Biphasic changes in autonomic nervous activity during pregnancy

C.-D. Kuo1 2*, G.-Y. Chen2 3, M.-J. Yang4, H.-M. Lo3 and Y.-S. Tsai5

1Cardiopulmonary Laboratory, Respiratory Therapy Department and 4Department of Obstetrics and Gynaecology, Veterans General Hospital-Taipei, Taipei, Taiwan, Republic of China. 2Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, Republic of China. 3Department of Medicine, Tao-Yuan General Hospital, Tao-Yuan, Taiwan, Republic of China. 5Department of Biomedical Engineering, Chung-Yuan Christian University, Chung-Li, Taiwan, Republic of China

*Corresponding author: Cardiopulmonary Laboratory, Respiratory Therapy Department, Veterans General Hospital-Taipei, Taipei, Taiwan 112, Republic of China

To understand the sequential response of the autonomic nervous system to pregnancy, we studied heart rate variability in 23 first trimester, 23 second trimester and 21 third trimester pregnant women. Twenty non-pregnant women were recruited as controls. Time and frequency domain measures of heart rate variability in three recumbent positions were compared. We found that normalized high-frequency power in the supine position increased significantly in the first trimester (42.2 (95% confidence interval (CI) 5.4) nu (normalized unit); P<0.05) compared with non-pregnant controls (33.0 (6.0) nu), and then decreased progressively in the second (27.3 (6.7) nu) and third (21.8 (6.0) nu; P<0.05) trimesters. The low-/high-frequency power ratio in the supine position decreased significantly in the first trimester (0.8 (0.3); P<0.05) compared with that of non-pregnant controls (1.1 (0.3)) and increased progressively in the second (1.5 (0.4)) and third (2.1 (0.8); P<0.05) trimesters. When the position was changed from the supine to the right lateral decubitus, the percentage change in normalized high-frequency power correlated significantly and negatively with normalized high-frequency power in the supine position in non-pregnant controls (r=-0.56, P=0.01) and in pregnant women in the first (r=-0.44, P=0.034), second (r=-0.68, P<0.001) and third (r=-0.68, P<0.001) trimesters. These results indicate that autonomic nervous activity shifted towards a lower sympathetic and higher vagal modulation in the first trimester, and changed towards a higher sympathetic and lower vagal modulation in the third trimester as gestational age increased. The balance between the haemodynamic changes of pregnancy and aortocaval compression caused by the enlarging gravid uterus may be responsible for the biphasic changes in autonomic nervous activity during pregnancy.

Br J Anaesth 2000; 84: 323–9

Keywords: heart, heart rate; parasympathetic nervous system; sympathetic nervous system; cardiovascular system, effects; pregnancy

Accepted for publication: November 1, 1999

Pregnancy is associated with substantial changes in the cardiovascular system. It has been noted that blood volume, cardiac output and stroke volume begin to change after the first trimester to accommodate the growing fetus.12 Systemic vascular resistance is also decreased in response to haemodynamic changes.3–5 As pregnancy advances, aortocaval compression from the gravid uterus gradually becomes evident, which may cause supine hypotensive syndrome in late pregnancy.6

In previous reports, decreased heart rate variability has been demonstrated during pregnancy, but there was no consensus as to the changes in autonomic nervous activity.7–11 Inadequate stratification of gestational stages might be the main cause of this discrepancy. In a previous study, we found that autonomic nervous activity was shifted to lower vagal and higher sympathetic modulation in late pregnancy.12 Aortocaval compression was suggested to be the main factor responsible for this change. This theory was supported by observations that moving to an upright position could lead to lessening of sympathetic activation13 and that delivery of the fetus led to return to normal autonomic nervous activity within 3 months.14

During the early stages of pregnancy, autonomic nervous activity may be expected to vary little from that of the non-pregnant woman because aortocaval compression is absent. However, haemodynamic studies during pregnancy suggest

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000
that autonomic nervous activity in the early stages of pregnancy is in fact different from the pre-pregnant state. As the autonomic nervous system plays an important role in adaptation of the maternal body to nurturing the fetus, it is important to understand the sequential changes in the autonomic nervous activity at various stages of pregnancy. Therefore, in this study, we have investigated the sequential changes in autonomic nervous activity during the three trimesters of pregnancy and between pregnant women in different trimesters and non-pregnant women.

**Subjects and methods**

This study was approved by the Hospital Committee for Human Investigation and informed consent was obtained from each subject before electrocardiographic recording. All pregnant women had a singleton vertex fetus with no obstetric or medical complications. They were advised to report symptoms of cardiovascular distress during the study, especially if they were supine. All women presented for study at the same time of day (14:00–16:00 after a light lunch at noon) to avoid the effects of circadian rhythms on heart rate variability. Those who drank any alcohol, were smokers, had any medical illness or who were receiving any medication were excluded.

The procedure for electrocardiographic recording and heart rate variability analysis was similar to our previous study. All subjects were instructed not to drink caffeinated beverages for at least 24 h before electrocardiographic recording. Three recumbent positions were assumed in random order by the subjects (supine, left lateral decubitus and right lateral decubitus). After 5 min rest in each position, a continuous analogue signal of lead II of the electrocardiogram was recorded over 15 min by the bedside electrocardiographic monitor (Model 90621A, Spacelabs Inc., Redmond, WA, USA) and transmitted to a personal computer for recording. If there was any sign or symptom of intolerance to the supine position such as restlessness, breathlessness, pallor, dizziness or faintness, the electrocardiographic recording was discontinued and the position of the pregnant woman was changed from supine to upright or lateral tilt.

As $2^m$ elements of data are needed by the fast Fourier transformation algorithm where $m$ is an integer, and as a short-term recording of several minutes is needed for analysis of both sympathetic and vagal nervous systems, the last stationary 512 RR intervals were used for calculation of the power spectrum by fast Fourier transformation (Mathcad, Mathsoft Inc., Cambridge, MA, USA). The direct current component was excluded before calculation of the power spectra. The area under the spectral peaks within the frequency range 0.01–0.4 Hz was defined as total power, the area under the spectral peaks within the range 0.04–0.15 Hz as low-frequency power and the area under the spectral peaks within the range 0.15–0.4 Hz as high-frequency power. Normalized high-frequency power (high-frequency power/total power) was used as an index of vagal modulation, normalized low-frequency power (low-frequency power/total power) as an index of sympathetic and vagal modulation and the low-/high-frequency power ratio as an index of sympathovagal balance. The mean, sd and coefficient of variation of the same 512 RR intervals were calculated using standard formulae.

To assess the effect on normalized high-frequency power of changing position from supine to lateral decubitus, we defined $nHFPR_{RS}$ and $nHFPL_{LS}$ according to the formulæ:

$$nHFPR_{RS} = 100\% \times \frac{nHFPR - nHFPS}{nHFPS}$$

$$nHFPL_{LS} = 100\% \times \frac{nHFPL - nHFPS}{nHFPS}$$

where $nHFPS$ = normalized high-frequency power in the supine position; $nHFPR$ = normalized high-frequency power in the right lateral decubitus position; $nHFPL$ = normalized high-frequency power in the left lateral decubitus position; and $nHFPR_{RS}$ and $nHFPL_{LS}$ = percentage changes in normalized high-frequency power when the position was changed from supine to right and left lateral decubitus positions, respectively. In the same manner, $nLFP_{RS}$, $nLFP_{LS}$, $LFP/HFPR_{RS}$ and $LFP/HFPL_{LS}$ were defined for assessment of the effect on normalized low-frequency power or low-/high-frequency power ratio of changing position from the supine to right or left lateral decubitus position.

Values of heart rate variability measures in both time and frequency domains are presented as mean (95% confidence interval (CI)). Analysis of variance on ranks (SigmaStat statistical software, Jandel Scientific, San Rafael, CA, USA) was used to compare measures of heart rate variability during different trimesters of pregnancy. Significant differences were analysed further by pairwise comparison using Dunn’s test. A Mann–Whitney rank sum test or unpaired t-test was used to compare measures of heart rate variability between pregnant women in different trimesters and non-pregnant women. Repeated measures analysis of variance on ranks was used to compare measures of heart rate variability in the three recumbent positions. The correlation between $nHFPR_{RS}$ (or $nHFPL_{LS}$) and $nHFPS$ was assessed by linear regression analysis in non-pregnant controls and pregnant women in different trimesters. $P<0.05$ was considered statistically significant.

We assumed that the expected difference in mean normalized high-frequency power was 10 normalized units (nu) and the expected $sd$ was 10 nu. Using an alpha level of 5%, a power of 80% and assuming 8% of subjects would be excluded from the final analysis because of intolerance caused by the supine hypotensive syndrome, we calculated that a sample of 20 patients would be required.

**Results**

Twenty-three pregnant women in the first, 23 in the second and 23 in the third trimesters, and 20 healthy age-matched
non-pregnant women were recruited to this cross-sectional study. Two pregnant women in the third trimester felt faint when they lay in the supine position. Therefore, 23 first trimester, 23 second trimester and 21 out of 23 third trimester pregnant women were included for data analysis. The age of the non-pregnant women and pregnant women did not differ significantly (Table 1).

Figure 1 shows representative power spectra of a non-pregnant woman and three pregnant women in the different trimesters of pregnancy in three recumbent positions. The power spectra of the pregnant women had a greater spectral density in the first trimester and a gradually decreased power spectral density in the second and third trimesters in all frequency ranges in the three recumbent positions. After normalization, the normalized high-frequency power in the first trimester was higher than that of non-pregnant controls, while the low-/high-frequency power ratio was lower than that of non-pregnant controls in the three recumbent positions. In the second and third trimesters, normalized high-frequency power decreased. The low-/high-frequency power ratio increased gradually as gestational age increased in the three recumbent positions.

Table 1 shows heart rate variability measures in the three recumbent positions in the non-pregnant women and in pregnant women in the three trimesters of pregnancy. In the time domain, mean RR interval in the three recumbent positions decreased progressively when gestational age increased. Mean RR interval in the second and third trimesters was significantly lower than that of non-pregnant controls in all recumbent positions. The SD and coefficient of variation of the RR intervals in the three recumbent positions also decreased progressively as gestational age increased. The SD of the RR intervals in the second and third trimesters was significantly lower than that of non-pregnant controls in both lateral decubitus positions. The coefficient of variation of the RR intervals in the third trimester in the right lateral decubitus position was significantly lower than that of non-pregnant controls.

In the frequency domain, total power and low-frequency power of the pregnant women in the three recumbent positions decreased progressively as gestational age increased. The SD of the RR intervals in the non-pregnant controls in both lateral decubitus positions. The coefficient of variation of the RR intervals in the third trimester in the right lateral decubitus position was significantly lower than that of non-pregnant controls.
positions decreased progressively as gestational age increased. Total power, high-frequency power and low-frequency power in the second and third trimesters were lower than those of non-pregnant controls in the three recumbent positions. The high-frequency power and normalized high-frequency power in the pregnant women increased in the first trimester compared with non-pregnant women, and then decreased progressively in the second and third trimesters. Similarly, normalized low-frequency power and the low-/high-frequency power ratio decreased in the first trimester compared with non-pregnant women, and then increased progressively in the second and third trimesters. In the supine position, normalized high-frequency power was significantly higher and low-/high-frequency power was significantly lower in the first trimester than in non-pregnant controls.

Table 2 shows the effect of position on autonomic nervous activity in pregnant women in different trimesters compared with non-pregnant women. The percentage change in normalized high-frequency power and the low-/high-frequency power ratio when the position was changed from the supine to the right or left lateral decubitus position in the first trimester was smaller than in non-pregnant controls.

When the position was changed from supine to right lateral decubitus, nHFP_{R/S} correlated significantly and negatively with nHFP_S in both non-pregnant controls and pregnant women in the three trimesters of pregnancy (left panel, Fig. 2). The slope of the regression between nHFP_{R/S} and nHFP_S decreased in the first trimester compared with non-pregnant women, and then increased progressively in the second and third trimesters of pregnancy, and the slope in the third trimester was greater than that in the second trimester (right panel, Fig. 2).

**Discussion**

Although investigators have found decreased heart rate variability during pregnancy, there was no consensus as to changes in autonomic nervous activity as pregnancy progressed. Vagal modulation was claimed to be increased, not changed or decreased, by different investigators compared with non-pregnant women. Inadequate stratification of gestational stages and insufficient numbers
Fig 2 Linear regression between nHFP_{R/S} (left panel, percentage change in normalized high-frequency power when the position was changed from supine to right lateral decubitus) or nHFP_{L/S} (right panel, percentage change in normalized high-frequency power when the position was changed from supine to left lateral decubitus) and nHFP_S (normalized high-frequency power in the supine position) in non-pregnant controls and pregnant women in the three trimesters.

Table 2 Percentage change in spectral heart rate variability measures in the three trimesters of pregnancy and in non-pregnant women when the position was changed from supine to lateral decubitus (mean (95% CI)). nHFP_{R/S} = percentage change in normalized high-frequency power when the position was changed from the supine to the right lateral decubitus; nHFP_{L/S} = percentage change in normalized low-frequency power when the position was changed from the supine to the left lateral decubitus; nLF_P_{R/S} = percentage change in normalized low-frequency power when the position was changed from the supine to the right lateral decubitus; nLF_P_{L/S} = percentage change in normalized low-frequency power when the position was changed from the supine to the left lateral decubitus; LFP/ HF_P_{R/S} = percentage change in low-/high-frequency power ratio when the position was changed from the supine to the right lateral decubitus; LFP/ HF_P_{L/S} = percentage change in low-/high-frequency power ratio when the position was changed from the supine to the left lateral decubitus.

<table>
<thead>
<tr>
<th></th>
<th>Non-pregnant</th>
<th>1st trimester</th>
<th>2nd trimester</th>
<th>3rd trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>nHFP_{R/S} (%)</td>
<td>49.5 (30.4)</td>
<td>23.5 (14.9)</td>
<td>76.4 (46.5)</td>
<td>64.4 (48.0)</td>
</tr>
<tr>
<td>nHFP_{L/S} (%)</td>
<td>32.0 (30.0)</td>
<td>14.3 (17.3)</td>
<td>77.9 (55.1)</td>
<td>86.2 (52.3)</td>
</tr>
<tr>
<td>nLF_P_{R/S} (%)</td>
<td>-7.5 (16.4)</td>
<td>-13.0 (12.2)</td>
<td>1.5 (20.2)</td>
<td>-0.7 (15.4)</td>
</tr>
<tr>
<td>nLF_P_{L/S} (%)</td>
<td>-7.3 (13.7)</td>
<td>0.1 (10.9)</td>
<td>12.9 (15.9)</td>
<td>9.3 (16.6)</td>
</tr>
<tr>
<td>LFP/HF_P_{R/S} (%)</td>
<td>-22.5 (28.2)</td>
<td>-19.5 (19.9)</td>
<td>-23.6 (20.7)</td>
<td>-14.8 (25.2)</td>
</tr>
<tr>
<td>LFP/HF_P_{L/S} (%)</td>
<td>-3.5 (35.8)</td>
<td>1.7 (21.9)</td>
<td>-9.1 (26.1)</td>
<td>-13.9 (25.3)</td>
</tr>
</tbody>
</table>

of patients might be the causes of these discrepancies. The response of the autonomic nervous system to haemodynamic changes and aortocaval compression which occurs during pregnancy may vary with the different stages of pregnancy.\(^1\)\(^-\)\(^6\) Thus, autonomic nervous activity should be studied separately in the different trimesters.

In this study, we demonstrated that autonomic nervous activity shifted to a higher vagal and lower sympathetic response of the autonomic nervous system to haemodynamic changes and aortocaval compression which occurs during the first trimester of pregnancy in the three recumbent positions, especially in the supine position. Several factors may be responsible for these changes. First, blood volume increases substantially during pregnancy,
starting as early as the sixth week of gestation and increasing rapidly until mid-pregnancy; thereafter it continues to increase but at a slower rate.1 This augmentation of blood volume may increase cardiac output early in pregnancy. Changes in blood volume and haemodynamics may reduce the workload of the heart and consequently shift the autonomic nervous system into a state of lower sympathetic and higher vagal modulation. Second, systemic arterial pressure begins to decrease during the first trimester and reaches a nadir in mid-pregnancy.2 The decline in systemic vascular resistance is probably caused by gestational hormones, increased concentrations of circulating prostaglandins, increased heat production by the developing fetus and development of a low-resistance circulation in the pregnant uterus.2–4 The decline in systemic vascular resistance may reduce the workload of the heart, leading to lower sympathetic and higher vagal modulation in the first trimester of pregnancy. Third, aortocaval compression is still negligible at this stage. Although the supine hypotensive syndrome may occur as early as the fifth month or when fetal movements are first perceived, it is not usually a problem until the eighth and ninth months of pregnancy.6,21 Finally, there may be psychological and mental factors that can influence autonomic nervous activity in the pregnant woman. As pregnancy is a joy to most women, the sense of happiness might manifest itself autonomically as increased vagal and decreased sympathetic modulation.

It has been demonstrated that higher vagal and lower sympathetic modulation can be induced by assuming the right or left lateral decubitus position in normal subjects compared with the supine position.22 A higher venous return and less workload in the right lateral decubitus position was suggested to be responsible for this autonomic nervous system response. If the vagal enhancing and sympathetic suppressing effect of pregnancy demonstrated in the first trimester of pregnancy were caused mainly by a higher venous return as a result of increased blood volume, and less workload caused by decreased vascular resistance, the beneficial effect of the right lateral decubitus position in the first trimester should be less prominent than in non-pregnant women. Venous return has already increased and the workload of the heart has already decreased in the first trimester of pregnancy. This saturation effect may also be the reason why autonomic nervous activity in the first trimester was significantly different from that of non-pregnant controls in the supine position, but not in the right or left lateral decubitus position. The finding that the slope of the regression between nHFP_{RS} and nHFP_{S} in the first trimester was smaller than in non-pregnant women could also be attributed to this saturation effect.

In the second trimester of pregnancy, although absolute powers of spectral heart rate variability decreased, the relative powers of spectral heart rate variability were not significantly different from that of non-pregnant controls. This could be explained by the beneficial effect of pregnancy on the autonomic nervous system in the first trimester being balanced by aortocaval compression caused by the progressively enlarging gravid uterus in the second trimester. As gestational age increases further, aortocaval compression caused by the enlarging gravid uterus further compromises venous return and cardiac output, leading to a shift in autonomic nervous activity towards an even higher sympathetic and lower vagal modulation in the third trimester of pregnancy. Similar trends in absolute powers of spectral heart rate variability were found in the study of Eneroth-Grimfors and colleagues10; however, normalized spectral powers and low-/high-frequency power ratios were not provided in their study.

The finding that nHFP_{RS} and nHFP_{LS} correlated negatively with nHFP_{S} suggests that those who have higher sympathetic and lower vagal modulation in the supine position may benefit from assuming lateral decubitus positions, especially in the second and third trimesters. The relief of aortocaval compression by assuming lateral decubitus positions may be responsible for the largest slope being the regression between nHFP_{RS} or nHFP_{LS} and nHFP_{S} in the third trimester.

In summary, we found biphasic changes in autonomic nervous activity during pregnancy. It was shifted significantly to a lower sympathetic and higher vagal activity in the first trimester of pregnancy and then to a higher sympathetic and lower vagal activity in the third trimester. The balance between the haemodynamic changes of pregnancy and aortocaval compression caused by the progressively enlarging gravid uterus may be responsible for these biphasic changes.

Acknowledgements
This work was supported by project VGHTH87-08-1 of the VGH-NTHU Joint Research Program and a research fund from Tao-Yuan General Hospital, Taiwan, Republic of China.

References
8 Ekholm EMK, Hartila J, Huikuri HV. Circadian rhythm of