 do 12 hodin a amplitudou vyšší než u 24-h složky, byly zjištěny v 25% údajů systolického tlaku, zaznamenaných během druhého a třetího trimestru. Takové ultradiánní složky byly zjištěny pouze u jedné z 36 simultánně zaznamenaných sérií dat srdeční frekvence. U 9 žen jsme měli k dispozici záznamy kardiiovaskulárních veličin v každém trimestru těhotenství, jejichž analýzou byla zjištěna v průběhu těhotenství větší variabilita v cirkadiánní amplitudě a akrofázi než v individuálním MESORu krevního tlaku. Fyziologické těhotenství odlišně ovlivňuje chronomy krevního tlaku a srdeční frekvence. Reprodukovatelný individuální MESOR krevního tlaku, získaný 24-h monitorováním v 15-minutových intervalech u hospitalizovaných těhotných žen, může být využit včasné diagnóze těhotenské gestózy, ale pro zjištění cirkadiánní hyperamplitudy krevního tlaku je potřebné monitorování delší než 48 hodin.

Acknowledgements

This study was supported by the U.S. National Institutes of Health (GM-13981); National Heart, Lung and Blood Institute (HL-40650); Minnesota Medical Foundation (SMF-745-88); Bulgarian Program for the study of the Human Brain (G-43); and the Fogarty International Center under the International Exchange Program.

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