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

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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 ($\beta = -0.09$, $P < 0.05$). However, this relationship was no longer significant after adjusting for RHR/HRR in a multivariable linear regression model ($\beta = -0.03$, $P = 0.29$). 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.

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INTRODUCTION

High levels of cardiorespiratory fitness (CRF) are associated with lower prevalence of cardiovascular morbidity and mortality (1,2). CRF reduces both traditional and nontraditional cardiovascular risk factors (3,4). Inflammation plays an important role in the development and progression of atherosclerosis, and C-reactive protein (CRP) is a strong predictor of cardiovascular events in healthy populations and in patients with coronary heart disease (5). Recently, many epidemiological and interventional studies have suggested that high CRF is associated with lower levels of CRP (6–8), and the inverse association between CRF and cardiovascular events is mediated in part by inflammatory factors (9).

Several mechanisms have been put forth in an attempt to explain the association between high CRF and low CRP levels. These include reduced body fat (10), improved antioxidant capacity (11), improved endothelial function (12), and improved insulin sensitivity (13). However, these factors do not fully explain the inverse relationship between CRF and CRP.

There is emerging evidence that autonomic nervous system function is related to inflammation (14–16). Experimental studies have reported that vagus nerve stimulation can modulate inflammatory cytokines through the cholinergic antiinflammatory pathway (17,18).

Individuals with high CRF have improved autonomic nervous system function as evidenced by increases in para-

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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 antiinflammatory 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 (m^2). 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 χ^2 test for categorical variables. Pearson's correlations and multiple linear regression analysis 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

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

	Q 1 (n = 604) <28 mL/kg/min	Q 2 (n = 639) 28.1–31.5	Q 3 (n = 595) 31.6–34.5	Q 4 (n = 618) >34.6	*P* values
Age (years)	60 ± 6[a]	57 ± 5	56 ± 4	55 ± 4	<0.001
BMI (kg/m^2)	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	3.6	<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) (mmHg)	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)[b]	0.12 (0.07–0.18)	0.10 (0.06–0.17)	0.09 (0.06–0.14)	0.08 (0.05–0.15)	<0.001
CRP (mg/dL)[c]	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[d]	0.72 ± 0.17	0.62 ± 0.15	0.58 ± 0.14	0.52 ± 0.14	<0.001

[a]Data are mean ± SD.
[b]Median and interquartile range.
[c]CRP, log transformed data due to skewed distribution.
[d]RHR/HRR, ratio of resting heart rate/heart rate recovery 1 min.

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 ($P < 0.01$) 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-

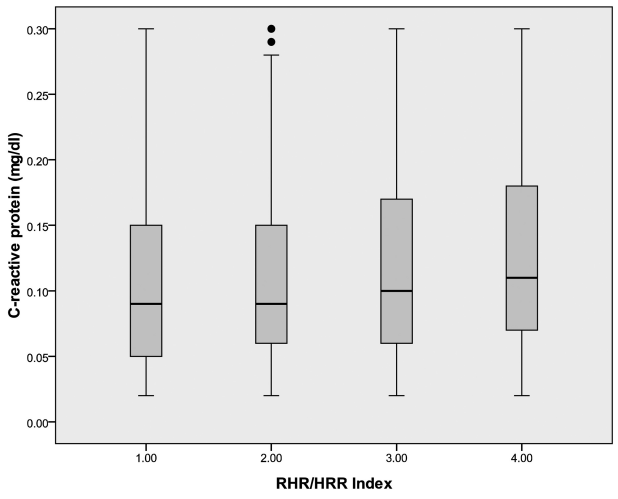

Figure 1. Box plot of CRP levels by quartiles of RHR/HRR index. The horizontal lines from the bottom to the top of the box plot display the 25th, median, and 75th percentiles ($P < 0.01$).

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

	Age	BMI	SBP	TC/HDL	TGs	Glucose	RHR/HRR	CRP
VO2 peak	–0.41[a]	–0.11[a]	–0.08[a]	–0.17[a]	–0.10[a]	–0.13[a]	–0.48[a]	–0.16[a]
RHR/HRR	0.36[a]	0.03	0.13[a]	0.12[a]	0.12[a]	0.23[a]	—	0.25[a]

[a]$P < 0.05$.

ducted 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 ± 0.6 versus 1.05 ± 0.4mg/dL, $P < 0.05$). While CRF was associated significantly with CRP (β = –0.10, $P < 0.05$) in multivariable models, CRF was not associated significantly with CRP when RHR/HRR was entered into the model (Table 5).

DISCUSSION

The major findings of this cross-sectional study were that subjects with high CRF exhibited low levels of CRP after adjusting for traditional risk factors and BMI. However, this relationship was dependent upon RHR/HRR, an index of autonomic nervous system function. Epidemiologic and interventional studies have noted that high CRF is associated with lower levels of CRP independent of body fat (6–8,22), and our results also support this. In addition, our findings suggest that a possible novel mechanism explaining reductions in inflammatory markers concomitant with high fitness may be improved by autonomic nervous system activity. To the best of our knowledge, this is the first large population study to report that the relationship between high CRF and low CRP is mediated by autonomic nervous system function. Vieira *et al*. (23) found in a cross section of 132 elderly subjects, HRR after exercise was 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 CRP, 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 cholinergic 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 3. Multiple linear regression analysis with CRP as the dependent variable without RHR/HRR.

Variables	β-coefficient	β (SE)	*P* values
Age	0.011	0.002	0.614
BMI	0.044	0.04	0.037
Glucose	0.056	0.001	0.009
SBP	–0.013	0.001	0.549
TC/HDL	0.109	0.009	<0.001
Smoker	–0.001	0.023	0.964
Hypertension	–0.041	0.026	0.046
Diabetes	0.003	0.040	0.901
VO2 peak	–0.122	0.002	<0.001

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

Variables	β-coefficient	β (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	–0.004	0.022	0.838
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 = 1995).

Variables	β-coefficient	β (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 sympathetic-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 *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 HRR 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 *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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