



Original Article

Effects of circuit exercise on autonomic nerve system of survivors after surgery of breast cancer

HYENG-CHEOL SHIN, MD¹⁾, JUNG-OK YANG, PhD²⁾, SEUNG-RYOL KIM, PhD³⁾*

¹⁾ Uva Breast Surgery Clinics, Republic of Korea

²⁾ Department of Kinesiology, Silla University, Republic of Korea

³⁾ Department of Physical Education, College of Sport Science, Dong-A University: 57 Nakdong-daero, 550 Beom-gil, Saha-gu, Busan 604-714, Republic of Korea

Abstract. [Purpose] This study aimed to investigate the effects of exercise on the autonomic nervous system of breast cancer survivors by measuring heart rate variability during an 8-week circulation exercise program. [Subjects and Methods] This intervention study included 22 volunteer female participants, younger than 65 years, who were selected from patients who had been diagnosed with carcinoma in situ and primary invasive breast cancer, stage I-III, in accordance with the American Joint Committee on Cancer (2009) and had undergone breast surgery. [Results] Despite the statistically significant differences in the low-frequency range (log), the high-frequency range (log), the standard deviation of the N-N interval, and the root mean square of differences values, which are heart rate variability indicators after exercise, between the two groups, no statistically significant difference was found in the low-frequency range/the high-frequency range values between the two groups. [Conclusion] The improvement in heart rate variability during the 8-week circulation exercise program confirms the increase in the activity of the autonomic nervous system of breast cancer patients after surgery.

Key words: Breast cancer, Circulation exercise program, Autonomic nervous system

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INTRODUCTION

Survivors of breast cancer usually experience muscular pain at the surgical site, limitation of motion of the shoulder joint, lymphedema secondary to axillary lymph node dissection and radiotherapy, fatigue, myasthenia gravis, lung function deterioration, and overall physical fitness deterioration secondary to systemic side effects of chemotherapy and radiotherapy. Psychologically, they experience mental symptoms and disorders such as depression and anxiety caused by excess stress during their diagnosis and treatment. The physical fitness and bodily functions of a patient with cancer may deteriorate secondary to surgery, chemotherapy, and continued decline in activity, which further leads to a rapid weakening of cardio-pulmonary and muscular system function. In addition, cancer-related fatigue and sleep disturbances are the most common symptoms experienced by patients who have undergone surgery, chemotherapy, or radiotherapy and are related to depression and anxiety disorders in the long term¹⁾. Fatigue is also correlated with decreased quality of living, depression, reduction in body weight, loss of appetite, etc²⁾.

Disharmony in the autonomic nervous system can appear as deterioration of heart rate variability (HRV) and weakening of the psychological and/or physical function, which affect each other³⁾; this disharmony is attributed to the integrated function of the autonomic nervous system with the endocrine system and the interaction of the autonomic nervous system with the central nervous system⁴⁾. The high-frequency (HF) value of the HRV (HRV-HF) of a woman 1 year post-breast cancer surgery was significantly lower than that of a healthy woman⁵⁾.

Such deterioration in the regulating ability of the autonomic nervous system is correlated with anxiety, depression, feel-

*Corresponding author. Seung-Ryol Kim (E-mail: srkimjp@hanmail.net)

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ings of fatigue, and sleep disturbances, which are common in survivors of breast cancer. If a high HRV-HF value is related to parasympathetic nervous system function, the death rate of metastatic breast cancer survivors was significantly lower than the control group by 25% during a central observation period of 7.9 years^{5, 6}. Based on these findings, deterioration in the autonomic nervous system and weakening of physical and mental functions of breast cancer patients can be expected.

According to previous studies, exercise has a statistically significant effect on the HRV of patients who were receiving rehabilitation due to myocardial infarction, chronic obstructive pulmonary disease, elderly patients, obese adolescents, and those in high-stress occupations⁷⁻¹³. However, in studies on healthy subjects and those with fibromyalgia, exercise did not have a statistically significant effect on HRV^{14, 15}. In studies where only strengthening exercise was done, without any aerobic exercise that can increase heart rate, or in studies where exercise duration was 8 weeks or shorter, exercise did not have any effect on HRV¹⁶. This study aimed to determine, through HRV, whether autonomic nervous system activity increases when a breast cancer patient at risk of autonomic nervous system deterioration (such as decline in physical fitness, depression, anxiety, and insomnia) performs aerobic exercises (which can increase the heart rate) along with strengthening exercises. An increase in autonomic nervous system activity through exercise is thought to be helpful in alleviating various physical and mental problems that breast cancer patients usually experience. Accordingly, in this intervention study, we intended to investigate through HRV the effect of exercise on the autonomic nervous system (which reflects the mental and physiological functions) in an integrated manner by letting survivors of breast cancer participate in an 8-week circulation exercise after the surgery.

SUBJECTS AND METHODS

The study was carried out in 22 volunteer female participants younger than 65 years who confirmed the intent and purpose of the experiment and signed participation consent. Participants were selected from patients who had been diagnosed with carcinoma in situ and primary invasive breast cancer, stage I-III, in accordance with the American Joint Committee on Cancer (AJCC, 7th Ed. 2009) and had undergone breast surgery located in City B. The clinical characteristics of the study participants are shown in (Table 1).

The subjects of this study were breast cancer patients, and the guidelines for the physical activities suitable for cancer patients as indicated by the American College of Sports Medicine (2010) were considered while creating the exercise programs. Regarding the intensity of the exercise, the Borg rating of perceived exertion was used. The exercise program is shown in (Table 2).

To adjust for the effect of circadian rhythm, HRV was measured by using CANS 3000 (Laxtha, Daejeon, Korea) between 2:00 and 6:00 p.m. after fasting for 2 hours or longer and resting for 10 minutes. The subjects were instructed not to drink alcohol a day before the measurement or smoke on the day of the measurement. The subjects were seated on chairs, and electrodes were attached on the area of the wrist joints and foot joints, and their HRVs were measured in stable state for 5 minutes. For temporal analysis of change in R-R interval, the standard deviation of the N-N interval (SDNN) was measured in 1/1,000 seconds (milliseconds), and this reflects the change brought about by the parasympathetic nervous system. The root mean square of successive differences (RMSSD) of continuous R-R interval was obtained in 1/1,000 seconds, and the low-frequency range (LF, 0.04-0.15 Hz), high-frequency range (HF, 0.15-0.4), and LF/HF ratio were measured.

All the data measured in this study were analyzed by using the SPSS version 23.0 for Windows (IBM, Chicago, IL, USA). A normality test and a homogeneity test between the two groups were carried out through a Shapiro-Wilk test, and a paired t-test of HRV values measured before and after the 8-week program was done to check the change in HRV before and after exercise within the exercise groups. Moreover, an independent t-test was conducted to check the difference between exercise and non-exercise groups. The significance level of all statistical analyses was set at $\alpha=0.05$.

RESULTS

The results of the analysis of the change in the LF range of the HRV within and between groups after participating in the 8-week circulation exercise are given in (Table 3). Before exercise, there was no statistically significant difference between the LF (log) values of the experimental and control groups, which showed average values of 5.58 and 5.11 ms², respectively; after exercise, there was a statistically significant difference between the LF (log) values of the two groups, which showed average values of 5.67 and 4.61 ms², respectively ($p=0.008$). However, the average LF (log) values of the experimental group before and after exercise were 5.58 and 5.67 ms², respectively, which showed no statistically significant difference.

The results of the analysis of the change in the HF range of the HRV within and between groups after participating in the 8-week circulation exercise are given in (Table 3). Before exercise, there was no statistically significant difference between the HF (log) values of the experimental and control groups, which showed average values of 5.68 and 4.86 ms², respectively; after exercise, there was a statistically significant difference between the HF (log) values of the two groups, which showed average values of 5.98 and 4.49 ms², respectively ($p=0.014$). However, the average HF (log) values of the experimental group before and after exercise were 5.68 and 6.00 ms², respectively, which showed no statistically significant difference.

The results of the analysis of the change in the LF/HF ratio of the HRV within and between groups after participating in the 8-week circulation exercise are given in (Table 3). Before exercise, there was no statistically significant difference between

Table 1. Clinical characteristics of the study objects

| Characteristics | Control group (n=10) | | Experimental group (n=12) | |
|-----------------------|---------------------------|----|---------------------------|------|
| | No. of subjects | % | No. of subjects | % |
| Average age | 49.2 (range, 35–60) years | | 46.3 (range, 35–66) years | |
| <50 years | 5 | 50 | 8 | 66.7 |
| >50 years | 5 | 50 | 4 | 33.3 |
| Lapse of period | 27.7 (range, 12–39) | | 20.3 (range, 6–48) | |
| <30 | 4 | 40 | 8 | 66.7 |
| >30 | 6 | 60 | 4 | 33.3 |
| Stage | | | | |
| 0 | 1 | 10 | 1 | 8.3 |
| 1 | 2 | 20 | 4 | 33.3 |
| 2 | 6 | 60 | 6 | 50 |
| 3 | 1 | 10 | 1 | 8.3 |
| Anti-cancer treatment | | | | |
| Yes | 7 | 80 | 10 | 83.3 |
| No | 3 | 20 | 2 | 16.7 |
| Radiotherapy | | | | |
| Yes | 8 | 30 | 11 | 91.7 |
| No | 2 | 70 | 1 | 8.3 |
| Operation method | | | | |
| Whole | 3 | 30 | 2 | 16.7 |
| Part | 7 | 70 | 10 | 83.3 |

Table 2. Exercise program

| Exercise frequency | Stage | Form | Time | Intensity | | | | |
|--------------------------|---|---|-----------------------------------|-----------|-----------|------------------------|--------------------------|--------|
| Three times a week | Warming up | Gymnastics and stretching (around the upper body) | | RPE 9–12 | | | | |
| | Main exercise | 15-min circulation exercise | 1. Shaking while running in place | 1st week | RPE 11–13 | | | |
| | | | 2. Flank | | | Familiarizing motions | 10 min, 3 times | |
| | | | 3. Running in place | | | 5-min course, 1 time | 10 min (30 s per motion) | |
| | | | 4. Squat | | | Motion practice | 15 min | 40 min |
| | | | 5. Walking in place | | | 5-min course, 3 times | 25 min | |
| | | | 6. Crunch | | | 5-min course, 2 times | 15 min | |
| | | | 7. Step | | | 10-min course, 2 times | 25 min | |
| | | | 8. Lunge | | | 5-min course, 1 time | 10 min | |
| | | | 9. Running with open arms | | | 10-min course, 1 time | 15 min | |
| 10. Back muscle exercise | | | 15-min course, 1 time | | | 15 min | | |
| Cooling down | Gymnastics and stretching (around the upper body) | | RPE 9–12 | | | | | |

RPE: rating of perceived exertion

the LF/HF values of the experimental and control groups, which showed average values of 1.18 and 1.45, respectively; after exercise, there was no statistically significant difference between the LF/HF values of the two groups, which showed average values of 0.95 and 1.58, respectively.

The results of the analysis of the change in the SDNN value of the HRV within and between groups after participating in the 8-week circulation exercise are given in (Table 3). Before exercise, there was no statistically significant difference between the SDNN values of the experimental and control groups, which showed average values of 42.15 and 34.29 ms,

Table 3. Change in the LF, HF, LF/HF, SFDNN, RMSSD range of the HRV within and between groups

| Group | | Pre | Post |
|--------------------------------|---------------------------|---------------|----------------|
| LF (log) (ms ²) | Control group (n=10) | 5.12 ± 0.83 | 4.61 ± 1.01** |
| | Experimental group (n=12) | 5.58 ± 0.65 | 5.67 ± 0.66 |
| HF (log) (ms ²) | Control group (n=10) | 4.86 ± 1.18 | 4.50 ± 1.63* |
| | Experimental group (n=12) | 5.68 ± 0.92 | 6.00 ± 0.92 |
| LF/HF (ms ²) | Control group (n=10) | 1.45 ± 0.68 | 1.58 ± 1.81 |
| | Experimental group (n=12) | 1.18 ± 0.95 | 0.95 ± 0.73 |
| SDNN (ms) | Control group (n=10) | 34.30 ± 14.21 | 30.68 ± 16.22* |
| | Experimental group (n=12) | 42.15 ± 13.31 | 45.14 ± 12.62 |
| RMSSD (ms) | Control group (n=10) | 27.07 ± 15.21 | 24.73 ± 22.18* |
| | Experimental group (n=12) | 38.75 ± 24.94 | 46.54 ± 24.45 |

LF: low-frequency; HRV: heart rate variability; HF: high-frequency; SDNN: standard deviation of the N-N interval; RMSSD: root mean square of successive differences.

Values are M ± SD. *, ** Significant difference compared with experimental (p<0.05, p<0.01)

respectively; after exercise, there was a statistically significant difference between the SDNN values of the two groups, which showed average values of 45.14 and 20.68 ms, respectively (p=0.029). However, the SDNN values of the experimental group before and after exercise were 42.15 and 45.14 ms, respectively, which showed no statistically significant difference.

The results of the analysis of the change in the RMSSD value of the HRV within and between groups after participating in the 8-week circulation exercise are given in (Table 3). Before exercise, there was no statistically significant difference between the RMSSD values of the experimental and control groups, which showed average values of 38.75 and 27.07 ms, respectively; after exercise, there was a statistically significant difference between the RMSSD values of the two groups, which showed average values of 46.54 and 24.21 ms, respectively (p=0.042). However, the RMSSD values of the experimental group before and after exercise were 38.75 and 46.54 ms, respectively, which showed no statistically significant difference.

DISCUSSION

In this study, there was a statistically significant difference between the LF (log) values of the experimental and control groups after exercise, which is attributed to the fact that the subjects of the study were breast cancer patients. Another study on healthy subjects reported that exercise did not have any significant effect on the LF (log) value¹⁵. However, in studies carried out in elderly people, obese adolescents, and those in high-stress occupations, exercise had a statistically significant effect on the LF (log) value^{7, 11-13}. A breast cancer patient undergoes diverse treatments such as surgery, radiotherapy, chemotherapy, and anti-hormone therapy, which have side effects including fatigue, deterioration of physical ability, insomnia, depression, and anxiety. Such side effects are thought to be caused by the deterioration of sympathetic nervous system activity due to by excess tension. Accordingly, although it is easy to evaluate the significance of improvement in the LF (log) value of a subject with low LF (log) value due to excess tension in the sympathetic nervous system, it is difficult to expect an improvement in the LF (log) value of a subject whose LF (log) value is within normal range. When sympathetic nervous system activity deteriorates because of excess tension, the ability to cope with a dangerous situation can deteriorate as well^{5, 17-19}. In this study, the LF values significantly increased, which signifies an increase in the activity of the sympathetic nervous system and is thought to improve the coping ability of the subject in protecting herself in a stressful or dangerous situation. Although there was a statistically significant difference between the LF (log) values of the two groups, there was no significant difference within the experimental group, which is due to the fact that the LF (log) value of the control group decreased from 5.11 ms before exercise to 4.61 ms after exercise. That is, the activity of the sympathetic nervous system is considered to naturally decrease due to excess tension of the sympathetic nervous system in a situation where stress continues. To increase the activity of the sympathetic nervous system significantly while overcoming the natural decrease in the activity of the sympathetic nervous system in a group similar to our experimental group, an exercise program with a duration not shorter than 12 weeks can be helpful¹⁰.

In this study, there was a significance difference between the HF (log) values. In studies on healthy subjects, exercise did not have any significant effect on the HF (log) value^{14, 15}. However, in studies on patients receiving rehabilitation because of chronic obstructive pulmonary disease or myocardial infarction, elderly people, obese adolescents, and those in high-stress occupations, exercise has a statistically significant effect on the HF (log) value, similar to this study^{7-9, 11-13}. As this study was carried out in breast cancer patients with decreased parasympathetic nervous system activity due to excess physical and mental stress environment, a significant change in the HF (log) value has been noted. In this study, the HF value, which represents the activity of the parasympathetic nervous system, was higher than that of the control group after exercise, and this is attributed to the normalization of the activity of the parasympathetic nervous system through exercise. This suggests

that the ability to recover from a stressful or dangerous situation to a normal condition has been improved¹⁹).

Although there was a statistically significant difference between the HF (log) values of the two groups, there was no significant difference within the experimental group. The reason can be inferred from the fact that the HF (log) value of the control group dropped from 4.86 ms before exercise to 4.49 ms after exercise. That is, the activity of the parasympathetic nervous system can naturally decrease in a situation where stress continues. To increase the activity of the parasympathetic nervous system significantly while overcoming the natural decrease in the activity of the parasympathetic nervous system in a group similar to our experimental group, an exercise program with a duration not shorter than 12 weeks can be helpful¹⁰).

In this study, no statistically significant difference was found between the LF/HF values of the two groups. Other studies did not find any statistically significant difference either^{15, 20, 21}). The LF/HF value represents the balance between the activities of the sympathetic nervous system and the parasympathetic nervous system within a human body. In this study, the average LF/HF values of the experimental and control groups before exercise were 1.18 and 1.45, respectively, and those after exercise were 0.95 and 1.58, respectively, which did not show any statistically significant change. The LF/HF value in this study shows that to balance the autonomic nervous system of a normal person before exercise, the activity of the parasympathetic nervous system should be higher than that of the sympathetic nervous system. That is, the LF/HF value of a normal person should not be higher than 1. The LF/HF value of the experimental group decreased below 1 to 0.96 after exercise. This means that the activity of the parasympathetic nervous system has increased in comparison to that of the sympathetic nervous system as a result of the exercise. Meanwhile, as there was no exercise treatment in the control group, the activity of the sympathetic nervous system has increased, thus losing the equilibrium and showing an LF/HF value of 1.58 after 8 weeks. This corresponds to the result of this study wherein the ratio of the sympathetic nervous system activity and that of the parasympathetic nervous system is not higher than 1, which means that the activity of the parasympathetic nervous system is higher.

In this study, there was a statistically significant increase in the SDNN value of the experimental group, which is the time-series measurement of the HRV, in comparison to that of the control group. This result is the same as those of other studies^{8, 9, 11}). However, contrary to the findings of our study, other studies reported that there was no change in the SDNN value even after the exercise program. These were studies carried out in healthy adults or children¹⁵) or where only strengthening exercise was done without performing any aerobic exercise that increases the heart rate^{11, 16}) could not find any statistically significant difference between the SDNN values measured before exercise and during the 4th and 8th weeks of medium-intensity exercise (3-km walking; speed, 6 km/hour, 3 times a week), they observed a change in the SDNN value after 12 weeks of exercise. A significant change in the SDNN value can be observed when the group at risk of deterioration of the autonomic nervous system included aerobic exercise. The SDNN value represents the overall activity of the autonomic nervous system including the sympathetic and parasympathetic nervous systems. This study shows that exercise increases the overall activity of the autonomic nervous system.

Although there was a statistically significant difference between the SDNN values of the two groups, there was no significant difference within the experimental group. The SDNN value of the control group decreased from 34.29 ms before exercise to 30.68 ms after exercise. The activity of the autonomic nervous system naturally decreases in situations with continuous stress. To overcome the natural decrease in the activity of the autonomic nervous system in a group similar to our experimental group, an exercise program with a duration not shorter than 12 weeks can be helpful¹⁰).

In this study, there was a statistically significant increase in the RMSSD value of the experimental group, which is the time-series measurement of the HRV, in comparison to that of the control group. This result is the same as those of other studies^{8, 9, 11}). However, contrary to the findings of our study, other studies reported no change in the RMSSD value even after the exercise program. These were studies carried out in healthy adults or children^{15, 16}) or where only strengthening exercise was done, without any aerobic exercise that increases the heart rate¹⁶). Liu et al.¹¹) observed a change in the RMSSD value after 12-week exercise. Significant changes in the HRV indicators, including the RMSSD value, were observed when the group at risk of deterioration of the autonomic nervous system included aerobic exercise for a certain period or longer. An RMSSD value represents the activity of the parasympathetic nervous system. As the effect of exercise on the autonomic nervous system was checked through the HF (which is a frequency-series analysis value), the RMSSD, which is a time-series analysis value, could confirm that exercise increases the activity of the parasympathetic nervous system.

Although there was a statistically significant difference between the RMSSD values of the two groups, there was no significant difference within the experimental group, which is due to the decrease in the RMSSD value of the control group from 27.07 ms before exercise to 24.21 ms after exercise. That is, the activity of the parasympathetic nervous system can naturally decrease in situations with continuous stress. To overcome the natural decrease in parasympathetic nervous system activity in groups similar to our experimental group, an exercise program with a duration of no less than 12 weeks can be helpful¹⁰). The results of previous studies and this study on breast cancer patients who are at risk of autonomic nervous system deterioration, such as decline in physical fitness, depression, anxiety, and insomnia, show a statistically significant increase in the activity of the autonomic nervous system, which implies that an exercise program with a duration not shorter than 12 weeks and includes aerobic and strengthening exercises can increase the activity of the autonomic nervous system in breast cancer patients after surgery.

Conflict of interest

The authors declare no conflicts of interest.

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