Arterial Wave Reflections During the Menstrual Cycle of Healthy Women
A Reproducibility Study

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Abstract—Increased wave reflection is an independent factor associated with cardiovascular diseases, risk, and mortality. The influence of the menstrual cycle on wave reflections and particularly on the reproducibility of their measurement has never been examined. The aim of the present study was to examine the reproducibility and variability of wave reflection indices in premenopausal healthy women during their menstrual cycle. Thirty-two women were examined at 3 phases of their menstrual cycle: days 1 to 2 (menstrual phase), days 6 to 14 (late follicular), and days 4 to 7 after ovulation (early luteal phase). Applanation tonometry of the radial artery and aortic pulse wave analysis were performed for the calculation of augmentation pressure, augmentation index, and timing of reflected waves. Reproducibility of these measures was evaluated by intraclass correlation coefficient and Bland-Altman analysis, whereas ANOVA was performed to assess their variability during the menstrual cycle. The SD of augmentation index differences between repeated measurements within the menstrual cycle ranged from 7.6% to 9.9%. Bland-Altman analysis indicated no evidence of systemic bias and no trend for the reproducibility of measurements to vary with their underlying mean value. Intraclass correlation coefficient indicated a moderate reproducibility of augmentation index and augmentation pressure (≥0.80) and a rather low reproducibility for timing of reflected waves (0.43). Mean augmentation pressure, augmentation index, and timing of reflected waves did not vary significantly during the menstrual cycle (ANOVA). Measurement of wave reflections at the same phase of the menstrual cycle or statistical adjustment could be suggested for optimal study design and data interpretation. (Hypertension. 2009;54:1021-1027.)

Key Words: applanation tonometry ■ augmentation index ■ arterial stiffness ■ transfer functions ■ central pressures ■ menstruation ■ repeatability

A ortic pulse wave analysis (PWA) can reveal important information regarding the mechanical properties of the arterial tree and the energetic coupling between the left ventricle and the arterial system.1 There is now ample evidence indicating that increased wave reflections have an unfavorable effect not only on left ventricle energetic load/burden and coronary flow but also on left ventricle structure and function.2–4 In addition, the pathophysiologic role of wave reflection has been documented in several diseases.5,6 More importantly, increased wave reflection is an independent factor associated with cardiovascular risk and mortality.6–8

Properties of reflected pressure waves, such as their amplitude/intensity and their timing/velocity, are primarily determined by vascular elasticity, peripheral resistance, heart rate, and left ventricle function. These properties can be expressed by indices obtained by PWA, namely, the augmentation index (AIx), augmentation pressure (AP), and the arrival time of reflected waves at central aorta (Tr), as described previously.9,10

Applanation tonometry with or without the use of transfer functions and PWA is a noninvasive technique most widely used for the assessment of arterial wave reflections. The reproducibility of wave reflection estimation by means of applanation tonometry and PWA has been examined previously under different pathophysiological conditions and in different populations.11–24 However, although the majority of clinical studies include premenopausal women, the influence of the menstrual phase on wave reflections and particularly on the reproducibility of their measurement has never been examined.

The purpose of the present study was to examine the variability of arterial wave reflection in premenopausal

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1021
healthy women during their menstrual cycle and to assess the reproducibility of wave reflection indices measured at different phases of the menstrual cycle.

Methods

Study Population
Thirty-two premenopausal women were recruited among volunteers from the outpatient population, staff, and visitors at a university hospital in Athens. All of the subjects were nonobese (body mass index: <30 kg/m²) with normal blood pressure (BP; brachial systolic/diastolic BP <140/90 mm Hg, respectively) and without any history of diabetes mellitus or cardiovascular, renal, and endocrine disease. Subjects under diet, as well as those using antioxidant vitamins, contraceptives, or any medication, were excluded. Only women with a stable ovulatory cycle duration over at least the last 2 months were eligible for the study. Estradiol and progesterone levels were measured at each visit by chemiluminescent microparticle immunoassay (Abbott ARCHITECT System; Abbott Diagnostics), with coefficients of variation at 7% for both hormones. The study protocol was approved by the local institutional committee on human research, and all of the participants gave informed consent before entering the study.

Study Protocol
All of the women were examined 3 times at the following 3 phases of their menstrual cycle: (1) days 1 to 2 (menstrual phase); (2) days 6 to 14 (late follicular phase); and (3) days 4 to 7 after ovulation (early luteal phase). The entry of each subject into the study was randomized. Examinations and data interpretation were performed by researchers who were unaware of the menstrual cycle phase. Applanation tonometry and data acquisition were performed by a single operator (G.G.).

All of the measurements were obtained in a quiet, temperature-controlled room (21°C to 23°C) at the same time of the day (8:00 AM to 9:00 AM). All of the women fasted and abstained from smoking, caffeine, and ethanol intake for ≥12 hours before the examination. The subjects were examined in a sitting position after ≥15 minutes of rest. Specific instructions were given to each volunteer to keep her everyday regular habits (ie, exercise) and nutrition unchanged during the study period.

Estimation of Wave Reflections and Central Hemodynamics
Noninvasive estimation of aortic pressure waveforms and PWA were performed by the SphygmoCor System (AtCor Medical Pty Ltd), as described previously.2,10 Radial pressure waves were recorded by a high-fidelity micromanometer placed on the tip of a hand-held tonometer (Millar Instruments). Central pressure waves were derived by use of transfer functions.28 Multiple recordings were performed in every subject to accomplish optimal quality control criteria, (quality index: >85%), in accordance with the recommendations of the instrument manual.26

The recorded waveforms were calibrated by using the brachial systolic and diastolic BPs, which were measured by cuff sphygmo- manometry according to the recommendations of the American Heart Association.27 Brachial BPs were measured using an automated digital oscillometric BP monitor (Omron HEM 705-CP, OMRON Matsusaka Corporation).

The calibrated aortic pressure waves were analyzed, and the following parameters were calculated: AIx, a surrogate of wave reflection intensity, was defined as the augmentation (AP) of aortic systolic BP, which is induced by the reflected waves, expressed as a percentage of pulse pressure (PP): AIx = 100 · AP/PP. Arrival time of reflected waves at the central aorta is directly related to pulse wave velocity, which is determined by arterial stiffness. Central systolic and diastolic BPs were also estimated. A more detailed description of the definition and the clinical relevance of the aforementioned parameters can be found elsewhere.2,10

Analysis of Reproducibility

Bland-Altman Analysis
Intraobserver reproducibility was evaluated using the method of Bland and Altman.28 According to this method, the differences between 2 repeated measurements, d = (X1 − X2), are plotted against their mean value, d = (X1 + X2)/2. The percentage of differences that lies between d−2 SD and d+2 SD (called “limits of agreement”) is determined. Bland-Altman plots are provided for paired measurements (phase 1 versus phase 2, phase 1 versus phase 3, and phase 2 versus phase 3) to investigate any possible tendency of differences between paired measurements to depend on the mean value of the measurements.

Intraclass Correlation Coefficient
Intraclass correlation coefficient (ICC) assesses the reproducibility of repeated measurements by comparing the variability of different measurements of the same subject to the total variation across all of the measurements and all of the subjects. ICC is calculated by the following formula: \[ s_{	ext{within}}^2/(s_{	ext{within}}^2 + s_{	ext{between}}^2), \]

where \( s_{	ext{within}} \) and \( s_{	ext{between}} \) are the between- and within-subject SDs of the measured variable, respectively. Values >0.70 indicate substantial reproducibility.29

Coefficient of Variation
The coefficient of variation (CV) was calculated according to the following formula: \[ CV = 100 \times s_w/\mu, \]

where \( s_w \) is the SD of the repeated measurements and \( \mu \) the mean value of the measurements within subjects.

Statistical Analysis
The continuous variables are expressed as mean±SD unless otherwise stated. Variable distributions were assessed for normality by the Shapiro-Wilk test. Differences during the menstrual cycle (follicular phase, ovulatory phase, and luteal phase) were assessed by ANOVA for repeated measurements, whereas multiple comparisons were performed by post hoc analysis (Bonferroni test). Nonparametric Friedman test was performed to assess hormonal level variation. \( P<0.05 \) was considered to represent statistical significance. Statistical analysis was performed using SPSS 15 (SPSS Inc).

Sample size was estimated according to the methodology proposed by Giraudeau and Mary for planning a reproducibility study.29 The proper number of subjects (n) and the number of replicates (which is k=3 in the present study) were determined so as to provide an expected ICC >0.60 with a narrow expected width of the 95% CIs. Thus, we estimated that 30 subjects with 3 repeated measurements per subject (resulting to a total of n·k=90 measurements) would be sufficient to provide values of ICC >0.60, which corresponds with the limit between “moderate” and “substantial” reproducibility. Initially, we included 32 subjects in the study, assuming that a possible dropout might occur.

Results
The mean age of the study population was 27±4.8 years, and the mean length of the subjects’ menstrual cycles was 29±2 days. All of the women tolerated the examinations well and completed the study protocol successfully. As expected, both estrogen and progesterone levels presented significant variation during the menstrual cycle (Table 1).

Peripheral and central systolic and diastolic BPs, as well as heart rate, did not vary significantly among the 3 phases of the study (Table 1). Also, there was no significant variation in AP, AIx, and Tr during the menstrual cycle (Table 1). Similarly, brachial and central pulse pressures, as well as pulse pressure amplification, remained statistically unchanged (Table 1).

Bland-Altman plots for AP, AIx, and Tr are shown in Figures 1, 2, and 3, respectively. Three pairs of repeated measurements for each parameter were evaluated, namely,
Table 1. Central Hemodynamics and Wave Reflection Indices Recorded at the 3 Phases of the Menstrual Cycle

<table>
<thead>
<tr>
<th>Variable</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial systolic BP, mm Hg</td>
<td>103.9±15.2</td>
<td>99.2±11.1</td>
<td>99.4±13.3</td>
<td>0.381</td>
</tr>
<tr>
<td>Brachial diastolic BP, mm Hg</td>
<td>67.1±9.8</td>
<td>64.4±9.0</td>
<td>64.5±10.0</td>
<td>0.384</td>
</tr>
<tr>
<td>Brachial PP, mm Hg</td>
<td>36.8±12.7</td>
<td>34.8±7.7</td>
<td>35±8.8</td>
<td>0.512</td>
</tr>
<tr>
<td>Aortic systolic BP, mm Hg</td>
<td>89.8±19.0</td>
<td>88.8±11.5</td>
<td>88.9±12.8</td>
<td>0.617</td>
</tr>
<tr>
<td>Aortic diastolic BP, mm Hg</td>
<td>68.2±10.0</td>
<td>65.4±9.1</td>
<td>65.3±9.7</td>
<td>0.573</td>
</tr>
<tr>
<td>Aortic PP, mm Hg</td>
<td>21.5±19.3</td>
<td>23.4±6.0</td>
<td>23.8±6.7</td>
<td>0.644</td>
</tr>
<tr>
<td>PP amplification*</td>
<td>1.42±0.41</td>
<td>1.51±0.19</td>
<td>1.51±0.22</td>
<td>0.298</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>72.7±12.3</td>
<td>73.6±8.5</td>
<td>80.6±21.2</td>
<td>0.078</td>
</tr>
<tr>
<td>AIx, %</td>
<td>14.1±11.5</td>
<td>14.0±12.8</td>
<td>13.9±11.4</td>
<td>0.861</td>
</tr>
<tr>
<td>AP, mm Hg</td>
<td>13.0±12.4</td>
<td>13.4±12.8</td>
<td>13.9±12.3</td>
<td>0.985</td>
</tr>
<tr>
<td>Tr, ms</td>
<td>151.4±19.1</td>
<td>147.7±15.3</td>
<td>143.1±22.9</td>
<td>0.406</td>
</tr>
<tr>
<td>Estradiol, pmol/L</td>
<td>36±13.4</td>
<td>116.5±21.2</td>
<td>132.5±11.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progesterone, nmol/L</td>
<td>0.25±0.02</td>
<td>0.20±0.40</td>
<td>11.6±2.76</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Phase 1 indicates menstruation phase; phase 2, late follicular phase; phase 3, early luteal phase. P<0.05 indicates overall significance of variation among the 3 repeated measurements (ANOVA). Values are presented as mean±SD except for estradiol and progesterone, which are presented as median±SE, because these variables are not normally distributed. *PP amplification is the ratio of brachial:central PP.

Discussion

The present study provides data regarding the reproducibility and variability of wave reflection estimation during the menstrual cycle. To our knowledge, it was demonstrated for the first time that intensity and timing of wave reflections remain statistically unchanged during the menstrual cycle of healthy women and that repeated measurements of wave reflection indices, such as AP, AIx, and Tr, present a moderate reproducibility.

Pressure wave patterns are modified not only by pathological or pharmaceutical factors,30 but also by nutritional habits,31 time of the day (e.g., circadian pattern of wave reflections),32 mental stress,33 and possibly by menstrual cycle. The aforementioned conditions may have an unfavorable effect on the reproducibility of these measurements, with the latter condition being still unexplored.

![Bland-Altman plots for repeated measurements of AP (Phases 1-2), AP (Phases 1-3), and AP (Phases 2-3)](image)

Figure 1. Bland-Altman plots for repeated measurements of AP during the menstrual cycle (A: phases 1 vs 2; B: phases 1 vs 3; C: phases 2 vs 3). The percentages indicate the percentage of the cases (pairs of measurements) that fall within the 2 SDs of the mean difference of all pairs. Phase 1 indicates menstruation phase; phase 2, late follicular phase; phase 3, early luteal phase.

Variation of Wave Reflections During Menstrual Cycle

It is known that natural hormonal fluctuations during the menstrual cycle are reflected in cardiovascular changes. However, limited and mostly controversial data exist regarding the effect of the menstrual cycle on arterial mechanical properties and function. It has been reported that a decrease in large-vessel endothelial function34 and radial arterial disten-
sibility occurs in the late luteal phase. Hayashi et al, in a small sample of 10 healthy young women, showed that elastic properties of central but not peripheral arteries fluctuate significantly with the phases of the menstrual cycle. On the contrary, Williams et al examined 15 healthy young women and found that aortic stiffness (estimated by carotid-to-femoral pulse wave velocity) did not vary significantly within the menstrual cycle. Similarly, Ounis-Skali et al found that
stiffness of central arteries does not differ between the follicular and midluteal phases of the menstrual cycle in healthy women. In the present study, intensity of reflected waves expressed by AP and AIx, as well as reflection timing, which relates to pulse wave velocity and, consequently, to arterial stiffness, remained statistically unchanged during the menstrual cycle of 32 young healthy women. Other than arterial stiffness, BP is another factor that influences wave reflections. However, we observed that both peripheral and central BPs remained statistically unchanged during the menstrual cycle, which accords to previous findings in a similar population.36 Finally, another potential factor that might affect wave reflection variation is heart rate, but it also remained unchanged during the menstrual cycle in our study. It should be underscored that the variation of wave reflections assessed by ANOVA during the menstrual cycle provides physiological information only, whereas the reproducibility analysis has totally methodological relevance. A significant fluctuation of both estradiol and progesterone across the 3 phases of the menstrual cycle was confirmed in our population. However, it appears that these hormonal changes during the regular menstrual cycle of healthy women do not affect wave reflection variation. Although various effects of hormonal therapies on arterial properties and wave reflections have been reported, the effect of endogenous fluctuations of hormonal levels on central hemodynamics during the menstrual cycle remains unclear.

Reproducibility of Wave Reflection Indices

It should be acknowledged that there is no one simple way to describe all of the important facets of the reproducibility. Some popular methods in the medical literature, such as indices of agreement (ie, the Pearson correlation coefficient \( r \) and the slope from linear regression analysis), may be inappropriate because they measure association and not concordance.41 Namely, one set of measurements may take systematically higher or lower values than another set and may still provide a very high but misleading \( r \) value. To overcome this limitation, the use of ICC has been proposed. ICC is used to assess agreement of quantitative measurements in the sense of consistency and conformity, whereas Bland-Altman analysis provides complementary information, because it assesses whether the variability or precision of a method is related to the value of the characteristic being measured. In this study, the calculated ICC indicated a moderate reproducibility for AIx and AP and a rather poor reproducibility for Tr. ICC values were similar to those obtained in other reproducibility studies of wave reflections.15 In addition, the coefficient of variation is an inappropriate index of variability when the values of the measured variable range close to 0. Consequently, the coefficient of variation might result in inaccurate and unreliable calculations for AP and AIx, which may range close to 0, especially in normal healthy subjects. This explains the particularly high SD of coefficients of variation reported in our study.

The SD of AIx differences between repeated (paired) measurements within the menstrual cycle ranged from 7.6% to 9.9% (Table 2). Previous reproducibility studies with a

### Table 2. Mean Difference±SD of Differences for Repeated Measurements of AIx, AP, and the Tr Between Different Phases of the Menstrual Cycle

<table>
<thead>
<tr>
<th>Difference Between Measurements</th>
<th>Phase 1 vs 2</th>
<th>Phase 1 vs 3</th>
<th>Phase 2 vs 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIx, %</td>
<td>−0.4±9.7</td>
<td>−0.9±7.6</td>
<td>−0.5±9.9</td>
</tr>
<tr>
<td>AP, mm Hg</td>
<td>0.1±8.1</td>
<td>0.3±6.8</td>
<td>0.2±9.8</td>
</tr>
<tr>
<td>Tr, ms</td>
<td>3.5±16.7</td>
<td>8.3±28.9</td>
<td>4.6±25.9</td>
</tr>
</tbody>
</table>

Phase 1 indicates menstruation phase; phase 2, late follicular phase; phase 3, early luteal phase.

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### Table 3. Mean Difference and SD of Repeated Measurements, With Different Time Intervals of AP and AIx at Various Populations

<table>
<thead>
<tr>
<th>Reproducibility Studies</th>
<th>Time Interval Between Measurements</th>
<th>Population</th>
<th>AP, mm Hg</th>
<th>AIx, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td></td>
<td></td>
<td>Mean Difference</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean Difference</td>
<td>SD</td>
</tr>
<tr>
<td>Wilkinson et al, 1998</td>
<td>Minimum 2 min</td>
<td>Various diseases</td>
<td>0.49</td>
<td>5.37</td>
</tr>
<tr>
<td>Siebenhofer et al, 1999*</td>
<td>Undefined</td>
<td>Healthy</td>
<td>0.40</td>
<td>6.40</td>
</tr>
<tr>
<td>Filovsly et al, 2000†</td>
<td>Minutes, undefined</td>
<td>Healthy</td>
<td>0.50</td>
<td>13.00</td>
</tr>
<tr>
<td>Filovsly et al, 2000†</td>
<td>Undefined</td>
<td>Healthy</td>
<td>0.20</td>
<td>5.40</td>
</tr>
<tr>
<td>Savage et al, 2002</td>
<td>2 min</td>
<td>Chronic renal failure and controls</td>
<td>0</td>
<td>4.00</td>
</tr>
<tr>
<td>Savage et al, 2002</td>
<td>2 to 16 wk, variable</td>
<td>Chronic renal failure and controls</td>
<td>−1.00</td>
<td>9.00</td>
</tr>
<tr>
<td>Pappaoannou et al, 2004</td>
<td>2 min</td>
<td>Cardiogenic shock</td>
<td>0.02</td>
<td>1.29</td>
</tr>
<tr>
<td>Matsui et al, 2004</td>
<td>4 wk</td>
<td>Hypertensive</td>
<td>0.50</td>
<td>5.90</td>
</tr>
<tr>
<td>Weber et al, 2004</td>
<td>Days, undefined</td>
<td>Undefined</td>
<td>1.20</td>
<td>−5.50</td>
</tr>
<tr>
<td>ter Avest et al, 2005</td>
<td>Minutes, &lt;30 min</td>
<td>Healthy</td>
<td>1.37</td>
<td>4.50</td>
</tr>
<tr>
<td>ter Avest et al, 2005</td>
<td>5 h</td>
<td>Healthy</td>
<td>4.80</td>
<td>4.00</td>
</tr>
<tr>
<td>Pappaoannou et al, 2007</td>
<td>1 wk</td>
<td>Healthy</td>
<td>5.50</td>
<td>5.20</td>
</tr>
<tr>
<td>Pappaoannou et al, 2007</td>
<td>1 h</td>
<td>Healthy</td>
<td>−2.10</td>
<td>5.20</td>
</tr>
<tr>
<td>Citty et al, 2007</td>
<td>Minutes, undefined</td>
<td>Patients, undefined</td>
<td>0.68</td>
<td>1.95</td>
</tr>
<tr>
<td>Citty et al, 2007</td>
<td>Minutes, undefined</td>
<td>Patients, undefined</td>
<td>−0.40</td>
<td>2.20</td>
</tr>
<tr>
<td>Frimodt-Moller et al, 2008</td>
<td>Days within a week, undefined</td>
<td>Chronic kidney disease</td>
<td>2.70</td>
<td>9.40</td>
</tr>
</tbody>
</table>

*Data show between-observer reproducibility.
†AIx was defined as 100 \( \cdot \frac{P_2}{P_1} \), where \( P_1 \) and \( P_2 \) are the corresponding BP values at the first and second inflection points at the systolic part of the pressure wave, respectively.
short time interval between repeated AIX measurements (seconds or minutes) have reported lower SD values (1.2% to 5.8%), indicating a higher reproducibility (Table 3). Nevertheless, the greater SDs in AIX differences that were reported in the present study are rather closer to those reported in reproducibility studies, with long-term time intervals (from days to weeks) between repeated measurements (Table 3).

It should be acknowledged that the reported reproducibility results are either operator dependent (intraobserver variations) and/or dependent on menstrual cycle variations, which cannot be disentangled by the present study design.

Perspectives
The properties of a statistical analysis using a measurement depend on the reproducibility coefficient value. The degree of a random error or noise in a measurement (ie, AP, AIX, or Tr) has a direct impact on correlation coefficients, regression model estimates, mean differences between groups, sensitivity and specificity, sample size, and power estimation. Because premenopausal women are included in most of the clinical studies, the effect of menstrual phases on the reproducibility of these measures should be known, and, more importantly, it should be taken into consideration not only in the design of the study but also in the interpretation of the data.

Conclusions
The results of the present study support that wave reflection indices do not vary significantly during the menstrual cycle of healthy premenopausal women, providing some additional evidence to an already controversial issue, namely, the effect of menstrual cycle on arterial properties. Nevertheless, our findings raise further questions of whether these hemodynamic and vascular characteristics are affected by menstrual irregularities. A moderate reproducibility of wave reflection indices was found during the menstrual cycle (eg, inasubject absolute differences of AIX up to 10% may be observed between different phases of the menstrual cycle). The importance of our findings mostly relates to future guidelines that should probably be followed in studies that include premenopausal women. Estimation of wave reflections at the same phase of the menstrual cycle or statistical adjustments could be suggested for optimal study design and data interpretation.

Disclosures
None.

References


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