Respiratory Care

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Changes in sympathetic nervous system activity in male smokers after moderate-intensity exercise

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BACKGROUND: This study aimed to investigate the effects of moderate-intensity exercise on the sympathetic nervous system of male smokers.

METHODS: Twenty-eight men (14 smokers and 14 non-smokers) aged 21–46 years were recruited for the study. The activity of the autonomic nervous system was measured by power spectral analysis of heart rate variability. Spectral power in the frequency domain was quantified by integrating the area under the curve of very-low-frequency power (0.007–0.035 Hz), low-frequency power (0.035–0.15 Hz), high-frequency power (0.15–0.5 Hz), and total power (0.007–0.5 Hz) bandwidths. We assessed heart rates, thermoregulatory sympathetic nervous system activity (very-low-frequency power/total power), sympathetic nervous system activity (low-frequency-power/high-frequency power or [very-low-frequency power + low-frequency power]/high-frequency power), and parasympathetic nervous system activity (high-frequency power/total power) of smokers before and after moderate-intensity exercise.

RESULTS: Smokers exhibited a greater degree of sympathetic nervous system activity (as quantified by very-low-frequency power/total power). The sympathetic nervous system activity of smokers (as indicated by [very-low-frequency power + low-frequency power]/high-frequency power) also showed a tendency to increase after exercise. Parasympathetic activity, as indicated by high-frequency power/total power, reduced after exercise in smokers. These findings are contrary to findings previously reported in obese

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participants.

CONCLUSIONS: Increased sympathetic nervous system activity, including thermoregulatory activity, might contribute to cachexia in smokers.

Key words: smoker, exercise, heart rate variability, autonomic responsiveness, power spectral analysis, very-low-frequency power, sympathetic nervous system activity, cachexia

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Introduction

Cachexia is a complex metabolic syndrome characterized by loss of muscle, with or without loss of fat mass, and is most often associated with underlying illness.[1] Many patients with chronic and end-stage diseases including infection, cancer, and congestive heart failure, demonstrate nutritional changes characteristic of cachexia.[1,2] Patients in the early stages of chronic obstructive pulmonary disease also display significant systemic features, such as reduced fat mass,[3] muscle loss, and skeletal muscle wasting.[4,5] The pathogenesis of these features is complex and may result from multiple factors, including energy imbalance, disuse atrophy, and systemic inflammation.[6] Furthermore, cigarette smoking, which is a major risk factor for chronic obstructive pulmonary disease, cancer, and congestive heart failure,[7] has been linked to reductions in body weight and body mass index.[8] These effects are thought to be due to increased energy expenditure and a reduction in appetite.[8] Thus, cigarette smoking may be associated with weight loss even before the development for chronic obstructive pulmonary disease or other pathologies.

Energy expenditure antagonizes the activity of the autonomic nervous system (ANS), which controls the heart rate (HR) and rhythm. The R-R interval, also known as the inter-beat interval, is determined by the net effect of sympathetic and parasympathetic inputs and can be measured on an electrocardiogram (ECG). Spectral analysis of heart rate variability (HRV) has gained general acceptance as an indicator of ANS function.[9] Power

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spectral analysis of HRV has demonstrated at least 2 distinct regions of periodicity within the ECG R-R interval: high-frequency (HF) power (>0.15 Hz), which solely reflects parasympathetic nervous system (PNS) activity, and low-frequency (LF) power (<0.15 Hz), which is dually mediated by sympathetic nervous system (SNS) and PNS activity.[9]

Previous studies using power spectral analysis have demonstrated that inactivity of the ANS, particularly the SNS, may indicate a risk of future weight gain and development of obesity.[10] Furthermore, recent obesity studies have suggested that very-low-frequency power (VLF; 0.007–0.035 Hz) of HRV is selectively lowered in obese individuals in response to several thermogenic perturbations such as acute cold exposure and food intake.[11, 12] This research has demonstrated that spectral analysis of VLF power of HRV can be used as a means of evaluating energy metabolism and thermoregulatory SNS function in humans.

To our knowledge, the effect of moderate-intensity exercise on the VLF power of HRV has not previously been investigated in smokers. The primary objective of this study was to evaluate the VLF activity of HRV in smokers and non-smokers after moderate-intensity exercise by means of power spectral analysis of HRV. We hypothesized that smokers would display continual hyperactive VLF power of HRV.

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Methods

Study Participants

Height- and weight-matched male non-smokers (n = 14) and smokers (n = 14) between the ages of 21 and 46 years were recruited for the study. In previous studies, ANS activity has been found to vary with body type. [10-12] Therefore, we matched body types among participants in order to isolate the effects of cigarette smoking. The smokers were asked about the duration and frequency of their smoking habit. The weight and fat-free mass of each volunteer were measured using a bioelectrical impedance analyzer (Inner Scan 50V; Tanita Corp, Tokyo, Japan). Body mass index and fat-free mass index were calculated as body weight/height^2 and fat-free mass/height^2, respectively. Participant demographics are presented in Table 1. Members of both the smoking and non-smoking groups were in good health and had no evidence of hypertension, cardiovascular disease, diabetes mellitus, or other disease. Every participant kept regular hours at the university and/or at jobs. None of the participants reported engaging in regular exercise. Each participant was instructed to avoid alcohol, coffee, and tea and to fast for 8 hours preceding the study to reduce the effects exerted by alcohol, caffeine, and food intake on the ANS. None of the participants reported a history of heavy drinking, a habit of staying up late, or engaging in extreme exercise the day before the study. Participants who smoked were also required to abstain

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from smoking for 8 hours before the study to limit the acute effects of cigarette smoking, such as increased HR, on the measurements.[13,14] The continuous exercise load used in this study was determined using the Karvonen formula so that the increased HR would place the same load on the bodies of smokers and non-smokers. On the day of the study, the participants stayed in a quiet, comfortable room with minimal stimuli from 2 to 6 pm. This period of the day was chosen to reduce the effects of the circadian rhythm on ANS activity. In accordance with previous studies,[11, 12] the temperature and humidity of the room were strictly regulated (Table 1), and all participants were dressed uniformly in T-shirts and shorts made of the same materials.

The Ethics Board of Kio University and the Hospital Ethics Committee of Tsu Seikyou Hospital approved the study protocol. Written informed consent was obtained from all study participants.

Experimental Procedures

Participants were seated in comfortable chairs and allowed to rest for at least 20 min before the start of the experiment. Each participant breathed in time with a metronome set at 15 beats/min to ensure that respiratory-linked variations in HR did not interfere with low-frequency (below 0.15 Hz) HR fluctuations from other sources. The respiratory rate was regulated for 10 min before the exercise commenced and during the recovery period.

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The regulation of respiration prevented placing a significant load on the participants during the exercise period. The recovery period lasted for 30 min after exercise. The target heart rate (HR_{target}) for the continuous exercise load was set using the Karvonen formula: $(HR_{max} - HR_{rest}) \times 60\%$ intensity + HR_{rest}. The intensity level was set at 60% of the estimated maximal HR, which was calculated as (220 − age). Moderate-intensity exercise was performed on a bicycle ergometer (Combi, Tokyo, Japan) and consisted of pedaling at 60 rpm. The initial power output was 25 W. Participants achieved 60% intensity within 5 min, and the exercise was continued at this intensity for a nother 15 min. The HR was continuously measured using the Sports Heart Rate product (S801i; Poler Electero Corp, Finland).

R-R interval power spectral analysis

Periodic components of HRV tend to aggregate within several frequency bands.[9] ANS activity can therefore be measured non-invasively by HRV power spectral analysis, which deconstructs a series of sequential R-R intervals into a sum of sinusoidal functions of different amplitudes and frequencies by the Fourier transform algorithm. In the present investigation, 3 frequency components of HRV were detected and analyzed. This approach has been used in basic medical science to assess a diverse range of conditions, and its validity and reliability have been confirmed in the literature.[11,12] The spectral powers in

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frequency domains were quantified by integrating the area under the curve for the following bandwidths: VLF power (0.007–0.035 Hz), reflecting energy metabolic and thermoregulatory sympathetic function; LF power (0.035–0.15 Hz), reflecting both SNS and PNS activity; HF power (0.15–0.5 Hz), which solely reflects PNS activity; and total power (TOTAL, 0.007–0.5 Hz), which represents overall ANS activity.[11,12] Thermoregulatory SNS activity was also calculated as the VLF/TOTAL ratio. SNS activities were calculated as the LF/HF and (VLF + LF)/HF ratio. In addition, PNS activity was calculated as the HF/TOTAL ratio. The rest period before moderate-intensity exercise (Pre-ex) was 5 min, and the recovery period after completion of exercise was divided into the following 5-minute stages: Post-1, 5 to 10 min; Post-2, 10 to 15 min; Post-3, 15 to 20 min; Post-4, 20 to 25 min; and Post-5, 25 to 30 min. The segments provide a direct view of time-series changes in ANS activity. Assessment of ANS activity omitted the 5-min period immediately following the exercise as the segments to be affected by breathing.

Statistical Analysis

Data analysis was performed using statistics software (SPSS 19.0, SPSS Chicago, Illinois). Differences between groups were analyzed by comparing the HR, VLF/TOTAL, LF/HF, (VLF + LF)/HF, and HF/TOTAL in the 6 time periods, respectively. Evaluations of these

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data distribution were analyzed by Kolmogorov-Smirnov test. The HR, VLF/TOTAL, LF/HF, (VLF + LF)/HF, and HF/TOTAL of subjects during the 6 periods were compared using Mann-Whitney's U test because a subset these data were the non-normal distribution. The results of these analyses were consistent in all cases. Data are expressed as the median (minimum, maximum) and are shown in box plots. Statistical significance was defined as $P < .05$.

Results

Figure 1 and Table 2 compare smokers and non-smokers during the 6 time periods with respect to HR, VLF/TOTAL, LF/HF, (VLF + LF)/HF, and HF/TOTAL. The VLF/TOTAL values were significantly higher in the smoking group during the Post-1 ($P = .005$) and Post-3 ($P = .005$) periods. LF/HF values were significantly higher in the smoking group during the Post-5 period ($P = .013$). (VLF + LF)/HF values were significantly higher in the smoking group during the Post-3 ($P = .022$) and Post-5 ($P = .048$) periods. HF/TOTAL was significantly lower in the smoking group in the Post-3 ($P = .022$) and Post-5 ($P = .048$) periods. VLF/TOTAL in the Pre-ex, Post-5, and (VLF + LF)/HF in the Post-2 time periods were higher in smokers than non-smokers. HF/TOTAL in the Post-2 period was lower in the smokers. None of the other measured parameters differed significantly.

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Discussion

Our findings indicate that after completion of moderate-intensity exercise, VLF/TOTAL and (VLF+LF)/HF were higher and HF/TOTAL was lower in smokers than in non-smokers with identical exercise loads. In addition, the VLF/TOTAL before exercise and the LF/HF, (VLF+LF)/HF after exercise were higher in smokers than in non-smokers. These findings are contrary to those previously reported for obese subjects.[11,12] Exercise in smokers may thus induce excessive increases in SNS activity, including thermoregulatory SNS activity.

The VLF activity of thermoregulatory sympathetic function reflects lipid metabolism. In obese individuals, VLF activity does not increase after thermogenic perturbations[11,12] and can be altered through dietary modification and exercise training.[15,16] VLF activity is associated with mutations in uncoupling proteins (UCP) and beta3-adrenergic receptors within adipose tissue.[17,18] The activation of UCP1, UCP2, and UCP3, which are located in white adipose tissue, brown adipose tissue, and skeletal muscle, respectively, converts energy from the substrate into heat without using ATP.[19] Thermoregulatory SNS activity significantly correlates with plasma leptin concentrations.[20] Thus, the current results suggest that the elevated VLF/TOTAL in smokers reflects increased thermoregulatory SNS activity, both before and after exercise,

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which may over-stimulate the catabolism of fat in adipose tissue.

In this study, the observed changes in VLF/TOTAL, LF/HF, (VLF+LF)/HF, and HF/TOTAL in smokers persisted for 30 min after completion of exercise. These changes affect the SNS via metaboreflex, baroreflex, and central command.[21] In a previous study, smokers were observed to have a higher resting energy expenditure mediated by caffeine as a thermogenic perturbation.[22] The use of caffeine and nicotine during casual physical activity have been observed to increase energy expenditure in smokers.[23] Analysis of expired gas has revealed that the total thermic response of smokers is significantly greater than that of non-smokers over a period of 4 to 24 hours.[24, 25] Normal-weight smokers have a higher energy expenditure at rest for 30 min after smoking than do obese smokers.[26] Therefore, the already over-activated SNS in normal-weight smokers may be further activated VLF/TOTAL, LF/HF, and (VLF+LF)/HF by exercise.

These findings are clinically important. We deduce that the SNS of smokers may mobilize against adipose tissue, triggering cachexia when calorie intake is deficient. Elevation of hypothalamic-SNS by leptin occurs indirectly through oxidation of fatty acids in muscle.[27] Smokers also experience muscle wasting[28] and loss of type 1 muscle fibers.[29] Furthermore, weight loss, including cachexia, is associated with increased morbidity and mortality.[30-32] Thus, normal-weight smokers may benefit from anti-smoking measures to prevent weight loss.

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These changes in ANS activity are presumably due to the action of nicotine. Participants in this study abstained from cigarette smoking for 8 hours to limit the acute effects of cigarette smoking. No significant differences were observed in the HR or LF/HF between smokers and nonsmokers during the 6 time-periods studied. This observation demonstrates that the acute effects of cigarette smoking were absent in these subjects. However, the effects of nicotine persist for at least 6 to 8 hours after cessation of smoking.[14] Nicotine activates sympathetic neurotransmission by inducing the release of ganglion catecholamine from postganglionic nerve endings.[33] In the present study, the LF/HF of the Post-1 period in smokers was lower than that in non-smokers, with an increase in the VLF/TOTAL. The SNS activity (VLF/TOTAL and [VLF+LF]/HF) of smokers remained elevated throughout the post-exercise period. Thus, the thermoregulatory SNS of smokers may more sensitive to nicotine than the LF/HF.

This study has several limitations. First, we did not conduct all tests at the same room temperature and humidity. Temperature and humidity do play a role in the activity of the ANS, so inconsistencies may be present in the results. Second, we did not directly measure lipid metabolism and cannot conclusively say that thermoregulatory SNS activity corresponds to lipid metabolism. To compensate, we used only healthy subjects with normal weights. Future studies should include subjects with cachexia, semi-starvation condition, or muscle atrophy. Additionally, metabolic and nutritional studies are required to confirm

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the relationship between SNS activity, body weight, and metabolic profiles.

Conclusions

Exercise was observed to induce hyperactivity of the SNS (thermoregulatory SNS and [VLF+LF]/HF) in smokers. Furthermore, HF/TOTAL did not return to pre-exercise levels after completion of exercise in smokers. This SNS hyperactivity in smokers may over-stimulate fat catabolism in adipose tissue over an extended period and trigger cachexia.

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Figure legends

Figure 1. Comparison of (A) heart rate, (B) ratio of the very-low-frequency component to total power, (C) ratios of low-frequency to high-frequency power components, (D) ratio of (very-low-frequency + low-frequency) to high-frequency power components, and (E) ratio of high-frequency component to total power in the smoking (▨) and non-smoking (□) groups. Pre-exercise was defined as the 5-minute time period before initiation of exercise. The post-exercise period was divided into 5-minute time periods covering the following times after exercise was stopped: post-1, 5 to 10 minutes; post-2, 10 to 15 minutes; post-3, 15 to 20 minutes; post-4, 20 to 25 minutes; and post-5, 25 to 30 minutes. Results are expressed as box plots for each group. The boxes show the first to third quartile, the horizontal line represents the median, and the vertical bars indicate the 10th to 90th percentiles. These 6 periods were analyzed by Mann-Whitney's U test in 6 periods, respectively. *$P < .05$, †$P < .1$.

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Table 1. Participant demographics*

	Non-smoker Group (n = 14)	Smoker Group (n = 14)
Age (years)	28.3 ± 7.2	27.6 ± 6.8
Height (cm)	168.3 ± 6.9	170.9 ± 6.4
Weight (kg)	65.4 ± 10.0	63.4 ± 8.9
Body Mass Index (kg/m^2)	23.0 ± 2.5	21.7 ± 2.8
Fat Free Mass (kg)	50.05 ± 6.4	49.2 ± 5.1
Fat-Free Mass Index (kg/m^2)	17.8 ± 1.4	16.8± 1.3
Room temperature (°C)	24.40 ± 1.53	24.04 ± 0.67
Humidity (%)	45.6 ± 4.3	44.3 ± 1.6
Cigarette smoking duration (years)	-	8.8 ± 6.5
Cigarettes/day	-	10.8 ± 7.5
Pack years	-	6.3 ± 9.9
Systolic blood pressure† (mmHg)	121.3 ± 7.1	116.9 ± 8.7
Diastolic blood pressure† (mmHg)	75.9 ± 8.0	69.7 ± 6.7

*Values are mean ± SD.

†Blood pressure was measured before exercise.

The only significant differences observed between the groups were duration of cigarette smoking, cigarettes/day, and pack years.

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Table 2. Comparison of combined heart rate variability in non-smokers and smokers over the course of 6 time-periods.

	Heart rate (beat/min)			VLF/TOTAL		
	Non-smokers	Smokers	*P*	Non-smokers	Smokers	*P*
Pre-Ex	63.0 (47, 76)	66.5 (50, 79)	.322	0.29 (0.09, 0.62)	0.38 (0.22, 0.56)	**.089**
Post-1	87.0 (66, 110)	85.0 (75, 98)	.963	0.24 (0.05, 0.50)	0.43 (0.18, 0.86)	**.005***
Post-2	85.5 (60, 103)	81.5 (68, 96)	.782	0.33 (0.16, 0.58)	0.41 (0.10, 0.55)	.129
Post-3	77.5 (53, 101)	78.5 (66, 93)	.982	0.31 (0.10, 0.48)	0.47 (0.18, 0.63)	**.005***
Post-4	76.0 (53, 94)	77.0 (58, 91)	.729	0.36 (0.12, 0.56)	0.37 (0.21, 0.64)	.462
Post-5	75.0 (50, 99)	75.5 (70, 92)	.549	0.28 (0.07, 0.68)	0.42 (0.29, 0.70)	**.054**

	LF/HF			(VLF+LF)/HF		
	Non-smokers	Smokers	*P*	Non-smokers	Smokers	*P*
Pre-Ex	2.55 (0.87, 6.71)	1.57 (0.60, 6.47)	.358	4.23 (1.82, 9.72)	4.14 (1.30, 15.47)	.783
Post-1	5.28 (1.73, 18.58)	4.62 (1.87, 17.10)	.613	7.10 (2.31, 37.18)	8.72 (4.45, 35.07)	.251
Post-2	3.78 (1.65, 10.50)	5.22 (2.25, 12.38)	.118	5.89 (2.18, 14.03)	9.82 (3.58, 19.54)	**.089**
Post-3	3.44 (0.88, 11.10)	4.37 (2.35, 12.42)	.183	4.66 (1.55, 17.90)	9.10 (4.65, 31.30)	**.022***
Post-4	2.64 (1.21, 8.62)	4.67 (1.72, 10.92)	.154	4.90 (2.54, 11.00)	8.19 (2.45, 22.50)	.118
Post-5	2.80 (1.46, 10.76)	4.70 (2.77, 9.26)	**.013***	4.55 (2.26, 19.73)	8.64 (6.61, 33.22)	**.048***

	HF/TOTAL		
	Non-smokers	Smokers	*P*
Pre-Ex	0.19 (0.09, 0.36)	0.20 (0.06, 0.43)	.783
Post-1	0.12 (0.03, 0.30)	0.10 (0.03, 0.18)	.251
Post-2	0.15 (0.07, 0.32)	0.09 (0.05, 0.22)	**.089**
Post-3	0.18 (0.05, 0.39)	0.10 (0.31, 0.18)	**.022***
Post-4	0.17 (0.08, 0.28)	0.11 (0.04, 0.29)	.118
Post-5	0.18 (0.05, 0.31)	0.10 (0.03, 0.13)	**.048***

Groups were compared with respect to heart rate, VLF/Total, LF/HF, (VLF + LF)/HF, and HF/Total using Mann-Whitney' U test in 6 periods, respectively. Values are the median (minimum, maximum). *P< .05. Bold typefaces are P< .1.

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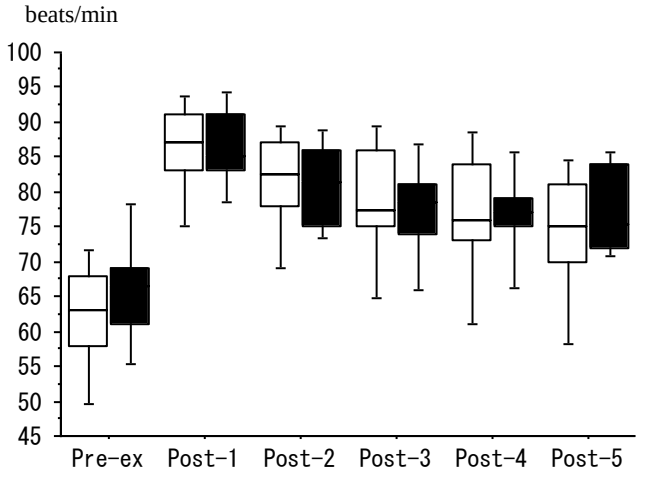
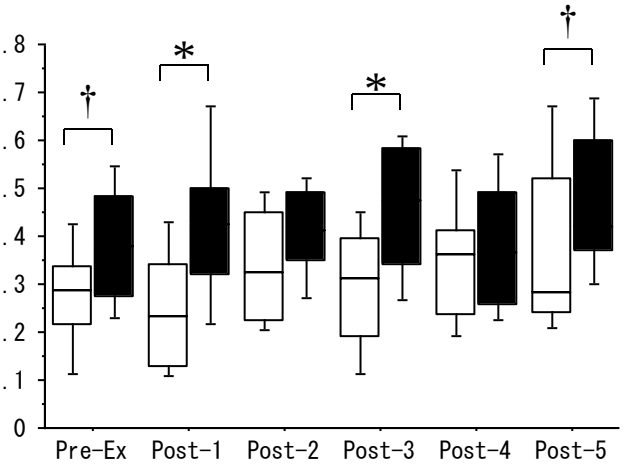
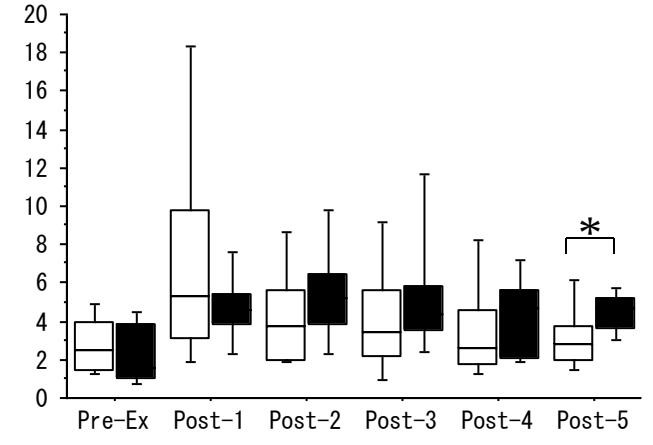
A. Heart Rate



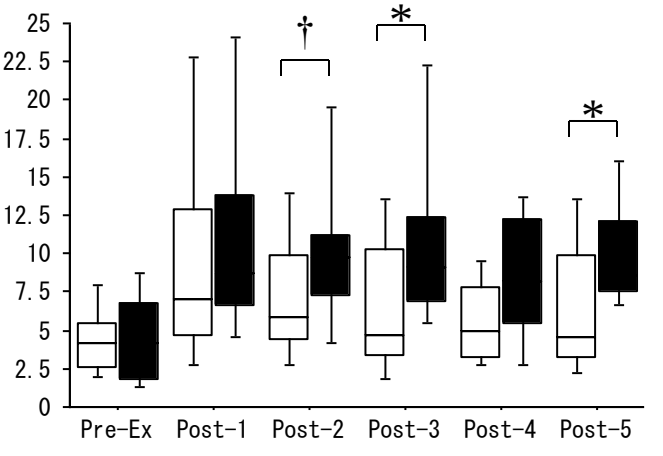
B. VLF/TOTAL



C. LF/HF



D. (VLF+LF)/HF



E. HF/TOTAL