Decreased large-artery stiffness in midluteal phase of the menstrual cycle in healthy women of reproductive age

Obniżona sztywność dużych naczyń tętniczych w fazie lutealnej w prawidłowym cyklu miesiączkowym u zdrowych kobiet w wieku reprodukcyjnym

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Abstract

Objectives: Sex hormones are specific factors contributing to the regulation of cardiovascular system. Studies on the effects of hormonal fluctuations during the menstrual cycle on hemodynamics and arterial stiffness in young women are limited and provide conflicting results.

Aim: The aim of the study was to assess arterial stiffness, peripheral/central blood (pBP and cBP) and pulse (pPP and cPP) pressures throughout the single, natural menstrual cycle (early follicular [EFP], late follicular [LFP] and midluteal [LP] phase).

Materials and methods: Forty two healthy, regularly menstruating women (28.6±5.1 yrs of age; BMI 22.0±3.5 kg/m2) were evaluated during EFP (Estradiol [E], FSH, LH, PRL, TSH, Testosterone [T], DHEAS, and SHBG), LFP (E, FSH, LH) and LP (Progesterone, E, FSH, LH). Transvaginal ultrasound was performed to confirm ovulatory cycle. Resting radial and aortic BP were assessed noninvasively and continuously using tonometric measurement of peripheral PP wave-PPW (Colin BMP7000, Japan) and on-line reconstruction of central PPW (Sphygmocor Mx, Australia) at EFP, LFP and LP. ANOVA and Friedman test were used in statistical analysis.

Results: There were no significant differences in systolic/diastolic BP and PP both at the periphery and at ascending aorta throughout the menstrual cycle. Comparable observations of no interphasal differences were noted for peripheral Augmentation Index (AI). Central AI and augmentation pressure (AP) were significantly lower in LP than in LFP (by 4%; p<0.05 and by 37%; p<0.05, respectively).

Conclusions: We demonstrated significant differences in mechanical properties of large arteries at the midluteal phase of natural menstrual cycle. We conclude that sex hormones may play role in the regulation of arterial stiffness in the reproductive age women.

Key words: **applanation tonometry** / **arterial stiffness** / **estrogen** / **menstrual cycle** / / **phases of the menstrual cycle** / **wave reflection** /

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Streszczenie

Hormony płciowe są ważnymi czynnikami biorącymi udział w regulacji funkcji układu krążenia. Dotychczasowe badania oceniające wpływ zmian stężeń hormonów płciowych w przebiegu fizjologicznego cyklu miesiączkowego na sztywność naczyń tętniczych oraz parametry hemodynamiczne są nieliczne i przedstawiają sprzeczne wniosków.

Cel pracy: *Celem pracy była ocena parametrów opisujących sztywność naczyniową oraz obwodowe i centralne ciśnienie tętnicze (pBP, cBP) i ciśnienie tętna (cPP, pPP) w przebiegu naturalnego cyklu miesiączkowego (we wczesnej fazie folikularnej [EFP], w późnej fazie folikularnej [LFP] i w fazie lutealnej [LP]).*

Materiał i metody: *Przebadano 42 regularnie miesiączkujące kobiety (średnia wieku 28,6±5,1 lat, BMI 22,0±3,5 kg/m2) we EFP (Estradiol [E], FSH, LH, PRL, TSH, Testosteron [T], DHEAS, SHBG), w LFP (E, FSH, LH) oraz LP (Progesteron, E, FSH, LH). W celu potwierdzenia cyklu owulacyjnego wykonano przezpochwowe badanie ultrasonograficzne. Ocenę pBP (tętnica promieniowa) i cBP (aorta wstępująca) wykonano w sposób nieinwazyjny metodą tonometrycznych pomiarów obwodowej fali tętna [PPW] (Colin BMP 7000, Japonia) z następową rekonstrukcją w czasie rzeczywistym centralnej PPW (Sphygmocor Mx, Australia) w fazie: EFP, LFP i LP. Analizę statystyczną wykonano przy pomocy testu ANOVA i testu Friedmana.*

Wyniki: *Nie zaobserwowano istotnych statystycznie różnic w wartościach skurczowego i rozkurczowego BP oraz PP na obwodzie i na poziomie tętnicy wstępującej w przebiegu cyklu miesiączkowego. Podobne wyniki świadczące o braku różnic między fazami cyklu uzyskano dla obwodowego wskaźnika wzmocnienia [AI]. Centralny AI oraz ciśnienie wzmocnienia [AP] były statystycznie istotnie niższe w LP w porównaniu z LFP (odpowiednio o 4%, p<0,05 oraz o 37%, p<0,05).*

Wnioski: *W przedstawionej pracy zaobserwowaliśmy występowanie istotnych różnic we właściwościach mechanicznych dużych naczyń tętniczych w środkowej fazie lutealnej fizjologicznego cyklu miesiączkowego. Przedstawione wyniki wskazują, iż hormony płciowe mogą brać udział w regulacji sztywności naczyń tętniczych u kobiet w wieku rozrodczym.*

Słowa kluczowe: **cykl miesiączkowy** / **estrogen** / **fazy cyklu miesiączkowego** / / **odbicie fali** / **sztywność naczyniowa** / **tonometria aplanacyjna** /

Introduction

Menstrual cycle has been thoroughly described in terms of complex hormonal fluctuations: rises in the periovulatory estradiol and luteal progesterone concentrations, paralleled by ovarian and endometrial changes. Estradiol and progesterone receptors were localized in the vascular smooth muscles and endothelium. Both in the experimental and clinical studies exogenous estradiol was shown to have vasodilatory effects acting indirectly, through nitric oxide and prostacyclin, or directly - modulating calcium channel activity in myocytes [1].

However large, randomized clinical studies in postmenopausal women treated with hormone replacement therapy demonstrated adverse effects of progestogens on vascular system. Medroxyprogesterone acetate antagonized vasodilatory effect of estrogens by inhibiting nitric oxide production and promoting vasoconstriction [2].

Non-invasive pulse wave analysis allows to assess arterial wave reflection and to quantify central arterial pressure and stiffness. Measurements of central pressures, when compared with peripheral ones, provide better markers for arterial elasticity and possible vascular damage. On the other hand, arterial stiffness is a well-validated noninvasive measure of cardiovascular risk and a good predictor for cardiovascular events [3, 4].

The effects of endogenous steroids on the cardiovascular system and its hemodynamic properties during the natural menstrual cycle in healthy women of reproductive age have not been investigated comprehensively. Only few studies have examined the associations between cyclic variations in sex hormones, pulse wave reflection and arterial stiffness.

Additionally, presented data are conflicting and the study groups relatively small [5-8].

Objectives

Therefore the aim of the current study was to evaluate peripheral and central hemodynamic characteristics and the mechanical properties of arterial vessels throughout the natural menstrual cycle at follicular, periovulatory and midluteal phases in healthy women of reproductive age.

Material and methods

Subjects:

Forty-two healthy regularly menstruating (29 ± 2 days) normotensive women (mean age 28.6 ± 5.1 years) were recruited to the study through announcements and educational action at the universities and colleges in Poznan in the period from 2011 till 2013. No female volunteers were recruited form the students and employees of Poznan University of Medical Sciences. None of the subjects had hyperandrogenemia, hyperandrogenism nor hyperprolactinemia diagnosed. No clinical signs and symptoms of any endocrinopathy were identified in all participants. Women with history of hypertension, diabetes mellitus, cardiovascular, renal, and neoplastic disease were not recruited to the study. Bioethics Committee at Poznan University of Medical Sciences approved the study protocol and a written informed consent was obtained from all participants. All subjects were not taking any form of hormonal contraception, other steroids nor any form of treatment to affect blood pressure and hormonal status for the preceding two months. None of the women declared to smoke.

Study protocol:

The study was conducted during the single, natural menstrual cycle at three time points corresponding to:

- Early follicular phase (EFP, between 3rd and 5th day of the menstrual cycle).
- Late follicular phase (LFP, between 11th and 14th day of the menstrual cycle).
- Midluteal phase (LP, between 19th and 22nd day of the menstrual cycle).

At the initial visit careful medical history was taken and the physical as well as gynecologic exam performed. Hormonal evaluations were performed at each visit and venous blood was collected between 7 and 9 a.m after an overnight fasting. Gynecological transvaginal ultrasound scan (Aloka ProSound α7; Aloka Co, Ltd, Tokio, Japan) was performed at the three described time points in order to assess the size and number of growing ovarian follicles, confirm the presence of corpus luteum and to assess changes in the endometrial texture and thickness. Evaluation of the cardiovascular system was performed on the same day, in the morning, at each of described time points of the menstrual cycle.

Hormonal assays:

Estradiol (E2), LH, FSH and progesterone (PROG; measured only in the mid-luteal phase) were determined by specific electrochemiluminescence assays (automated Cobas e601 immuno-analyzer, Roche Polska sp z o.o., Warsaw, Poland). Testosterone, TSH, prolactin, DHEAS, and SHBG were assessed only at the early follicular phase with specific electrochemiluminescence assays as described above.

Evaluation of the cardiovascular system:

Blood pressure and pulse wave measurements were performed in the morning hours in the supine position, after 15 minute rest. Radial and aortal blood pressures were assessed noninvasively and continuously using tonometric measurement of peripheral pulse pressure wave (PPW) with piezoelectric wrist tonometer (Colin BMP7000, Japan). The brachial blood pressure recorded with oscillometric method (M-5, Omron Healthcare, Kyoto, Japan) was used for the calibration. On-line real-time reconstruction of central PPW was performed (Sphygmocor Mx, Australia) with the use of validated transfer function after acquisition of ten sequential pulse wave forms [4, 9, 10].

The measurements were performed at each phase of the menstrual cycle and the following derived hemodynamic parameters were analyzed:

- Peripheral (radial) blood pressure (peripheral Systolic Pressure – pSP, peripheral Diastolic Pressure – pDP).
- Central (aortic) blood pressure (central Systolic Pressure – cSP, central Diastolic Pressure – cDP).
- Peripheral pulse pressure (pPP) defined as the difference between pSP and pDP.
- Central pulse pressure (cPP) defined as the difference between cSP and cDP.
- Augmentation Pressure (AP), a descriptor of arterial stiffness derived from central pulse wave analysis, describes the portion of the cSP contributed by the early reflected wave.

- Augmentation index (AI) defined as the difference between the first (early) and the second (late) systolic peaks on the arterial waveform expressed as a percentage of pulse pressure (peripheral – pAI, recorded on the radial pressure waveform, and central – cAI, recorded on the reconstructed aortic pressure waveform). AI is considered as the indirect descriptor of wave reflection, arterial stiffness as well as the predictor of adverse cardiovascular events [11].

AI and AP are related to the reflected pressure waves from the peripheral arterial system, either as in a direct increase in pressure at the heart from the reflected wave (AP) or as a percentage of pulse pressure (AI).

Statistical analysis:

Statistical analysis was performed after checking the normality of data distribution (Shapiro-Wilk test), with the ANOVA test (normal distribution) or Friedman test (no normal distribution) with the appropriate post-hoc tests. $p < 0.05$ was considered as statistically significant. The results are presented as mean ± standard deviation (SD).

Results

Group characteristics

Table I lists the clinical and hormonal characteristics of the study subjects.

Table I. Clinical and hormonal characteristics of the study subjects.

Characteristic	Mean +/- SD
Age [yrs]	28.6 ± 5.1
Weight [kg]	62.2 ± 10.9
Height [cm]	168 ± 6
BMI [kg/m²]	22.0 ± 3.5
Testosterone [ng/ml]	0.33 ± 0.14
SHBG [nmol/l]	70.0 ± 31.6
DHEAS [µmol/l]	6.5 ± 2.5
PRL [ng/ml]	14.1 ± 6.8
TSH [µIU/ml]	1.83 ± 0.89

BMI – body mass index

Biphasic nature of the menstrual cycle in all study subjects, with well depicted luteal phase was confirmed with hormonal and ultrasound evaluations (Table II).

Heart Rate (HR) is a parameter that may significantly affect other hemodynamic phenomena and thus variability of the HR during the menstrual cycle should be excluded in order to conduct further statistical analysis. We found no statistically significant differences in HR values between researched phases of the menstrual cycle (EFP vs. LFP vs. LP ; HR = 71.6 ± 9.3/min vs. 71.0 ± 8.9/min vs. 72.2 ± 9.3/min, respectively; p=ns).

Peripheral blood pressure

There were no significant differences in the peripheral (radial artery) blood pressure (systolic, diastolic, pulse) between the three phases of the menstrual cycle (EFP vs. LFP vs. LP;

Table II. Hormonal and sonographic characteristics of the study subjects at the investigated phases of the menstrual cycle (EFP – early follicular phase, LFP – late follicular phase, LP – midluteal phase).

Phase of the menstrual cycle Characteristic	EFP	LFP	LP
Estradiol [pg/ml]	44.2 ± 15.5	218.8 ± 140.0	177.3 ± 90.35
FSH [mIU/ml]	6.9 ± 4.9	5.5 ± 3.7	3.6 ± 1.1
LH [mIU/ml]	5.9 ± 2.5	14.4 ± 15.5	5.7 ± 2.9
Progesterone [ng/ml]	not measured	not measured	13.2 ± 6.1
Endometrial thickness [mm]	4.0 ± 2.2	8.7 ± 2.2	11.3 ± 1.9

pSP 105.4 ± 9.7 mmHg vs. 105.9 ± 9.4 mmHg vs. 104.4 ± 11.1 mmHg, respectively, p=ns ; pDP 63.9 ± 7.3 mmHg vs. 64.3 ± 8.3 mmHg vs. 63.7 ± 7.8 mmHg, respectively, p=ns ; pPP 41.6 ± 6.4 mmHg vs. 41.6 ± 7.7 mmHg vs. 40.7 ± 6.1 mmHg, respectively, p=ns; presented in Figure 1).

Central blood pressure

Similarly, no interphasal differences were obtained for central blood pressure parameters corresponding to the pressure in the ascending aorta. Central systolic, diastolic and pulse pressure showed no statistically significant differences at the three time points investigated (EFP vs. LFP vs. LP ; cSP 90.9 ± 9.1 mmHg vs. 92.0 ± 9.4 mmHg vs. 89.7 ± 10.0 mmHg respectively, p=ns; cDP 64.9 ± 7.5 mmHg vs. 65.4 ± 8.3 mmHg vs. 64.7 ± 7.9 mmHg respectively, p=ns and, cPP 26.1 ± 4.6 mmHg vs. 26.7 ± 5.3 mmHg vs. 25.0 ± 3.7 mmHg respectively, p=ns ; presented in Figure 2).

Parameters describing pulse pressure waveform and arterial stiffness

Peripheral augmentation index (pAI) showed no significant differences between the three selected phases of the menstrual cycle (LFP vs. EFP vs. LP; pAI = 55.6 ± 11.8% vs. 57.4 ± 12.2% vs. 54.2 ± 10.7% respectively, p=ns; presented in Figure 3). The pulse pressure wave analysis demonstrated statistically significant differences in the values of parameters describing central vascular stiffness at the investigated menstrual phases. Central AI had significantly lower values in the midluteal phase of the menstrual cycle compared to the late follicular phase (by 4%; cAI LFP vs. LP = 113.4 ± 12.5% vs. 109.0 ± 10.4%; p<0.05). There were no statistically significant differences in cAI between the early and late follicular as well as the early follicular and midluteal phases (cAI EFP vs. LFP = 111.3 ± 12.0 % vs. 113.4 ± 12.5%, p=ns; cAI EFP vs. LP = 111.3 ± 12.0 % vs. 109.0 ± 10.4 %, p=ns; Figure 4).

Augmentation pressure (AP) was significantly lower in the midluteal phase when compared to the late follicular phase of the menstrual cycle (by 37% ; AP LFP vs. LP = 3.1 ± 3.0 vs 1.9 ± 2.3, p<0.05). There were no differences in AP between the early and late follicular as well as the early follicular and midluteal phases of the menstrual cycle (cAP EFP vs. LFP = 2.6 ± 2.7 mmHg vs. 3.1 ± 3.0 mmHg, p=ns; cAP EFP vs. LP = 2.6 ± 2.7 mmHg vs. 1.9 ± 2.3 mmHg, p=ns; Figure 5).

Discussion

In the present study we have observed no differences in the peripheral and central blood pressures (both systolic, diastolic, and pulse) measured at three phases of the natural menstrual cycle: early follicular, late follicular, and midluteal in young and healthy females. Interestingly the pulse pressure wave analysis demonstrated that at the level of ascending aorta the lowest vascular stiffness (described by central augmentation index [AI] and augmentation pressure [AP]) was recorded in the midluteal phase. There was no interphasal difference in the vascular stiffness measured at the radial artery (peripheral AI).

Early studies on the menstrual fluctuations of peripheral blood pressures showed that there is a significant rise in the systolic blood pressure in the early [12] and late follicular (periovulatory) phase [13], presumably due to increasing estradiol concentrations. Other investigators reported the decrease in radial diastolic blood pressure in midluteal phase of the cycle. [14] In a more recent study Adkisson et al., showed on a group of 23 women that the lowest peripheral blood pressures, both systolic and diastolic, were recorded in the late follicular phase of the cycle. That reduction in blood pressures correlated inversely with the periovulatory increase in serum concentrations of a potent vasodilator - nitric oxide. [5] However these observations were not confirmed by others. [6, 7, 15]
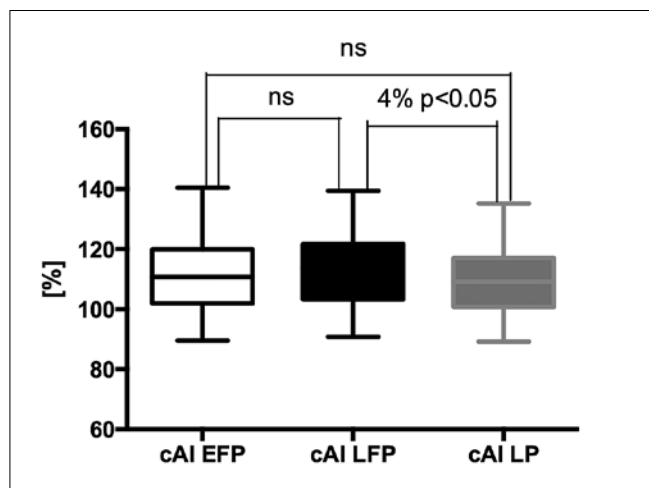
Our results, to our knowledge derived from the largest female population studied up to date, also demonstrate no changes in peripheral blood pressures. Well-described physiological hormonal fluctuations - estradiol rise in the late follicular phase and progesterone increase in the luteal phase seemed to have no significant effect on radial arteries. Short-term, cyclic hormonal fluctuations in the natural cycle may have no significant effects on pressures. However we must take into consideration that peripheral blood pressure shows relatively large variability and is influenced by complex internal regulatory mechanisms and many various external factors. Thus significant changes, possibly very small, might be only shown on much larger female populations investigated.

Peripheral systolic blood pressure (usually measured at the brachial artery or as in our study at the radial artery) is not the direct and perfect surrogate for the central pressure (aorta or the central arteries), because of peripheral amplification. There are multiple studies demonstrating that central blood pressure better correlates with endothelial dysfunction, subendocardial ischemia, atherogenesis and is a stronger, more sensitive predictor for cardiovascular morbidity and mortality than traditional peripheral blood pressure. [16, 17] This was proven both in the diseased as well as in healthy populations. [18]
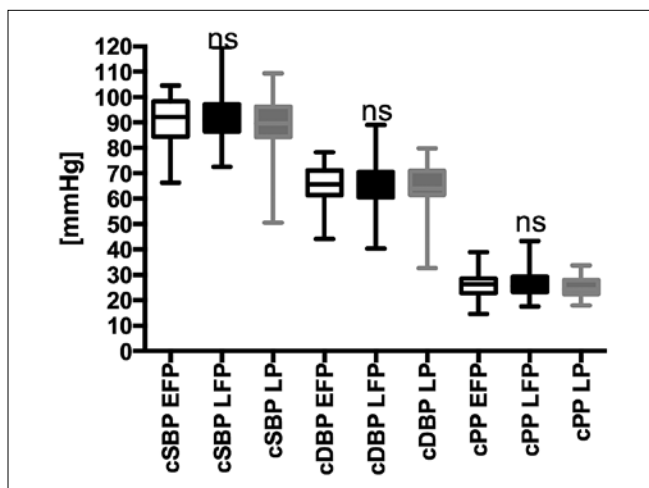
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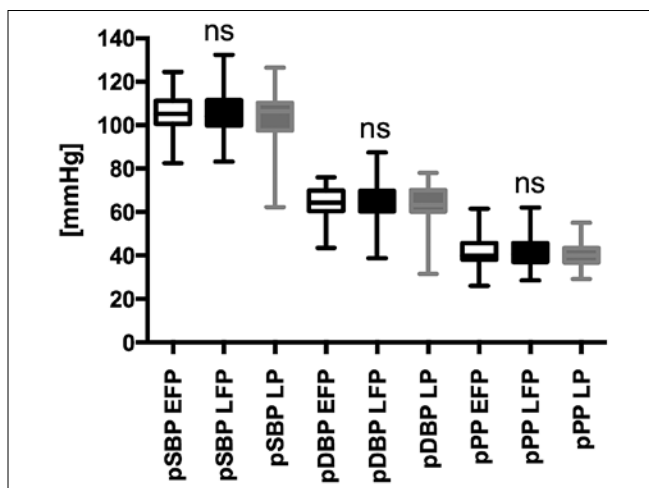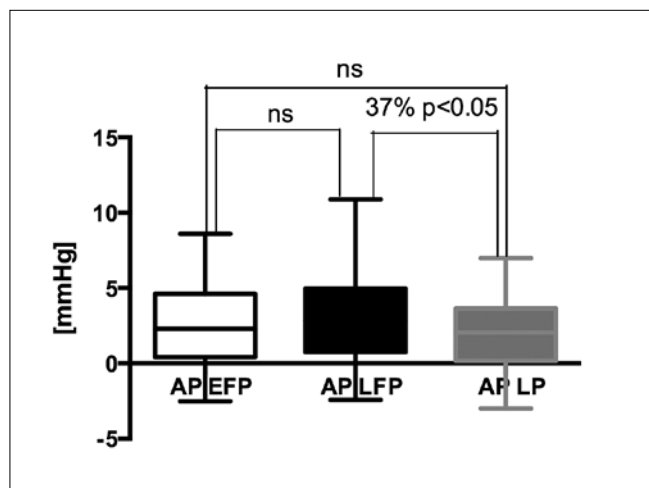

Figure 1. Peripheral blood pressure (systolic – pSBP, diastolic – pDBP, and pulse – pPP) at the early follicular (EFP), late follicular (LFP), and midluteal phase (LP) of the menstrual cycle. Results shown as mean +/- SD.
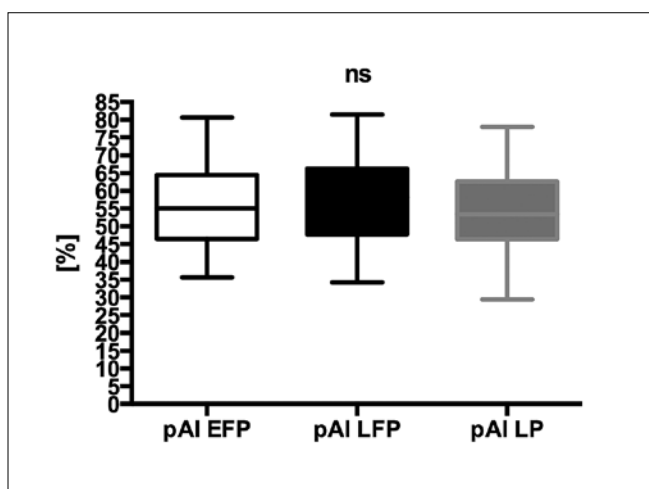

Figure 2. Central blood pressure (systolic – cSBP, diastolic – cDBP, and pulse – cPP) at the early follicular (EFP), late follicular (LFP), and midluteal phase (LP) of the menstrual cycle. Results shown as mean +/- SD.

Figure 3. Peripheral Augmentation Index (pAI) at the early follicular (EFP), late follicular (LFP), and midluteal phase (LP) of the menstrual cycle. Results shown as mean +/- SD.

Figure 4. Central Augmentation Index (cAI) at the early follicular (EFP), late follicular (LFP), and midluteal phase (LP) of the menstrual cycle. Results shown as mean +/- SD.

Figure 5. Augmentation Pressure (cAP) at the early follicular (EFP), late follicular (LFP), and midluteal phase (LP) of the menstrual cycle. Results shown as mean +/- SD

Development of noninvasive and affordable technologies causes that measurements of central vascular pressures are increasingly used, however the number of studies assessing central pressures during the natural menstrual cycle in young and healthy females is limited. In the already mentioned study Adkisson et al., parallel to the decrease in radial pressures in the periovulatory period, observed the lowest values of aortic, both systolic and diastolic, pressures at the late follicular phase of the menstrual cycle. During the early luteal phase central blood pressures remained in the lower ranges, significantly below the values recorded at the beginning of the cycle [5]. Nevertheless these findings were not confirmed by other groups, with no differences observed throughout the menstrual cycle [7, 15]. Similarly, in our study central blood pressures (systolic, diastolic, and pulse pressure), measured at the level of ascending aorta did not differ significantly between the phases of menstrual cycle. Normal transitory surges of estradiol and progesterone had no significant effects on

aortic pressures. To date only one study demonstrated changes in the central pressures in premenopausal females. [5] However the study was performed on only 23 women, of much younger age than our population (mean age below 20) with no hormonal (only estradiol measured) and sonographic confirmations of ovulation. On contrary our studied subjects had biphasic, ovulatory cycles that were thoroughly documented with hormonal evaluations and sonographic examinations identifying dominant follicle and corpus luteum.

Analysis of the central pressure waveform allows to derive the parameters describing arterial stiffness: AP and AI. Arterial stiffness influences the velocity of the reflected wave from the peripheral vascular system and hence affects central pressures. Augmentation pressure is the additional pressure added to the forward wave by the reflected wave and AI is the ratio between AP and pulse pressure (central or peripheral). Both descriptors of arterial stiffness are good, independent predictors for adverse cardiovascular events [19].

We have observed no fluctuations in peripheral AI throughout the menstrual cycle, however we have demonstrated that central vascular stiffness decreased during the luteal phase. Previous studies on arterial stiffness during the menstrual cycle are limited and present contradictory results. Papaioannou et al. found no significant changes in arterial stiffness during the menstrual cycle using applanation tonometry on a group of 32 women [7]. Comparable findings of no differences in central AI (though on carotid artery) between different phases of the menstrual cycle were presented by others [15]. Opposing results of the decrease in arterial stiffness toward the end of the follicular phase prior to ovulation were presented by Adkisson et al [5]. This group suggested that at least in part the mechanism responsible is related to estrogen–mediated increase in nitric oxide production and bioavailability. However this study showed no comparable temporal changes in central or peripheral stiffness when measuring pulse wave velocity [5]. Similar results of an increase in vascular elasticity in the periovulatory phase were also presented by other groups, that used different methodologies. Using simultaneously ultrasound and applanation tonometry, Hayashi et al showed cyclical changes in carotid arterial compliance, with highest values in periovulatory phase. The fluctuation in carotid arterial elasticity correlated with the changes in the estrogen to progesterone ratio [6]. Other studies evaluating the whole body arterial compliance also demonstrated an increase in arterial compliance in the periovulatory period [20]. Only one recent study, performed on 10 healthy nulliparous women presented observations in accordance with our findings [8]. Robb et al observed a significant decline in AI (by almost 65%) in the luteal phase when compared with the periovulatory period using similar methodology. These conflicting results could have been due to different methodologies used, heterogeneity of populations studies and low numbers, not even approaching normal distribution, of the populations studied.

Estradiol and progesterone receptors were localized in the vascular cells, including endothelium and vascular smooth muscles [1]. Experimental studies, both in human and animal models, demonstrated that estrogens increased vasodilator responses, lowered coronary vascular resistance, diminished myocardial ischemia, decreased inflammation and atherosclerosis [21]. Estrogens improve vascular reactivity, by promoting vasodilation through nitric oxide (NO) and prostacyclin (PGI_2) produc-

tion, and by inhibiting the production of vasoconstrictors such as endothelin (ET-1) and angiotensin. These effects were exerted on both genomic as well as non-genomic mechanism via membrane estrogen receptors [21]. Thus we might have expected the lowest vascular resistance and highest compliance at the time of the periovulatory estradiol peak, i.e. in the late follicular phase of the natural cycle. However, other endogenous steroids, predominantly progesterone, may also exert direct effects on the vascular system or modulate estrogen-induced effects. Thus the interplay between estradiol and progesterone may be more important than the concentrations of estradiol alone. In the animal models progesterone induces NO-dependent relaxation of aorta and peripheral arteries, increases PGI_2 production and has anti-atherogenic effect [22]. Nevertheless progesterone is less potent vasodilator than estradiol and in some models it was also shown to antagonize the vasoprotective effects of estrogens [23].

Our results demonstrating the lowest arterial stiffness in the midluteal phase, characterized by the highest progesterone levels and estradiol concentrations in the upper ranges, suggest some additive effects of both hormones on vascular compliance at the central arteries. However lack of all progesterone measurements does allow for the detailed analysis of estrogen to progesterone ratios on hemodynamic parameters and vascular stiffness.

Data from randomized studies in postmenopausal women treated with hormone replacement therapy, showing that exogenous estrogens increased arterial distensibility, and that this beneficial effect was counteracted by progesterone should not be directly linked to our observations [2, 24]. Age-related changes in steroid receptors, their distribution and/or affinity may contribute to the differences in vascular reactivity. Moreover age-related vascular remodeling and changes in the structure of blood vessels may result in different responses to endogenous as well as exogenous hormones [1].

Conclusion

In conclusion the present study demonstrates significant differences in mechanical properties of large arteries throughout the natural menstrual cycle in young and healthy females, reflected by changes in the central pulse waveform. Conversely there were no changes in the peripheral blood pressure nor in peripheral arterial stiffness detected. Significant differences in hemodynamic parameters during the menstrual cycle, though small, might be taken into account when performing cardiovascular assessment in reproductive age women. Further studies, on larger population with complete hormonal evaluation are needed to confirm our findings.

Oświadczenie autorów:

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