Changes in baroreceptor sensitivity for heart rate during normotensive pregnancy and the puerperium

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ABSTRACT

Normal pregnancy is associated with marked changes in cardiovascular haemodynamics, which in part may be due to changes in autonomic control mechanisms. Baroreflex sensitivity for heart rate (BRS) was calculated in the supine and standing positions using power spectral analysis of pulse interval (PI) and systolic blood pressure (SBP) in 16 normotensive pregnant women and 10 normotensive non-pregnant controls. The pregnant women were studied on three occasions during their pregnancy (early, mid- and late gestation) and once during the puerperium. Supine total SBP variability increased between early and late pregnancy by 79% [95% confidence intervals (CI) 30%, 145%; P < 0.001], and supine high-frequency PI variability decreased by 75% (CI 51%, 88%; P < 0.001). Supine BRS fell by 50% (P < 0.001), with values returning to early-pregnancy levels in the puerperium, which were similar to those recorded in the control group. Standing SBP variability and BRS values were unchanged during pregnancy and post partum. The low/high frequency ratio of PI variability, taken as a surrogate measure of sympathovagal balance, increased by 137% (CI 42%, 296%; P < 0.01) in the supine but not the standing position from early to late pregnancy. This was due to a decrease in high-frequency variability rather than to an increase in low-frequency variability, suggesting that these changes may have been due to vagal withdrawal rather than increased sympathetic activity. Normotensive pregnancy is associated with a marked decrease in supine BRS, although the exact mechanisms for these changes remain unclear. Further studies are required to define whether changes in BRS and sympathovagal tone in early pregnancy can be used to predict the onset of pregnancy-induced hypertension.

INTRODUCTION

Normal pregnancy is accompanied by marked alterations in the maternal circulation, including an increase in cardiac output of about 45% [1] and a decrease in peripheral vascular resistance, manifest by a progressive fall in blood pressure (BP) in the first and second trimesters [2]. These cardiovascular changes are accompanied by changing levels of various pressor hormones and vasoactive metabolites. The activity of the renin–angiotensin system is increased and plasma levels of angiotensin II are elevated, although there is a marked

Key words: baroreceptor sensitivity, blood pressure, pregnancy.

Abbreviations: BP, blood pressure; BRS, baroreflex sensitivity; CI, confidence intervals; DBP, diastolic BP; HF, high frequency; LF, low frequency; MANOVA, multivariate analysis of variance; n.u., normalized units; PI, pulse interval; SBP, systolic BP; VLF, very low frequency.

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diminution in pressor responsiveness to angiotensin II, with this loss of response reaching a maximum during mid-pregnancy and returning towards non-pregnant values thereafter [3].

The action of the autonomic nervous system is thought to be essential for the circulatory adaptations seen in pregnancy, but its actual role is poorly understood [4]. Sympathetic nervous system activity assessed by measurement of plasma catecholamine levels has produced conflicting results, demonstrating either normal concentrations of plasma noradrenaline and adrenaline [5,6] or reduced levels of noradrenaline [7] in pregnant women compared with non-pregnant controls. Similarly, blockade of the adrenergic system [8], measurement of dopamine β-hydroxylase activity [9] and simple non-invasive cardiovascular reflex tests known to increase sympathetic nervous system activity and/or vagal activity have not produced conclusive results. Ekholm et al. [4] employed a range of standard cardiovascular reflex tests to assess autonomic function before, during and after pregnancy, and demonstrated that parasympathetic responsiveness decreased during pregnancy, returning to normal after delivery.

The primary role of the arterial baroreflex is the immediate and short-term adjustment of BP following perturbations around an existing mean pressure. The Oxford phenylephrine ‘ramp’ method [10] for studying the baroreceptor heart rate reflex relates the change in pulse interval (PI) (R–R interval, in ms) to the change in systolic arterial pressure (mmHg) produced by an intravenous injection of phenylephrine. The slope of the regression line for the change in systolic BP (SBP) in relation to the change in PI is linear; the steepness of the slope (expressed as ms of increase in R–R interval per mmHg rise in systolic arterial pressure) gives an index for the baroreflex control of heart rate by largely vagal mechanisms [11]. Due to the invasive nature of this technique only a few cross-sectional studies have been performed in pregnancy. Seligman [12] and Leduc et al. [13] used this method, and found that baroreflex sensitivity (BRS) decreased from term to the post-partum period in normotensive pregnancy. In contrast Valdes et al. [14], in a longitudinal study through pregnancy and the puerperium, found a progressive blunting of the heart rate response to tilt as pregnancy progressed, suggesting a decrease in BRS in late pregnancy. Yoshimura et al. [15] examined angiotensin sensitivity in the 20th and 30th weeks of gestation and found that BRS was significantly greater in early than in late pregnancy.

More recently, power spectral analysis of BP and heart rate variability [16] has proved useful in evaluating cardiovascular autonomic activity. Power spectral analysis of BP and PI in the frequency domain produces a power spectrum from which it is possible to express the variability of the signals as a function of their frequency content. The power spectrum of PI variability normally demonstrates two significant peaks: at high frequency (HF) centred around a frequency of 0.15–0.4 Hz, synchronous with respiration and thought to be vagally mediated, and at low frequency (LF), centred around 0.05–0.15 Hz, which is predominantly sympathetically mediated [16,17]. The LF peak of BP variability is thought to represent sympathetic tone, while the HF component is believed to result from mechanical changes in intrathoracic pressure associated with respiration [18,19]. A third peak of very-low-frequency (VLF) variability can be seen in both spectra, centred on 0.02–0.05 Hz and thought to represent changes in vaso-motor tone. A quantitative assessment of the overall gain of the baroreceptor mechanisms can be obtained by simultaneous spectral analysis of PI and BP variabilities [20]. This gain, which is represented by the index α, can be computed for either LF or HF components or their mean, and therefore is descriptive of the overall activity of the baroreflex. Its numerical value is provided by the square root of the ratio of the powers of PI to corresponding BP spectral components.

A number of studies have addressed the issue of the validity of spectral methods of assessing BRS compared with the older pharmacological method. Three studies [20–22] have described a close relationship between BRS values derived from spectral analysis and those obtained from pharmacological BP manipulation using classical methodology. It may be that the former technique is more descriptive of the arterial baroreflex at rest rather than the artificially stimulated conditions of the pharmacologically induced ramp method. Ekholm et al. [23] studied autonomic nervous control in mid-pregnancy using spectral analysis of heart rate variability and demonstrated that normal pregnancy is associated with diminished heart rate variability, indicating decreased parasympathetic tone at rest. To our knowledge there is no published work comparing invasive and non-invasive methods of analysis of BRS in the pregnant state.

The aims of the present study were to use spectral analysis of PI and BP variability to assess the potential alterations in cardiac BRS and sympatho–vagal balance occurring during normotensive pregnancy. We also wished to assess the response of the sympathetic nervous system to orthostatic stress during pregnancy.

** METHODS**

**Subjects**

A total of 16 normotensive non-smoking women, eleven of whom were nulliparous, were randomly selected from standard antenatal clinics. Their mean (± S.D.) age was 26.3 ± 5.7 years (range 15–38 years), and their mean (± S.D.) body mass index at the time of booking was 23.2 ± 4.4 kg/m². There was no evidence of pregnancy-induced hypertension throughout their pregnancies, ac-
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to the standard ISSHP definition [24]. All pregnancies were singleton, and the average birth weight was 3.56 ± 0.43 kg.

Subjects were studied at three time points during their pregnancy: early gestation (T1; 16 ± 2 weeks; range 11–18 weeks), mid-gestation (T2; 27 ± 1 weeks; range 26–29 weeks), and late gestation (T3; 36 ± 1 weeks; range 34–40 weeks). They were also studied on one occasion in the post-partum period (PP; 6 ± 2 weeks; range 4–9 weeks).

In addition, 10 healthy, normotensive, non-pregnant women [eight nulliparous; mean age 29.7 ± 6.4 years (range 15–38 years); body mass index 23.2 ± 3 kg/m²] were recruited from laboratory, administrative and nursing staff to serve as controls, and were studied on one occasion. The control group was similar to the study group with regard to age, and to supine BP and PI values (post-partum values).

No woman was known to be suffering from any cardiovascular, metabolic or renal disease, or was taking any regular medication, including the oral contraceptive pill.

Measurements

All studies took place in the morning in a quiet room with an ambient temperature (thermostatically controlled) between 20 and 22 °C. Subjects were advised to have a light breakfast and to refrain from taking alcohol or caffeine-containing products for at least 12 h prior to the study.

All subjects were positioned supine and allowed to rest for 10 min before beginning the study. Studies within the Department have shown there to be no significant differences in BRS values measured in the 30 ° left lateral position and the supine position (n = 6; mean BRS: left lateral, 15.3 ± 2.8 ms/mmHg; supine, 16.2 ± 2.5 ms/mmHg; P > 0.4). The subjects were then fitted with chest leads for recording of a continuous surface ECG (model CR7; Cardiac Recorders Ltd., London, U.K.). The appropriate-sized finger cuff of a Finapres 2300 non-invasive beat-to-beat BP recording device (Ohmeda Monitoring Systems, Englewood, CO, U.S.A.) was fitted to the middle finger of the right hand, which was rested throughout the study on an adjustable support at the level of the heart. Respiratory rate was monitored with a Piezo-electric transducer (Gould; model 2202.09), and although respiratory rate was not controlled with a metronome, subjects were asked to breathe at a respiratory rate greater than 15 breaths/min.

Following achievement of a satisfactory BP signal from the Finapres and the stabilization of SBP with < 10% variation over a 5-min recording, three periods of continuous BP and heart rate measurements were recorded, each of 5 min duration. Subjects then stood, and a single 5 min recording was obtained (with the right arm supported at heart level) starting 30–60 s after attainment of upright posture to allow for stabilization of BP and heart rate. Only one recording was made in the upright position, since it was uncomfortable for pregnant subjects to remain standing for longer than this. During each period of recording the servo self-adjust mechanism of the Finapres was disabled, but was recalibrated between each recording.

The Local Ethics Committee approved the study design, and all subjects gave written informed consent.

Data analysis

The analogue outputs from the Finapres and the ECG signal were routed to a dedicated personal computer fitted with a 12-bit analogue–digital converter sampling at 200 Hz per channel. Purpose-written software permitted the recording, calibration and editing of the digitalized signal and the derivation for later off-line analysis of beat-to-beat systolic, mean arterial and diastolic BP (DBP), together with the PI from both the Finapres and ECG signals.

Power spectral analysis was performed on the baseline recordings after low-pass filtering with an eighth-order Butterworth digital filter with a cut-off frequency of 20 Hz. Recordings with more than four ectopic beats (of which there were two) were rejected. The beat-to-beat recordings of BP and PI were interpolated with a third-order polynomial and then resampled at a rate of 2 samples/s to render signals with a uniform time base. Linear trends were removed and a 20% tapering cosine window was applied at the extremities of both signals. The signals were transformed to the frequency domain with a fast Fourier transform algorithm using 512 samples. Separate power spectra were computed for BP and PI, and the BRS α index (BRS α) was computed from the mean of the square roots of the ratios of the spectral powers of BP and PI in the LF (0.05–0.15 Hz) and HF (0.15–0.40 Hz) bandwidths, as proposed by Lucini et al. [25]. The cross-spectrum was smoothed with a nine-point triangular window yielding spectral and coherence function estimates with 14 degrees of freedom per record used [26]. The coherence function varies between 0 and 1, and is a method of expressing the amount of linear coupling between two signals in the frequency domain. It is comparable to the correlation coefficient in classical regression analysis, except that it is computed for each frequency region [27].

Each spectral component was represented in absolute units, and the LF and HF components of both BP and PI variability were also represented as normalized units (n.u.), obtained by the following equation. [16,17]:

\[
P_{\text{n.u.}} = P / (\sigma - P_{\text{VLF}}) \times 100
\]

P (n.u.) represents the variability of either the LF or HF components in n.u., P represents LF or HF absolute variability, σ represents total variability, and P_{VLF} indicates the variability of the VLF component. All values
have units of either ms² (PI variability) or mmHg² (BP variability) [16,17]. The use of n.u. allows comparison among subjects when large inter-individual variabilities exist [28], as is the case for PI variability, and these units also minimize the influence of VLF variability. It has been suggested that spectral analysis of PI variability may reflect the balance between sympathetic (reflected by LF variability) and vagal (reflected by HF variability) discharges directed to the heart [29], and that the LF/HF ratio of PI variability may be a convenient index of such an interaction [17].

Quoted BP values are taken as the means for all recordings taken from the Finapres for the 15 min supine and 5 min standing recordings.

**Statistics**
The results are presented as the median and total range for non-normally distributed data. The *a priori* criterion was the comparison of T1 with T3 and PP. Each variable was analysed using repeated-measures MANOVA (multivariate analysis of variance) to test for an overall effect of time. The Wilks’ Lambda test statistic was used to investigate within-subject effects.

All of the outcome variables were inspected for evidence of an underlying normal distribution. The small sample size meant that this was done by subtracting the appropriate cell mean from each observation and then pooling these deviations for each outcome. Natural logarithmic transformations could then be applied to achieve marginal normality, with the assumption that this would provide an approximate multivariate normal distribution.

When an overall statistically significant effect was found, T1 was compared with T3 and PP using Student’s paired *t*-tests to obtain estimates of the mean difference between the time points. Where the data had been log-transformed, a percentage change in the geometric mean was calculated. In addition, 95% confidence intervals (CI) for these differences are reported.

Supine and standing measurements were compared at T1 and PP for PI values, PI variability and BRS. All orthostatic comparisons were carried out using paired Student’s *t*-tests, with log-transformed data where appropriate.

Statistical significance was taken at the 5% level. MANOVA was carried out using SAS v6.12, with Minitab release 12.1 used for all other analyses.

**RESULTS**
All pregnant subjects completed the four study sessions for both supine and standing recordings, and the complete results for all 16 subjects were included in the analysis. No woman showed evidence of supine hypertension or developed orthostatic intolerance, and all remained normotensive throughout pregnancy.

**BP changes during pregnancy**
There were significant changes with time in supine SBP and DBP during pregnancy (MANOVA: SBP, *P* < 0.05; DBP, *P* < 0.01; Table 1). Supine DBP rose between early pregnancy (T1) and late pregnancy (T3) by 5 (95% CI 1, 9) mmHg (*P* < 0.05) (Table 1). No statistically significant variations were seen in standing BP, and orthostatic BP tolerance was maintained throughout pregnancy. Post-partum supine SBP and DBP values were similar to values in the control group (Table 1).

**PI changes during pregnancy**
The supine PI values varied significantly during pregnancy (*P* < 0.0001), decreasing by 124 (95% CI 74, 175) ms between T1 and T3 (*P* < 0.001), whilst standing values remained unchanged. Again, in the post partum period values were similar to those of the control group (Table 1). Standing heart rate was significantly greater than supine values at T1 and post partum (*P* < 0.001), with similar orthostatic changes in heart rate to those of the control group.

**BP variability**
Total supine BP variability (power) altered significantly during pregnancy (*P* < 0.01), increasing by 79% (95% CI 30%, 145%) between T1 and T3 (*P* < 0.01), although no such changes occurred for total BP variability measured in the standing position (Table 2). Looking at the different spectral powers, the supine LF component changed with time (*P* < 0.001), with a significant increase in variability between T1 and T3 of 68% (95% CI 14%, 48%) (*P* < 0.05) (Table 2 and Figure 1). No overall change was seen in standing BP variability during pregnancy and the post partum period.

When the data were normalized (n.u.) to eliminate variations due to the VLF band, there was an overall increase in standing normalized LF variability with time (*P* < 0.05; MANOVA), but the normalized HF variability decreased (*P* < 0.05; MANOVA), with a significant fall between T1 and PP (*P* < 0.01) (Table 2).

**PI variability**
No change occurred during pregnancy in total supine PI variability (*P* = 0.12) or in PI LF variability (*P* = 0.08). Absolute supine PI HF variability did alter as pregnancy progressed (*P* < 0.01), with a statistically significant decrease of 75% (95% CI 51%, 58%) (*P* < 0.01) between T1 and T3 (Table 3 and Figure 2). In the standing position no overall change in total PI variability was noted during pregnancy, although both LF and HF variability changed with time (*P* < 0.01 and *P* < 0.05 respectively).
Table 1  SBP, DBP and PI during pregnancy and post partum
Supine values were taken as the mean of the three 5-min recordings made prior to standing. Standing values were taken as the mean of the 5-min recording after standing. See the text for definition of time periods T1–T3 and PP. Values are means ± S.D. Statistical significance: *P < 0.05; **P < 0.01 compared with T1; †P < 0.05 control compared with PP; ‡P < 0.05 supine compared with standing.

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>PP</th>
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<tr>
<td><strong>SBP (mmHg)</strong></td>
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<tr>
<td>Supine</td>
<td>104 ± 13</td>
<td>96 ± 12</td>
<td>99 ± 15</td>
<td>101 ± 16</td>
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<tr>
<td>Standing</td>
<td>116 ± 10</td>
<td>119 ± 16</td>
<td>122 ± 12</td>
<td>115 ± 19</td>
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<td><strong>DBP (mmHg)</strong></td>
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<tr>
<td>Supine</td>
<td>47 ± 8</td>
<td>45 ± 8</td>
<td>52 ± 9*</td>
<td>51 ± 10</td>
</tr>
<tr>
<td>Standing</td>
<td>62 ± 6</td>
<td>61 ± 9</td>
<td>66 ± 7</td>
<td>68 ± 12</td>
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<tr>
<td><strong>PI (ms)</strong></td>
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<tr>
<td>Supine</td>
<td>845 ± 91</td>
<td>753 ± 94</td>
<td>721 ± 63**</td>
<td>875 ± 80</td>
</tr>
<tr>
<td>Standing</td>
<td>659 ± 75‡</td>
<td>639 ± 82</td>
<td>633 ± 56</td>
<td>659 ± 83‡</td>
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</tbody>
</table>

Table 2  Changes in BP variability during pregnancy and after standing
Data are median (range). VLF component, 0.02–0.05 Hz; LF component, 0.05–0.15 Hz; HF component, 0.15–0.4 Hz. See the text for definition of time periods T1–T3 and PP. Absolute values are given in units of mmHg^2. Normalized values are a percentage of total variability. Statistical significance: *P < 0.05; **P < 0.01 compared with T1.

<table>
<thead>
<tr>
<th>BP variability</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>PP</th>
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<tbody>
<tr>
<td><strong>Total variability (mmHg^2)</strong></td>
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<tr>
<td>Supine</td>
<td>24.5 (7.8, 48.1)</td>
<td>31.3 (15.0, 68.4)</td>
<td>44.0 (15.3, 99.1)**</td>
<td>29.8 (3.4, 44.9)</td>
</tr>
<tr>
<td>Standing</td>
<td>28.8 (14.3, 56.7)</td>
<td>36.5 (16.0, 86.2)</td>
<td>37.6 (23.9, 83.2)</td>
<td>43.8 (14.8, 104.3)</td>
</tr>
<tr>
<td><strong>Absolute VLF (mmHg^2)</strong></td>
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<tr>
<td>Supine</td>
<td>9.1 (1.7, 18.6)</td>
<td>12.5 (3.6, 27.7)</td>
<td>15.0 (4.0, 26.7)**</td>
<td>11.2 (0.6, 20.5)</td>
</tr>
<tr>
<td>Standing</td>
<td>10.1 (2.8, 21.4)</td>
<td>10.1 (3.9, 34.1)</td>
<td>11.4 (5.9, 27.3)</td>
<td>11.0 (4.4, 35.6)</td>
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<tr>
<td><strong>Absolute LF (mmHg^2)</strong></td>
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<tr>
<td>Supine</td>
<td>5.1 (1.2, 13.7)</td>
<td>5.9 (2.5, 16.2)</td>
<td>8.1 (3.0, 21.1)*</td>
<td>6.0 (0.8, 9.7)</td>
</tr>
<tr>
<td>Standing</td>
<td>8.4 (3.9, 21.4)</td>
<td>11.0 (3.9, 34.6)</td>
<td>10.4 (7.2, 34.5)</td>
<td>14.0 (5.4, 58.6)</td>
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<tr>
<td><strong>Absolute HF (mmHg^2)</strong></td>
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<tr>
<td>Supine</td>
<td>1.6 (0.6, 2.8)</td>
<td>1.2 (0.2, 2.9)</td>
<td>1.3 (0.3, 8.6)</td>
<td>0.9 (0.2, 2.5)</td>
</tr>
<tr>
<td>Standing</td>
<td>3.0 (1.2, 7.6)</td>
<td>2.5 (1.1, 6.7)</td>
<td>2.7 (1.1, 9.2)</td>
<td>2.4 (1.1, 5.0)</td>
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<tr>
<td><strong>Normalized LF (%)</strong></td>
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<tr>
<td>Supine</td>
<td>39.3 (7.4, 56.1)</td>
<td>35.6 (15.3, 59.1)</td>
<td>34.9 (20.9, 49.6)</td>
<td>30.0 (11.5, 49.3)</td>
</tr>
<tr>
<td>Standing</td>
<td>43.1 (24.4, 71.3)</td>
<td>45.5 (31.5, 68.5)</td>
<td>46.0 (28.0, 61.6)</td>
<td>54.4 (36.5, 72.9)</td>
</tr>
<tr>
<td><strong>Normalized HF (%)</strong></td>
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</tr>
<tr>
<td>Supine</td>
<td>10.8 (2.0, 36.6)</td>
<td>5.7 (1.1, 19.5)</td>
<td>4.9 (1.2, 19.7)</td>
<td>5.4 (1.4, 33.2)</td>
</tr>
<tr>
<td>Standing</td>
<td>16.9 (3.9, 36.8)</td>
<td>13.6 (4.0, 27.3)</td>
<td>12.8 (4.7, 18.8)</td>
<td>8.6 (3.8, 27.1)**</td>
</tr>
</tbody>
</table>

When normalized PI values were calculated, there were no significant changes with time in supine normalized LF or HF variability, but both standing normalized LF and HF values did alter significantly [normalized LF, P < 0.05; normalized HF, P < 0.01; Table 3]. Standing normalized LF variability decreased by 44% (CI 26%, 58%) between T1 and T3 (P < 0.001), and standing normalized HF variability decreased by 46% (CI 27%, 40%) between T1 and PP (P < 0.001; Table 3).

Standing values for HF and normalized HF variability were lower, and those for normalized LF variability were higher, than supine values at T1 and PP for the pregnancy group (all P < 0.001), with similar orthostatic changes being seen in the control group.

Changes in BRS
Supine BRS values changed significantly during pregnancy (P < 0.001), falling by 50% (CI 33%, 63%)
between T1 and T3 (P < 0.001) and returning to early-gestation levels in the post-partum period (Table 4).

Standing BRS levels did not change throughout pregnancy, and were similar to those for the non-pregnant controls (Table 4). Standing BRS values at T1 and PP were significantly lower than supine values (P < 0.001), with similar orthostatic differences in BRS seen in the controls (P < 0.001). There were no significant differences in supine or standing BRS values between post-partum values and those of the control group.
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Figure 2  PI variability during pregnancy
Vertical axes are log scales. Vertical bars represent ± 1 S.E.M.

Table 4  Changes in BRS during pregnancy and after standing
Data are median (range). Statistical significance: ** P < 0.01 compared with T1; ‡P < 0.05 supine compared with standing.

<table>
<thead>
<tr>
<th></th>
<th>BRS (ms/mmHg)</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>PP</th>
<th>MANOVA Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total BRS</td>
<td>Supine</td>
<td>19.5 (10.0, 34.1)</td>
<td>9.6 (5.9, 25.1)</td>
<td>9.1 (6.4, 16.8)**</td>
<td>19.2 (8.9, 38.9)</td>
<td>&lt; 0.01 19.4 (11.0, 30.2)</td>
</tr>
<tr>
<td></td>
<td>Standing</td>
<td>6.2 (4.1, 11.3)‡</td>
<td>6.7 (2.5, 11.3)</td>
<td>7.1 (4.7, 13.8)</td>
<td>7.0 (4.0, 9.7)‡</td>
<td>0.558.0 (5.2, 11.6)‡</td>
</tr>
<tr>
<td>BRS LF</td>
<td>Supine</td>
<td>11.6 (5.7, 33.2)</td>
<td>6.4 (4.5, 20.6)</td>
<td>6.6 (4.1, 15.5)**</td>
<td>12.9 (4.3, 29.9)</td>
<td>&lt; 0.01 14.1 (6.5, 20.3)</td>
</tr>
<tr>
<td></td>
<td>Standing</td>
<td>7.1 (3.0, 14.2)‡</td>
<td>6.5 (2.9, 12.1)</td>
<td>6.3 (2.9, 10.3)</td>
<td>7.6 (4.6, 8.8)‡</td>
<td>0.30 7.8 (5.2, 12.2)‡</td>
</tr>
<tr>
<td>BRS HF</td>
<td>Supine</td>
<td>22.5 (11.1, 53.4)</td>
<td>12.8 (6.3, 32.0)</td>
<td>11.5 (5.7, 22.2)**</td>
<td>26.6 (13.5, 58.2)</td>
<td>&lt; 0.01 24.9 (12.1, 40.1)</td>
</tr>
<tr>
<td></td>
<td>Standing</td>
<td>5.7 (3.8, 9.5)‡</td>
<td>7.5 (2.0, 10.6)</td>
<td>8.5 (4.8, 17.3)**</td>
<td>5.9 (3.4, 10.7)‡</td>
<td>&lt; 0.01 7.8 (3.2, 11.1)‡</td>
</tr>
</tbody>
</table>

LF/HF PI ratio
The PI power LF/HF ratio was used as a surrogate marker of sympathovagal balance. This changed significantly during pregnancy in both the supine and standing positions (supine, P < 0.05; standing, P < 0.001; Table 3).

From T1 to T3 the supine LF/HF ratio increased by 137% (CI 42%, 296%) (P < 0.05), returning to early-pregnancy levels in the post-partum period. If the normalized LF and HF bandwidths were examined, the increase in the supine LF/HF ratio was found to be due to a decrease in HF power rather than to an increase in LF power (Table 3). The changes in standing LF/HF ratio showed a marked increase of 108% (CI 50%, 189%) (P < 0.001) between T1 and PP, which resulted mainly from a decrease in HF power. There was no significant difference in supine or standing LF/HF ratios between controls and post-partum values for the pregnancy group.

DISCUSSION
The changes in supine BP and PI seen during normal pregnancy in the present study are consistent with changes recorded by others, with both SBP and DBP tending to fall in early pregnancy, reach a nadir in the second trimester and return towards pre-pregnancy levels at term [30–33]. MacGillivray et al. [33] noted that BPs observed at 6 weeks post partum were equivalent to pre-pregnancy BP levels, but in our study post-partum standing DBP was significantly lower than control values, suggesting that the time span for cardiovascular responses to return to their pre-conception level may be longer than 6 weeks. The increase in heart rate during pregnancy is also well documented [34], and this was confirmed for the supine position, but not the standing position, in the present study.

Cardiovascular responses to orthostatic stress are mediated by both the arterial baroreceptor and the cardiopulmonary reflex arcs [35]. Our results confirm that orthostatic BP tolerance is maintained during pregnancy, with orthostatic increases in SBP and DBP of similar magnitude to those reported by Redman et al. [36]. The post-partum orthostatic changes and the values recorded in the control group are also in keeping with those found by others [37,38] using similar methodology. Although the present study demonstrated an increase in heart rate on standing at all gestational time points, the change was less pronounced in late pregnancy; this is in accordance with other work which has shown that sequential responses to standing at different periods of
pregnancy are clearly different, with progressive attenuation of heart rate responses as gestation advances [4,14,39].

The significant fall in supine HF PI variability seen as pregnancy progressed was associated with an increase in heart rate; this has been noted previously [21] and is suggestive of a decrease in vagal tone in advanced pregnancy. Ekholm et al. [4], in a longitudinal study of autonomic cardiovascular responses in pregnancy, were able to demonstrate a significant decrease in parasympathetic responsiveness in early and mid-pregnancy, but with some restoration in the third trimester. The same group also employed the technique of spectral analysis to evaluate changes in autonomic cardiovascular control in a cross-sectional study during mid-pregnancy, and clearly demonstrated diminished heart rate variability, suggesting either a decrease in parasympathetic tone or an increase in sympathetic nervous system activity. The former would seem more likely, since Airaksinen et al. [40] showed that the heart rate response to deep breathing, an index of cardiac parasympathetic efferent activity, was progressively diminished during normal and diabetic pregnancy. The decrease in standing normalized LF PI variability in late pregnancy compared with early gestation is suggestive of a decrease in cardiac sympathetic tone during late pregnancy. Nisell and co-workers [39] measured arterial noradrenaline levels in pregnant women during late pregnancy and post partum, and found that tilting induced smaller increases in noradrenaline levels during pregnancy than post partum. The significant change seen in normalized HF PI variability in our study, with a trend towards a fall as pregnancy progressed, could be suggestive of vagal tone withdrawal. These changes in HF PI variability could also be explained by stretch of the sino−atrial node associated with the volume expansion seen in pregnancy, since Horner et al. [41] have demonstrated similar changes in HF PI variability with mechanical stretch of the sino−atrial node in an animal model. However, it is unlikely that this fully explains the changes in PI variability seen, as the volume expansion associated with pregnancy would have occurred by about 20 weeks, with little further change until very late pregnancy [42]. Hence the changes in PI variability that we demonstrated between T1 and T3 occurred when the intravascular volume, although expanded compared with the post-partum and control states, was relatively static.

The increase in mean total supine BP variability observed as pregnancy progressed reverted to non-pregnant control values in the post-partum period, as did the changes in supine HF PI variability, suggesting that, if these changes are related to autonomic nervous control, this reverts to the non-pregnant state by about 6 weeks post partum. The significant increase in absolute supine LF BP power between early and late pregnancy and its fall in the post-partum period may suggest an increase in sympathetic vasomotor tone during pregnancy, as others have proposed [43].

The increase in supine BP and decrease in PI variability, especially in the HF band, seen as pregnancy progressed is consistent with the observed fall in supine baroreceptor control of heart rate demonstrated in the present study, although the exact mechanisms for these changes are unclear. They cannot be accounted for by essential or pregnancy-induced hypertension, a family history of hypertension (in view of the reversible nature of the changes demonstrated) or other factors, such as exercise or diabetes, that are known to be associated with decreased BRS activity. Central or peripheral BRS resetting could occur independent of BP changes, due to neurohumoral and paracrine factors associated with pregnancy. Increased systemic levels of angiotensin II are found during normal pregnancy, and it has been shown that angiotensin II can inhibit peripheral cardiac vagal activity [44,45] and also may have a selective effect on the arterial baroreflex via central nervous system mechanisms [46].

We have used surrogate markers of changes in sympathetic and vagal tone during pregnancy to assess changes in cardiovascular responses, but the latter are also heavily influenced by increased blood volume, decreased peripheral vascular resistance and hormonal changes that occur during pregnancy. Multi- and single-unit muscle sympathetic nerve activity provides a more accurate assessment of sympathetic activity, and recent work has demonstrated greater resting sympathetic output in women with pregnancy-induced hypertension than in those with normal pregnancies [47,48].

Several studies have shown that respiratory rate and tidal volume exert major influences on PI fluctuations [49,50], which could have significant effects on PI variability if this is to be used as a surrogate measure of sympathovagal balance. Tidal volume and pulmonary ventilation at rest increase during pregnancy, but respiratory rate remains unchanged [51]. Therefore changes in respiratory pattern should increase rather than decrease HF PI variability, and this will not explain the lower HF PI variability observed. Although all our subjects maintained a respiratory rate of between 13 and 15 breaths/min to minimize any potential changes due to respiration in the HF spectral band, the spectral power of respiration in relation to the cardiovascular changes seen was not analysed. Some subjects may have had to increase their usual respiratory rate to meet these criteria, and hence the changes demonstrated in the LF and HF PI variability may have resulted from changes in autonomic function associated with this manoeuvre. However, increasing the respiratory rate from 10 to 15 to 20 breaths/min has been shown to have no effect on LF or HF PI or BP variability [52].

Limitations of the present study include the absence of pre-conception data, since it is unclear how early in
pregnancy changes in autonomic cardiovascular control may occur. Similarly, the correct time to make post-partum measurements is unclear, since autonomic changes may persist long after the conventional 6-week post-partum period and may also be influenced by factors such as lactation. The study was not able to extensively investigate the underlying mechanisms influencing BP and PI variability during pregnancy, and specific studies are required to study volume and autonomic nervous changes in relation to our findings.

In conclusion, we have shown that supine normotensive pregnant women demonstrate a decrease in BRS for heart rate with advancing gestation, and that this appears to be related to a withdrawal of vagal tone, rather than an increase in sympathetic tone. These changes are reversed in the post-partum period. Further studies are now needed to see if changes in BRS can be used as early indicators of the development of pregnancy-induced hypertension.

REFERENCES


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