Title

Altered autonomic nervous system activity in women with unexplained recurrent pregnancy loss

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Abstract

Aim: Autonomic nervous system activity was studied to evaluate the physical and mental state of women with unexplained recurrent pregnancy loss (RPL).
Methods: Heart rate variability (HRV) is a measure of beat-to-beat temporal changes in heart rate and provides indirect insight into autonomic nervous system tone and can be used to assess sympathetic and parasympa- thetic tone. We studied autonomic nervous system activity by measuring HRV in 100 women with unexplained RPL and 61 healthy female volunteers as controls. The degree of mental distress was assessed using the Kessler6 (K6) scale.
Results: The K6 score in women with unexplained RPL was significantly higher than in control women. HRV evaluated on standard deviation of the normal-to-normal interval (SDNN) and total power was significantly lower in women with unexplained RPL compared with control women. These indices were further lower in women with unexplained RPL ≥4. On spectral analysis, high-frequency (HF) power, an index of parasympa- thetic nervous system activity, was significantly lower in women with unexplained RPL compared with control women, but there was no significant difference in the ratio of low-frequency (LF) power to HF power (LF/HF), an index of sympathetic nervous system activity, between the groups.
Conclusions: The physical and mental state of women with unexplained RPL should be evaluated using HRV to offer mental support. Furthermore, study of HRV may elucidate the risk of cardiovascular diseases and the mechanisms underlying unexplained RPL.

Key words: anxiety, autonomic nervous system, depression, heart rate variability, recurrent pregnancy loss.

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Introduction

Recurrent pregnancy loss (RPL) is defined as the loss of two or more consecutive and clinically recognized pregnancies.[1] The causes of RPL are classified as genetic, anatomic, endocrinologic, immunologic, microbiologic, environmental, and so on.[2,3] It is, however, estimated that almost half of RPL remain unexplained.

We have reported that women with unexplained RPL have elevated blood flow resistance in the uterine arteries[4] and progressing stiffness in systemic arteries.[5] Impaired uterine perfusion, which is caused by unspecified factors, may be involved in pregnancy loss.

Women who have experienced a pregnancy loss are more likely to experience an adverse mental health problem such as depression and anxiety following the loss.[6,7] Approximately 50% of women with a history of pregnancy loss experience difficulty in psychological adjustment, leading to depression and/or anxiety lasting for several months.6 Indeed, approximately 25.0% of Japanese women are known to have a high level of anxiety equivalent to typical psychiatric outpatients.[8]

Symptoms of depression and major depressive disorder have been identified as potential risk factors for coronary heart disease.[9] Individuals with high anxiety are at increased risk of coronary heart disease, congestive heart failure, stroke, fatal ventricular arrhythmia, and sudden cardiac death. Anxiety and depression, which is often observed in women with RPL, is also suggested to be an independent predictor of adverse cardiovascular events.[5,10,11]

Heart rate variability (HRV) is a measure of beat- to-beat temporal changes in heart rate and provides indirect insight into autonomic nervous system tone. Analysis of HRV has been reported to be a reliable non-invasive technique to quantify cardiovascular autonomic regulatory responses to autonomic regulatory mechanisms. Several time-domain measures are recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology for descriptive statistical methods.[12] These indices of HRV are markers to assess sympathetic and parasympathetic tone.

The severity and extent of coronary atherosclerosis were related to a shift of cardiac autonomic regulation towards sympathetic predominance in asymptomatic subjects without evidence of myocardial ischemia.[13] Depressed parasympathetic modulation was associated with worse early outcome in patients with acute large artery atherosclerotic infarction.[14]

Reduction of HRV has been reported in several cardiovascular and non-cardiovascular diseases.[12] Reduction of HRV is also associated with generalized anxiety disorder, and individuals with comorbid major depression may be distinguished based on indices of HRV from non-comorbid patients.[15] Thus, HRV is considered to be a psychophysiological marker of physical and mental wellbeing. To our knowledge, however, there are few studies on the probable correlation between autonomic nervous system activity and RPL. Therefore, we studied autonomic nervous system activity to evaluate the physical and mental state of women with unexplained RPL in the present study.

Methods

Patients

One hundred women with unexplained RPL (RPL group; n = 100) treated at Okayama University Hospital were enrolled in this study. Women with uterine anomaly, impaired glucose tolerance, abnormal thyroid function, anti-phospholipid antibodies, or other obvious diseases causing pregnancy loss such as diabetes mellitus and thrombophilia, and mental diseases such as depression and anxiety neurosis were excluded from the study. In the present study, anti- phospholipid antibodies included anti-cardiolipin antibodies (IgG and IgM) and anti-β2 glycoprotein I antibodies detected on ELISA (MBL, Nagoya, Japan, and Yamasa, Choshi, Japan, respectively),lupus anticoagulant detected on diluted Russell viper venom time, anti-phosphatidylserine/prothrombin antibodies, and anti-phosphatidylethanolamine antibodies detected on ELISA (SRL, Tokyo, Japan). Healthy female volunteers were also recruited as a control group (n = 61). Informed consent was obtained from each woman and the protocol was approved by the local institutional review board.

Methods

Pulse analyzer (TAS9, YKC Co., Tokyo, Japan) was used to record surface electrocardiography (ECG) in the sitting position for 5 min after 10 min of rest in a quiet room at 25°C. On continuous ECG, each QRS complex is detected, and the normal-to-normal (NN) interval, that is, all intervals between adjacent QRS complexes resulting from sinus node depolarization, is determined.[12] The standard deviation of the NN interval (SDNN), the simplest variable of time domain, was calculated. This index reflects all the cyclic components responsible for variability in the period of recording.

Conversion from the time domain to frequency domain analysis is made possible using Fourier transformation. Power spectra obtained from spectral analysis (frequency domain methods) were defined as two components: 0.04–0.15 Hz (low frequency: LF) and 0.15–0.4 Hz (high frequency: HF). HF power was shown to be almost entirely mediated by activity of the parasympathetic nervous system,[12] whereas LF power reflects the mixed modulation of parasympathetic and sympathetic activities.[12] The ratio of LF power to HF power (LF/HF) is considered to reflect a sympathetic predominance.[12] Total power (5 min total power) represents the variance of NN intervals over the temporal segment, which is a similar index to SDNN. SDNN is known to be correlated with total power.[12]

Screening for non-specific psychological distress and serious mental illness was done using the Kessler 6 (K6) scale.[16] The degree of mental distress was assessed using the K6 screening scale, with higher scores indicating depression or anxiety disorder.

The specific grief after miscarriage is evaluated in women with unexplained RPL using the Perinatal Grief Scale (PGS), which was designed to measure grief after perinatal loss and has good reliability and validity.[17]

Statistical analysis

SPSS ver.21 (IBM Japan, Tokyo, Japan) was used to analyze the data. Differences in variables between women with unexplained RPL were analyzed on Mann–Whitney U-test. Correlations between continuous variables were evaluated using Pearson's coefficients. Multiple regression analysis was used to evaluate the influence of background factors on each HRV index. Statistical significance was assumed for $P < 0.05$.

Results

Physical finding and mental state

There were no significant differences in age, height, bodyweight, body mass index (BMI), and systolic and diastolic blood pressures between women with unexplained RPL and control women (Table 1). The time from the day of the last pregnancy loss and that of HRV measurement was 34.8 ± 55.3 weeks (range, 1–304 weeks). K6 score in women with unexplained

RPL(3.9±4.0) was significantly higher than in control women(2.1±2.3). The PGS score in women with unexplained RPL was 71.7 ± 20.2. There was no significant correlation between K6 or PGS score and time from day of last pregnancy loss to HRV measurement. There was a positive correlation between K6 and PGS scores ($r = 0.68$, $P < 0.01$) in women with unexplained RPL.

Heart rate variability

There was no significant difference in heart rate between women with unexplained RPL and control women (Table 2). SDNN, total power, LF, and HF were significantly lower in women with unexplained RPL compared with control women. There was no significant difference in LF/HF between women with unexplained RPL and control women.

Number of pregnancy losses

We divided women with unexplained RPL into three groups according to the number of pregnancy losses and compared various indices of HRV and mental state with control women (Table 2). There was no significant difference in heart rate between each group of women with unexplained RPL and control women. SDNN and total power, however, in women with unexplained RPL ≥4 were significantly lower than in control women. LF and HF in women with unexplained RPL≥4 were also significantly lower than in control women, whereas there was no significant difference in LF/HF between women with unexplained RPL and control women.

Although the K6 score in each group of women with unexplained RPL was higher than in control women, a significant difference was observed between women with sequential RPL = 3 and control women. There was no significant difference in PGS among the three groups of women with unexplained RPL.

Live birth

There was no significant difference in HRV indices between unexplained RPL women with a past history of live birth and those without (Table 3).

HRV indices and K6 or PGS score

There were no significant correlations between SDNN, total power, LF, or HF and the K6 score (Table 4). In contrast, LF/HF, which reflects a sympathetic predominance, was weakly but significantly associated with K6 score among total subjects and especially among women with unexplained RPL. There was a weak but significant correlation between LF/HF and PGS score among women with unexplained RPL (Table 5).

Multiple regression analysis

Multiple regression analysis was performed to evaluate the influence of various factors including age, BMI, systolic blood pressure, and K6 score, and PGS score on each index of HRV in women with unexplained RPL and control women. Among women with unexplained RPL, LF/HF = 3.755 + 0.175 × K6 score (standardized coefficient, β= 0.50; $P = 0.004$). In contrast, no significant associations between K6 score and LF/HF were found among control women. There were no significant associations between various factors and the other indices of HRV.

Discussion

In the present study, we found that HRV was altered in women with unexplained RPL. Reduction of HRV, which was represented by decreases of SDNN, total power, LF, and HF, was observed in women with unexplained RPL. These findings were more prominent in women with unexplained RPL ≥4. LF/HF, which reflects activation of sympathetic nerve system, in women with unexplained RPL was similar to that in control women. Decreased HF and unchanged LF/HF, however, may indicate a relative shift of sympatho- parasympathetic balance towards sympathetic predominance.

Reduced HRV is known to lead to immune dysfunction and inflammation attributable to the downstream effects of a poorly functioning cholinergic anti- inflammatory reflex.[18] It is known that HRV is inversely correlated with inflammatory markers such as interleukin-6 and C-reactive protein in healthy individuals, as well as in those with cardiovascular dis- eases.[19] Immune dysfunction and inflammation associated with altered autonomic nervous system should be investigated in women with unexplained RPL.

The involvement of the autonomic nervous system in uterine perfusion has not been fully elucidated although we have reported impaired uterine perfusion in women with unexplained RPL.[4] Abnormal uterine perfusion is associated with the development of hypertensive pregnancy disorders. Preeclamptic pregnancy is known to be associated with increased sympathetic and decreased parasympathetic state.[20] Altered autonomic nervous system activity during pregnancy may be associated with adverse uterine environment and subsequent pregnancy loss.

We have reported that some women with unexplained RPL have arterial stiffness,[5] which is a possible risk for cardiovascular disease. Autonomic nervous system plays an important role in blood pressure regulation. It has been suggested that increased sympathetic outflow is evident in borderline hypertension, but in longstanding hypertension, the absolute sympathetic tone is not increased and may even be decreased.[21] Depressed parasympathetic modulation was associated with worse early outcome in patients with large artery atherosclerosis.[14]

It has been reported that reduction of the absolute power of LF and HF is observed in diabetic patients without evidence of autonomic neuropathy.[12] There is no significant difference in LF/HF, however, between these patients and healthy controls. Thus, the initial manifestation of this neuropathy is likely to involve both efferent limbs of the autonomic nervous system. To date, however, studies examining HRV in patients with existing cardiovascular disease have produced inconsistent results.[22]

In the present study, women with unexplained RPL had increased K6 score, which indicates distress and dormant anxiety and depression in these women. In a previous study, a total of 15.4% of the Japanese women with RPL were estimated to have diagnosable depression or anxiety disorders.[16] In the present study, increased K6 score and decreased HRV indices including SDNN, total power, LF, and HF were observed in women with unexplained RPL, especially in those with RPL ≥3. This suggests an association between mental state and sympatho-parasympathetic balance. Because there is a weak but significant association between K6 score and LF/HF, psychological distress is likely to be involved in sympathetic predominance in women with unexplained RPL.

Depression is known to be accompanied by dysfunction of the cardiac autonomic nervous system.[22] SDNN and HF were reported to be lower in the depression group compared with the control group. LF and LF/HF in the depression group were reported to be higher than in the control group.

In the present study, reduced HRV, which is represented by decrease of SDNN, total power, LF, and HF, was prominent in women with unexplained RPL. Women with RPL sometimes experience post- traumatic stress disorder (PTSD). Patients with PTSD are known to have reduced HRV.[23] It has been reported that otherwise healthy, non-medicated patients with anxiety disorders have reduced HRV.[18] Reduced HRV has important functional significance for motivation to engage in social situations, social approach behaviors, self-regulation and psychological flexibility in the face of stressors.[18] Patients with generalized anxiety disorder are known to have reduced HRV, while these patients with comorbid depression had further reductions in HRV.[15]

The results of several studies suggest that patients with mood and anxiety disorders may be at increased risk of cardiovascular disease as a result of decreased HRV.[21] Anxiety could play a more important role than depression as a psychosomatic element in the pathogenesis of hypertension. More than 20 studies reported abnormalities of HRV in anxiety, and patients with heart disease and anxiety are at increased risk for morbidity and mortality.[24]

Chronic work stress is known to cause large imbalance of autonomic nervous system, associated with a reduction of HRV during work, leisure time, and sleep on work days.[25] It has been reported that subjects who complained of poor sleep quality, which is associated with job stress, had a reduced HF component during standing rest.[25] Job strain was also associated with increases in the LF/HF ratio during working hours.[25]

The systematic review by Jarczok et al. showed that adverse psychosocial work conditions are negatively associated with function of autonomic nervous system, according to HRV indices.[26] Overall, nine of all studies reported a negative and significant association between vagally mediated HRV and measures of stress at work,while eight of all studies reported a negative and significant association with mixed sympathetic and parasympathetic measures of HRV. In the majority of studies that examined the association of HRV and work stress, greater work stress was associated with lower HRV.[27]

Physical and chemical work environments (i.e. exposure to occupational toxicants and hazardous environments), psychosocial workload (i.e. job stressors), and working time (i.e. shift work) has been examined and identified as having associations with decreased HF.[25]Therefore, parasympathetic nervous system activity should be focused on to protect cardiovascular health at work and also unexplained pregnancy loss.

Stress is one of the major threats to physical and mental health.28 Training programs, such as exercise training and mental training, have been trialed to induce adaptive physiological response to psychosocial stressor. Measurement of HRV may help in the selection of these training programs for use in women with unexplained RPL. Indices of HRV may also be useful to evaluate the effects of these training programs in women with unexplained RPL.

Pregnant women with previous but not current anxiety and their children are known to have low HRV.[29] Children with low HRV tend to show more fearfulness.[29] These findings have implications for measuring HRV and investigating risk of anxiety disorders in children of women with unexplained RPL.

The clinical significance of mental state and cardio- vascular risk factors in women with unexplained RPL remains to be clarified. We believe, however, that the physical and mental state of women with unexplained RPL should be evaluated on HRV in order to offer mental support and evaluate the risk of cardiovascular diseases. Furthermore, study of HRV may elucidate the mechanism of pregnancy loss and thereby lead to selection of appropriate therapy in at least some women with unexplained RPL.

Disclosure

There are no conflicts of interest to declare.

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Table 1. Physical finding of women with unexplained recurrent pregnancy loss

	Control (n=61)	Recurrent pregnancy loss (n=100)	p value
Age	34.9±5.6 〔27-45〕	36.3±5.0 〔21-45〕	n.s.
Height (cm)	158.3±6.3	158.6±4.6	n.s.
Body weight (kg)	52.2±7.0	53.3±7.2	n.s.
Body mass index	20.8±2.7	21.3±2.7	n.s.
Systolic blood pressure (mmHg)	113.9±14.0	117.9±10.3	n.s.
Diastolic blood pressure (mmHg)	69.9±8.0	70.6±9.6	n.s.
Kessler 6	2.1±2.3	3.9±4.0*	<0.05
Perinatal Grief Scale	n.a.	71.7±20.2	n.a.

mean±S.D., n.s.: not significant.

Table 2. Heart rate variability and mental state

	Control	Recurrent pregnancy loss			
	(n=61)	Total (n=100)	Twice (n=48)	Three times (n=43)	Four times or more (n=9)
Heart rate (bpm)	71.3±7.6	73.4±9.6	72.8±9.0	73.8±10.3	73.2±11.2
SDNN (ms)	56.5±30.6	46.6±25.2**	47.1±29.1**	47.8±22.5	37.9±11.6*
Total power (ms^2)	1,602.0±1283.2	1,182.0±1706.7**	1,421.4±2359.5	1,024.5±678.9**	658.2±367.9**
LF (ms^2)	612.5±764.8	394.1±747.1*	475.2±1044.9	345.3±271.0	194.7±98.3*
HF (ms^2)	491.8±606.3	370.5±745.7*	472.8±1038.0	298.0±275.3	171.6±129.5*
LF/HF	1.8±1.6	1.6±1.8	1.5±1.6	1.8±2.1	1.7±1.2
Kessler 6	2.1±2.3	3.9±4.0*	3.3±3.5	4.5±4.1*	4.3±6.4
Perinatal Grief Scale	n.a.	71.7±20.2	72.0±18.2	71.1±18.8	72.4±40.2

mean±S.D., vs. control：*p<0.05, **p<0.01.

SDNN: Standard deviation of all NN intervals, LF: Low frequency, HF: High frequency, LF/HF: Low-frequency/high-frequency ratio, K6: Kessler 6, na: not available.

Table3. Heart rate variability in women with unexplained recurrent pregnancy loss

	Without live birth (n=72)	With live birth (n=28)	p value
SDNN	47.6±28.7	43.8±12.5	n.s
Total power	1,295.5±1,982.1	890.4±477.1	n.s
LF	442.9±872.3	268.4±150.4	n.s
HF	401.2±857.8	291.6±308.0	n.s
LF/HF	1.6±1.5	1.8±2.4	n.s

mean±S.D., n.s.: not significant.

SDNN: Standard deviation of all NN intervals, LF: Low frequency, HF: High frequency,

LF/HF: Low-frequency/high-frequency ratio, TP: Total power, K6: Kessler 6, PGS: Perinatal Gief Scale, na: not available.

Table 4. Correlations between various indices and score of Kessler 6

	Total (n=161)		Control (n=61)		Recurrent pregnancy loss (n=100)	
	r	p value	r	p value	r	p value
SDNN	-0.02	0.84	0.27	0.22	-0.03	0.82
Total power	-0.09	0.37	0.30	0.16	-0.11	0.36
LF	-0.08	0.42	0.16	0.47	-0.08	0.48
HF	-0.09	0.39	0.25	0.24	-0.11	0.35
LF/HF	0.24	0.02	-0.15	0.51	0.32	0.01

SDNN: Standard deviation of all NN intervals, LF: Low frequency, HF: High frequency,
LF/HF: Low-frequency/high-frequency ratio.

Table 5. Correlations between various indices and score of Perinatal Grief Scale

	Recurrent pregnancy loss (n=100)	
	r	p value
SDNN	-0.04	0.74
Total power	-0.09	0.46
LF	-0.08	0.48
HF	-0.13	0.29
LF/HF	0.27	0.03

SDNN: Standard deviation of all NN intervals, LF: Low frequency, HF: High frequency,
LF/HF: Low-frequency/high-frequency ratio.