Peripheral haemodynamics and renal function in relation to the menstrual cycle

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1. The objective of this study was to investigate whether the luteal phase of the menstrual cycle differs from the follicular phase by the development of a state of general vascular relaxation.

2. Once in the follicular and once in the luteal phase of the menstrual cycle, we measured by non-invasive techniques: arterial blood pressure (by finger blood pressure measurements), vascular tone (by pulse-wave velocity and plethysmography), blood flow to skin (by laser-Doppler), blood flow to forearm (by plethysmography) and blood flow to kidneys (by para-aminohippurate clearance), and the glomerular filtration rate (by inulin clearance). The data points obtained in the luteal phase were compared with those in the follicular phase by non-parametric tests.

3. Arterial blood pressure, vascular tone and the blood flows to the forearm and kidneys were comparable in the two phases of the menstrual cycle. In contrast, the blood flow to the skin was consistently lower, and the glomerular filtration rate higher in the luteal phase of the menstrual cycle.

4. The results of the present study do not support our hypothesis of a general vascular relaxation in the luteal phase of the menstrual cycle. The lower skin flow in the luteal phase may be an adaptation needed to ensure the higher core temperature of 0.3-0.5°C in the luteal phase. The higher glomerular filtration rate was in most cases paralleled by a higher renal blood flow in the luteal phase. This suggests that the higher glomerular filtration rate is secondary to a selective vasorelaxation of the afferent renal arterioles.

INTRODUCTION

Several studies have shown that systemic haemodynamics and volume homoeostasis in women are related to the menstrual cycle. The mean arterial blood pressure (MAP) was found to be lower [1], and the plasma renin activity and creatinine clearance higher in the luteal phase (LP) than in the follicular phase (FP) of the menstrual cycle [2, 3]. In addition, the osmotic thresholds for thirst and vasopressin release were reported to have decreased in the LP [4]. From a theoretical point of view, all these changes could be viewed as compensatory mechanisms triggered by a decline in filling pressure of the arterial tree [5]. Such a state may develop in a healthy person, when the arterial/arteriolar tone slackens.

The steroid environment in the LP differs from that in the FP primarily by the presence of progesterone in the former. Both progesterone [6, 7] and 17β-oestradiol [8] can independently induce vascular relaxation. However, these data have been obtained either from animal studies [7] or in vitro using human placental arteries and veins [6]. Moreover, it is incorrect simply to extrapolate these results to the complex endocrine environment of the LP.

Our objective was to investigate in vivo whether the hormonal environment in the LP induces a general vascular relaxation in humans. To this end we measured the differences between the LP and FP in venous and arterial tone and in the blood flow to three vascular beds: skin, forearm and kidney. We also determined the glomerular filtration rate (GFR) and filtration fraction.

SUBJECTS AND METHODS

Experiments were performed in nine healthy volunteers (<40 years of age) with a regular menstrual cycle of 28 ± 2 days and evidence of ovulation, indicated by a mid-luteal serum progesterone concentration >5 ng/ml [9]. All participants gave written informed consent and the study was approved by the hospital’s medical-ethical committee. Measurements were taken once in the FP, between the fourth and 10th days, and once in the LP, between the 20th and 24th days of the cycle. The subjects’ characteristics are listed in Table 1.

Key words: forearm blood flow, inulin clearance, menstrual cycle physiology, para-aminohippurate clearance, sex hormones, skin microcirculation, vascular tone.
Abbreviations: ERPF, effective renal plasma flow; FBF, forearm blood flow; FP, follicular phase; GFR, glomerular filtration rate; LP, luteal phase; MAP, mean arterial pressure; PAH, para-aminobenzoic acid; RBF, renal blood flow.
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The two measurements were taken randomly. This implied that four subjects started the measurements in the FP whereas five subjects started in the LP.

Methods

All investigations were performed in a temperature-controlled room (24–25°C) and at the same time of day. The subjects were asked not to smoke, not to drink beverages containing caffeine or alcohol on the day of measurements and not to eat during the last 3 h before the measurements. We took precautions to minimize external disturbances during the measurements. The measurements were started after an acclimatization period of at least 30 min; they were performed with the subject in the supine position and the arm under investigation at heart level. Before the acclimatization period, a 20-gauge catheter was inserted into a vein of the left forearm for infusion of para-aminohippurate sodium (PAH) and inulin (see renal haemodynamics).

The arterial wall distensibility was assessed by measuring the pulse-wave velocity. The pulse-wave velocity is based on the time needed for an arterial pulse to travel over a standardized distance in a given artery [transit time (ms)]. The transit time provides information on the average elastic state of the artery over that particular distance [10]. The transit time in this study was taken as the mean of three to five successive heartbeats. A change in transit time within a subject provides an accurate estimate for a change in the overall arterial distensibility in that subject, because the length of the arterial tree remains constant. The opening of the aortic valves (R-top in ECG signal) was taken as the starting point. The onset of the distension waveform, assessed by Vessel Wall Tracking, at a defined site on the right common femoral artery, was taken as the end-point. Vessel Wall Tracking is an ultrasound technique which enables the transcutaneous measurement of the vessel diameter and diameter change during consecutive heartbeats [10, 11].

Renal haemodynamics, i.e. effective renal plasma flow (ERPF) and GFR, were measured by continuous infusion of PAH (MSD, West Point, PA, U.S.A.) and inulin (Inutest; Laevosan Gesellschaft, Linz, Austria), respectively. After the bolus injection, a continuous infusion was initiated using a syringe pump (Terumo SYC-521; Terumo Corporation, Tokyo, Japan) [12]. After an equilibration period of 120 min, a total of four blood samples were collected in heparinized glass tubes (Monoject; Sherwood Medical, St Louis, MO, U.S.A.) at 10 min intervals. Once blood for measurements of progesterone and 17β-oestradiol was withdrawn in a vacutainer glass tube (Monoject). The blood samples were centrifuged at 4°C for 10 min at 1500 g directly after sampling. All plasma and serum samples were stored at −20°C before assay. In the plasma samples both PAH and inulin were measured as detailed elsewhere [13, 14]. Serum progesterone and 17β-oestradiol were measured using commercially available radioimmunoassay kits: RSL direct progesterone and RSL direct 17β-oestradiol kit (ICN Biomedicals, CA, U.S.A.), respectively. The clearances of PAH and inulin were calculated by dividing the product of infusion rate and infusate concentration by the mean of plasma PAH and plasma inulin concentration, respectively. Assuming an extraction ratio for PAH of 90% [15], we calculated renal plasma flow and renal blood flow (RBF) using the formulas: 10/9 × ERPF and 10/9 × ERPF/(1 − Haematocrit), respectively. We calculated renal vascular resistance using the formula: (MAP/RBF) × 80000. The filtration fraction was obtained by taking the ratio of the inulin clearance (GFR) and the renal plasma flow.

We determined thermoregulatory skin perfusion using laser-Doppler fluxmetry (Periflux PF3; Perimed, Järfälla, Sweden), with probe PF 308, wide-band (12 kHz) mode, and time constant 0.2 s. Measurements were performed at the volar side of the endphalanx and dorsal side of the interphalanx of the right third finger. The mean value of 2 min recording was used for off-line analysis. Flux values were expressed in arbitrary units (Pu); calibrated to the periflux motility standard. Biological zero values, obtained during arterial occlusion, were subtracted from the measured laser-Doppler fluxmetry
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levels. Skin temperature was measured at the dorsal side of the interphalanx of the right fourth finger using a Hewlett Packard 78214C monitor (Hewlett Packard, Böblingen, Germany).

Total forearm blood flow (FBF) was determined using ECG-triggered strain-gauge venous occlusion plethysmography (Periflow; JSI, Beerse, Belgium) and has been described in detail elsewhere [16]. In short, the cuff for venous occlusion was placed just above the elbow. A mercury strain-gauge was placed around the arm, 3–5 cm distal to the lateral humeral epicondyle. The hand circulation was stopped by inflating a wrist cuff to suprasystolic pressure, starting 1 min before each FBF measurement. Hence, FBF represents predominantly muscle blood flow [17]. FBF was measured over a period of 4 min. The mean of the last 2 min was used for calculations. A flow curve encompassed the time interval of five heartbeats, during which venous occlusion (50 mmHg) was applied over three heartbeats. Thus, on average, we measured 12 inflow curves/min.

MAP (mmHg) and heart rate (beats/min) were measured non-invasively over a 1 min period on the third finger of the left hand using a blood pressure monitor (Finapres; Ohmeda, Englewood, CO, U.S.A.).

Venous compliance was determined as described elsewhere [16]. To measure venous pressure and to take blood samples, we inserted a 20-gauge catheter into a vein of the right forearm. A pressure transducer was placed 5 cm below the sternal angle. Intravenous pressure was measured with a Hewlett Packard 78205C pressure monitor. Forearm volume changes were measured using mercury strain-gauge venous occlusion plethysmography as described above. Measurements began 30 min after venepuncture. First, the upper arm cuff was inflated to a cuff pressure of 25 mmHg and was kept inflated for 3 min. This time interval was chosen to reach a steady state in arm volume and pressure. Thereafter, the cuff was deflated for 2 min to minimize accumulation of interstitial fluid due to capillary filtration. The concomitant changes in volume and intravenous pressure during each cuff pressure step were derived from the values measured just before and after deflation of the cuff. Subsequently, the same procedures were followed to obtain volume/pressure ratios during cuff pressures of 30, 35, 40 and 50 mmHg. Venous compliance was defined as the slope of the relationship, calculated by linear regression, of the forearm volume (dV, ml/100ml) on the ordinate with the venous pressure (dP, mmHg) on the abscissa.

Statistical analysis

Differences between LP and FP were analysed by the Wilcoxon matched-pairs signed-ranks test. Correlations between concomitantly measured variables in the FP and LP, and between differences in potentially related variables were tested by Spearman’s rank correlation analysis. In the comparisons, a P-value of less than 5% was considered statistically significant.

We calculated detectable changes in the mean of variables (n=9, α=0.05 and β=0.10), assuming a normal distribution of the data. The minimum detectable changes were 23%, 4%, 48%, 9% and 6% for the venous compliance, transit time, FBF, ERPF and GFR, respectively.

RESULTS

Table 1 lists the general characteristics of the study population and the serum levels of 17β-oestradiol and progesterone in the FP and LP, respectively. In seven of nine cases, serum levels of 17β-oestradiol were higher in the LP than in the FP (P=0.14). In both the FP and LP the 17β-oestradiol varied over a wide range. In the LP, progesterone also varied over a wide range.

Medians (and ranges) for haemodynamic and renal variables are listed in Table 2. The most relevant variables are also shown in Fig. 1. Skin blood flow and skin temperature were consistently lower, and the GFR higher in the LP. None of the other variables differed significantly between the LP and the FP. Neither the absolute values in the LP nor the magnitude of the change relative to the FP of all variables listed in Table 2 correlated with the serum level of progesterone in the LP, with the change in serum level of 17β-oestradiol between FP and LP, or with the ratio of progesterone and 17β-oestradiol in the LP.

DISCUSSION

The objective of this study was to determine whether there are signs of vascular relaxation in the LP of the menstrual cycle. Arterial blood pressure, vascular tone and the blood flows to the forearm and kidneys were comparable in the LP and FP. In contrast, skin thermoregulatory blood flow was consistently lower, and the GFR higher in the LP of the menstrual cycle.

The LP is not only characterized by the appearance of progesterone in the peripheral blood, but also by a highly variable serum level of 17β-oestradiol, known to be a significant modulator of vascular tone. Most studies on vascular effects in response to oestrogen have shown a vasodilatory action [8]. In our study the luteal value for serum 17β-oestradiol was higher in seven out of nine subjects when compared with that in the FP (Table 1). We did not find a correlation between the change in serum level of 17β-oestradiol between the two phases, and all the haemodynamic and renal variables measured.

Based on reported studies [6–8], we expected to see an increase in both the venous compliance and arterial distensibility leading to a fall in pulse-wave velocity and a rise in transit time, respectively.
Table 2. Medians (with ranges) for haemodynamic variables and kidney function during the FP and LP of the menstrual cycle (n=9). Median differences [with 95% confidence interval] are listed. Changes in LP relative to FP were evaluated using the Wilcoxon matched-pairs signed-ranks test. Pu, perfusion units.

<table>
<thead>
<tr>
<th></th>
<th>FP</th>
<th>LP</th>
<th>Median difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous compliance x 100</td>
<td>5.3</td>
<td>6.6</td>
<td>+0.7</td>
<td>0.33</td>
</tr>
<tr>
<td>(ml 100ml⁻¹ mmHg⁻¹)</td>
<td>(4.8-8.0)</td>
<td>(4.4-8.8)</td>
<td>[-1.7--+3.0]</td>
<td></td>
</tr>
<tr>
<td>Transit time (ms)</td>
<td>207</td>
<td>202</td>
<td>0</td>
<td>0.78</td>
</tr>
<tr>
<td>(194-217)</td>
<td>(195-221)</td>
<td></td>
<td>[-13--+7]</td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>87</td>
<td>87</td>
<td>0</td>
<td>0.18</td>
</tr>
<tr>
<td>(75-97)</td>
<td>(61-93)</td>
<td></td>
<td>[-13--+3]</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>61</td>
<td>64</td>
<td>+6</td>
<td>0.31</td>
</tr>
<tr>
<td>(49-71)</td>
<td>(55-75)</td>
<td></td>
<td>[-7--+7]</td>
<td></td>
</tr>
<tr>
<td>Laser-Doppler fluxmetry_{renal} (Pu)</td>
<td>54.2</td>
<td>29.6</td>
<td>-17.8</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>(16.7-124)</td>
<td>(9.5-59.8)</td>
<td>[-66.4--+5.8]</td>
<td></td>
</tr>
<tr>
<td>Laser-Doppler fluxmetry_{renal} (Pu)</td>
<td>6.2</td>
<td>5.0</td>
<td>-0.4</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>(2.1-13.2)</td>
<td>(1.5-26.1)</td>
<td>[-7.9--+2.0]</td>
<td></td>
</tr>
<tr>
<td>Temperature skin (°C)</td>
<td>31.4</td>
<td>27.0</td>
<td>-1.9</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>(27.6-33.5)</td>
<td>(24.1-32.2)</td>
<td>[-4.8--+0.6]</td>
<td></td>
</tr>
<tr>
<td>Forearm blood flow</td>
<td>2.7</td>
<td>1.8</td>
<td>-0.4</td>
<td>0.10</td>
</tr>
<tr>
<td>(ml/min 100ml⁻¹)</td>
<td>(1.2-5.4)</td>
<td>(1.2-2.4)</td>
<td>[-1.0--+0.4]</td>
<td></td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>112</td>
<td>123</td>
<td>+7</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>(96-129)</td>
<td>(105-129)</td>
<td>[0--+11]</td>
<td></td>
</tr>
<tr>
<td>RBF (ml/min)</td>
<td>852</td>
<td>889</td>
<td>+24</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>(670-1006)</td>
<td>(666-1063)</td>
<td>[-26--+110]</td>
<td></td>
</tr>
<tr>
<td>Renal vascular resistance</td>
<td>8955</td>
<td>7499</td>
<td>-376</td>
<td>0.21</td>
</tr>
<tr>
<td>(dys⁻¹ cm⁻²)</td>
<td>(7131-10420)</td>
<td>(6291-10575)</td>
<td>[-2040--+374]</td>
<td></td>
</tr>
<tr>
<td>Filtration fraction (GFR/RPF)</td>
<td>0.21</td>
<td>0.22</td>
<td>+0.01</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>(0.17-0.27)</td>
<td>(0.19-0.30)</td>
<td>[0.0--+0.02]</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Skin blood flow [measured by laser-Doppler fluxmetry (LDF)] (a), FBF (b) GFR (c) and RBF (d) during the menstrual cycle. Each pair of open circles represents one subject, a filled square represents the median of that menstrual phase. FP, follicular phase; LP, luteal phase; M, menstrual period; O ovulation.
However, our measurements suggested that neither the venous compliance nor the arterial distensibility had changed consistently in the LP. Other studies investigating venous distensibility during the menstrual cycle show conflicting data [18, 19]. The reproducibility of pulse-wave velocity measurements can be adversely affected by changes in arterial blood pressure [20]. Because of the lack of consistent change in MAP in our study, we did not correct for coincidental fluctuations in blood pressure.

Vasodilatation in response to a fall in arteriolar tone can be expected to give rise to hyperperfusion in muscle and skin tissue for example. Instead, we found a consistent reduction in skin thermoregulatory blood flow and a trend towards lower perfusion rates in forearm muscle during the LP. Other investigators have not found a consistent change in venous compliance nor the arterial distensibility [21]. Because of the lack of consistent change in MAP in our study, we did not correct for coincidental fluctuations in blood pressure. Investigating venous distensibility during the menstrual cycle show conflicting data [18, 19]. The fall in skin thermoregulatory blood flow as observed in the present study is possibly related to the well-known 0.3-0.5°C increase in core temperature during the LP. This increase in core temperature may result from either a raised metabolic rate or an increase in thermal body insulation. It follows that the higher body temperature is probably an intended effect in response to a rise in the set-point of the thermoregulatory centre in the medulla oblongata. This effect can be obtained by a fall in thermoregulatory skin flow (arteriovenous shunt flow) [29]. The blood flow to the skin of the fingertip is more influenced by thermoregulation than is the case on the dorsal side of the finger, where arteriovenous shunts are relatively scarce. The consistent fall in just the fingertip flow supports the view that the observed changes in skin flow reflect those in thermoregulation.

To our knowledge the cyclicity in the GFR has never been evaluated by measuring serum inulin clearance; in other words, all data on this topic reported so far are based on GFR markers such as creatinine clearance or 51Cr-EDTA clearance. We showed a 10% rise in median GFR in conjunction with a trend towards higher RBF and lower renal vascular resistance in the LP. Other investigators reported either a similar cyclicity [3, 31-33] or lack of cyclicity [34], probably due to differences in methodology. The combined increase in both GFR and RBF in five of six subjects supports the view that the mechanism of this increase is afferent arteriolar dilation. However, this requires further study.

The observed blood flow patterns to muscle, skin and kidney do not support our hypothesis of a general vascular relaxation in the LP. Since we studied the blood flows to only three vascular beds, it was impossible to draw conclusions about changes in total peripheral resistance with the menstrual cycle. However, it has been demonstrated that total peripheral resistance decreases in the LP of the menstrual cycle [35].

A limitation of these in vivo experiments is the relatively high variability resulting from the combination of biological variation (2-week interval) and the use of indirect measurement techniques. In our institute, this combined variability is associated with coefficients of variation ranging from 10 to 25% [16, 36]. Since the measurements were paired and performed by the same investigator, we expected to minimize this problem. Table 2 shows the 95% confidence intervals of the median differences for each of the measured variables. Although some variables are characterized by relatively wide intervals (modest power), others show relatively narrow intervals. The minimum detectable changes mentioned above do support these findings and illustrate, in combination with the actual measured changes, the possibility of a type II error.

In conclusion, the present data do not support the concept of a general vascular relaxation during the LP of the menstrual cycle. Thermoregulatory blood flow in the skin was most probably diminished in the LP, in order to raise the core temperature. Post-ovulatory vasodilatation of afferent renal arterioles could be responsible for the raised GFR, and possibly the endocrine environment of the LP induces selective vasorelaxation in certain vascular beds.

ACKNOWLEDGMENTS

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