Sampling Requirements for Ambulatory Blood Pressure Monitoring in the Diagnosis of Hypertension in Pregnancy

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Abstract—Previous studies on ambulatory blood pressure monitoring as a potential screening test for hypertension in pregnancy have not carefully considered sampling requirements. We have examined the impact of duration and frequency of blood pressure sampling in the reproducibility of mean values in pregnancy. We analyzed 2430 blood pressure series sampled every 20 minutes during the day and every 30 minutes at night for 48 hours every 4 weeks from the first obstetric visit until delivery in 235 normotensive and 168 hypertensive pregnant women. Blood pressure series were decimated to generate shorter series with data sampled every 1, 2, 3, or 4 hours for 48 hours, as well as at the original rate for the first 24 hours. Reproducibility of mean blood pressure as well as sensitivity and specificity in the diagnosis of hypertension were compared between the original and the decimated series. Sensitivity and specificity of the 24-hour blood pressure mean are similar for the values calculated from the original series and for those obtained from shorter profiles up to data sampled every 3 hours but reduced by 5% to 12% when diagnosis is based on data sampled at 20- to 30-minute intervals for the first 24 hours. Results also indicate that the 24-hour blood pressure mean is better reproduced with data sampled at 3-hour intervals for 48 hours than by data sampled at 20- to 30-minute intervals for 1 day only. This study demonstrates that reproducibility of mean blood pressure values is more dependent on duration of sampling than on sampling rate. (Hypertension. 2003;42:000-000.)

Key Words: blood pressure ■ pregnancy ■ hypertension, pregnancy ■ preeclampsia ■ blood pressure monitoring, ambulatory

Pregnancies complicated by hypertension contribute markedly to perinatal morbidity and mortality rates. Because an elevated blood pressure (BP) after 20 weeks of gestation in a previously normotensive woman is common to the definition of both gestational hypertension and preeclampsia, the issue of whether the development of these complications may be predicted on the basis of BP obtained during conventional antenatal visits has been addressed in several retrospective as well as prospective studies. Recent studies have tried to overcome the poor results from isolated conventional BP measurements in detecting hypertensive complications in pregnancy by relying on ambulatory BP monitoring (ABPM). By the use of ABPM, differences between healthy and complicated pregnancies in the circadian pattern of BP, previously documented for the second trimester of pregnancy, can be observed as early as in the first trimester of pregnancy, quite before the actual clinical diagnosis of gestational hypertension or preeclampsia takes place for most pregnant women investigated. As in the general nonpregnancy practice, the most common approach has been to rely for diagnosis on the arithmetic mean of all values determined by ABPM. However, the use of the 24-hour mean of BP does not provide a proper approach for an individualized early diagnosis of hypertension in pregnant women. Poor results from the diagnostic test based on mean BP values have led many authors to extrapolate erroneously that ABPM is not a valid approach in pregnancy.

Most studies conducted so far have been performed with ABPM for 24 hours. In the general practice, definitions of “normal” ABPM, criteria for diagnosis of hypertension, and assessment of antihypertensive therapy have been established on the basis of mean values determined from data gathered every 15 to 30 minutes over a single 24-hour span, a sampling scheme also used in most studies on pregnant women. Sampling requirements for the use of ABPM in the diagnosis of hypertension, however, have not yet been carefully taken into consideration. Along these lines, some advantages of 48-hour sampling instead of the most common 24-hour monitoring span in terms of reproducibility of results have been previously documented.

The objective of this study was to assess the impact of duration and frequency of BP sampling in the reproducibility of mean BP values, as well as in their sensitivity and specificity in the diagnosis of hypertension in pregnancy. In particular, we studied clinically healthy pregnant women and women who had gestational hypertension or preeclampsia, who were systematically studied by 48-hour ABPM from the first obstetric visit to the hospital until delivery.
Methods

Subjects
We studied 403 (207 primipara) untreated white pregnant women (235 normotensive, 128 who had gestational hypertension, and 40 who had preeclampsia) who fulfilled all required criteria for this trial (see below). Gestational hypertension was defined as conventional BP values $\geq 140$ or $90$ mm Hg for systolic (SBP) or diastolic BP (DBP), respectively, after the 20th week of gestation, and/or a hyperbaric index (area of BP excess above the upper limit of a time-varying tolerance interval $^{25,26}$) consistently above the threshold for diagnosis of hypertension in pregnancy $^{12}$ after the 20th week of gestation for further corroboration. Preeclampsia was defined as gestational hypertension and proteinuria $\geq 300$ mg in 24 hours of urine collection. Further details on the women participating in this prospective protocol on BP variability throughout gestation have been provided previously. $^{26,27}$ Inclusion criteria were the absence of any condition requiring the use of antihypertensive medication, maternal age (18 to 40 years), and gestational age ($\leq 16$ weeks at the time of inclusion). Exclusion criteria were multiple pregnancy, chronic hypertension, chronic liver disease, kidney disease, any disease requiring the use of anti-inflammatory medication, diabetes or any other endocrine disease such as hyperthyroidism, and intolerance to the use of an ABPM device. The State Ethics Committee of Clinical Research approved the study. All women signed consent forms before entering the study.

BP Assessment
In this trial, the SBP, DBP, and heart rate (HR) of each woman were scheduled to be measured by ABPM every 20 minutes during the day (7 AM to 11 PM) and every 30 minutes during the night for 48 consecutive hours with a validated $^{28}$ SpaceLabs 90207 device (SpaceLabs Inc) at the time of recruitment and then every 4 weeks until delivery. Subjects were instructed to go about their usual activities with minimal restrictions but to follow a similar schedule during the 2 consecutive days of ABPM and to avoid the use of over-the-counter and other medication for the duration of the trial. BP series were eliminated from analysis (a total of 79) when the women showed an irregular rest-activity schedule during the 2 days of sampling, an odd sampling with spans of $>3$ hours without BP measurement, or a night resting span $<6$ hours or $>12$ hours. The total number of valid BP series provided by the 403 women under investigation fulfilling all mentioned requirements set a priori was 2430.

Statistical Methods
Original oscillometric data from each BP series were edited according to commonly used criteria for the removal of outliers and measurement errors. $^{29}$ BP series were decimated to generate shorter series, with data sampled at half-hour, 1-, 2-, 3-, or 4-hour intervals for 48 hours. We also analyzed data obtained at the original rate for just the first 24 hours. Reproducibility of the 24-hour mean BP as well as sensitivity and specificity in the diagnosis of hypertension were compared between the values obtained from the complete (original time series) and the decimated series. The limits of agreement between the 24-hour mean value obtained from the original BP series and from each of the decimated series were calculated by use of the method of Bland and Altman. $^{30,31}$ Changes in sensitivity and specificity of the test for diagnosing hypertension based on the 24-hour BP mean as a function of the decimation process were evaluated and graphically shown by comparing receiver operating characteristic (ROC) curves obtained for SBP and DBP in each trimester of pregnancy, taking into account the predictable BP changes along gestation, as previously documented. $^{27}$

An expanded Methods section can be found in an online supplement available at http://www.hypertensionaha.org.

Results
Individual values of the 24-hour BP mean for each of the 2430 series obtained from the women participating in this trial were compared between the original undecimated series and each of the decimated series. The limits of agreement are shown in Figures 1 and 2 for SBP and DBP, respectively.

Figure 1. Bland-Altman plots for assessing agreement in the estimation of the 24-hour mean of SBP from data originally sampled by ambulatory monitoring every 20 to 30 minutes for 48 consecutive hours and from data sampled every half-hour, every hour, every 2 hours, every 3 hours, and every 4 hours for 48 consecutive hours or at the original sampling rate of 20 to 30 minutes for the first 24 hours in 403 pregnant women who provided 2430 ambulatory blood pressure profiles.
Each Bland-Altman graph represents the difference between the 24-hour mean value calculated from the original series and the 24-hour mean value calculated from the decimated series (in the vertical axis), plotted against the average of those two values (in the horizontal axis). The average of those differences is represented by the continuous horizontal line in each graph, and the values of these averages are provided in the first numerical column of the Table. The average of the differences ranges, depending on the loss of either duration or frequency of sampling, between 0.4 mm Hg (for data sampled at the original rate for 1 day only) and 1.0 mm Hg (for SBP sampled every hour for 48 hours). Although these values are apparently very low, all are significantly different from zero (P < 0.001 in all cases). The dashed lines in each graph represent the values of the

| Data was sampled every 20 minutes during the day (7 AM to 11 PM) and every 30 minutes at night for 48 consecutive hours and from data sampled at other less-dense sampling schemes in 403 pregnant women who provided 2430 ambulatory blood pressure profiles. Coverage is defined as the percentage of patients with a difference within the mean ± 2SD. |
average difference ± 2 SD. The values of SD are provided in the second column of the Table.

Figures 1 and 2 indicate that the values of the difference in 24-hour mean between the original and the decimated series are equally distributed around the average difference across the range of BP values. Accordingly, the degree of disagreement is not dependent on the actual value of mean BP. The graphs in Figures 1 and 2 also indicate that the degree of disagreement in the estimation of the 24-hour mean between the original and the decimated series gradually increases with the decimation process and, therefore, with the reduction in the frequency of sampling. The information in the Table, as a complement to Figures 1 and 2, also indicates that the range of values for the difference in 24-hour mean gradually increases as one decreases the frequency of sampling. The length of this range of differences is relatively small when the rate of sampling is within 1 datum per hour but very high when the frequency of sampling decreases to 1 datum every 3 to 4 hours. Results in the Table also indicate that the percentage of women with a difference within the average ± 2 SD (here defined as coverage) is always close to the expected value of 95%.

With respect to the impact of duration of sampling on the estimation of the 24-hour BP mean, results in Figures 1 and 2 as well as the information provided in the Table indicate that the BP mean from the original BP series are better reproduced with data sampled up to at 3-hour intervals for 48 hours (left graph on the bottom in Figures 1 and 2) than by data obtained at the original sampling rate of 20- to 30-minute intervals for just the first 24 hours (right graph on the bottom in Figures 1 and 2). The length of the range of values for the difference in 24-hour mean between the complete and decimated series is larger for all the data sampled during the first day than for the data sampled every 3 hours for 48 hours, both for SBP and DBP.

The impact of the disagreement in the estimation of the 24-hour BP mean as a function of the decimation process was evaluated by comparing the sensitivity and specificity in the diagnosis of hypertension in pregnancy. The graphs in Figure 3 provide the ROC curves for the 24-mean of SBP (top) and DBP (bottom) obtained in different trimesters of pregnancy from data sampled by ABPM every 20 to 30 minutes for 48 consecutive hours, every hour for 48 hours, every 3 hours for 48 hours, or every 20 to 30 minutes for 24 hours only. Figure 3 shows that the ROC curves are virtually equivalent at all stages of pregnancy for the complete undecimated data and for the data obtained at lower rates up to data sampled every 3 hours. Sensitivity and specificity, however, are reduced by 5% to 12%, mainly during the second half of pregnancy, when diagnosis is based on data sampled at 20- to 30-minute intervals for the first 24 hours only. Results and conclusions derived from Figures 1 through 3 and the Table for the 24-hour mean of BP are similar for the diurnal and nocturnal means of BP, calculated for each individual BP profile as a function of the actual schedule of diurnal activity and nocturnal rest of every woman investigated.

**Discussion**

In patients with chronic hypertension, the correlation between the BP level and the current target organ damage and the
eventual cardiovascular risk and long-term prognosis is closer for ABPM than for clinical measurements. ABPM is characterized by higher reproducibility as compared with conventional measurements, is not subject to digit preference and observer bias, and is apparently not subject to the transient rise of a patient’s BP in response to the clinical surroundings or the presence of the observer (the “white-coat” effect). There are, however, some problems associated with ABPM. Tolerance of the technique has been discussed as a possible limitation, mostly because ABPM could induce modest sleep disturbances. Moreover, there seems to be low individual reproducibility of the circadian profile in BP by repeated ABPM performed on the same patients, although results again show clear advantages of ABPM over office values in terms of reproducibility.

Some investigators have attempted to extrapolate the advantages of ABPM in general practice to the diagnosis of hypertension in pregnancy. Kyle et al investigated the effectiveness of second-trimester 24-hour mean of BP as a screening test for preeclampsia. They reported that the awake SBP was significantly higher at 18 and 28 weeks of gestation in those women who had subsequent development of gestational hypertension. Despite this difference in BP, the best predictive measurement with regard to BP was mean arterial BP at 28 weeks of gestation, providing a sensitivity of 65%, specificity of 81%, and a positive predictive value of 31% for the prediction of gestational hypertension. Daytime or night-time values of BP did not provide a better diagnosis. Brown et al reported a sensitivity of 70% when a cutoff value of 62 mm Hg for the nocturnal mean of DBP was used for predicting gestational hypertension or preeclampsia. While all these studies are based on ABPM done for 24 hours only, the most extended conclusion so far is that due to poor results in the diagnostic test based on the BP mean, ABPM does not provide a proper approach for the early identification of preeclampsia, and it should not be used in pregnancy. Against the common approach of relying on the 24-hour mean of ABPM, the combined approach of establishing tolerance intervals for the circadian variability of BP as a function of gestational age and then computing the hypobaric index (area of BP excess above the upper limit of the tolerance interval) by comparison of any patient’s BP profile with those intervals, has been shown to provide high sensitivity and specificity for the early detection of pregnant women who will have subsequent development of gestational hypertension or preeclampsia as well as a proper approach for the prediction of the outcome of pregnancy.

Results from this trial on the impact of the duration and frequency of BP sampling on the reproducibility of mean values indicate that parameters calculated from the ABPM profile are much more dependent on duration of sampling than on sampling rate. Thus, Figures 1 and 2 indicate that the 24-hour mean of BP can be better estimated by expanding the length of the monitoring span to 48 hours, even by markedly reducing the frequency of sampling up to only 1 value every 3 hours. Results in the Table indicate that the range of error in the estimation of the 24-hour mean of BP can be >20 mm Hg when calculation is based on data sampled by ABPM over 1 single day only. Although such a potential error is clearly unacceptable in clinical practice, Figure 3 shows that sensitivity and specificity in the diagnosis of hypertension in pregnancy are affected by reducing the duration of sampling but not by reducing the sampling rate. These results may explain in part the somehow negative results of previous studies on the evaluation of ABPM in pregnancy relying on 24-hour sampling. Figures 1 and 2 indicate that there is no particular trend (either positive or negative) that would allow a mathematical correction in the estimation of the mean BP when duration of sampling is restricted to 24 hours only. The average difference, as indicated in the Table, is close to zero. Therefore, the impact on sensitivity is expected to be low, as shown in Figure 3. Results from Figure 3 further indicate that values of sensitivity and specificity of the test based on the 24-hour mean for the diagnosis of hypertension in pregnancy increase with gestational age. These values are higher at all stages of pregnancy for SBP than for DBP, corroborating earlier findings.

Hypertensive patients, including women with gestational hypertension or preeclampsia, appear to have a greater day-to-day variability in BP than normotensive subjects. Although most studies assessing the circadian BP profile have used 24-hour ABPM, as a compromise with practicality, monitoring over at least 48 hours has been shown to present advantages in the analysis of BP variability, diagnosis of disease, and evaluation of a patient’s response to treatment. The individualized estimation of rhythm characteristics become more reliable; new end points are obtained, such as the circadian period, which cannot usually be estimated from 24-hour records. Previous findings suggested that ABPM done only for 24 hours may be too short to characterize accurately the features of the day-night variation in BP, including the “precise period of that variation. Moreover, there may be relatively large day-to-day changes in blood pressure, due in part to differences in day-to-day schedule, which are at least partly accounted for by sampling over 48 hours or even longer spans. Along these lines, it has been recently demonstrated that in patients evaluated by ABPM for the first time, there is a highly significant reduction during the second day of monitoring as compared with the first in the diurnal mean of BP. This “ABPM effect” increases SBP and DBP, on the average, by 7 and 5 mm Hg, respectively, during the first 4 hours of measurement, and it remains as statistically significant for at least the first 9 hours of sampling. As a consequence of the decrease in BP during diurnal activity but not during nocturnal resting hours, 35% of the patients characterized as dippers (patients with >10% decline in the nocturnal relative to the diurnal BP mean) during the first day of ABPM became nondippers in the second day of measurement. This result additionally justifies the lack of reproducibility in the estimation of the 24-hour mean of BP when sampling is restricted to 1 single day.

**Perspectives**

This study on women systematically studied by 48-hour ABPM throughout gestation indicates that reproducibility of mean BP values is more dependent on duration of sampling than on sampling rate. Thus, the diurnal, nocturnal, and 24-hour means of BP are better reproduced from data sampled every 3 hours for 48 hours than from data sampled...
at 20- to 30-minute intervals for 24 hours only. Results further indicate that ABPM for 24 hours may be insufficient for a proper diagnosis of hypertension in pregnancy. Expanding the length of monitoring, even at a lower sampling rate, could potentially increase patient compliance while rendering ABPM a proper approach for early diagnosis of hypertension in pregnancy.

References

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