The Inverse Association between Cardiorespiratory Fitness and C-Reactive Protein Is Mediated by Autonomic Function: A Possible Role of the Cholinergic Antiinflammatory Pathway

Sae Young Jae,1 Kevin S Heffernan,2 Eun Sun Yoon,1 Moon-Kyu Lee,3 Bo Fernhall,4 and Won Hah Park5

1The Health and Integrative Physiology Laboratory, Department of Sports Informatics, University of Seoul, Seoul, South Korea; 2Tufts Medical Center, Division of Cardiology, Boston, Massachusetts, United States of America; 3Center for Health Promotion, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; 4Department of Kinesiology and Community Health, University of Illinois, Urbana-Champaign, Illinois, United States of America; and 5Sports Medicine Center Department of Physical Medicine and Rehabilitation, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

INTRODUCTION

Although studies have shown an inverse association between cardiorespiratory fitness (CRF) and C-reactive protein (CRP) levels, the underlying mechanisms are not fully understood. There is emerging evidence that autonomic nervous system function is related to CRP levels. Because high CRF is related to improved autonomic function, we hypothesized that the association between high CRF and low CRP levels would be affected by autonomic nervous system function. Cross-sectional analyses were conducted on 2,456 asymptomatic men who participated in a medical screening program. Fasting blood samples for cardiovascular disease risk factors were analyzed, and CRF was measured by maximal exercise treadmill test with expired gas analysis. We used an index of cardiac autonomic imbalance defined as the ratio of resting heart rate to 1 min of heart rate recovery after exercise (RHR/HRR). CRF was significantly correlated with CRP (r = –0.16, P < 0.05), and RHR/HRR (r = –0.48, P < 0.05), while RHR/HRR was significantly correlated with CRP (r = 0.25, P < 0.05). In multivariable linear regression models that adjusted for age, body mass index; smoking, disease status, medications, lipid profiles, glucose, and systolic blood pressure, CRF was inversely associated with CRP (β = –0.09, P < 0.05). However, this relationship was no longer significant after adjusting for RHR/HRR in a multivariable linear regression model (β = –0.03, P = 0.29). These results suggest that autonomic nervous system function significantly affects the relationship between CRF and inflammation in middle-aged men. Thus, physical activity or exercise training may favorably affect the cholinergic antiinflammatory pathway, but additional research is needed to confirm this finding.

© 2009 The Feinstein Institute for Medical Research, www.feinsteininstitute.org

Address correspondence and reprint requests to Won Hah Park, Sports Medicine Center Department of Physical Medicine and Rehabilitation, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, 50 Ilwon-Dong, Kangnam-Gu, Seoul, South Korea 135-710. Phone: 82-2-3410-3840; Fax: 82-2-3410-6689; E-mail: wonhah.park@samsung.com.

Submitted June 30, 2009; Accepted for publication July 1, 2009; Epub (www.molmed.org) ahead of print July 6, 2009.
sympathetic tone and decreases in sympathetic tone (19,20). Therefore, it is possible that physical activity and/or high CRF-related improvement in autonomic function may favorably affect the cholinergic anti-inflammatory pathway, but this possibility has not been tested. Given the interrelations between CRF, CRP, and autonomic function, we sought to test the hypothesis that the association between high CRF and low CRP levels would be affected by autonomic nervous system function.

**MATERIALS AND METHODS**

**Study Population**

We used data from subjects who visited the multidisciplinary health promotion center, Samsung Medical Center, Seoul, between January 2003 and December 2003 for routine medical checkup. Our analysis included 2,456 male subjects (mean age 57 ± 5 years) who had undergone graded exercise testing without angina symptoms and/or abnormal electrocardiographic changes. Subjects with exercise-induced angina or abnormal electrocardiographic changes (more than 1 mm of horizontal or downsloping ST segment depression) were not included as these conditions could be secondary to some form of cardiovascular disease. Other exclusion criteria included subjects with a diagnosis of coronary heart disease, stroke, arterial fibrillation, or ST segment depression during exercise testing. The presence of diabetes was defined as a fasting glucose ≥126 mg/dL, or self-reported physician-diagnosed diabetes, or self-reported use of an oral hypoglycemic agent. Hypertensive subjects were defined by a resting blood pressure ≥140/90 mmHg or self-reported use of antihypertensive medications. Written informed consent was obtained from all subjects before health screening, and the study was approved by the medical center institutional review board.

**Data Collection**

Resting heart rate was measured in the supine position using an electrocardiogram (Hewlett-Packard ECG M 1700A, Hewlett-Packard Corporation, Palo Alto, CA, USA) following at least 5 min of quiet rest. Subjects performed treadmill exercise testing using the Bruce protocol. Expired gases were collected breath-by-breath using a one-way valve and analyzed using a metabolic cart (Jaeger Oxycon Delta, Germany). VO2 peak (mL/kg/min) was defined as the highest value recorded during test. Exercise heart rate was measured using 12-lead electrocardiography, and maximal heart rate was defined as the highest value achieved during the test (Quinton Q-4500, Bothell, WA, USA). Exercise tests were stopped if one of the following criteria was present: a rating of perceived exertion >17, if the subject achieved >90% of age-predicted maximal heart rate, if the subject was too fatigued to continue walking safely on the treadmill, >250 mmHg of systolic blood pressure, typical chest pain, severe arrhythmias, or ST segment changes. Heart rate recovery (HRR) was calculated as the difference between maximum HR during the test and HR 1 min after cessation of exercise. The recovery protocol consisted of 1 min light walking (1.2 mph of speed and 0% of grade) immediately after peak exercise testing followed by 3 min of seated rest.

We used an index of resting heart rate (RHR)/HRR for the assessment of integrative autonomic nervous system function, because increased RHR may suggest enhanced sympathetic dominance of the autonomic nervous system, and delayed HRR is an index of impaired parasympathetic activity (21).

Body mass index was calculated as weight (kg) divided by height (m²). Resting blood pressure was measured in seated position using an automated blood pressure monitor (Dinamap PRO 100, Milwaukee, WI, USA) during quiet rest. Blood samples were collected following a 12-h overnight fast prior to all exercise testing, and analyzed at the hospital clinical laboratory. Total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) were analyzed enzymatically using a Hitachi 747 (Tokyo, Japan) analyzer. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Glucose levels were determined using the glucose oxidase method (Hitachi 747, Tokyo, Japan). High sensitivity CRP was measured using a CRP (II) Latex X2 turbidimetric method (Hitachi 747, Tokyo, Japan). Inter- and intra-assay coefficients of variation were <5% for all blood variables.

Data are expressed as mean ± SD for continuous variables, and as proportions for categorical variables. Because the distribution of CRP was highly skewed, we used the log transformation of these variables. Following log transformation, a constant was added to each log transformed value to ensure that all values were greater than zero. To test for associations between CRF, autonomic function, and CRP, subjects were divided into groups according to quartiles of peak oxygen uptake and RHR/HRR index. Characteristics were compared between the groups using analysis of variance for continuous variables and the χ² test for categorical variables. Pearson’s correlations and multiple linear regression analyses were used to determine the association between CRF, autonomic function, and CRP. The selection of variables for entrance into the multivariate model was based on the univariate analysis and collinearity among variables. Our multiple regression models were to adjust for potential confounding factors with and without RHR/HRR index. Given potential relationships between hypertension, diabetes, and CRP, we conducted secondary analysis (excluding subjects with hypertension and diabetes) to determine whether or not associations prevail. Statistical significance was set at P < 0.05 for all data. Statistical analyses were performed using the SPSS 14.0 (SPSS, Chicago, IL, USA).

**RESULTS**

The characteristics of patients across quartiles of peak oxygen uptake are presented in Table 1. Subjects in the high quartile of fitness had a more favorable traditional coronary heart disease risk
factor profile for such variables as age, body mass index (BMI), HDL-C, systolic blood pressure (SBP), triglycerides (TGs), total cholesterol (TC)/HDL-C ratio, glucose, CRP, RHR, HRR, and RHR/HRR index. Subjects in the high quartile of fitness had a significantly lower rate of hypertension and diabetes than subjects in the low quartile of fitness. CRP data are significantly different across groups (Figure 1, $P < 0.01$). The levels of CRP in the highest quartile of RHR/HRR index were significantly higher than the levels observed across all other quartiles of RHR/HRR index (see Figure 1).

CRF was correlated significantly with body mass index (BMI) ($r = -0.11$, $P < 0.05$), CRP ($r = -0.16$, $P < 0.05$), and RHR/HRR ($r = -0.48$, $P < 0.05$), while RHR/HRR was correlated significantly with age ($r = 0.36$, $P < 0.05$), glucose ($r = 0.23$, $P < 0.05$), and CRP ($r = 0.25$, $P < 0.05$) (Table 2). In multivariable linear regression models that adjusted for age, BMI, smoking, disease status, medications, lipid profiles, glucose, and systolic blood pressure, CRF was associated inversely with CRP ($\beta = -0.09$, $P < 0.05$) (Table 3). However, this relationship was no longer significant after adjusting for RHR/HRR in a multivariable linear regression model ($\beta = -0.03$, $P = 0.29$) (Table 4).

Because of the relationship between hypertension, diabetes, and CRP, we con-

### Table 1. Characteristics of the subjects according to quartiles of peak oxygen uptake ($n = 2,456$).

| Quartile | n (n = 604) | 28 mL/kg/min | 28.1–31.5 | 31.6–34.5 | >34.6 | P values |
|----------|------------|-------------|-----------|----------|------|---------|
| Age (years) | 60 ± 6 | 57 ± 5 | 56 ± 4 | 55 ± 4 | <0.001 |
| BMI (kg/m²) | 24.9 ± 2 | 24.8 ± 2 | 24.6 ± 2 | 24.3 ± 2 | <0.001 |
| Smoker (%) | 27.0 | 20.2 | 19.5 | 20.7 | 0.005 |
| Hypertension (%) | 17.7 | 16.3 | 12.2 | 14.1 | 0.042 |
| Antihypertensive drugs (%) | 17.7 | 14.7 | 13.9 | 11.2 | 0.013 |
| Diabetes (%) | 9.4 | 6.6 | 8.9 | 6.0 | <0.001 |
| Oral hypoglycemic drugs (%) | 9.9 | 6.0 | 6.9 | 2.4 | <0.001 |
| SBP (mmHg) | 125.8 ± 20 | 124.2 ± 18 | 121.7 ± 18 | 121.8 ± 18 | 0.001 |
| Diastolic blood pressure (DBP) | 78.9 ± 12 | 78.6 ± 11 | 78.1 ± 11 | 78.1 ± 12 | 0.475 |
| TC (mg/dL) | 204.9 ± 38 | 205.5 ± 33 | 204.7 ± 33 | 203.3 ± 31 | 0.711 |
| HDL-C (mg/dL) | 47.2 ± 12 | 48.0 ± 10 | 50.6 ± 12 | 51.3 ± 12 | <0.001 |
| LDL-C (mg/dL) | 139.3 ± 34 | 140.9 ± 32 | 140.3 ± 31 | 138.5 ± 30 | 0.546 |
| TGs (mg/dL) | 160.8 ± 80 | 161.7 ± 85 | 145.4 ± 74 | 143.6 ± 76 | <0.001 |
| TC/HDL-C ratio | 4.5 ± 1.1 | 4.4 ± 1.0 | 4.2 ± 0.9 | 4.1 ± 0.9 | <0.001 |
| Glucose (mg/dL) | 112.9 ± 32 | 107.9 ± 29 | 110.6 ± 36 | 103.8 ± 27 | <0.001 |
| CRP (mg/dL) | 12.0 (0.07–0.18) | 10.0 (0.06–0.17) | 9.9 (0.06–0.14) | 9.8 (0.05–0.15) | <0.001 |
| CRP (mg/dL) | 1.24 ± 0.4 | 1.18 ± 0.4 | 1.16 ± 0.4 | 1.06 ± 0.4 | <0.001 |
| RHR (bpm) | 65 ± 9 | 64 ± 10 | 63 ± 9 | 61 ± 8 | <0.001 |
| HRR (bpm) | 19 ± 9 | 23 ± 9 | 24 ± 8 | 26 ± 8 | <0.001 |
| RHR/HRR index | 0.72 ± 0.17 | 0.62 ± 0.15 | 0.58 ± 0.14 | 0.52 ± 0.14 | <0.001 |

aData are mean ± SD.
bMedian and interquartile range.
cCRP, log transformed data due to skewed distribution.
dRHR/HRR, ratio of resting heart rate/heart rate recovery 1 min.

---

**Figure 1.** Box plot of CRP levels by quartiles of RHR/HRR index. The horizontal lines from the bottom to the top of the box plot display the 25th, median, and 75th percentiles ($P < 0.01$).
duced secondary analysis in a subset of subjects without hypertension and diabetes ($n = 1,995$). After excluding subjects with hypertension and diabetes, we found that subjects in the highest quartile of RHR/HRR had higher CRP levels than those in the lowest quartile of RHR/HRR ($1.32 \pm 0.6$ versus $1.05 \pm 0.4 \text{mg/dL}$, $P < 0.05$). While CRF was associated significantly with CRP ($\beta = -0.10$, $P < 0.05$) in multivariable models, CRF was not associated independent of lower CRP levels after adjustment for exercise capacity. In an experimental study, Heffernan et al. (24) showed that improved vagal modulation in African Americans stemming from resistance exercise training was associated with a reduction in CRF, independent of changes in body fat. Therefore, our results support the possibility that exercise/physical activity may increase activity of the cholinergic antiinflammatory pathway as suggested by Tracey et al. (18).

The cholinoergic antiinflammatory pathway fosters communication between the autonomic and immune systems whereby vagal stimulation by inflammatory cytokines produces reflexive antiinflammatory effects (25). Acetylcholine released from the vagus nerve binds to nicotinic receptors on macrophages, halting proinflammatory cytokine production (18). Conversely, reduced vagal tone directly contributes to a heightened inflammatory state and end-organ damage (26,27), and is associated with the development of diabetes (28). Both increased inflammation and/or impaired autonomic function have been suggested as independent predictors of cardiovascular events. Interventions that increase cardiac vagal modulation and reduce inflammation may, therefore, have significant clinical utility for preventing future cardiovascular and metabolic disease.

Numerous studies have suggested that higher levels of physical activity and/or cardiorespiratory fitness are associated with lower risk of cardiovascular disease (12) and type 2 diabetes (29). Individuals with high CRF have improved autonomic nervous system function as evidenced by increases in parasympathetic tone and decreases in sympathetic tone (19). The mechanism responsible for improved autonomic function in individuals with high CRF has not been elucidated clearly. A strong relationship exists between arterial stiffness and baroreflex sensitivity. Stiffening of the vessels housing barosensory

### Table 2. Correlations of selected cardiovascular risk factors with CRP, peak oxygen uptake, and index of RHR/HRR.

| Variables     | β-coefficient | β (SE) | $P$ values |
|---------------|---------------|--------|------------|
| Age           | -0.041        | 0.002  | 0.513      |
| BMI           | -0.052        | 0.009  | 0.190      |
| Glucose       | -0.123        | 0.008  | <0.001     |
| VO2 peak      | -0.103        | 0.005  | <0.001     |

Table 3. Multiple linear regression analysis with CRP as the dependent variable without RHR/HRR.

| Variables     | $\beta$-coefficient | $\beta$ (SE) | $P$ values |
|---------------|----------------------|--------------|------------|
| Age           | 0.011                | 0.002        | 0.614      |
| BMI           | 0.044                | 0.04         | 0.037      |
| Glucose       | 0.056                | 0.001        | 0.009      |
| BP            | -0.018               | 0.004        | <0.001     |
| TC/HDL        | 0.109                | 0.009        | <0.001     |
| Smoker        | -0.001               | 0.023        | 0.964      |
| Hypertension  | -0.041               | 0.026        | 0.046      |
| Diabtes       | 0.003                | 0.040        | 0.901      |
| VO2 peak      | -0.102               | 0.020        | <0.001     |

### Table 4. Multiple linear regression analysis with CRP as the dependent variable with RHR/HRR.

| Variables     | $\beta$-coefficient | $\beta$ (SE) | $P$ values |
|---------------|----------------------|--------------|------------|
| Age           | -0.028               | 0.002        | 0.213      |
| BMI           | 0.053                | 0.004        | 0.010      |
| Glucose       | 0.025                | 0.001        | 0.266      |
| SBP           | -0.023               | 0.001        | 0.261      |
| TC/HDL        | 0.096                | 0.009        | <0.001     |
| Smoker        | -0.005               | 0.022        | 0.839      |
| Hypertension  | -0.032               | 0.026        | 0.115      |
| Diabetes      | 0.007                | 0.039        | 0.736      |
| VO2 peak      | -0.042               | 0.002        | 0.082      |
| RHR/HRR       | 0.214                | 0.065        | <0.001     |

### Table 5. Multiple linear regression analysis with CRP as the dependent variable with RHR/HRR in subjects without hypertension and diabetes ($n = 1,995$).

| Variables     | $\beta$-coefficient | $\beta$ (SE) | $P$ values |
|---------------|----------------------|--------------|------------|
| Age           | -0.037               | 0.002        | 0.154      |
| BMI           | 0.043                | 0.005        | 0.067      |
| Glucose       | 0.026                | 0.001        | 0.262      |
| SBP           | -0.002               | 0.001        | 0.935      |
| TC/HDL        | 0.096                | 0.010        | <0.001     |
| Smoker        | -0.003               | 0.026        | 0.884      |
| VO2 peak      | -0.031               | 0.002        | 0.255      |
| RHR/HRR       | 0.183                | 0.075        | <0.001     |
regions (that is, carotid and aorta) coupled with regional atherosclerotic development seen with aging and disease may depress mechanotransduction of these stretch receptors, resulting in a reduction of baroreceptor afferent firing per given unit of arterial pressure change, less inhibition of sympathetic outflow, and lessened amplification of cardiac vagal tone (30). Chronic/habitual exercise has been shown to reduce arterial stiffness and improve baroreceptor sensitivity (31), which may have a favorable effect on sympathetically-parasympathetic interaction. In addition to this peripheral mode of action, it is possible that exercise has direct central effects on autonomic regulation. Nelson et al. (32) has demonstrated that aerobic/endurance training alters dendritic fields of neurons within the posterior hypothalamic area, periaqueductal gray, cuneiform nucleus, and nucleus of the \textit{tractus solitarius} of rats, crucial regions responsible for neural cardiorespiratory regulation. Given the cross-sectional nature of our study, we cannot speak to the mechanisms underlying autonomic modulation with physical activity/exercise. However, our large cross section results do confirm that individuals with high fitness levels have significantly improved autonomic modulation as reflected by lower RHR/HRR.

In this paper, we propose a new measure of autonomic balance. Many commonly used noninvasive measures of autonomic function assess only parasympathetic modulation. However, autonomic dysfunction may be attributable either to enhanced sympathetic activity and/or to blunted parasympathetic activity. Increased RHR reflects enhanced sympathetic dominance of the autonomic nervous system while delayed RHR is an index of impaired parasympathetic activity (21). Elevated RHR is associated with progression of carotid atherosclerosis, increased arterial stiffness, and increased CRP (33,34). Large epidemiologic studies also have shown that RHR is an independent predictor of cardiovascular and all cause mortality (33). Slow HRR after exercise is associated with several negative health outcomes, including impaired fibrinolysis, increased CRP, carotid atherosclerosis, and arterial stiffness (35–38). HRR also is a predictor of incident diabetes mellitus, metabolic syndrome, and ultimately mortality (39–41). Individuals with high CRF have faster HRR and lower RHR (42,43), resulting in lower RHR/HRR. Therefore, we propose that combining RHR and HRR may be a clinically/physiologically relevant composite index with elevated values reflecting a general sympathovagal imbalance. Further studies are needed to examine this index in experimental design.

A limitation of our data is that we did not control for diet status and medication use (that is, β-blockers, aspirin, and statins), which may potentially be confounding factors. Given the cross-sectional nature of our study, it cannot be determined whether improved autonomic function in individuals with high fitness is the cause or effect of cholinergic antiinflammatory activity. Also, these results may not be generalized to women. A strength of this study is the use of directly measured peak oxygen uptake for CRF and a large sample size.

In conclusion, the association between higher CRF with lower CRP levels is dependent on autonomic function. These results suggest that autonomic nervous system function affects the relationship between cardiorespiratory fitness and inflammation significantly. Thus, physical activity/exercise training may affect the cholinergic antiinflammatory pathway favorably, but additional research is needed to confirm this novel finding.

**DISCLOSURE**

The authors declare that they have no competing interests as defined by \textit{Molecular Medicine}, or other interests that might be perceived to influence the results and discussion reported in this paper.

**REFERENCES**

1. Myers J, et al. (2002) Exercise capacity and mortality among men referred for exercise testing. \textit{N. Engl. J. Med.} 346:793–801.
2. Laukkanen JA, et al. (2001) Cardiovascular fitness as a predictor of mortality in men. \textit{Arch. Intern. Med.} 161:825–31.
3. Cornelissen MR, Gulati M, Greenland P (2005) Prevalence and cardiovascular disease correlates of low cardiorespiratory fitness in adolescents and adults. \textit{JAMA.} 294:2981–8.
4. Kasapis C, Thompson PD. (2005) The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. \textit{Am. Coll. Cardiol.} 45:1563–9.
5. Ridker PM. (2008) High-sensitivity C-reactive protein as a predictor of all-cause mortality: implications for research and patient care. \textit{Clin. Chem.} 54:234–7.
6. Church TS, et al. (2002) Associations between cardiorespiratory fitness and C-reactive protein in men. \textit{Arterioscler. Thromb. Vasc. Biol.} 22:1869–76.
7. Jae SY, Heffernan KS, Lee MK, Fernhall B, Park WH. (2008) Relation of cardiorespiratory fitness to inflammatory markers, fibrinolytic factors, and lipoprotein(a) in patients with type 2 diabetes mellitus. \textit{Am. J. Cardiol.} 102:700–3.
8. Jae SY, et al. (2006) Effects of lifestyle modifications on C-reactive protein: contribution of weight loss and improved aerobic capacity. \textit{Metabolism.} 55:825–31.
9. Mora S, Cook N, Buring JE, Ridker PM, Lee IM. (2007) Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. \textit{Circulation.} 116:2110–18.
10. Nicklas BJ, You T, Pahor M. (2005) Behavioural treatments for chronic systemic inflammation: effects of dietary weight loss and exercise training, \textit{CMAJ.} 172:1199–209.
11. Powers SK, Ji LL, Leeuwensemble C. (1999) Exercise training-induced alterations in skeletal muscle antioxidant capacity: a brief review. \textit{Med. Sci. Sports Exerc.} 31:987–97.
12. Leung FP, et al. (2008) Exercise, vascular wall and cardiovascular disease: an update (part 1). \textit{Sports Med.} 38:1009–24.
13. Messier V, Malita FM, Rabasa-Lhoret R, Brochu M, Karelis AD. (2008) Association of cardiorespiratory fitness with insulin sensitivity in overweight and obese postmenopausal women: a Montreal Ottawa New Emerging Team study. \textit{Metabolism.} 57:1293–8.
14. Lanza GA, et al. (2006) Relation of heart rate variability to serum levels of C-reactive protein in patients with unstable angina pectoris. \textit{Am. J. Cardiol.} 97:1702–6.
15. Sloan RP, et al. (2007) RR interval variability is inversely related to inflammatory markers: the CARDIA study. \textit{Mol. Med.} 13:178–94.
16. Lampert R, et al. (2008) Decreased heart rate variability is associated with higher levels of inflammation in middle-aged men. \textit{Am. Heart J.} 156:759.e1–7.
17. Borovikova LV, et al. (2000) Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature. 405:458-62.
18. Tracey KJ. (2007) Physiology and immunology of the cholinergic anti-inflammatory pathway. JCI. 117:289-96.
19. Rennie KL, et al. (2003) Effects of moderate and vigorous physical activity on heart rate variability in a British study of civil servants. Am. J. Epidemiol. 157:135-43.
20. Blomquist CG, Saltin B. (1983) Cardiovascular adaptations to physical exercise. Annu. Rev. Physiol. 45:169-89.
21. Lahiri MK, Kannankeril PJ, Goldberger JJ. (2008) Cardiac vagal activity following resistance exercise is associated with carotid atherosclerosis. Atherosclerosis. 196:256-61.
22. Ford ES. (2002) Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. Epidemiology. 13:561-8.
23. Vieira VJ, Valentine RJ, McAuley E, Evans E, Woods JA. (2007) Independent relationship between heart rate recovery and C-reactive protein in older adults. J. Am. Geriatr. Soc. 55:747-51.
24. Heffernan KS, et al. (2009) Cardiac vagal activity following resistance exercise training in young African American and white men. Am. J. Physiol. Regul. Integr. Comp. Physiol. 296:1096-105.
25. Tracey KJ. (2002) The inflammatory reflex. Nature. 420:853-59.
26. Thayer JF, Lane RD. (2007) The role of vagal function in the risk for cardiovascular disease and mortality. Biol. Psychol. 74:224-42.
27. Gidron Y, Kupper N, Kwaijtaal M, Winter J, Dehniel J. (2007) Vagus-brain communication in atherosclerosis-related inflammation: a neuroimmunomodulation perspective of CAD. Atherosclerosis. 195:e1-9.
28. Carnethon MR, Craft LL. (2008) Autonomic regulation of the association between exercise and diabetes. Exerc. Sport Sci. Rev. 36:12-8.
29. Gill JM, Cooper AR. (2008) Physical activity and prevention of type 2 diabetes mellitus. Sports Med. 38:807-24.
30. Joynner, MJ. (2000) Effect of exercise on arterial compliance. Circulation. 102:1214-5.
31. Delay G, Picard G, Taylor JA. (2009) Arterial baroreflex control of cardiac vagal outflow in older individuals can be enhanced by aerobic exercise training. Hypertension. 53:826-32.
32. Nelson AJ, Juraska JM, Musch TJ, Iwamoto GA. (2003) Neuroplastic adaptations to exercise: neuronal remodeling in cardiorespiratory and locomotor areas. J. Appl. Physiol. 99:2312-22.
33. Fox K, et al. (2007) Resting heart rate in cardiovascular disease. J. Am. Coll. Cardiol. 50:823-30.
34. Rogowski O, et al. (2007) Heart rate and microinflammation in men: a relevant atherothrombotic link. Heart. 93:940-4.
35. Jae SY, et al. (2008) Association between heart rate recovery after exercise testing and plasminogen activator inhibitor 1, tissue plasminogen acti-