fasted for at least 12 h before each test. All haemodynamic and hormonal measurements were performed as follows: (1) after measuring body composition, the subject was placed in the supine position and fitted with electrocardiographic and blood pressure devices (brachial and radial); (2) after a 20-min resting period, we measured spontaneous baroreflex sensitivity (SBRS) by the sequence method, BRS by the Valsalva manoeuvre, and carotid and brachial haemodynamics as described below; (3) after a 15-min resting period, blood was drawn for the measurement of hormone levels.

### Measurements

*Body composition.* Body composition was determined using bioelectric impedance as described elsewhere (Houtkooper *et al.* 1992).

*Heart rate and brachial arterial blood pressure.* We measured heart rate and brachial blood pressure at rest non-invasively using a limb-lead electrocardiograph and a semi-automated device (Form ABI; Colin Medical) in the supine position. Brachial blood pressure values were determined in triplicate (Perloff *et al.* 1993).

*Cardiovagal BRS.* We used the sequence method and the Valsalva manoeuvre to estimate cardiovagal BRS. To determine SBRS, we recorded R–R intervals and SBP for 5 min with the subjects in the supine position. Respiratory rate was controlled at a frequency of 0.25 Hz during the measurements. We determined arterial blood pressure waveforms and R–R intervals using arterial tonometry (Jentow-7700; Nihon Colin, Komaki, Japan) and standard lead electrocardiography (Life Scope 11; Nihon Koden, Tokyo, Japan), respectively. Both R–R intervals and arterial blood pressure waveforms were sampled at 1000 samples per second by connecting each device to a computer using an A/D converter (Maclab/400; AD Instruments, NSW, Australia). Prior to analysis, both R–R intervals and arterial blood pressure waveforms were visually inspected for artefacts.

Spontaneous baroreflex sensitivity was assessed using a modification of a previously reported procedure (Bertinieri *et al.* 1985, 1988). Briefly, we identified baroreflex sequences (three or more beats relating to R–R intervals and progressively spontaneously changing SBP of the same detection, *lag 1*) in which SBP progressively increased followed by a lengthening of the R–R interval (up-sequence) or SBP progressively decreased with a subsequent shortening of the R–R interval (down-sequence). Next, we determined the slope of the linear relationship between the R–R intervals and SBP at these points. The minimum changes observed were 1 mmHg for SBP and 1 ms for the R–R interval. Linear regressions relating SBP to the R–R interval were plotted for each sequence; only those sequences with linear $r$ values >0.85 were accepted. The results for a 5-min period were averaged to provide a single data set for up- or down-sequence SBRS.

To perform the Valsalva manoeuvre, subjects exhaled forcefully through a mouthpiece connected via a rubber tube to an analog manometer. Subjects were instructed to exhale until reaching a mouth pressure of 40 mmHg. Three 10-s Valsalva manoeuvres were performed, separated by 3-min recovery periods. We used the slope method to assess cardiovagal BRS during phase IV arterial pressure elevations. We used linear regression analysis to calculate the magnitude of the increases in R–R intervals as a function of the elevations in systolic pressures. We used a minimum of four consecutively increasing systolic pressure levels and the corresponding changes in R–R intervals. SBP levels regressed linearly against the corresponding (*lag 1*) R–R intervals, began to lengthen, and continued to increase to the maximal SBP elevation. Only linear $r$ values ≥0.85 were considered a valid sequence. An average of three trials was examined for each subject.

*Carotid arterial distensibility and structural indices.* We used the carotid arterial distensibility coefficient (DC) to estimate carotid arterial distensibility. The combination of ultrasound imaging of the common carotid artery with simultaneous applanation tonometry yielded the arterial pressure from the contralateral carotid artery. These measurements allow the non-invasive determination of carotid arterial DC (Reneman *et al.* 1986, 2005). Carotid artery diameter and intima-media thickness (IMT) were measured from images derived from ultrasonography using a machine equipped with a high-resolution linear-array transducer. A longitudinal region of the cephalic portion of the common carotid artery was imaged 1–2 cm proximal to the carotid bulb. Computer images were digitized with a media converter and analysed using image analysis software (NIH image 1.62). Minimal and maximal lumen diameters, measured from the media-adventitia border of the near wall to the intima-lumen interface of the far wall, were identified by scrolling through images acquired at 33-ms intervals. At least 10 measurements of minimal and maximal lumen diameters and carotid artery IMT were taken at each segment, and the mean values were used for analysis. All image analyses were performed by a single investigator, who was blinded to the menstrual phase assignments. Carotid arterial pressure waveforms and amplitudes were taken from the common carotid artery using a pencil-type probe incorporating a high-fidelity strain-gauge transducer

(SPT-301; Millar Instruments) (Miyachi *et al.* 2003, 2004). As the baseline levels of carotid blood pressure were subjected to hold-down forces, we calibrated the pressure signal obtained by tonometry by equating the carotid mean arterial (MAP) and diastolic blood pressure (DBP) to the values obtained for the brachial artery as described elsewhere (Armentano *et al.* 1995). The right and left carotid arterial blood pressures were almost equal when investigated previously (unpublished data). Carotid arterial DC was calculated using the following equation (Reneman *et al.* 1986, 2005):

$$DC = [(CSAs - CSAd)/CSAd]/\Delta P$$

where $\Delta P$ is the carotid arterial pulse pressure (PP) and CSAs and CSAd are the cross-sectional areas at the maximal systolic expansion and minimal diastolic relaxation of the carotid artery, respectively.

*Ovarian hormones.* To measure serum oestradiol and progesterone concentrations, a 5-mL fasting blood sample was taken from the antecubital vein in each menstrual phase. Blood was centrifuged at 3000 rpm for 15 min. All serum samples were distributed into appropriate preservation tubes and stored at −80 °C until analysed. Serum oestradiol and progesterone concentrations were measured using commercially available radioimmunoassay kits (Mitsubishi BCL, Tokyo, Japan). To eliminate intra-assay variability, all samples were analysed within the same batch; intra-assay variability was <5%.

### Statistical analysis

All data are presented as the mean ± SE. Differences in values measured across the menstrual cycle were assessed by one-way analysis of variance (ANOVA) with repeated measures. For significant $F$ values in ANOVA, a *post-hoc* test using the Newman–Keuls method was used to identify significant differences between the mean values. The level of significance was set at $P < 0.05$.

## Results

### Ovarian hormones and body composition

All subjects were nulliparous, with a mean cycle length of 28 ± 2 days. Body weight, per cent body fat, and serum ovarian hormone measurements are summarized in Table 1. Serum oestradiol and progesterone concentrations changed significantly throughout the menstrual cycle, consistent with the predicted fluctuations for each cycle phase (oestradiol: $F = 9.3$, $P < 0.05$, progesterone: $F = 13.9$, $P < 0.05$). Serum oestradiol concentrations were higher during the O and EL phases than in other phases ($P < 0.05$). Serum progesterone concentrations were significantly higher in the EL phase in comparison with the other phases ($P < 0.05$). Body weight and per cent body fat did not change significantly during the menstrual cycle.

### Heart rate and arterial blood pressure

Neither the resting heart rate, brachial arterial blood pressure (SBP, DBP, MAP and PP), nor the carotid arterial blood pressure (SBP and PP) in each menstrual phase changed significantly during the menstrual cycle (Table 2).

### Carotid arterial distensibility

The diastolic lumen diameter and IMT of the carotid artery did not change significantly during the menstrual cycle (Table 2). Measurements of the changes in carotid arterial DC throughout the five phases (Fig. 1) demonstrated that the carotid arterial DC decreased after ovulation (in the EL and LL phases). The carotid arterial DC values in each phase of the menstrual cycle were 52.4 ± 4.9, 52.7 ± 4.4, 57.6 ± 4.4, 46.0 ± 4.0 and 45.1 ± 3.0 ($\times 10^{-3}$ kPa$^{-1}$) in the M, F, O, EL and LL phases, respectively (ANOVA; $F = 6.37$, $P < 0.05$). *Post-hoc* comparisons indicated that the O phase value was significantly higher than that of the EL and LL phases ($P < 0.05$).

**Table 1** Physiological characteristics of subjects

| Variables | M | F | O | EL | LL |
|---|---|---|---|---|---|
| Age (years) | 21 ± 1 | – | – | – | – |
| Height (cm) | 159 ± 1 | – | – | – | – |
| Weight (kg) | 52 ± 1 | 52 ± 1 | 52 ± 1 | 52 ± 1 | 52 ± 1 |
| % Fat | 26 ± 1 | 27 ± 1 | 26 ± 1 | 26 ± 1 | 26 ± 1 |
| Oestradiol (pg mL$^{-1}$) | 41 ± 9 | 50 ± 7 | 137 ± 27* | 129 ± 19* | 66 ± 12 |
| Progesterone (ng mL$^{-1}$) | 0.8 ± 0.1 | 0.8 ± 0.3 | 0.7 ± 0.1 | 10.7 ± 29** | 3.3 ± 0.6 |

Data are expressed as the mean ± SE.
M, menstrual phase; F, follicular phase; O, ovulatory phase; EL, early luteal phase; LL, late luteal phase; *$P < 0.05$ vs. M, F and LL phase; **$P < 0.05$ vs. all other phases.

**Table 2** Heart rate, central and peripheral arterial blood pressure, and carotid artery structural indices

| Variables | M | F | O | EL | LL |
|---|---|---|---|---|---|
| Heart rate (bpm) | 53 ± 1 | 52 ± 2 | 54 ± 2 | 54 ± 1 | 55 ± 1 |
| Brachial SBP (mmHg) | 102 ± 3 | 100 ± 3 | 102 ± 3 | 100 ± 3 | 101 ± 3 |
| Brachial DBP (mmHg) | 61 ± 1 | 57 ± 2 | 59 ± 2 | 59 ± 2 | 58 ± 2 |
| Brachial MAP (mmHg) | 77 ± 2 | 74 ± 2 | 76 ± 3 | 73 ± 3 | 75 ± 2 |
| Brachial PP (mmHg) | 42 ± 3 | 42 ± 3 | 43 ± 2 | 41 ± 2 | 43 ± 3 |
| Carotid SBP (mmHg) | 95 ± 2 | 93 ± 2 | 92 ± 2 | 94 ± 3 | 95 ± 2 |
| Carotid PP (mmHg) | 37 ± 2 | 37 ± 2 | 36 ± 1 | 39 ± 2 | 37 ± 1 |
| Carotid artery diameter (mm) | 5.40 ± 0.10 | 5.56 ± 0.10 | 5.46 ± 0.08 | 5.53 ± 0.11 | 5.55 ± 0.07 |
| Carotid artery IMT (mm) | 0.47 ± 0.11 | 0.46 ± 0.02 | 0.47 ± 0.02 | 0.46 ± 0.01 | 0.46 ± 0.01 |

Data are expressed as the mean ± SE.
M, menstrual phase; F, follicular phase; O, ovulatory phase; EL, early luteal phase; LL, late luteal phase; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; Carotid artery diameter, carotid artery diastolic lumen diameter; IMT, intima-media thickness.

### *Cardiovagal BRS*

Up- and down-sequence SBRS did not change significantly during the menstrual cycle (Fig. 1). Up-sequence SBRS values were 35.3 ± 3.8, 38.5 ± 3.0, 38.0 ± 3.5, 36.2 ± 3.8 and 33.6 ± 3.9 (ms $mmHg^{-1}$) in the M, F, O, EL and LL phases, respectively ($F = 0.35$, $P = 0.84$). Down-sequence SBRS values were 33.0 ± 3.1, 37.7 ± 5.5, 37.3 ± 4.4, 35.1 ± 5.1 and 34.3 ± 4.7 (ms $mmHg^{-1}$) in the M, F, O, EL and LL phases, respectively ($F = 0.59$, $P = 0.67$). BRS, estimated by the Valsalva manoeuvre, also did not change significantly during the menstrual cycle (Fig. 1), with values of 9.5 ± 1.9, 9.4 ± 1.3, 8.7 ± 0.6, 10.2 ± 1.7 and 8.7 ± 0.5 (ms $mmHg^{-1}$), respectively ($F = 0.52$, $P = 0.73$).

## Discussion

The salient findings of the present study were as follows. First, carotid arterial distensibility varied significantly throughout the menstrual cycle. Second, cardiovagal BRS remained constant throughout the menstrual cycle. These findings suggest that the fluctuations in carotid arterial distensibility induced by the menstrual cycle do not influence cardiovagal BRS in young women.

Cardiovagal BRS did not change significantly during the menstrual cycle. In previous animal studies, oestrogenic intravenous injections produced significant increases in vagal BRS (Mohamed *et al.* 1999, Saleh & Connell 1999). In humans, however, it is unclear if ovarian hormone variation throughout the menstrual cycle influences cardiovagal BRS. While Minson *et al.* (2000) could not observe any differences in cardiovagal BRS (Oxford method) between the early follicular and mid-luteal phases, Fuenmayor *et al.* (2000) demonstrated that the Valsalva ratio was higher in the late luteal phase than in the early follicular phase. The results in these studies cannot, however, be correlated with either ovarian hormone levels, such as oestrogen and progesterone, or the balance between these hormones, because the menstrual cycle was divided into only two phases. Using the Oxford method, the Valsalva manoeuvre and sequence methods, Tanaka *et al.* (2003) recently examined changes in cardiovagal BRS throughout the menstrual cycle, which was divided into three phases (early follicular, when oestradiol and progesterone are low; pre-ovulation, when the oestradiol is high and progesterone is low; and mid-luteal, when both oestradiol and progesterone are high). Their results demonstrated that baroreflex sensitivities to hypertensive stimuli (phenylephrine and the Valsalva manoeuvre) were enhanced in the preovulation phase. In addition, they observed a significant correlation between plasma oestradiol concentrations and BRS to hypertensive stimuli, a result that differs significantly from our data. This discrepancy may result from differences in the magnitude of oestradiol increases. As our subjects were young women (approximately 20 years old), the serum oestradiol concentrations in the

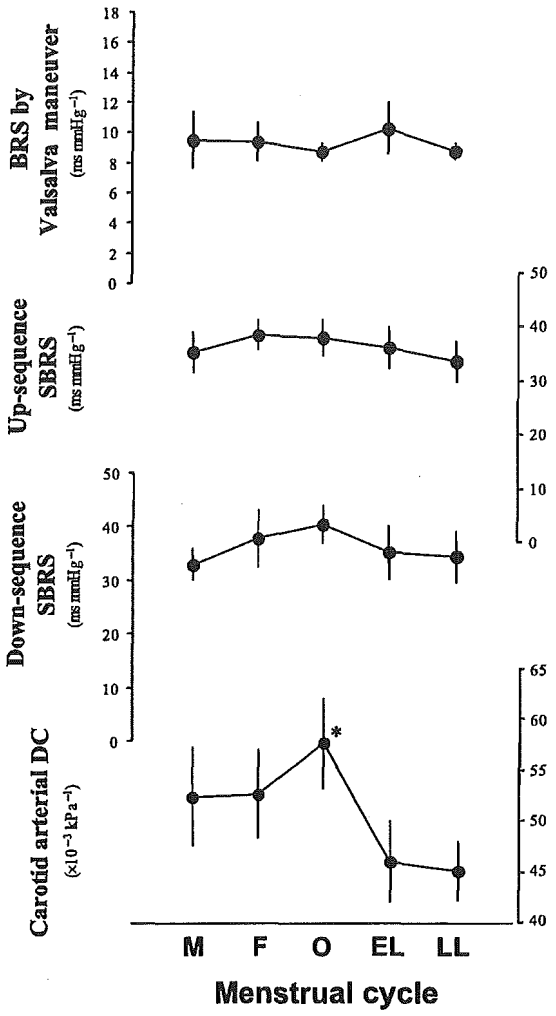


**Figure 1** Changes in cardiovagal BRS and carotid arterial distensibility. $*P < 0.05$ vs. the values measured for the EL and LL phases. M, menstrual phase; F, follicular phase; O, ovulatory phase; EL, early luteal phase; LL, late luteal phase; DC, distensibility coefficient.

ovulatory phase (O) were lower (137.2 ± 27.0 pg $mL^{-1}$) than those reported by Tanaka *et al.* (210.7 ± 16.5 pg $mL^{-1}$).

In the present study, a lack of correlation between cardiovagal BRS and carotid distensibility changes was observed. The amounts of change in carotid arterial distensibility throughout the menstrual cycle (27.7%, O phase vs. LL phase) were smaller than those of ageing (Reneman *et al.* 1986) and hormone replacement therapy (Moreau *et al.* 2003); therefore, it is likely that the amounts of change in carotid arterial distensibility during the normal menstrual cycle were not sufficient to induce significant changes in cardiovagal BRS.

As other reasons why the relationship between changes in carotid arterial distensibility and cardiovagal BRS during the menstrual cycle were lacking, the effects of ovarian hormones on neural components of the baroreflex loop (sensitivity of baroreceptor, central integration and sensitivity of effect or organ) might be related. In rats, oestrogen modulated cardiovagal BRS via oestrogen receptors in the cardiovascular centre (Saleh & Connell 2000), and the expression levels of the oestrogen receptor in the brainstem changed throughout the oestrous cycle (Haywood *et al.* 1999). A change in cardiovagal BRS may not necessarily be synchronized with the fluctuations in the blood oestrogen level if there is a temporal difference between the elevation of blood oestrogen levels and the enhancement of oestrogen receptor expression in the cardiovascular center. In this context, Kornet *et al.* (2005) provided the new elegant approach with which the component of neural control of BRS could be assessed. This was achieved by the quantification of the sensitivity of baroreflex control of the heart rate by considering the carotid arterial diameter/R–R interval relationship ('stretch-derived' BRS) through continuous monitoring of the carotid arterial diameter (by ultrasound) and the arterial waveform. Clarification of the actions of ovarian hormones on the interrelation of neural and mechanical components of the baroreflex loop will be enabled by using this method.

Carotid arterial DC changed significantly in a manner dependent on the menstrual cycle phase: increasing in the menstrual and follicular phases, peaking in the ovulatory phase, and decreasing significantly in the early and late luteal phases. These alterations in carotid arterial distensibility are consistent with changes in whole-body and radial arterial compliance varying with the menstrual cycle, as reported elsewhere (Giannattasio *et al.* 1999, Williams *et al.* 2001). However, Willekes *et al.* (1997) reported that carotid arterial distensibility did not change during the menstrual cycle. No clear explanation is at hand for this discrepancy.

Multiple studies have suggested that oestrogen improves vascular endothelial function by enhancing endothelial nitric oxide synthase activity, nitric oxide release (Knot *et al.* 1999, Geary *et al.* 2000), prostacyclin release (Orshal & Khalil 2004), and the vasodilator action of endothelial-dependent hyperpolarization factor (Liu *et al.* 2001) and also by inhibiting endothelin-1 production (Akishita *et al.* 1998). In addition, oestrogen inhibits the influx of $Ca^{2+}$ into vascular smooth muscle cells (Murphy & Khalil 2000). All in all, these oestrogenic actions should lead to an increase of arterial distensibility. In contrast, progesterone has an inhibitory effect on oestrogen-mediated endothelial-dependent vasodilation (Williams *et al.* 1998). In addition, it was reported that, in the human female, muscle sympathetic nervous activity was significantly higher in the mid-luteal phase than in the early follicular phase

 

during the normal menstrual cycle (Minson *et al.* 2000). These factors might interact to change arterial distensibility.

Brachial blood pressure did not change during the menstrual cycle, although carotid arterial distensibility changed significantly. And although increased distensibility of the elastic artery should be accompanied by reduced SBP and increased DBP when the change (or difference) in arterial distensibility is great (e.g. in ageing), it is appropriate to interpret this to mean that physiological changes in arterial distensibility attributable to the menstrual cycle phase do not influence blood pressure levels. Indeed, it has been reported that whole-body arterial compliance varied significantly but the arterial blood pressure did not change during the menstrual cycle (Williams *et al.* 2001). Other factors (e.g. autonomic nervous function, vasoactive substance and blood volume) might also be associated with regulation of the blood pressure.

There are several limitations in the present study. First, only cardiovagal BRS was estimated. It will be necessary to examine the effects of ovarian hormones on sympathetic BRS. It has been reported that sympathetic BRS in the mid-luteal phase was significantly higher than that seen in the early follicular phase (Minson *et al.* 2000). Second, it is possible that the distance between the carotid bulb (where baroreceptors are located) and the common carotid artery (carotid arterial distensibility was measured) would explain the lack of correlation observed between the changes in cardiovagal BRS and carotid distensibility. However, it is difficult to evaluate the carotid arterial structures and dynamics in the bulb by means of the two-dimensional ultrasound device, and previous studies (Bonyhay *et al.* 1996, Monahan *et al.* 2001) on the association between carotid arterial distensibility (or compliance) and cardiovagal BRS have measured carotid artery elastic properties in common carotid arteries but not in the carotid bulb.

In summary, we examined during the menstrual cycles of young women, the relationship between the changes in cardiovagal BRS and carotid arterial distensibility, one of the factors controlling cardiovagal functions. Carotid arterial distensibility changed significantly in a manner dependent on ovarian hormone changes, but cardiovagal functions remained constant throughout the menstrual cycle. Therefore, these results suggest that the fluctuations in carotid arterial distensibility observed during the menstrual cycle do not influence resting cardiovagal BRS in young women.

## Conflict of interest

There are no conflicts of interest for our work.

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