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ORIGINAL ARTICLE

Perioperative heart rate variability analysis to evaluate autonomic activity in gynecologic patients

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Abstract

Background: Women often experience medically unexplained symptoms as they age, and their possible causes include changes in autonomic activity. Heart rate variability is a relevant marker for autonomic function.

Methods: The autonomic activities of patients who underwent gynecologic surgery were prospectively measured and evaluated by menopausal status. Parameters included the standard deviation of the mean R-to-R intervals (SDNN) and index of the sympathetic nervous system (SNS) function. Patients also evaluated the severity of their headache, hot flashes, anxiety, irritability, fatigue and shoulder stiffness using the visual analog scale (VAS-P, VAS-H, VAS-A, VAS-I, VAS-F and VAS-S, respectively). Measurements were conducted shortly before, immediately after, and 1 week after surgery.

Results: The study cohort (N = 101) consisted of 14 premenopausal, 39 surgically menopausal, and 48 naturally menopausal patients. At 1 week after surgery, surgically menopausal patients had significantly smaller mean SDNN than premenopausal patients. Surgically menopausal patients also showed significant correlation between the SNS index and VAS-I and VAS-F.

Conclusions: The SNS index in surgically menopausal patients can be a promising tool for evaluating the severity of menopausal symptoms. Parasympathetic nerve activity decreased immediately after the operation in the surgical menopausal group. Therefore, early hormone replacement therapy may be necessary in surgical menopause group.

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Key words: menopausal patients; gynecologic surgery; autonomic activity; heart rate variability; visual analog scale.

Introduction

Women experience hormonal imbalance challenges in many occasions. Typical examples of such challenge occur during menopausal transition. Menopausal symptoms are wide-ranging, including episodic sensations of warmth on the chest, neck, and face (hot flashes), shoulder stiffness, irritability, headache, anxiety, and depression. The mechanisms underlying these medically unidentified symptoms have not been clearly elucidated. Several studies suggest that they are associated with changes in autonomic activity. For example, hot flashes are associated with reduced parasympathetic tone[1]. Alternatively, hot flashes and sleep disturbance may be associated with sympathetic activation[2, 3].

The time interval between heartbeats is not constant but varies naturally from beat to beat all the time. This variation in heart rate is termed heart rate variability (HRV). Recently, the analysis of HRV metrics has been applied to the evaluation of autonomic activity. HRV analysis enables to separate and quantify the contributions of the sympathetic and parasympathetic branches of the autonomic nervous system. For

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example, HRV analysis was shown to be an effective tool for stratifying the risk of disease progression in patients with chronic stable angina treated with percutaneous coronary revascularization[4]. In the field of gynecology, HRV metrics were analyzed to investigate their utility in predicting menopausal symptoms and cardiovascular risk[1, 5-7]. Available literature reveals various efforts to identify the clinical utility and implications of HRV measurement in menopause. However, few studies have reported the results of perioperative HRV analysis in the evaluation of autonomic activity in women. Moreover, no studies have reported the results of perioperative HRV analysis in female patients by type of menopausal status, to the best of our knowledge. Hot flashes, shoulder stiffness, and other medically unexplained symptoms show large interindividual variability in severity and frequency, and the effects of their treatment are mostly evaluated based on self-reported outcomes in the absence of standard and objective criteria.

We recruited the female patients undergoing surgical treatment at our department, and measured HRV metrics to assess their autonomic function before and after surgery. The severity of their menopausal symptoms was subjectively evaluated using the visual analog scale (VAS), and their possible correlations with HRV variables were investigated.

Materials and Methods

1 Study Patients

This study included 101 patients who underwent surgery between February 2020 and December 2020 at the Department of Obstetrics and Gynecology, Hirosaki University Hospital, Aomori, Japan. This study was approved by the Ethics Committee of Hirosaki University Hospital, and all study patients provided written informed consent before participation. (IRB number 2019-1109)

2 Methods

The patients were divided for analysis into three groups by menopausal status: premenopausal, surgically menopausal, and naturally menopausal. Here, surgical menopause was defined as patients who were premenopausal at the time of the surgery and underwent bilateral oophorectomy during the study. VAS-based subjective ratings of menopausal symptoms and HRV-based evaluation of autonomic function were performed. These evaluations were conducted shortly before, immediately after, and 1 week after surgery. Patient background data including age, blood pressure, heart rate, indication for operation and usage of antihypertensive drugs that suppress sympathetic nerves were collected from medical record. Patients who provided the results of evaluation shortly before and immediately after surgery were included in further analysis.

(1) Heart Rate Variability Analysis

HRV metrics were evaluated according to international guidelines and studies reported in the literature[8,9]. HRV measurement was conducted using a health assessment system (Heart Rhythm Scanner PE; Biocom Technologies, Poulsbo, WA) according to the procedure reported in the literature[10,11]. Specifically, HRV was measured as described below.

Patients were asked to lie at rest in the supine position and gently breathe in and out in a quiet room in the afternoon. The HRV measurement sensor was attached to the tip of the finger to detect fluctuations in peripheral blood flow. Blood flow fluctuations were reflected in the photoplethysmography (PPG). PPG signals were analyzed to provide beat-to-beat intervals.

The following HRV metrics were analyzed in this study: MeanRR, SDNN, RMSSD, pNN50, LH/HF, and TP. MeanRR represented the mean R-to-R interval over 5 minutes (ms), and SDNN represented the standard deviation of the mean

R-to-R intervals (ms). RMSSD was the root mean square of differences between adjacent R-to-R intervals. pNN50 indicated the proportion of differences between adjacent R-to-R intervals exceeding 50 msec (%). RMSSD and pNN50 were indicators of vagal tone. In the frequency domain, the power spectral densities of the very low frequency (VLF, 0.0033–0.04 Hz), low frequency (LF, 0.04–0.15Hz), and high frequency (HF, 0.15–0.4Hz) bands were estimated, and the ratio of LF to HF was determined (LF/HF). High and low LF/HF ratios indicate the dominance of sympathetic and parasympathetic contribution to cardiac control, respectively. TP represented the total power of the spectrum, or the sum of VLF, LF, and HF. Moreover, the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) indices proposed by Matsumoto et al[12], were evaluated. Specifically, the SNS index was defined as (VLF + LF)/HF, and the PNS index was defined as HF/TP.

(2) Visual Analog Scale Measurements

On the same day as HRV measurements, patients were asked to evaluate their symptoms using the VAS scale. The VAS scale used in this study was a straight line of a given length with anchor statements of "no pain (= 0)" at the left-most end and "worst condition imaginable (= 10)" at the far right. The target symptoms included headache (VAS-P), hot flashes (VAS-H), anxiety (VAS-A), irritability (VAS-I), shoulder stiffness (VAS-S), and fatigue (VAS-F). The results were evaluated taking note of previous studies[13-17].

3 Statistical Analysis

Comparisons between the three groups were performed using one-way analysis of variance (ANOVA), and changes over time in each group were assessed using repeated measures ANOVA and Tukey's multiple post hoc tests used for comparison between the groups. Correlations between the autonomic activity parameters (MeanRR, SDNN, RMSSD, pNN50, LH/HF, TP, SNS index, and PNS index) and the VAS scores were analyzed using Pearson's correlation analysis. Statistical significance was defined as $P < 0.05$. Statistical analyses were conducted using the SPSS® software Version 25.0 (SPSS Inc., Chicago, IL).

Table 1. Patient backgrounds

Type of disease	N=101
Endometrial cancer	42
Ovarian cancer	22
Uterine benign tumor	17
Ovarian benign tumor	8
Uterine cervical cancer	6
Uterine cervical neoplasia	4
Others	2

The causes for their operations are summarized in Table 1.

Results

The study cohort consisted of 14 premenopausal, 39 surgically menopausal, and 48 naturally menopausal women. The causes for their operations are summarized in Table 1. Cancers (endometrial, ovarian, and uterine cervical) accounted for 69.3% (n = 70) of the operations. Antihypertensive drugs that suppress sympathetic nerves were used in the 29 patients who consisted of 2 premenopausal, 8 surgically menopausal, and 19 naturally menopausal women. Study patients were asked to undergo evaluations three times. However, 27 (26.7%) had the first and second evaluations only and skipped the last ones because of their schedules. These 27 patients consisted of 9 premenopausal, 10 surgically menopausal, and 8 naturally menopausal women. Patients with two evaluations only accounted for the majority (64.3%) of the premenopausal group.

The data taken shortly before surgery, immediately after surgery, and 1 week after

Table 2. The result of HRV analysis and VAS in three groups before surgery

	Premenopausal group (N=14)		Surgically menopausal group (N=39)		Naturally menopausal group (N=48)		
	Average	SD	Average	SD	Average	SD	P-value
Age (years)	42.6	4.7	47.3	5.7	63.2	7.9	<0.0001
Systolic blood presuure (mmHg)	126.7	16.6	128.2	16.4	128.6	16.9	0.929
Diastolic blood pressure (mmHg)	75.1	13.2	78.3	11.2	73.5	12.3	0.175
Heart rate (bpm)	72.4	8.3	80.8	12.3	76.2	12.2	0.052
HRV analysis							
Mean RR (ms)	839.6	103.0	761.4	121.8	807.5	131.7	0.076
SDNN (ms)	48.7	27.2	32.9	18.4	33.5	25.4	0.064
RMSSD (ms)	36.1	41.3	24.9	24.3	23.0	28.6	0.312
p NN50 (%)[a,b]	9.5	12.7	3.3	7.6	1.9	3.0	0.001
LF/HF	3.9	4.5	3.2	5.9	3.2	4.7	0.869
TP (ms^2)	610.9	526.1	502.2	1172.4	726.3	2987.2	0.893
SNS Index	12.4	14.8	13.2	26.5	19.7	69.0	0.796
PNS Index	0.2	0.1	0.2	0.1	0.1	0.1	0.120
VAS							
VAS-F (Fatigue)	3.2	2.3	2.9	2.5	2.8	2.7	0.868
VAS-S (Shoulder stiffness)	2.5	2.9	1.7	2.4	1.3	1.9	0.207
VAS-H (Hot flash)	1.9	2.6	1.4	1.7	1.6	2.4	0.727
VAS-P (Pain ; Headache)	1.9	3.2	0.9	1.5	1.0	1.7	0.183
VAS-A (Anxiety)	4.5	3.3	2.5	2.4	2.6	3.0	0.053
VAS-I (Irritability)	1.5	2.6	1.0	1.7	1.0	1.9	0.616

[a] p=0.01 premenopausal group had statistical difference as compared to surgically menopausal group.
[b] p<0.001 premenopausal group had statistical difference as compared to Naturally menopausal group.

Table 3. The result of HRV analysis and VAS in three groups immidiately after surgery

	Premenopausal group (N=14)		Surgically menopausal group (N=39)		Naturally menopausal group (N=48)		
	Average	SD	Average	SD	Average	SD	P-value
Age (years)	41.8	4.6	47.3	5.6	63.2	7.9	<0.0001
Systolic blood presuure (mmHg)	125.3	19.6	118.3	16.2	122.8	15.6	0.284
Diastolic blood pressure (mmHg)	72.5	17.2	75.5	12.9	88.2	102.1	0.632
Heart rate (bpm)[a]	76.7	10.4	86.9	12.3	78.8	10.2	0.001
HRV analysis							
Mean RR (ms)[b,c]	795.1	105.8	703.9	99.0	772.5	108.8	0.003
SDNN (ms)	52.0	37.6	36.8	29.6	47.3	56.1	0.433
RMSSD (ms)	41.6	51.9	30.1	42.9	46.3	80.8	0.492
p NN50 (%)	2.4	4.1	1.5	3.2	3.2	7.8	0.381
LF/HF	4.4	3.2	4.5	5.2	3.4	3.3	0.393
TP (ms^2)	925.1	1241.0	444.9	740.1	1007.1	2968.2	0.454
SNS Index	21.3	24.8	16.5	26.2	16.2	18.5	0.753
PNS Index	0.1	0.1	0.2	0.1	0.1	0.1	0.408
VAS							
VAS-F (Fatigue)	3.3	3.2	3.2	2.6	2.9	2.5	0.817
VAS-S (Shoulder stiffness)	1.6	1.5	1.4	2.1	1.8	2.1	0.604
VAS-H (Hot flash)	2.4	2.6	1.3	1.9	1.5	2.1	0.297
VAS-P (Pain ; Headache)	1.5	2.3	0.7	1.5	0.6	1.4	0.152
VAS-A (Anxiety)	2.8	2.9	3.2	2.7	3.9	3.4	0.446
VAS-I (Irritability)	1.1	1.9	1.4	1.9	1.5	2.8	0.810

[a] p=0.013 surgically menopausal group had statistical difference as compared to premenopausal group.
[b] p=0.017 surgically menopausal group had statistical difference as compared to premenopausal group.
[c] p<0.001 surgically menopausal group had statistical difference as compared to naturally menopausal group.

surgery (age, blood pressure, heart rate, autonomic activity variables and VAS scores) are summarized in Table 2, Table 3, and Table 4, respectively, together with the results of ANOVA analysis among groups. In the preoperative evaluation (Table 2), the surgically menopausal and naturally menopausal groups had significantly smaller pNN50 values than the premenopausal group

Table 4. The result of HRV analysis and VAS in three groups one week after surgery

	Premenopausal group (N=14)		Surgically menopausal group (N=39)		Naturally menopausal group (N=48)		
	Average	SD	Average	SD	Average	SD	P-value
Age (years)	39.6	5.3	47.1	5.9	62.9	7.9	<0.0001
Systolic blood presuure (mmHg)	112.8	16.8	123.3	13.8	121.4	12.3	0.274
Diastolic blood pressure (mmHg)	67.2	11.1	73.2	13.0	68.0	8.3	0.132
Heart rate (bpm)	73.0	9.2	76.3	13.4	74.9	10.9	0.804
HRV analysis							
Mean RR (ms)	833.6	119.4	811.6	143.5	819.1	127.3	0.935
SDNN (ms)[a,b]	78.1	69.9	40.5	19.9	38.4	31.8	0.032
RMSSD (ms)	77.3	108.2	29.1	21.2	31.6	47.4	0.091
p NN50 (%)	11.6	12.2	8.4	14.9	4.3	8.8	0.221
LF/HF	4.0	2.4	2.0	1.7	2.2	2.2	0.108
TP (ms^2)[c,d]	2922.6	3664.5	409.5	324.8	561.3	1177.1	<0.0001
SNS Index	10.7	6.8	7.4	8.0	9.8	11.9	0.597
PNS Index	0.1	0.2	0.2	0.1	0.2	0.1	0.595
VAS							
VAS-F (Fatigue)	1.0	1.7	2.7	2.0	3.2	2.8	0.174
VAS-S (Shoulder stiffness)	1.4	1.9	1.0	1.6	1.7	2.4	0.426
VAS-H (Hot flash)	0.8	1.8	1.3	2.2	2.1	2.8	0.314
VAS-P (Pain ; Headache)	0.8	1.8	1.0	2.2	0.8	2.1	0.957
VAS-A (Anxiety)	1.8	2.9	2.5	2.7	3.7	3.4	0.200
VAS-I (Irritability)	0.8	1.8	1.2	2.1	1.1	2.6	0.947

a,b,c,d p<0.001 surgically menopausal and naturally menopausal groups had statistical difference as compared to premenopausal group.

($P < 0.01$ and $P < 0.001$, respectively). The MeanRR and SDNN values were smaller (though not significantly so) for the surgically menopausal group compared with other groups. In addition, the VAS-A scores were greater (though not significantly so) for the premenopausal group compared with other groups. In the evaluation immediately after surgery (Table 3), the surgically menopausal group had significantly smaller MeanRR than premenopausal group and naturally menopausal group (P =0.017 and P=0.001, respectively). The surgically menopausal group had significantly larger heart rate than premenopausal group (P=0.013) In the evaluation 1 week after surgery (Table 4), the surgically menopausal and naturally menopausal groups had significantly smaller SDNN and TP than the premenopausal group (P<0.001 for all comparisons). We performed the same study for the naturally menopausal group with or without the drugs that suppress sympathetic nerves separately, and the results were consistent.

The data of the premenopausal group, surgically menopausal group, and naturally menopausal group (age, blood pressure, autonomic nervous variables, and VAS scores) are shown in Table 5, Table 6, and Table 7, respectively, along with the results of repeated measures ANOVA. Only the data obtained from the patients in whom measurement was performed at three time points were analyzed.

Table 6 shows the result of surgically menopausal group. The surgically menopausal group showed a statistical difference in heart rate between immediately postoperative and 1-week postoperative time points (P = 0.008). The surgically menopausal group also showed a statistical difference in MeanRR and LH/HF ratio between immediately postoperative and 1-week postoperative time points (P = 0.004 and P = 0.013, respectively). The premenopausal group and naturally menopausal group exhibited no statistically significant differences in any variables examined across the measurement time points (Table 5 and 7).

As a result of the correlation analysis, SNS index in surgically menopausal group at immediately after operation had statistically

Table 5. The result of HRV analysis and VAS in premenopausal group (N=5)

	Before surgery		Immediately after surgery		One week after surgery		
	Average	SD	Average	SD	Average	SD	P-value
Age (years)	39.6	5.3	–	–	–	–	–
Systolic blood presuure (mmHg)	130.8	15.6	121.6	17.5	112.8	16.8	0.271
Diastolic blood pressure (mmHg)	81.0	9.3	68.0	14.4	67.2	11.1	0.158
Heart rate (bpm)	75.3	5.4	78.4	11.6	73.0	9.2	0.651
HRV analysis							
Mean RR (ms)	799.9	59.6	777.2	105.4	833.6	119.4	0.668
SDNN (ms)	62.5	38.8	61.1	47.4	78.1	69.9	0.859
RMSSD (ms)	55.7	68.7	59.1	62.1	77.3	108.2	0.906
p NN50 (%)	10.7	13.3	3.6	5.8	11.6	12.2	0.470
LF/HF	5.3	5.0	4.1	2.2	4.0	2.4	0.805
TP (ms^2)	949.2	531.7	721.6	654.2	2922.6	3664.5	0.254
SNS Index	21.3	22.0	11.4	6.7	10.7	6.8	0.425
PNS Index	0.1	0.1	0.1	0.1	0.1	0.2	0.800
VAS							
VAS-F (Fatigue)	2.8	1.5	1.6	2.2	1.0	1.7	0.319
VAS-S (Shoulder stiffness)	3.0	3.5	1.0	1.7	1.4	1.9	0.435
VAS-H (Hot flash)	3.0	3.5	2.0	2.5	0.8	1.8	0.456
VAS-P (Pain ; Headache)	3.8	4.5	1.8	2.2	0.8	1.8	0.322
VAS-A (Anxiety)	6.8	4.1	3.2	3.3	1.8	3.0	0.103
VAS-I (Irritability)	3.0	3.5	1.0	2.2	1.6	2.6	0.365

The premenopausal group exhibited no statistically significant differences in any variables examined across the measurement time points.

Table 6. The result of HRV analysis and VAS in surgically menopausal group (N=29)

	Before surgery		Immediately after surgery		One week after surgery		
	Average	SD	Average	SD	Average	SD	P-value
Age (years)	46.8	6.4	–	–	–	–	–
Systolic blood presuure (mmHg)	131.3	18.3	119.6	19.1	124.0	13.7	0.064
Diastolic blood pressure (mmHg)	80.7	12.9	76.4	13.6	74.0	12.6	0.205
Heart rate (bpm)[a]	81.5	14.2	89.6	13.6	76.8	13.4	0.004
HRV analysis							
Mean RR (ms)[b]	761.9	142.7	684.4	104.2	806.2	143.0	0.005
SDNN (ms)	34.7	21.7	39.3	34.0	40.2	20.2	0.725
RMSSD (ms)	30.1	29.3	34.7	49.5	29.4	21.6	0.839
p NN50 (%)	4.7	9.2	1.9	3.7	8.7	15.1	0.076
LF/HF[c]	2.4	3.6	4.8	5.4	1.9	1.6	0.016
TP (ms^2)	628.5	1473.9	479.3	686.7	398.4	325.1	0.671
SNS Index	9.8	19.2	14.6	19.8	7.1	7.9	0.246
PNS Index	0.2	0.2	0.2	0.2	0.2	0.1	0.284
VAS							
VAS-F (Fatigue)	2.5	2.0	2.8	2.7	2.8	2.0	0.816
VAS-S (Shoulder stiffness)	1.3	1.9	1.2	2.1	1.0	1.6	0.873
VAS-H (Hot flash)	1.2	1.5	1.3	2.1	1.4	2.2	0.963
VAS-P (Pain ; Headache)	0.7	1.3	0.7	1.4	1.0	2.2	0.753
VAS-A (Anxiety)	1.9	1.9	3.3	2.8	2.6	2.7	0.174
VAS-I (Irritability)	0.7	1.0	1.4	1.9	1.2	2.1	0.327

[a] p=0.008 The surgically menopausal group showed a statistical difference in heart rate between immediately postoperative and 1-week postoperative time points

[b] p=0.004 The surgically menopausal group showed a statistical difference in Mean RR between immediately postoperative and 1-week postoperative time points

[C] p=0.013 The surgically menopausal group showed a statistical difference in LH/HF ratio between immediately postoperative and 1-week postoperative time points

significant correlation with VAS-I ($P=0.004$, $r=0.441$) (Figure 1). In addition, SNS index in surgically menopausal group at 1-week after operation had statistically significant correlation with VAS-F ($P=0.046$, $r=0.373$) (Figure 2). Other autonomic activity parameters include SNS index in other group had no significant correlation with any VAS scores.

Table 7. The result of HRV analysis and VAS in naturally menopausal group (N=40)

	Before surgery		Immediately after surgery		One week after surgery		
	Average	SD	Average	SD	Average	SD	P-value
Age (years)	63.3	7.3	–	–	–	–	–
Systolic blood presuure (mmHg)	128.2	16.8	122.7	15.7	121.6	12.4	0.122
Diastolic blood pressure (mmHg)	72.8	10.5	92.7	114.9	68.3	8.1	0.229
Heart rate (bpm)	76.6	12.6	79.8	10.5	74.9	11.0	0.141
HRV analysis							
Mean RR (ms)	803.0	132.0	764.5	111.2	819.6	128.9	0.134
SDNN (ms)	34.4	27.9	50.7	61.5	38.7	32.2	0.220
RMSSD (ms)	24.8	31.9	51.4	89.3	32.0	48.0	0.139
p NN50 (%)	1.9	3.1	3.8	8.7	4.4	8.8	0.282
LF/HF	2.6	2.4	3.3	3.6	2.3	2.2	0.263
TP (ms^2)	834.3	3371.4	1138.6	3310.9	570.9	1191.0	0.671
SNS Index	20.7	77.7	14.8	17.8	9.9	12.0	0.593
PNS Index	0.1	0.1	0.2	0.2	0.2	0.1	0.509
VAS							
VAS-F (Fatigue)	2.5	2.5	3.0	2.7	3.2	2.8	0.543
VAS-S (Shoulder stiffness)	1.2	1.7	2.0	2.1	1.6	2.4	0.262
VAS-H (Hot flash)	1.3	2.1	1.4	2.0	2.1	2.8	0.271
VAS-P (Pain ; Headache)	0.9	1.5	0.4	1.0	0.8	2.1	0.277
VAS-A (Anxiety)	2.5	3.1	3.9	3.6	3.7	3.5	0.170
VAS-I (Irritability)	1.1	2.0	1.5	2.7	1.1	2.6	0.724

The naturally menopausal group exhibited no statistically significant differences in any variables examined across the measurement time points.

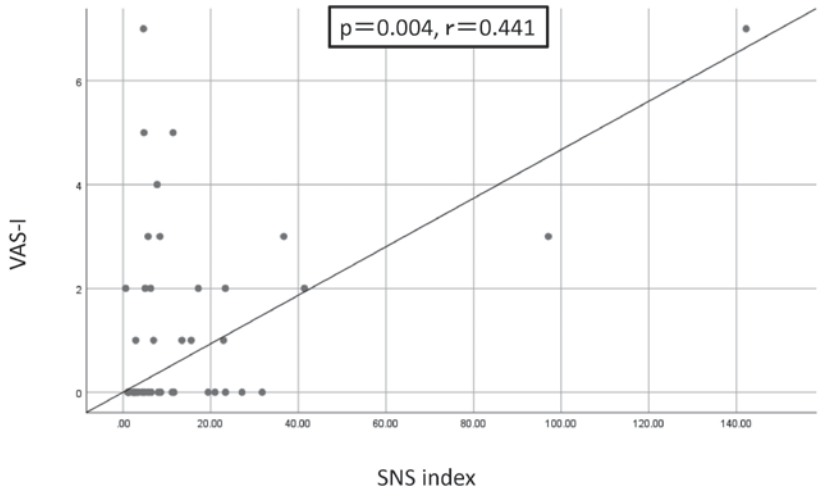

Figure 1 Relationship between VAS-I and SNS Index at immediately after operation (N=39)
SNS index in surgically menopausal group at immediately after operation had statistically significant correlation with VAS-I (P =0.004, r = 0.441).

Discussion

This study investigated the pre- and postoperative conditions of gynecologic patients by menopausal status. The surgically menopausal and naturally menopausal groups had lower pNN50 values than the premenopausal group shortly before and 1 week after surgery. pNN50 is an indicator of vagal tone[18]. Given the fact that the premenopausal group exhibited a large but temporary decrease in pNN50 immediately after surgery, the relatively small changes in pNN50 may be of minor clinical significance.

In the evaluation 1 week after surgery, the surgically menopausal and naturally menopausal groups had significantly smaller SDNN than the

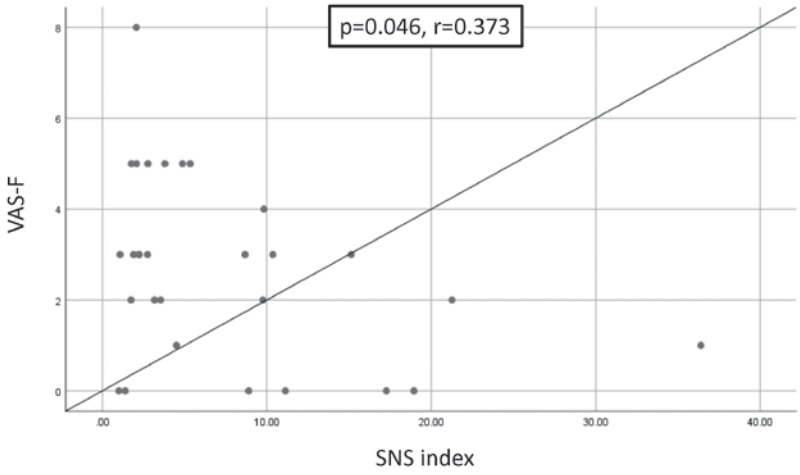

Figure 2 Relationship between VAS-F and SNS Index at 1-week after operation (N=29)
SNS index in surgically menopausal group at 1-week after operation had statistically significant correlation with VAS-F (P =0.046, r = 0.373).

premenopausal group. SDNN values predict both morbidity and mortality and higher SDNN values (typically above 100 ms) indicate better health[18]. Admitted that the higher mean age of the surgically menopausal and naturally menopausal groups (47.3 and 63.2 years, respectively, versus 42.6 years of the premenopausal group at baseline) may suggest that they were at a higher cardiac risk than the premenopausal group, our data suggested that menopausal women, especially surgically menopausal women, should deserve medical attention for their elevated cardiac risk. This is consistent with the finding that women who had surgically induced menopause before the age of 45 years were at a higher risk of death than age-matched controls[19], suggesting that menopause-related changes in autonomic activity may increase cardiac mortality.

In the surgically menopausal group, heart rate and LH/HF ratio showed temporary increase immediately after surgery, but returned to the preoperative levels after 1 week. On the contrary, MeanRR and pNN50 showed temporary decrease immediately after surgery, though the decrease of pNN50 was not significant. These results may be due to activation of sympathetic nerve activity and decrease of parasympathetic nerve activity. The clinical significance and implications of these changes are still unknown, but it seems important that these changes were not seen in the other groups. Interesting insight into these changes may be gleaned by collecting data from long term after surgery.

There were no significant correlations between the VAS scores and autonomic activity metrics in the naturally menopausal and premenopausal groups. However, SNS index in surgically menopausal group immediately after operation had statistically significant correlation with VAS-I. SNS index in surgically menopausal group at 1-week after operation had statistically significant correlation with VAS-F. Since LH/HF and parasympathetic activity variables, such as RMSSD, pNN50 and PNS index, did not show significant correlations with the VAS scores, the SNS index may be a useful variable in evaluating the autonomic activity in surgically menopausal patients. The diagnosis of climacteric disorder is based on symptoms. Of course, diagnosis of exclusion of depression and thyroid disease is indispensable. The SNS index may be a useful tool in the quantitative evaluation of climacteric disorder because the SNS index was correlated with VAS.

What are the reasons for showing postopera-

tive HRV changes and the correlation between SNS index and VAS in surgically menopausal patients? The first reason may be the stress by surgical invasion. The age and the degree of surgical invasion were not matched in this study. In order to solve this problem, it is necessary to make a study that matches the age and degree of surgical invasion. The second reason is an abrupt ovarian dysfunction. Estrogen deficiency is known to have various effects. Dyslipidemia, hypertension, diabetes, osteoporosis, cardiovascular disease are a representative disease of estrogen deficiencies. The decrease of estrogen in naturally menopause is slow and mild compared with that of surgical menopause. In meta-analysis, the pooled relative risk of bilateral oophorectomy before 50 years old on cardiovascular disease was 4.55 (95%confidence interval, 2.56-8.01) [20]. Therefore, we think that the results of this study are mainly due to the rapid decrease in estrogen. Parasympathetic nerve activity decreased immediately after the operation in the surgical menopausal group. Therefore, early hormone replacement therapy may be necessary in surgical menopause group.

In the paucity of studies of perioperative HRV power spectral analysis in gynecologic patients, this study was one of the first to evaluate autonomic activity by menopausal status, and shed light on the clinical utility of HRV metrics, especially in surgically menopausal patients.

Limitations: This study has several limitations. The premenopausal group was much smaller than other groups, and this sample size imbalance reduced the statistical power of the study. Specifically, the majority of the premenopausal group patients participated in two measurements only. A greater number of patients in the premenopausal group would have yielded more accurate statistical findings.

Another limitation is that age is not controlled for in this study. Many HRV variables are age dependent, and older individuals typically show lower HRV than younger people, although several studies showed that MeanRR, RNSSD, LH/HF, and other HRV metrics were independent of age[21]. Future research that includes age-matched healthy controls may help overcome this problem.

A third limitation relates to the patient reporting tool. This study employed the VAS scale because of its ease of use. Although the VAS scale was originally developed for assessing pain levels, it is widely used for other psychophysical measurements including anxiety, irritability, and fatigue[13-17]. For psychometric analyses, validated patient reporting tools have been developed including the Self-rating Depression Scale and Quick Inventory of Depressive Symptomatology Self-report (QIDS-SR) for the assessment of depression[22, 23]. For future psychometric measurements, universally accepted self-report measures should be used in combination with the VAS scale.

The future development of objective autonomic activity parameters may help circumvent the problems of subjective assessment and provide globally acceptable instruments. Our study was among the first efforts towards that goal.

Conclusions: Many medically unexplained symptoms that perimenopausal and postmenopausal patients and other gynecologic patients experience are presumably the result of complex interactions between physical, emotional, environmental, lifestyle, and social factors. These symptoms may be partly associated with disorders of sex hormone status and autonomic control, which adversely influence the cardiovascular, respiratory, immunological, neurological, gastrointestinal, endocrinological, reproductive, and other systems. Medically unexplained symptoms are characterized by interindividual variability of the site of onset and severity. The set of objective metrics for autonomic activity reported here will provide a promising tool for assessing a variety of medically unexplained symptoms.

The positive results presented here warrant a further study in women undergoing childbirth, a situation where sex hormone levels change considerably in a manner similar to menopausal transition. The research methods employed here can also be applicable to the research on the impact of autonomic activity by physical exercise, drugs, aromatherapy treatment, essential oils, and other products.

Disclosure statement

All authors have no conflicts of interest directly relevant to the content of this article.

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