行政院國家科學委員會專題研究計畫　成果報告

規律運動訓練計畫對乳癌婦女疲憊症狀、身體功能及血清 Cytokine 濃度改善成效系列研究

計畫類別：整合型計畫
計畫編號：NSC93-2321-B-038-006-
執行期間：93 年 08 月 01 日至 95 年 01 月 31 日
執行單位：臺北醫學大學護理學系

計畫主持人：蔡仁貞
共同主持人：陳炳常，陳保羅，許準榕，邱仲峰，林建煌，呂思潔

報告類型：精簡報告

處理方式：本計畫可公開查詢

中　華　民　國 95 年 4 月 28 日

摘要

本研究針對 Stage I, II 或 IIIa 乳癌婦女於化學治療期間疲憊程度、血清 cytokines 濃度及身體功能之變化進行觀察，並分析規律運動訓練對乳癌婦女之影響。本研究採類實驗性研究設計，將個案以隨機方式分配至運動組與控制組，運動組個案參與每週 3 次，每次 30 分鐘，共 12 週之走步機運動訓練。研究工具包括：走步機運動測試（Treadmill Exercise Test）、簡明疲憊量表（Brief Fagitue Inventory）、及 Enzyme-linked Immunosorbent Assay Kits，以測驗血清 IL-1β, IL-6, TNF-α cytokines 濃度。本計劃於個案接受第一次化學治療後第一週，化學治療期間第 8 及 12 週進行資料收集，運動介入措施於化療後第一週開始進行。

研究期間共有 33 位個案完成資料收集（18 位運動組，15 位控制組），運動組之個案疲憊程度、身體功能（VO_2max）均有明顯改善。而控制組疲憊程度於第 8 週相較於化療第一週顯著上升，身體功能則未有顯著變化。在血清 cytokines 濃度方面，運動組 TNF-α 血清濃度於第 8 週及 12 週均較運動介入前顯著降低，然在控制組並未觀察到顯著改變。在運動組個案中，血清 TNF-α 濃度變化與疲憊降低程度呈現顯著相關。

此外，運動組血清 IL-6 濃度於研究計劃期間，並未有顯著變化。然而，相較於化療第 1 週，控制組血清 IL-6 濃度於第 8 及 12 週均有顯著上升的情形。在血清 IL-1β 濃度方面，無論在實驗組或控制組，均未觀察到顯著的改變。經由以上結果，研究者建議針對乳癌婦女接受化學治療期間進行適度運動訓練，可增進其身體功能、減輕疲憊程度，並協助降低血清 TNF-α 濃度。

關鍵字：乳癌、血清素 cytokines、疲憊、運動訓練

Abstract

This study was conducted to develop an aerobic exercise training program and to asses the effect of exercise training on fatigue and cytokine levels in breast cancer women receiving adjuvant chemotherapy. A randomized, controlled research design was used. Data were collected within one week after chemotherapy but before beginning the exercise intervention, the 8^{th} and 12^{th} weeks of the intervention. Woman diagnosed with stage I, II or IIIa breast cancer, age between 30 and 69 years old, and accept into a program of adjuvant chemotherapy were recruited. A least one week after initiation of the chemotherapy, all subjects performed a graded exercise test. Concentration of serum IL-1β, IL-6, and TNF-α of the subjects were determined using DuoSet enzyme-linked immunosorbent assay kits. The Brief fatigue Inventory was used to measure the severity of fatigue. The exercise training program consists of 20 to 30 minutes of supervised walking exercise on a treadmill, 3 times each week for 12 weeks.

Thirty-three subjects completed the 12-weeks study (18 in the exercise group and 15 in the control). Levels of fatigue were reduced in the exercise participants in the 12^{th} week of the study. Whereas, fatigue severity of the control group increased from the start of chemotherapy to the 8^{th} week of chemotherapy but did not change from the 8^{th} week to the 12^{th} week. At the end of intervention, the exercise participants showed an increase in their physical fitness as indicated by the volume of oxygen intake. The control group did not show an increase in physical fitness. The mean plasma of TNF-α concentration decreased significantly from the start to the 8^{th} and 12^{th} weeks of chemotherapy in exercise participants, whereas it did not change in the control. Change in mean fatigue scores compared to the start of chemotherapy were paralleled to the change of plasma INF-α concentrations in exercisers at the end of the

study.

The plasma IL-6 concentrations following the initiation of chemotherapy were not significant different between the two groups. No significant different was found in the change in IL-6 over time in exercisers, whereas it increased in the control. No significant different was found in the change of IL-1β over time for either group. Result from this study suggested that a moderate exercise program for breast cancer women undergoing chemotherapy may heighten their physical capacity, decrease concentration of TNF-α cytokines and levels of fatigue.

Key words: breast cancer, fatigue, cytokines, exercise training

Introduction

Fatigue is a common problem among women undergoing treatment for breast cancer and may endure for months or years following completion of treatment in some patients. The majority of breast cancer women experienced fatigue regardless of diagnosis, stage of disease, or type of treatment (Morrow et al., 2002; Schwartz, 1999). Because of its prevalence, it is often reported as the symptom that is the most distressing and causes the greatest amount of interference with daily life (Mendoza et al., 1998). Fatigue may affect cognition, reduce functional ability and impair one's ability to interact with family and friends (Cimprich, 1992; Pickard-Holley, 1991).

Although fatigue has been associated with inadequate nutrition, sleep, disease-related biochemical changes and reduce levels of activity; the etiology of cancer related fatigue remains unclear (Schwartz, 1999). Cytokines are also proposed to be associated with symptoms of fatigue (Kurzrock, 2001). Elevation blood levels of IL-1β, IL-6, TNF-α have been observed in patients receiving treatment for cancer who reported feeling fatigued (Bower et al., 2002; Morrow et al., 2002).

Fatigue in human may be defined as a subjective of overwhelming, sustained exhaustion and decreased capacity for physical and mental work that is not relieved by rest. This definition has both subjective and objective elements, and any explanation of the pathophysiology of this symptom account for both dimensions (Piper, 1992). A critical aspect of cancer induced fatigue is the consistent observation that eved by rest, suggesting that cancer-related fatigue probably involves

inflammatory responses (Ardies, 2002). However, few studies have looked at cytokine response and adaptation to long-term physical training in patients with chronic disease (Pedersen, 2000). The cytokine response to endurance exercise remains controversially, depending on the levels and duration of physical activity. Larsen and colleagues (2002) observed a decrease in TNF-α levels (from 29.9±22.4 to 25.2±15.2pg/ml) in men with congestive heart failure (CHF) after 12 weeks exercise training. In a study by Gielen and colleagues (2003), exercise training significant reduced the expression of TNF-α, IL-6, IL-1β in CHF patients after 6 months exercise training.

Effects of exercise in patients undergoing cancer treatment and cancer survivors have been studied in several experimental studies. These studies tested an aerobic exercise intervention (e.g., cycling, walking, or patient selected activities) and followed exercise prescription guideline suggested by the American College of Sport Medicine (2000). Each study prescribed 3 to 5 days per week of an aerobic activity that can be maintained continuously for 20 to 60 minutes at a moderate intensity. Exercise intensity depending on patient's current fitness level and severity of side effects from treatment. Guidelines include 50% to 75%VO_2max or heart rate reserve, 60% to 80% maximal heart rate, or a Rating of Perceived Exertion of 11-14. These studies have shown that many breast cancer survivors, even during adjuvant therapy, can adhere to a conventional exercise prescription. Program ranged from 6 to 12 weeks of exercise for patients during breast cancer treatment, and 8 to 24 weeks for breast cancer patients after treatment. All studies showed significant beneficial effects of exercise in multiple domains of functioning, reduction in fatigue or emotional distress (Dimeo at al., 1999; Mock et al., 1994; Schwartz, 2000, Winningham, 2001).

Methods

Research Design

A randomized, controlled research design was used to examine the effects of exercise training on fatigue and cytokine levels in breast cancer patients who undergoing adjuvant chemotherapy. Data were collected within one week after chemotherapy but before beginning the exercise intervention (O_1), the 8^{th} (O_2) and 12^{th} (O_3) weeks of the exercise training program.

Subject and setting

Women with breast cancer who were evaluated for postsurgery adjuvant chemotherapy protocols in a university-based teaching hospital were recruited in this study. Subject selection criterions were: age between 30 and 69 years old; have been diagnosed with stage I, II or IIIa breast cancer; and accept into a program of adjuvant chemotherapy. Exclusion criterions included: a history of cardiovascular disease, pulmonary disease, or skeletolmuscular disease. This study had been approved by the Institutional Review Board of the teaching hospital and informed consent was obtained from all participants.

Exercise Tests

All subjects underwent a physical evaluation. A least one week after initiation of the chemotherapy, all subjects performed a graded exercise test using the Balke protocol on a Schiller Treadmill (Cardiovit CS-100) fitted with an Schiller electrocardiogram monitor and controller (Schiller AG, Basel, Switzerland). Patients who show abnormalities on the exercise EKG were excluded from this study. The Balke protocol was selected due to its moderate intensity increases per stage (ACSM, 2000). The subjects will performed the second test at the end of the study. Functional capacity of each subject was determined based on the results of individual exercise tests.

Blood Sample Measurements

To concentration of IL-1β, IL-6, and TNF-α in the serum of the subjects were determined using commercial available DuoSet enzyme-linked immunosorbent assay kits (R & D Systems, Minneapolis, MN). Blood samples were drawn from subjects within one week following chemotherapy at the 3 data collection times of the study. All blood sample measurements were preformed with subjects in a 12-h fasted between 8:00 and 10:00 in the morning.

The Brief Fatigue Inventory

The Brief fatigue Inventory (BFI) was used to measure the severity of fatigue and interference caused by fatigue. The BFI has nine items, with the items measured on 0-10 numeric rating scales. Three items ask patients to rate the severity of their fatigue at its "worst," "usual," and "now" during normal waking hours, with 0 being "no fatigue" and 10 being "fatigue as bad as you can imagine." Six items assess the amount that fatigue has interfered with different aspects of the patient's life during the past 24 hours. The interference items are measured on a 0-10 scale, with 0 being "doses not interfere" and 10 being "completely interfere." Concurrent validity was established by showing that the BFI is closely related to existing instruments that measure fatigue. Two previously validated measures, POMS-fatigue and the fatigue subscale of the Functional Assessment of Cancer Therapy (FACT), were used in the analysis. The BFI was significantly correlated with both the FACT ($r = -0.88$, $p<0.001$) and the POMS ($r = 0.84$, $p<0.001$) fatigue subscales.

Demographic and Laboratory Data Collection Form

Additional data on possible confounding variables including: age, employment, marital status, stage of diagnosis, and type of chemotherapy were analyzed for each subject. These data were collected in a structure data collection form.

Experimental Groupings and Trials

Prior to initial the randomized-control trail, the investigator obtained informed consent from subjects then randomly assign them into one of the two experimental groups: a control group and a moderate intensity exercise training group. The exercise training program consists of 10 minutes warm up, 20 to 30 minutes of supervised walking exercise on a treadmill, and 10 minutes cool down three times each week for 12 weeks.

During walking exercise, the subjects maintained about 60-70% maximal heart rate reserve. To ensure compliance with the exercise prescription, exercise heart rate for each subject will be continuously monitored by a well-trained research assistant. In addition, subject's blood pressure and values of RPE will be taken every 10 minutes during exercise to ensure the safety of the exercise participants. Subjects in the control group remained their usual lifestyle and receive standard care given by the staff in the outpatient oncology clinic. Regular follow-up through outpatient department or by telephone interview was arranged every 4 weeks for the control group.

Statistical Analysis

Values were expressed as mean ± standard deviations in this study. Independent t-tests, Mann-Whitney U test, or Chi-square test were preformed to analyze the differences among baseline data between groups. Pre-training versus post-training and between group differences in physical capacity, concentration of cytokines, and levels of fatigue at 8-week and 12-week were analyzed using repeated-measures analysis of variance and the post-hoc tests. A p-value of < 0.05 was considered to be statistically significant.

Result and Discussion

At the beginning of the study, 40 subjects were recruited in this study (22 in the

exercise group and 18 in the control). Of these, 4 exercises and 3 nonexercisers dropped out during the study period, resulting in 33 subjects completing the 12-weeks study (18 in the exercise group and 15 in the control). The mean age of the subjects was 51 years (range of 30-69). Treatment for chemotherapy lasted 12 to 24 weeks. No statistical difference was found between the groups in age, weight, stage of cancer, and type of treatment at the baseline (Table 1).

The subjects' age, stage of cancer, and type of chemotherapy were not significantly related to fatigue severity or disruptiveness score across the three assessment times ($p > 0.05$). Levels of fatigue were reduced in the exercise participants in the 12^{th} week of the study (O_3). Whereas, fatigue severity of the control group increased from the start of chemotherapy (O_1) to the 8^{th} week of chemotherapy (O_2) but did not change significantly from the 8^{th} week (O_2) to the 12^{th} week (O_3) ($p = 0.43$).

At the end of intervention, the exercise participants showed an increase in their physical fitness as indicated by the volume of oxygen intake (VO_2max). The control group did not show an increase in physical fitness (Table 3). The mean plasma of TNF-α concentration decreased significantly from the start (O_1) to the 8^{th} (O_2) and 12^{th} weeks (O_3) of chemotherapy in exercise participants, whereas it did not change in the control. This change in the mean plasma TNF-α concentration between the two groups was significantly different (Table 4). In addition, change in mean fatigue scores compared to the start of chemotherapy were paralleled to the change of plasma INF-α concentrations in exercisers at the end of the study ($r = 0.44$, $p = 0.03$).

The plasma IL-6 concentrations following the initiation of chemotherapy (O_1) were not significant different between the two groups. No significant different was found in the change in IL-6 over time in exercisers, whereas it increased in the control. No significant different was found in the change of IL-1β over time for either group

(Table 4).

Results of this study suggested that chemotherapy led to an increase in the circulating levels of IL-6, as well as increased ratings of fatigue. A moderate exercise program for breast cancer women undergoing chemotherapy may heighten their physical capacity, decrease concentration of TNF-α cytokines and levels of fatigue. Future studies are needed to examine the long tern effects of exercise intervention on inflammation and complaints of fatigue in breast cancer women receiving chemotherapy.

Reference

American College of Sports Medicine (2000). ACSM's guidelines for exercise testing and prescription. ACSM: Baltimore, MD.

Ardies, C. M. (2002). Exercise, cachexia, and cancer therapy: A molecular Rationale. Nutrition and Cancer, 42(2), 143-157.

Bower, J. E., Ganz, P. A., Aziz, N., Fahey, J. L.(2002). Fatigue and proinflammatory cytokine activity in breast cancer survivors. Pschosomatic Medicine, 64, 604-611.

Burnham, T. R., Wilcox, A. (2002). Effects of exercise on physiological and psychological variables in cancer survivors. Medicine & Science in Sports & Exercise, 34(12), 1863-1867.

Cimprich, B. (1992). Attentional fatigue following breast cancer surgery. Research Nursing and Healthy, 15, 199-207.

Courneya, K. S. (2003). Exercise in cancer survivors: An overview of research. Medicine & Science in Sports & Exercise, 35(11), 1846-1852.

Courneya, K. S., Mackey, J. K., Bell, G. J., Janes, L. W., Field, C. J., Fairey, A. S. (2003). Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: Cardiopulmonary and quality of life outcomes. Journal of Clinical Oncology 21(9), 1660-1668.

Courneya, K. S., Mackey, J. K., McKenzie, D. C. (2002). Exercise for breast cancer survivors. The Physician and Sportsmedicine, 130(8), 33-42.

Crevenna, R., Schmidinger, M., Keilani, M., Nuhr, M., Zoch, C., Zielinski, C. (2003). Aerobic exercise as additive palliative treatment for a patient with advanced hepatocellular cancer. Wiener Medizinische Wochenschrift 153, 237-240.

Dimeo, F. C. (2001). Effects of exercise on cancer-related fatigue. Cancer, 92(8), 1689-1693.

Dimeo, F., Rumberger, B. G., Keul, J. (1998). Aerobic exercise as therapy for cancer fatigue. Medicine & Science in Sports &Exercise, 30(4), 475-478.

Dimeo, F. C., Stieglitz, R. D., Novelli-Fischer, U., Fetscher, S., Keul, J. (1999). Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. Cancer, 85(10), 2273-2277.

Escalante, C. P. (2003). Treatment of cancer-related fatigue: an update. Support Care Cancer, 11, 79-83.

Gielen, S., Adams, V., Mobius-Winkler, S., Linke, A., Erbs, S., Yu, J., Kempf, W., et al. (2003). Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. Journal of American College of Cardiology, 42(5), 861-868.

Greenberg, D. B., Gray, J. L., Mannix, C. M., Eisenthal, S., Carey, M. (1993). Treatment-related fatigue and serum interleukin-1 levels in patients during external beam irradiation for prostate cancer. Journal of Pain and Symptom Management, 8, 196-200.

Gutstein, H. B. (2001). The biologic basis of fatigue. Cancer, 92(6), 1678-1683.

Hickok, J. T., Morrow, G. R., McDonald, S., Bellg, A. J. (1996). Frequency and correlates of fatigue in lung cancer patients receiving radiation therapy: Implications for management. Journal of Pain and Symptom Management, 11, 370-377.

de Jong, N., Candel, M. J. J. M., Schouten, H. C., Huijer Abu-Saad, H., Courtens, A. M. (2004). Prevanlence and course of fatigue in breast cancer patients receiving adjuvant chemotherapy. Annals of Oncology 15, 896-905.

Kolden, G. G., Strauman, T. J., Ward, A., Kuta, J., Woods, T. E., Schneider, K. L., et al. (2002). A pilot study of group exercise training (get) for women with primary breast cancer: feasibility and health benefits. Psycho-Oncology 11, 447-456.

Kurzrock, R. (2001). The role of cytokines in cancer-related fatigue. Cancer, 92(6), 1684-1688.

Larsen, A. I., Lindal, S., Aukrust, P., Toft, I., Aarsland, T., Dickstein, K. (2002). Effect of exercise training on skeletal muscle fibre characteristics in men with chronic heart failure: Correlation between skeletal muscle alterations, cytokines and exercise capacity. International Journal of Cardiology, 83, 25-32.

Mendoza, T. R., Wang, X. S., Cleeland, C. S., Morrissey, M., Jhonson, B. A., Wendt, J. K., Huber, S. L. (1999). The rapid assessment of fatigue severity in cancer patient. Cancer, 85(5), 1186-1196.

Mock, V. (1996). The benefits of exercise in women with breast cancer: Rehabilitation through exercise. In: Dow KH (Ed.) Contemporary issues in breast cancer(pp.99-106). Boston: Jones & Bartlett.

Mock V., Burke, M. B., Sheehan, P. K., et al. (1994). A nursing rehabilitation program for women with breast cancer receiving adjuvant chemotherapy. Oncology Nursing Forum, 21, 899-908.

Mock V., Dow, K. H., Meores, C., et al. (1997). Effects of exercise on fatigue, physical functioning, and emotional distress during radiation therapy for breast cancer. Oncology Nursing Forum, 24(6), 991-1000.

Moldoveanu, A. I., Shephard, R. J., Shek, P. N. (2001). The cytokine response to physical activity and training. Sports Medicine, 31(2), 115-144.

Morrow, G. R., Andrews, P. L. R., Hickok, J. T., Roscoe, J. A., Matteson, S. (2002). Fatigue associated with cancer and its treatment. Support Care Cancer, 10, 389-398.

Nieman, D.C., Cook, V. D., Henson, D. A., Suttles, J., Rejeski, W. J., Ribisl, P. M., Fagoaga, O. R., Nehlsen-Cannarella, S. L. (1995). Moderate exercise training and natural killer cell cytotoxic activity in breast cancer patients. International Journal of Sports Medicine 16, 334-337.

Pedersen, B. L. (2000). Exercise and cytokines. Immunology and Cell Biology, 78, 532-535.

Pick-Holley, S. (1991). Fatigue in cancer patients. Cancer nursing, 14,13-19.

Rao, V. S. R., Dyer, C. E., Jameel, J. K. A., Drew, P. J., Greenman, J. (2006). Potential prognostic and therapeutic roles for cytokines in breast cancer (Review). Oncology reports 15, 179-185.

Rayson, D., Reyno, L. (2003). Exercise and cancer: no pain, some gain? Journal of Clinical Oncology, 21(9), 1651-1652.

Schwartz, A. L. (2000). Daily fatigue patterns and effect of exercise in women with breast cancer. Caner Practice 8(1), 16-24.

Schwartz, A. L. (1999). Fatigue medicines the effects of exercise on quality of life. Quality of Life Research 8, 529-538.

Schwartz, A. L. (2000). Exercise and weight gain in breast cancer patients receiving chemotherapy. Caner Practice 8(5), 231-237.

Schwartz, A. L., Mori, M., Gao, R., Nail, L. M., King, M. E. (2001). Exercise reduces daily fatigue in women with breast cancer receiving chemotherapy. Medicine & Science in Sports &Exercise, 33(5), 718-723.

Segal, S., Evans, W., Johnson, D., Smith, J., Colletta, S., Gayton, J., et al. (2001). Structured exercise improves physical functioning in women with stages I and II breast cancer: Results of a randomized controlled trial. Journal of Clinical Oncology 19(3), 657-665.

Tsavaris, N., Kosmas, C., Vadiaka, M., Kanelopoulos, P., Boulamatsis, D. (2002). Immune changes in patients with advanced breast cancer undergoing chemotherapy with taxanes. British Journal of Cancer 87, 21-27.

Winningham, M. L. (2001). Strategies for managing cancer-related fatigue syndrome. Cancer, 92(4), 988-997.

Table 1. Patient Demographics

Variables	Exerciser (n = 18)	Control group (n = 15)	Total (n = 33)
	n(%)	n(%)	n(%)
Age (yr)[a]	49.8±9.0	52.5±11.2	
Weight (kg)[a]	63.8±10.7	64.2±11.6	
Marital status			
Married	14(78)	12(80)	26(79)
Single/divorced	4(22)	3(20)	7(21)
Employment status			
Full-time	9(50)	7(47)	16(48)
Part-time	4 (22)	3(20)	7(21)
Unemployment/retired	5(28)	5(33)	10(31)
Education			
College degree or above	9(50)	7(47)	16(48)
High school	9(50)	8(53)	17(52)
Stage of cancer			
I	6(33)	4(27)	10(30)
II	7(39)	6(40)	13(40)
IIIa	5(28)	5(33)	10(30)
Type of chemotherapy			
CA	8(44)	6(40)	14(42)
CAF	5(28)	4(27)	9(27)
CMF	4 (22)	3(20)	7(21)
Other	1(6)	2(13)	3(10)

[a] : Values for mean±standard deviation

CA = Cyclophosphamide/Doxorubicin;

CAF = Cyclophosphamide/Doxorubicin/Finorouracil;

CMF = Cyclophosphamide/Methotrexate/Fiuorouracil

Table 2. Fatigue severity of the subjects receiving chemotherapy

Group	Time	Worst Fatigue	Usual Fatigue	Fatigue Now	Interference Score
Exercisers	O_1	5.4±1.3	4.5±1.7	4.6±1.9	4.0±1.6
(n = 18)	O_2	4.7±1.5	3.7±1.2	4.3±2.0	3.6±1.8
	O_3	4.3±1.7[a]	3.4±1.0[a]	3.6±1.3[a]	3.0±1.3[a]
Control group	O_1	5.2±1.9	4.3±1.7	4.7±1.6	3.9±1.5
(n = 15)	O_2	6.4±1.4[b]	5.6±0.8[b]	4.8±1.9	4.2±1.4
	O_3	5.7±2.0	5.0±1.5	4.6±1.2	4.4±1.2

[a]: decreased as compared to O_1 within the group ($p < 0.05$)

[b]: increased as compared to O_1 within the group ($p < 0.05$)

O_1: one week following the initiation of chemotherapy

O_2: the 8th week of the study

O_3: the 12th week of the study

Table 3. Physical capacity of the subjects

Group	Volume of oxygen intake (ml/kg/min)		
	O_1	O_3	O_1- O_3
Exercisers (n = 18)	20.1±4.5	24.5±5.2[a]	4.4±3.2[b]
Control group (n = 15)	19.2±2.3	19.5±3.0	0.7±1.2

[a] $p < 0.05$ as compared to O_1 within the group

[b] $p < 0.05$ as compared to the change between groups

O_1: one week following the initiation of chemotherapy

O_3: the 12th week of the study

Table 4. Plasma cytokine concentrations of the subjects

Group	Time	TNF-α (pg/ml)	IL-6 (pg/ml)	IL-1β (pg/ml)
Exercisers	O_1	114.3±19.1	52.4±13.4	74.7±19.2
(n = 18)	O_2	100.5±18.7[a]	58.2±13.2	69.0±13.5
	O_3	97.4±22.3[a]	57.6±15.9	68.9±18.5
Control group	O_1	112.2±24.1	54.4±12.1	72.8±21.3
(n = 15)	O_2	109.9±22.4	67.6±13.3[b]	71.6±17.5
	O_3	107.8±30.0	73.0±12.5[c]	72.1±20.9

[a]: decreased as compared to O_1 within the group ($p < 0.05$)

[b]: increased as compared to O_1 within the group ($p < 0.05$)

[c]: increased as compared to O_1 within the group ($p < 0.01$)