Blood pressure and heart rate variability in early pregnancy in rats

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Slangen, Brigitte F. M., Iris C. M. Out, Ben J. A. Janssen, and Louis L. H. Peeters. Blood pressure and heart rate variability in early pregnancy in rats. Am. J. Physiol. 273 (Heart Circ. Physiol. 42): H1794–H1799, 1997.—Changes in the autonomic control of the circulation may contribute to the maternal hemodynamic adaptation to early pregnancy. To evaluate this, we studied mean arterial pressure (MAP) and heart rate (HR) in chronically instrumented, conscious rats in early (days 4, 6, 8, and 10) and late (day 18) pregnancy (n = 8) and in nonpregnant rats (n = 9). MAP and HR were recorded on a beat-to-beat basis and analyzed by spectral analysis. Spectral density power was calculated in low- (0.047–0.305 Hz), mid- (0.305–0.598 Hz), and high-frequency (0.598–1.494 Hz) bands, which contain oscillations that are among others related to myogenic-, sympathetic/vagal-, and vagal/respiration-related influences, respectively. In addition, baroreceptor reflex sensitivity was determined from spontaneous variations in MAP and HR by a sequential time series method and by calculating the transfer gain between MAP and HR in the midfrequency band. Mean values of HR and MAP did not differ between the two groups on day 4. In the pregnant group, MAP fell gradually over days, whereas HR had significantly increased only on day 18. Overall variability in MAP and HR (expressed as coefficients of variation) did not change during pregnancy. Baroreceptor reflex sensitivity did not differ between the groups and did not change with advancing pregnancy. Spontaneous oscillations of MAP and HR at low, mid, and high frequencies were not different between pregnant and nonpregnant rats on days 4 to 10. On day 18, spectral density power of MAP, but not of HR, in the high-frequency band had significantly increased in pregnant rats only, most likely reflecting the increased impact of breathing on MAP fluctuations. We conclude that, with the methods employed, we could not discern any changes in baroreflex sensitivity and MAP and HR variability in pregnancy. This would imply that changes in autonomic activity do not contribute appreciably to the hemodynamic adaptations in early rat pregnancy.

autonomic nervous system; baroreflex; spectral analysis; mean arterial pressure variability

HEMODYNAMIC ADAPTATION to early human as well as early rat pregnancy is characterized by a fall in blood pressure and total peripheral resistance, together with a rise in cardiac output and stroke volume (10, 29). This high-flow, low-resistance circulation is accompanied by an elevated plasma renin activity (6, 10), suggesting that early pregnancy hemodynamics may be associated with a relative vascular underfill (28). However, in the rat, this relative vascular underfill does not trigger a rise in heart rate (HR), although cardiac contractility increases (3). This finding suggests that reflex regulation of HR changes during early pregnancy. Studies on baroreceptor reflex function and autonomic tone in pregnancy have revealed contradictory results. In human pregnancy, neither catecholamine levels nor HR variability have changed (1, 14), suggesting an unaltered sympathoadrenal function. On the other hand, autonomic function tests indicate a decreased parasympathetic responsiveness (12, 13). An increase in baroreflex-mediated bradycardia in rat (7) and human pregnancy (23) as well as unchanged baroreflex control in rat pregnancy (8, 16) have been reported. These discrepancies might be due to differences in methodology using autonomic function tests or pharmacological interventions (7, 8, 12, 13, 16, 23). In addition, most studies focused on late pregnancy (11, 12, 14, 23) or at the end of the first trimester (13), when most of the hemodynamic adaptations are already fully developed (10).

Recently, methods have been developed to assess autonomic influences and the cardiac baroreflex gain from computer analysis of spontaneously occurring changes in arterial blood pressure and HR (2, 5, 24). These methods are attractive, because they provide information about cardiovascular control without pharmacological or mechanical manipulation of the baroreflex and the autonomic nervous system. Spectral analysis of beat-to-beat fluctuations in HR and mean arterial pressure (MAP) may provide insight into the sympathetic and parasympathetic influences on the cardiovascular system (30). Generally, two or more different frequency bands are identified. In conscious, unrestrained rats, it was demonstrated that spectral power of MAP in midfrequencies (0.27–0.74 Hz) depends primarily on the activity of sympathetic nerve fibers. The baroreflex accounts for ~50% of this power (4, 22). The spectral power of HR in midfrequencies seems to be determined by vagal rather than sympathetic influences (25). Efferent vagal influences are responsible for a fraction of the high-frequency (0.75–3 Hz) power of MAP and HR, but a large part of these fluctuations are due to the mechanical impact of breathing (4, 21, 25). Low-frequency (0.08–0.18 Hz) oscillations of MAP result primarily from vasomotion (21, 22, 26).

Baroreceptor reflex sensitivity can be determined from spontaneous variations in MAP and HR by a sequential time series method (2, 20, 24) or by calculating the transfer gain between MAP and HR in defined frequency ranges (4, 15, 27).

Using the aforementioned techniques, we evaluated whether changes in autonomic nervous activity or baroreceptor reflex sensitivity contribute to the hemodynamic adaptation in early pregnancy. To this end, we assessed HR and MAP on a beat-to-beat basis in chronically instrumented, conscious pregnant rats,
along with nine nonpregnant rats. Measurements were performed on days 4, 6, 8, 10, and 18 of pregnancy, because the majority of the hemodynamic adaptations in rat pregnancy take place between days 4 and 10 of pregnancy (29). In addition, day 18 of pregnancy was included, because HR increases in late pregnancy (29).

MATERIALS AND METHODS

Surgical Procedures

Seventeen female Wistar rats (Winkelmann, Borchen, Germany) were studied at the age of 3–4 mo. All procedures were approved by the Institutional Animal Care and Use Committee of the University of Limburg, Maastricht. Rats were kept on a 12:12-h light-dark cycle. Rats were mated with a male, and presence of a sperm plug was defined as day 1 of pregnancy. On this day, surgery was performed aseptically. With the rat under ketamine (40 mg/kg) and xylazine (4 mg/kg) anesthesia, a polyethylene catheter (0.28 mm ID, 0.61 mm OD) was advanced into the abdominal aorta via the femoral artery, as described previously (29). The catheter was exteriorized between the scapulae, filled with heparinized saline (5 IU/ml), and plugged with a stainless steel pin.

Data Acquisition and Analysis

Measurements were performed on days 4, 6, 8, 10, and 18 or 19 of pregnancy (n = 8) and in a nonpregnant group (n = 9). On experimental days, the arterial catheter was connected to a pressure transducer (Statham). The signal was sampled continuously at 1,000 Hz, and beat-to-beat values were stored on disk for off-line analysis. Recordings were started after ~30 min, when the rat was resting quietly and stable tracings had been obtained for at least 15 min. Then data sampling was performed for a period of 20–30 min. The beat-to-beat registration of MAP and HR was replayed on screen for visual inspection. Data segments with artifacts due to obstruction of the arterial catheter were eliminated. We calculated mean (±SD) HR and MAP for the 20- to 30-min experimental period, as well as overall variability, expressed as the coefficients of variation (CV; standard deviation divided by mean times 100%).

Two pregnant and two nonpregnant rats could not be studied on day 18 postsurgery because of catheter failure.

Spectral Analysis

Spectral density power of the various frequency components of MAP and HR was calculated using a fast Fourier transformation (21). For this analysis technique equidistantly sampled data are required. Therefore, the beat-to-beat data points were converted into equidistant time series using an algorithm that extracted from sequential 200-ms time windows the maximum value of each parameter. The resulting (5 Hz) time series were divided into half-overlapping sequential sets of 512 data points. Before calculation of spectral density power, each segment was subjected to linear trend removal and cosine tapering of the first and last 60 data points. From sections of 512 values, the power and frequency of every spectral component was calculated (Fig. 1). Three frequency bands were defined, as indicated in Fig. 1. A low-frequency band (LF: 0.047 to 0.305 Hz) representing oscillations in MAP that primarily result from vasomotion (21, 22, 26), a midfrequency band (MF: 0.305–0.598 Hz) containing oscillations in MAP predominantly resulting from sympathetic influences (4, 22, 30) and oscillations in HR that may stem from parasympathetic influences (25), and a high-frequency band (HF: 0.598–1.494 Hz) containing oscillations in MAP that are associated with respiration (4, 21, 25).

Calculation of Baroreceptor Reflex Sensitivity

Time series method. Baroreceptor reflex sensitivity was determined from spontaneous fluctuations in MAP and HR using a time series method recently validated for rats (24). In short, beat-to-beat values of MAP and pulse interval (60,000/HR) were low-pass filtered using a 10-beat moving-average function. The filtered signal was searched for ramps of decreasing or increasing MAP of four beats or more. When a ramp was detected, MAP and HR were averaged over the 10 beats preceding and 10 beats following the ramp.

![Figure 1](http://ajpheart.physiology.org/)
ramp was found, then the slope between the MAP ramp and pulse interval change at delays of 3, 4, and 5 beats was determined. Baroreceptor reflex sensitivity was calculated as the average value of these three slopes.

Transfer function analysis. In addition, baroreceptor reflex sensitivity was calculated as the transfer gain between MAP and HR oscillations in the MF band (4, 15, 27). The basic assumption that underlies this approach is that the system linking MAP and HR responds linearly (15). In addition to the transfer gain, this analysis enables the calculation of two other parameters. The first is a coherence function, which provides an assessment of the linear relationship between MAP and HR at each frequency. Coherence can have a value between 0 and 1 and is a frequency-domain estimate of the degree that the HR variance can be explained by linear operation of the MAP variance. The coherence is 1 if no other variable than MAP affects the HR oscillations (4). The second parameter is a phase function, which represents the temporal relationship between the MAP and HR signals in the frequency domain. The phase value indicates the portion of the period corresponding to the frequency f, of which the output signal HR is delayed relative to the input signal MAP. A positive phase indicates that the HR oscillations at frequency f precede those of MAP. Finally, for each rat, the results obtained from these analysis techniques were averaged over the sequential data segments to reduce the variance.

Statistical Analysis

We used nonparametric analysis of variance for repeated measures (Friedman test) to assess whether significant changes occurred within each group. If so, Wilcoxon's signed rank test was used for specific between-period comparisons. Day 4 was selected as the reference day because the pregnant and nonpregnant groups were comparable on that day (Mann-Whitney U-test). Differences between the pregnant and nonpregnant groups were analyzed by Mann-Whitney U-test. Data are expressed as means ± SD, unless stated otherwise. Differences were considered significant when the P was <0.05.

RESULTS

Steady-State Values of Hemodynamic Parameters

Table 1 lists mean values of and overall variability in MAP and HR obtained during the 20- to 30-min recording sessions on the experimental days. Mean values of HR and MAP did not differ between the two groups on day 4. In the pregnant group, MAP decreased gradually from day 6 of pregnancy onward (from 125 ± 12 mmHg by day 4 to 101 ± 10 mmHg by day 18). HR had only increased in late pregnancy (from 373 ± 21 beats/min by day 4 to 408 ± 24 beats/min by day 18). In the nonpregnant group no significant changes were observed over time. The overall CV of MAP and HR remained unchanged throughout the experimental period in both groups.

Spectral Analysis

Average spectra of MAP and HR obtained in pregnant and nonpregnant rats are given in Fig. 2. In both groups, the spectral power of MAP was lowest in the HF, intermediate in the MF, and highest in the LF band. The LF and MF bands contained clear peaks centered at ~0.13 and ~0.45 Hz, respectively. Spectral power of HR was low in both the HF and MF bands. Most variability was observed in the LF band. No differences were observed between pregnant and nonpregnant rats, except for day 18. MAP spectra, but not HR spectra, obtained in 18-day pregnant rats showed increased power in the HF band. No changes were observed in the nonpregnant group.

Table 1. Hemodynamic values in pregnancy

<table>
<thead>
<tr>
<th></th>
<th>day 4</th>
<th>day 6</th>
<th>day 8</th>
<th>day 10</th>
<th>day 18</th>
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</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>P</td>
<td>373 ± 21</td>
<td>375 ± 9</td>
<td>377 ± 10</td>
<td>374 ± 16</td>
<td>408 ± 24*</td>
</tr>
<tr>
<td>NP</td>
<td>358 ± 21</td>
<td>369 ± 26</td>
<td>365 ± 21</td>
<td>359 ± 11</td>
<td>368 ± 25</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>125 ± 12</td>
<td>112 ± 28*</td>
<td>107 ± 9*</td>
<td>110 ± 7*†</td>
<td>101 ± 10†</td>
</tr>
<tr>
<td>NP</td>
<td>121 ± 8</td>
<td>112 ± 7</td>
<td>109 ± 3</td>
<td>113 ± 6</td>
<td>117 ± 7</td>
</tr>
<tr>
<td>CV of HR, %</td>
<td></td>
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<tr>
<td>P</td>
<td>4.1 ± 1.4</td>
<td>3.9 ± 1.2</td>
<td>4.2 ± 1.2</td>
<td>3.6 ± 0.5</td>
<td>3.2 ± 0.5</td>
</tr>
<tr>
<td>NP</td>
<td>4.6 ± 1.3</td>
<td>5.0 ± 2.0</td>
<td>3.7 ± 0.8</td>
<td>4.2 ± 1.4</td>
<td>4.4 ± 1.1</td>
</tr>
<tr>
<td>CV of MAP, %</td>
<td></td>
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<tr>
<td>P</td>
<td>3.7 ± 0.7</td>
<td>4.1 ± 0.9</td>
<td>3.8 ± 0.4</td>
<td>4.0 ± 0.4</td>
<td>3.8 ± 1.2</td>
</tr>
<tr>
<td>NP</td>
<td>3.6 ± 0.5</td>
<td>3.5 ± 0.5</td>
<td>3.3 ± 0.6</td>
<td>3.6 ± 1.0</td>
<td>3.7 ± 1.0</td>
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<tr>
<td>n</td>
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<td>8</td>
<td>8</td>
<td>8</td>
<td>6</td>
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<tr>
<td>NP</td>
<td>9</td>
<td>9</td>
<td>9</td>
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<td>7</td>
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</tbody>
</table>

Values are means ± SD; n, number of rats. HR, heart rate; MAP, mean arterial pressure; CV, coefficient of variation. Each variable was subjected to 2-way analysis of variance by ranks (Friedman test). Pregnant (P) group: P < 0.05 for HR; P < 0.01 for MAP. *P < 0.05 compared with day 4 by Wilcoxon's signed rank test. †P < 0.05 compared with nonpregnant (NP) rats by Mann-Whitney U-test.

Baroreceptor Reflex Sensitivity

Time series method. In pregnant rats (day 4 of pregnancy) the baroreceptor reflex sensitivity index, calculated from spontaneous fluctuations in pressure, was 0.49 ± 0.23 ms/mmHg and did not change during pregnancy. Values for nonpregnant rats changed little with time and were not different from the pregnant group (Table 2). These baroreceptor reflex sensitivity values are comparable to those previously reported for male Wistar-Kyoto rats (24).

Transfer gain. Average coherence, gain, and phase spectra are summarized in Table 2 and did not differ between groups. No changes were observed during pregnancy. Coherence between MAP and HR was >0.5 Hz in all frequency bands. Phase estimates were positive in all frequency bands, indicating that HR oscillations at these frequencies precede those of MAP.

DISCUSSION

The purpose of this study was to investigate whether autonomic control of MAP and HR, as assessed by their spontaneous variability, changes during early pregnancy in rats. Our results demonstrate that MAP and HR variability and baroreceptor reflex sensitivity do not change during early pregnancy in the rat. MAP has decreased by day 10 of pregnancy compared with that of the control group, whereas HR has increased by day 18 of pregnancy. These findings are in agreement with previous studies (7, 29). Overall variability (CV) of...
MAP and HR did not change with advancing pregnancy and was comparable in pregnant and nonpregnant rats. Also, the LF, MF, and HF components of MAP spectra did not change in early pregnancy. These results indicate unchanged vasomotion and sympathetic and respiratory influences on MAP during pregnancy, respectively. In addition, unchanged LF, MF, and HF components of HR spectra suggest that (para)sympathetic and respiratory influences on HR remain unaltered during pregnancy in rats, respectively. The only change observed in our study was an increase in the power of the HF band of the MAP spectrum on day 18 of pregnancy. Because MAP oscillations in this frequency band are mainly related to respiration (22, 25), we speculate that in our pregnant rats elevated intrathoracic pressure, caused by the rapidly growing conceptus in late pregnancy, may have magnified the impact of breathing on pressure oscillations. The breathing frequency did not change as evidenced by the fact that the HF band remained centered at ~1 Hz. This does not exclude the possibility that breathing excursions may have become more profound.

Our present findings in late-pregnant rats are in agreement with those of Barron et al. (1) in human pregnancies. Their observation of comparable catecholamine levels in late-pregnant and postpartum populations suggests that pregnancy does not alter sympathoadrenal function (1). However, hormone levels may not be conclusive, and interpretation of plasma catecholamine levels is complicated by methodological pitfalls in sample collection and measurement (17). In other studies in human pregnancy using cardiovascular autonomic function tests (12, 13) or spectral analysis of HR (11, 14), pregnancy seemed to be associated with a decreased parasympathetic responsiveness from the first trimester onward (13), persisting in the second trimester. Additionally, these studies observed an increased sympathetic activity during late pregnancy. The results of our study in rats are consistent with these findings in humans.
Baroreceptor reflex sensitivity in pregnancy (11–13), and returning to prepregnant levels in the third trimester (13, 14). It was suggested that the fall in parasympathetic tone accounted for the known variability. Thus our data in rats do not support a lower parasympathetic responsiveness of HR and add to the existing data that no changes can be observed in early pregnancy.

Baroreceptor reflex sensitivity determined by the time series method and by the transfer gain remained unaltered during pregnancy. In early pregnancy, basal MAP decreased while HR remained unchanged. This may reflect a leftward shift of the MAP-HR curve due to a downward resetting of the baroreflex. Only in late pregnancy had HR increased, however, without change in baroreceptor reflex sensitivity. Our results on the cardiac baroreflex in late pregnancy are in agreement with previous studies in late-pregnant rats (8, 16). Hines and Barron (16) demonstrated similar HR responses to increments in blood pressure after phentolamine administration in late-pregnant and virgin rats. It was also observed that sinoaortic denervation had similar effects on baseline blood pressure in pregnant and virgin rats (16). Others have also reported unchanged baroreflex sensitivity during late pregnancy in studies where isolated carotid sinus manipulation was employed to vary the reflex response (18, 19). In addition, we observed no changes in the cardiac baroreflex in early pregnancy when most of the hemodynamic changes develop. In contrast, other authors (7, 23) have reported an increase in baroreflex sensitivity to infusions of vasoactive agents in pregnant women at term and in late-pregnant rats. Reasons for the discrepancies regarding gestational effects on autonomic function and baroreflex sensitivity of HR are unclear but may relate to species difference, effects of anesthesia, variations in experimental design, and altered sensitivity to vasoactive agents. Our study was performed in chronically instrumented animals that were fully recovered from surgery, and we examined autonomic function in the basal, unstimulated state in the period in which most of the hemodynamic adaptations are achieved (early pregnancy, 29). It would be most reliable to measure sympathetic nervous activity using direct methods such as measurement of sympathetic nerve activity; however, this method is not suitable for long-term recordings in the same animal. We preferred the use of spectral analysis and baroreceptor reflex sensitivity measurements from spontaneous variations in blood pressure and HR for several reasons. First, the administration of vasoactive substances to compare changes in HR as a consequence of imposed blood pressure changes could influence the baroreceptor reflex by a direct effect on receptor or effector sites. Second, the influence of these substances on the conceptus itself and the changed sensitivity of the vessel wall to vasoactive substances in pregnancy (7) may invalidate comparisons with nonpregnant rats. Third, autonomic nervous function and baroreceptor reflex sensitivity are measured in the physiological blood pressure range. Finally, these methods do not impose any extra stress on the animals. However, we cannot exclude the possibility that baroreceptor control of sympathetic nerve activity to peripheral organs is modified. Interestingly, it has been demonstrated by Crandall and Heesch (8) that renal sympathetic outflow in response to a hypotensive challenge is impaired in late-pregnant rats.

The calculation of the transfer function between pressure and HR to assess baroreceptor reflex sensitivity has been validated in humans (27). In the present study in rats, however, the phase relationship between MAP and HR in the MF range was always positive. This finding indicates that HR oscillations at this frequency range are probably responsible for the oscillations in MAP. Thus the transfer gain between MAP and HR in the MF range is not a suitable index for baroreceptor reflex sensitivity in the rat (24). Recent studies have indicated that oscillations lower than

Table 2. Baroreceptor reflex sensitivity in pregnancy

<table>
<thead>
<tr>
<th></th>
<th>day 4</th>
<th>day 6</th>
<th>day 8</th>
<th>day 10</th>
<th>day 18</th>
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<tbody>
<tr>
<td>BRS, ms/mmHg</td>
<td></td>
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<tr>
<td>P</td>
<td>0.49 ± 0.23</td>
<td>0.56 ± 0.19</td>
<td>0.55 ± 0.14</td>
<td>0.46 ± 0.12</td>
<td>0.51 ± 0.21</td>
</tr>
<tr>
<td>NP</td>
<td>0.67 ± 0.36</td>
<td>0.66 ± 0.30</td>
<td>0.67 ± 0.23</td>
<td>0.74 ± 0.35</td>
<td>0.71 ± 0.40</td>
</tr>
<tr>
<td>Transfer gain, %</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>P</td>
<td>2.60 ± 0.76</td>
<td>2.98 ± 0.76</td>
<td>3.14 ± 0.71</td>
<td>2.75 ± 0.41</td>
<td>4.20 ± 1.25</td>
</tr>
<tr>
<td>NP</td>
<td>2.94 ± 0.89</td>
<td>3.61 ± 1.84</td>
<td>3.10 ± 1.34</td>
<td>3.16 ± 0.75</td>
<td>4.17 ± 1.63</td>
</tr>
<tr>
<td>Phase, s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.65 ± 0.18</td>
<td>0.70 ± 0.15</td>
<td>0.56 ± 0.36</td>
<td>0.56 ± 0.20</td>
<td>0.66 ± 0.23</td>
</tr>
<tr>
<td>NP</td>
<td>0.70 ± 0.31</td>
<td>0.71 ± 0.27</td>
<td>0.79 ± 0.28</td>
<td>0.76 ± 0.23</td>
<td>0.47 ± 0.26</td>
</tr>
<tr>
<td>Coherence</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>P</td>
<td>0.70 ± 0.03</td>
<td>0.71 ± 0.02</td>
<td>0.70 ± 0.06</td>
<td>0.69 ± 0.04</td>
<td>0.71 ± 0.07</td>
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<tr>
<td>NP</td>
<td>0.69 ± 0.05</td>
<td>0.73 ± 0.04</td>
<td>0.74 ± 0.04</td>
<td>0.70 ± 0.07</td>
<td>0.66 ± 0.09</td>
</tr>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>6</td>
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</tbody>
</table>

Values are means ± SD; n, number of rats. BRS, baroreflex sensitivity. Transfer gain, phase, and coherence between MAP and HR are in the midfrequency band (0.305–0.598 Hz). Each variable was subjected to 2-way analysis of variance by ranks (Friedman test).
those in the MF range might be responsible for the baroreflex changes (9).

In summary, the present data suggest unaltered activity of the autonomic regulation of blood pressure and HR during early pregnancy in rats. We speculate that the high-flow, low-resistance circulation in early pregnancy with its higher demand for intravascular fluid develops so slowly that the concomitant volume retention is adequate at any time to preserve the mean circulatory filling pressure and with it, venous return. This low rate of change with time may be even of vital importance for pregnancy because a too rapid rate of change carries the risk of a stress response with a higher sympathetic tone and with it a compromise of the blood supply to the implantation sites.

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