PREDICTABLE BLOOD PRESSURE VARIABILITY IN CLINICALLY HEALTHY HUMAN PREGNANCY

Diana E. Ayala and Ramón C. Hermida


ABSTRACT

Conventional time-unspecified single measurements of blood pressure (BP) and heart rate (HR) may be misleading since they may be influenced, among other factors, by the patient’s emotional state, position, diet, and external stimuli. All of these effects depend upon the stages of a (mathematical) spectrum of rhythms and trends with age. The evaluation of predictable variability in BP and HR by 1) the use of fully ambulatory devices, and 2) chronobiologic data processing, assesses early cardiovascular disease risk, e.g., in pregnancy. We have used this approach to quantify changes in 24-hour synchronized (circadian) characteristics of BP and HR in two consecutive pregnancies of a clinically healthy woman (DEA). BP and HR were automatically monitored, with few interruptions, at 1-hour intervals, and for a total of 76 days of monitoring in each pregnancy. Circadian parameters of BP and HR were computed for each single day of measurement by the least-squares fit of a 24-hour cosine curve. Regression analysis of parameters thus obtained revealed patterns of variation of circadian rhythm-adjusted means and amplitudes with gestational age. This longitudinal study confirms and extends to ambulatory everyday life conditions the predictable pregnancy-associated variability in BP and HR and also allows the establishment of prediction and confidence limits for cardiovascular parameters in a healthy pregnancy.

KEY WORDS

Human pregnancy, blood pressure, heart rate, healthcare, biomedical signal processing, rhythmometry, clinical assessment.

INTRODUCTION

Ambulatory and non-invasive BP monitoring is increasingly used in the diagnosis and treatment of hypertension. The use of rhythmometric methods for analysis of time series with sparse and non-equidistant observations in combination with automatic and portable recording systems has already proved its value in assessing the antihypertensive efficacy of a prescribed drug not only for groups but also on an individualized basis [16]. The major interest in BP readings comes as a need to better understand and to more accurately diagnose clinical high BP states. Hypertension is a common chronic condition that may affect up to 25% of the adult population [27]. The major importance of this condition is that it is a risk factor for premature cardiovascular disease, especially strokes and heart attacks [20]. Treatment of high BP by pharmacologic methods lowers the incidence of these major complications and may prolong life [16]. Accordingly, there has been a strong incentive to identify individuals with high BP and to provide them with an
appropriate treatment.

A group of particular interest is that of pregnant women. This is due to the fact that pregnancies complicated by an elevated BP and the occurrence of preeclampsia contribute markedly to perinatal mortality [12]. It also appears that a history of preeclampsia or at least of gestational hypertension in a prior pregnancy places the pregnant woman and her offspring at a high risk for a later development of high BP 7 to 12 years later [26]. In order to prevent the occurrence of gestational hypertension or even preeclampsia, several tests have been designed, with various degrees of specificity and sensitivity. Gant et al. [14] proposed the rollover test for predicting the development of acute hypertension in pregnancy. Hayashi et al. [17] applied the angiotensin II response test in relation to positional change. Several authors have found a reduced drop in BP by night in preeclamptic patients [21,23], whereas others even report an inversion of the circadian pattern of change in BP associated with preeclampsia [7,22]. Such studies have usually been carried out during the second or third trimester of pregnancy. Physiologic changes, however, already occur early in human pregnancy [9,10].

So far, the BP and HR assessment in pregnant women has relied mostly on a few measurements taken in the physician's office. Such measurements may be misleading because BP and HR vary according to a spectrum of rhythms (the circadian in particular) and because measurements may be influenced, among other factors, by the patient's emotional state, position, diet, and external stimuli [16]. Self-measurement, if done systematically, offers an alternative, but it interferes with daytime activities and is not feasible during sleep. Moreover, the variability of BP, even among healthy individuals, is such that the identification and the proper definition of high BP is highly ambiguous, mainly when relying on single time-unspecified measurements. Even when based, not on one or two, but on a mean of several casual rather than systematic measurements, a BP found to be "high" or "low" is often unreliable. This is due both to the large variability of BP and the circumstance that unusually high or low values may occur only at certain times that may not be covered by casual sampling [11], as in the case of nightly hypertension.

The development of automatic instrumentation for indirect non-invasive ambulatory BP monitoring makes possible to follow the time course of BP variation around the clock in large groups [25]. The use of these monitors has provided a method of BP assessment that may compensate for some of the limitations of office and even self-measurements. Moreover, there is evidence that ambulatory BP measurements correlate better with target organ damage than do office BP values [13].

For the study of BP, the use of presently available automatic, fully ambulatory recording systems greatly facilitates data collection and, in combination with proper software, the interpretation of results. This approach can be useful in assessing early cardiovascular disease risk in pregnancy. We here report results from an ongoing study aiming at the provision of reference standards for BP and HR in the course of a healthy pregnancy by the use of this combined hardware-software approach. In particular, we quantified changes in circadian characteristics of BP and HR in two consecutive pregnancies of a clinically healthy woman [4,5,6].

**SUBJECT AND METHODS**

A clinically healthy pregnant woman (DEA) used an ABPM-630 (manufactured by Colin Medical Instruments Inc., Komaki City, Japan) to monitor her BP and HR at ~1-hour intervals with few interruptions. For the first pregnancy, she monitored herself for 47 consecutive days between the 9th and the 16th weeks of pregnancy, and for about 7 consecutive days each month thereafter until the day of delivery [4,5,6]. For the second
pregnancy, and starting on the first gestational week, she monitored herself for 2 out of each 6 days during the whole pregnancy, for a total of 76 days.

The instrument is a small (165 x 36 x 89 mm), lightweight (830 g, including battery and gas cartridge) fully ambulatory monitor carried in a special shoulder pouch designed for pregnancy monitoring. This monitor is powered by CO₂ cartridges for cuff inflation and is battery-operated for the management of data collection, scheduling and storage in a solid-state memory that can hold over 600 sets of measurements. The instrument uses both an oscillometric and auscultatory (Riva Rocci-Korotkoff) method of measuring BP. Both approaches also provide a measure of HR. Additionally, four control keys allow the subject to enter information with a previously agreed code to identify the times of food intake, activity and position (walking, running, sitting, sleeping), drug administration (if any), etc. Data can be easily transfer from the memory cassette to a computer by the use of an AA-200 Colin Analyzer and software specifically designed by us for that purpose. After coding, data were analyzed on a Macintosh IIIF by rhythmometric procedures [2,3,18] and by multiple regression analysis.

Circadian parameters of BP and HR were first computed for each single day of measurement by the least-squares fit of a 24-hour cosine curve. By this approach one obtains, for the period considered, an estimate of 1) the MESOR (midline estimating statistic of rhythm, in brief M), a rhythm-adjusted mean, defined as the average value of the rhythmic function (e.g., cosine curve) fitted to the data; 2) the amplitude (A), half the extent of rhythmic change in a cycle approximated by the fitted cosine curve; and 3) the acrophase (θ), lag from a defined reference timepoint (usually local midnight when the period of the fitted curve is 24 hours) of the crest time in the cosine curve fitted to the data [2,18]. The circadian parameters that obtained were used to establish their pattern of variation along gestational age by polynomial regression analysis.

RESULTS

Results of linear regression on the daily M of systolic and diastolic BP and HR as a function of gestational age for the 47-day span of continuous monitoring between the second and fourth months of the first pregnancy indicate a statistically significant linear decrease in systolic and diastolic BP (correlation coefficient with gestational age r=-.620 and -.559, respectively; P<.001 in both cases), but not statistically significant change in HR (r=.017, P=.913). The variation of circadian A along gestational age for the span considered is not statistically significant for BP (r=-.135, P=.368 for systolic; r=.081, P=.585 for diastolic), but borderline significant for HR (r=-.271, P=.065).

When considering the whole monitoring span for the first pregnancy, the variation of circadian Ms along gestational age can not longer be explained by the fit of a linear trend. The predictable variability of circadian BP M can be approximated by a second order polynomial model on gestational age: a steadily linear decrease in systolic (Figure 1) and diastolic BP (Figure 2) up to the 22nd week of pregnancy is followed by an increase in BP up to the day of delivery, with final BP values similar to those found early in pregnancy. Circadian BP A is slightly decreasing with advancing gestational age (r=-.089, P=.444 for systolic BP; r=.049, P=.676 for diastolic BP).

With respect to HR, the circadian M increases up to the 23rd week and slightly decreases thereafter, as approximated by a second-order model of variation (multiple correlation coefficient r=.284, P=.047). Values just before delivery are also similar to those found early in pregnancy. There is no significant change in the circadian A of HR.
Figure 1: Variation of circadian MESOR (M) of systolic blood pressure along gestational age in the first pregnancy of a clinically healthy women.

Multiple correlation coefficient $r = .551$, $P < .001$
(from 2nd order polynomial model)

Figure 2: Variation of circadian MESOR (M) of diastolic blood pressure along gestational age in the first pregnancy of a clinically healthy women.

Multiple correlation coefficient $r = .570$, $P < .001$
(from 2nd order polynomial model)
These results have been corroborated by the data monitored along the second pregnancy of the same woman. Regression analysis on the circadian BP Ms indicate again a second-order model of variation on gestational age for systolic (Figure 3) and diastolic (Figure 4) BP. Moreover, the second-order models approximating BP variability in the two pregnancies have similar coefficients for gestational age (P=.668 and .669 for first and second order coefficients, respectively, for systolic BP, Figure 3; P=.339 and .397 for first and second order coefficients, respectively, for diastolic BP, Figure 4), but lower BP values throughout the second pregnancy. This consistent and statistically significant decrease of about 8 mm Hg (P<.001) for systolic BP and 4 mm Hg (P<.001) for diastolic BP in the course of the second pregnancy could be due not only to the expected decrease in BP for subsequent pregnancies as compared to the first, but also to the average added intake of 625 mg/day of calcium during most of the second pregnancy.

It is important to note that the total range of variation observed in the circadian M (computed in each case from data representing about 24 hours of measurements) is of 23 and 21 mm Hg for systolic and diastolic BP, respectively, in the first pregnancy, and of 27 and 21 mm Hg for systolic and diastolic BP in the second pregnancy. This range is about three times larger if we considered individual observations instead of circadian Ms.

DISCUSSION

Earlier transverse studies of BP during human pregnancy and an earlier quasi-longitudinal study of a pregnancy associated with diabetes [8] are here complemented by the longitudinal monitoring of a clinically healthy pregnancy. These longitudinal results can be compared with those of an earlier hybrid (transverse and longitudinal) study [12] on 22 women studied in at least two different stages of their pregnancy. Since not all women pro-

Figure 3: Variation of circadian MESOR (M) of systolic blood pressure along gestational age in two consecutive pregnancies of a clinically healthy woman.

- First pregnancy  $y = 127,47 - 0,33730x + 1,0239e^{-3x^2}$  $R^2 = 0,304$
- Second pregnancy  $y = 116,80 - 0,30248x + 9,1364e^{-4x^2}$  $R^2 = 0,439$
Figure 4: Variation of circadian MESOR (M) of diastolic blood pressure along gestational age in two consecutive pregnancies of a clinically healthy women.

- First pregnancy: $y = 82.655 - 0.27619x + 8.1668e^{-4}x^2$  $R^2 = 0.325$
- Second pregnancy: $y = 73.319 - 0.21506x + 6.4676e^{-4}x^2$  $R^2 = 0.472$

Provided profiles at the same gestational age, a normalization procedure was used: as a first approximation, the rate of change per week was calculated assuming linearity, for each woman separately, and assigned to each gestational week between the dates of monitoring. These rates of change per week were further averaged for each week across all women [12]. This approach clearly showed, for systolic and diastolic BP, statistically significant changes: a decrease between the 12th and the 15th weeks, and an increase between the 30th and 32nd weeks. In the case of HR, the increase could not be shown to be of statistically significance in any particular gestational week [12]. The trends obtained on the basis of this hybrid study are also apparent in the longitudinal monitoring investigated herein [4,5].

The critical thresholds for BP of 140/90 systolic/diastolic BP as recommended by the World Health Organization [1] do not account for the large range of variation seen in these variables within a day. Usual tests for detecting hypertension based on differences larger than 20 mm Hg in casual measurements are not longer valid in assessing gestational hypertension, since those differences can be found in a healthy pregnancy as indicated herein, not only for casual measurements, but also for the more stable and less noisy circadian Ms. On the other hand, the angiotensin sensitivity test is not always reliable in identifying pregnant women at risk of developing gestational hypertension [12].

In dealing with apparently healthy individuals, one important factor usually ignored when studying biologic variables within conventional physiologic normal ranges is the timing of a clinical measurement in relation to biologic rhythms. Time-varying reference limits that adjust for the rhythmic behavior of BP and HR have accordingly been suggested [15]. These reference standards are derived from data provided by healthy peer groups taking into consideration changes in mean and variance as a function or rhythm stage.
From this point of view, the study here presented represents a double example of longitudinal monitoring in a healthy pregnancy, keeping the everyday life conditions by the use of a fully ambulatory and non-invasive BP monitor. Non-invasive BP monitoring combined with the proper rhythmometric analysis on dense and long data series offers a complementary and early cardiovascular risk assessment in pregnant women.

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