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Association of In Vivo Beta-Adrenergic Receptor Sensitivity with Inflammatory Markers in Healthy Subjects

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Abstract

Objective—Several stress-related states and conditions that are considered to involve sympathetic over-activation are accompanied by increased circulating levels of inflammatory immune markers. Prolonged sympathetic over-activity involves increased stimulation of the β -adrenergic receptor. While prior research suggests that one mechanism by which sympathetic stimulation may facilitate inflammation is via β -adrenergic receptor activation, little work has focused on the relationship between circulating inflammatory immune markers and β -adrenergic receptor function within the human body (in vivo). We examined whether decreased β -adrenergic receptor sensitivity, an indicator of prolonged β -adrenergic over-activation and a physiological component of chronic stress, is related to elevated levels of inflammatory immune markers.

Methods—Ninety-three healthy participants aged 19–51 years underwent the chronotropic 25 dose (CD₂₅) isoproterenol test to determine in vivo β -adrenergic receptor function. Circulating levels of C-reactive protein (CRP), interleukin 6 (IL-6) and soluble tumor necrosis factor receptor 1 (sTNF-R1) were determined.

Results— β -adrenergic receptor sensitivity was lower in people with higher CRP concentrations ($r = .326$, $P = 0.003$). That relationship remained significant after controlling for socio-demographic and health variables such as age, gender, ethnicity, body mass index (BMI), mean arterial blood pressure (MAP), heart rate (HR), leisure-time exercise (LTE) and smoking status. No significant relationship was found between CD₂₅ and IL-6 or sTNF-R1.

Conclusions—This study demonstrates a link between in vivo β -adrenergic receptor function and circulating inflammatory immune markers in humans. Future studies in specific disease states may be promising.

Keywords

β -adrenergic receptor; chronotropic 25 dose; C-reactive protein; cytokines; inflammation; isoproterenol

INTRODUCTION

Sympathetic over-activity has been related to a wide range of pathological states and conditions. Prolonged sympathetic over-activity involves increased stimulation of the β -

adrenergic receptor which leads to reduced β -adrenergic receptor function (1–4). Altered β -adrenergic receptor function has been implicated in the pathophysiology of ischemic heart disease, heart failure, metabolic syndrome and hypertension (1, 5–10) and is considered a risk factor for cardiovascular disease (CVD) by increasing myocardial energy production, oxidative stress and enhancing apoptotic pathways (4). Prolonged β -adrenergic stimulation, indicated by decreased in vitro or in vivo assessed β -adrenergic receptor sensitivity (3, 11), has also been related to psychopathological factors such as anxiety, prolonged life stressors, hostility, depression, as well as the procoagulant response to acute stressors (12–19). CVD and numerous of the above mentioned states and conditions are related to stress. Thus, prolonged β -adrenergic stimulation—accompanied by down regulation of β -adrenergic receptor sensitivity – has been considered a physiological component of chronic stress resulting from chronically increased stress hormones (i.e. catecholamines) (3, 11, 20).

Increased inflammatory immune markers are frequently observed in states and conditions associated with sympathetic over-activity. For example, C-reactive protein (CRP), an acute phase protein which is considered a stable marker for inflammation, has been related to increased risk for CVD, hypertension and metabolic syndromes (21–24). Pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor (TNF)- α affect CRP production (25, 26) and have also been linked to CVD as well as Alzheimer's disease and cancer (27–29). In addition, stressful experiences, negative emotions and symptoms of depression and anxiety have been associated with elevated levels of CRP and pro-inflammatory cytokines (30–33). Because of bidirectional relationships between depression/anxiety and CVD, immunological dysregulation has been considered a possible link between mood disorders and CVD (34–36).

Increased concentrations of inflammatory markers in clinical conditions may in part result from sympathetic over-activation. Prolonged sympathetic activation, accompanied by altered catecholamine and glucocorticoid circulation, facilitates inflammation through the induction of cytokines, CRP and the activation of the corticotrophin-releasing hormone/substance P/histamine axis (25). Altered β -adrenergic receptor function may be one sympathetic factor that underlies such a dysfunctional sympathetic immune interface. The β -adrenergic receptor group consists of three subtypes (β_1 , β_2 , β_3 ; 28) and mediates several catecholamine-induced end organ sympathetic responses such as vasodilatation and heart rate increase, but also a variety of immune functions including immune cell trafficking, adhesion, and increased pro-inflammatory cytokine secretion due to the adrenergic receptor activation of leukocytes and adipocytes (3, 11, 37–41). A pro-inflammatory effect of β -adrenergic receptor activation is suggested by in vitro findings demonstrating that pro-inflammatory responses in human monocytes are mediated by a β -adrenergic mechanism (42). Additionally, research in rodents found that chronic β -adrenergic stimulation using isoproterenol, a non-selective β -adrenergic receptor agonist, is sufficient to induce pro-inflammatory cytokine expression (43, 44) and that the intra-cerebroventricular application of isoproterenol induces IL-1 β mRNA in several regions of the rat brain (45). In clinical samples, the link between β -adrenergic receptor function and inflammation was suggested by studies showing that β -blocker treatment reduces CRP concentrations in coronary heart disease (46) as well as after acute myocardial infarction (47). Finally, CRP concentrations in twins were predicted by genetic variants in the catecholaminergic/ β -adrenergic pathway (48).

β -adrenergic responsiveness has frequently been assessed in vitro by measuring isoproterenol-induced cyclic adenosine monophosphate (cAMP) production in human lymphocytes (49, 50). Studies using this technique reveal associations of lymphocyte β -adrenergic receptor function with tension-anxiety, prolonged stressors, hostility, depression, as well as the procoagulant response to acute stressors (12–17). However, there are

limitations to using in vitro assessment as an indicator for human β -adrenergic receptor sensitivity. β -adrenergic receptor function in lymphocytes indicate the ratio of isoproterenol-stimulated cAMP to basal cAMP on lymphocytes, but does not directly reflect the in vivo status because the neurohormonal environment of a peripheral cell receptor such as on lymphocytes may differ from a post-synaptic cell receptor (3). Moreover, although under basal conditions β -adrenergic receptor function in lymphocytes may reflect β -adrenergic receptor function within the body, the validity of β -adrenergic receptor function in lymphocytes can be undermined because stressors and sympathetic arousal may stimulate a redistribution of lymphocyte subsets, due to a partially β -adrenergic mediated release of lymphocytes from the spleen and lymphatic nodes (49–52).

One technique for measuring β -adrenergic receptor function in vivo involves assessing the *chronotropic 25 dose* (CD₂₅). CD₂₅ refers to the dose of isoproterenol, which is necessary to increase heart rate by 25 beats per minute. Low CD₂₅ values indicate high receptor sensitivity (49, 53). Correlational studies indicate an inverse relationship between CD₂₅ and lymphocyte β -adrenergic sensitivity (54). Studies using the CD₂₅ method in humans have found relationships of β -adrenergic receptor function with Type A behavior pattern, anxiety, hostility as well as decreased maximal heart rate with aging (55–60).

While prior studies suggest that β -adrenergic receptor manipulation alters immune parameters and that sympathetic nervous system abnormalities and inflammation often overlap, studies have rarely addressed the functional relationship between in vivo β -adrenergic receptor function and inflammatory markers in humans. Therefore, we examined the association of CD₂₅ with the inflammatory markers CRP, IL-6 and sTNF-R1 in a sample of healthy unmedicated adults. We hypothesized that reduced β -adrenergic receptor sensitivity (i.e., higher chronotropic 25 dose values) is related to increased levels of CRP, IL-6 and sTNF-R1.

METHODS

Participants

Participants were healthy volunteers from a larger study on health, stress and ethnicity. The study was approved by the University of California, San Diego (UCSD) Institutional Review Board. The study group for isoproterenol testing consisted of 39 women (19 African Americans and 20 white participants) and 54 men (24 African Americans and 30 whites) between 19 and 51 years (see Table 1 for sample characteristics). Participants were recruited between 2006 and 2010 using advertisements and announcements. Exclusionary criteria were: Current diagnoses of a clinical illness other than hypertension, history of psychosis or sleep disorder, current alcohol or drug abuse, moderate or heavy smoking (>10 cigarettes/day), increased caffeine intake (>600 mg/day), hormonal medication (including the contraceptive pill or hormone replacement therapy), blood pressure (BP) 170/105 mm Hg, severe obesity (class II obesity, body mass index (BMI) 35) and any medication use. Two subjects with antihypertensive medication were accepted for participation and enrolled after a 3-week drug washout period supervised by the study physician.

Procedure

After prescreening, physical examination by a physician, and giving informed consent, participants arrived between 4:00 PM and 5:00 PM at the UCSD General Clinical Research Center. The isoproterenol stimulation test was conducted in the evening between 7:00 PM and 9:00 PM. To avoid effects of pain caused by needle sticks on inflammatory parameters, all blood samples were obtained through an intravenous catheter, which was placed after arrival between 4:00 PM and 5:00 PM. To yield more reliable measures of inflammatory

parameters, we used average values which resulted from analyzing 3 blood samples. Blood samples were taken in the evening at about 7:00 PM, at 10:30 PM before lights were turned off and at 6:30 AM after subjects were wakened at 6:00 AM.

Isoproterenol Stimulation Test and Chronotropic 25 Dose

Participants were connected to an electrocardiogram monitor to measure heart rate. After a 30-min rest and assessment of basal heart rate, an intravenous low-dose bolus (0.1 μ g) of isoproterenol was administered to ensure that no adverse reactions to the drug occurred. Following the 0.1 μ g bolus, subjects were infused with incremental bolus doses (0.25, 0.5, 1.0, 2.0, 4.0 μ g) until an increase of heart rate by 25 beats/min above basal heart rate was observed or until the 4.0 μ g bolus was completed. The maximum heart rate after each bolus was calculated as the mean of the three shortest R-R intervals in the electrocardiogram. There was a 5-min time interval between bolus injections. Standardized calculation of CD₂₅ values was performed as described previously (49, 53).

Immunological Measures

Plasma was stored at -80°C until thawed for assay. CRP was assayed using the high sensitivity Denka-Seiken method (61). IL-6 and sTNF-R1 were determined using commercial ELISAs according to the manufacturer's instructions (Quantikine, R&D Systems, MN). Intra- and inter-assay coefficients of variation were $<3\%$ for CRP and $<5\%$ for sTNF-R1 and IL-6, respectively. Assay sensitivities were <0.05 mg/L for CRP, <0.72 pg/mL for IL-6 and <0.61 pg/mL for sTNF-R1.

Covariates

Socio-demographic and health-related variables such as age, gender, ethnicity, BMI, smoking status (smoker/non-smoker), physical activity (weekly-activity-score of the Godin Leisure Time Exercise Questionnaire (LTE), (62)), blood pressure and heart rate (HR) may be related to β -AR function (3, 55, 56, 63, 64) and may also be confounded with concentrations of circulating inflammatory immune markers (65–69). Thus, these variables were considered as control variables in adjusted regression models.

Statistical Analyses

The statistical analyses were carried out with SPSS version 17.0 for Windows (Chicago, SPSS, Inc.). Occasional missing values occurred due to heterogeneous technical difficulties and multiple assessments. The rate of missing values for each of the three immunological measures was between 2.2 % and 7.5 % for CRP, between 6.5 % and 8.6 % for IL-6 and between 1.1 % and 7.5 % for sTNF-R1. Regarding covariates, the rate of missing values was 7.5 % for mean arterial blood pressure (MAP) and 7.5 % for LTE. CD₂₅ values and immunological parameters above 3 standard deviations were considered to be extreme outliers and treated as missing values. The rate of extreme outliers was 3.2 % for CD₂₅, between 3.2 % and 4.3 % for CRP measures, between 2.2 % and 6.4 % for IL-6 measures and 0.0 % for sTNF-R1 measures (Note: CRP scores indicated no potentially ongoing acute phase response since all scores were below 10 mg/L, 70).

To avoid disproportional high rates of missing data due to averaging immunological values from three assessments, missing values of single immunological assessments were replaced by multiple imputation (MI) if complete data for the two other assessments were available. MI was conducted with the use of NORM software version 2.03 (71). MI is considered a "state of the art" method to deal with missing data and is superior to traditional missing data techniques (72, 73). For the imputation process, observed data from all study variables were included. To avoid biased estimations, the MI procedure was run after exclusion of extreme

outliers and missing values which were due to outliers were not imputed. Missing values for covariates (MAP and LTE) were also imputed. We conducted five imputations followed by five independent statistical analyses (74–76). Descriptive statistics and results from these five analyses were combined according to Rubin's rules (77). Correlation coefficients were Z-transformed before combining (78) and subsequently back transformed (79). LTE values and immunological data were log-transformed before MI since these variables were not normally distributed (tested by Kolmogorov–Smirnov tests) and skewed data may bias the estimations (73, 80). After each imputation procedure, immunological data were antilog-transformed before calculating average values which were again log-transformed to reach normal distribution for further analyses.

Pearson correlation analyses were performed to examine potential bivariate associations between CD₂₅ and inflammatory markers. Hierarchical linear regression analyses were conducted to examine relationships between CD₂₅ (step 2) and inflammatory markers (dependent variables) after adjusting for covariates (step 1). Our final regression models included 84 observations for CRP, 74 observations for IL-6 and 88 observations for sTNF-R1.

RESULTS

Mean values and standard deviations for demographic and biological variables are shown in Table 1. Bivariate relationships between study variables are presented in Table 2. With respect to CD₂₅ and inflammatory markers, correlation analyses revealed a significant linear association between CD₂₅ and CRP. Among all study variables, CRP showed the strongest relationship with CD₂₅ ($r = .326$, $P = 0.003$) (Figure 1). A hierarchical regression analysis was used to examine if the observed association between CD₂₅ (step 2) and CRP (dependent variable) remained significant after entering potential covariates on step 1. Results for step 1 indicated that this model significantly accounted for variance in CRP ($P < 0.001$; $R^2 = .336$) with BMI ($\beta = 0.394$, $P = 0.002$) and age ($\beta = 0.246$, $P = 0.04$) being significant predictors of CRP but not sex ($\beta = -0.062$, $P = 0.48$), ethnicity ($\beta = 0.045$, $P = 0.70$), smoking status ($\beta = -0.027$, $P = 0.79$), LTE ($\beta = -0.056$, $P = 0.39$), MAP ($\beta = 0.084$, $P = 0.45$) and HR ($\beta = -0.004$, $P = 0.92$). Results for step 2 indicated that the inclusion of CD₂₅ significantly accounted for variance in CRP even after taking potential confounders into account (β for CD₂₅ = 0.220, $P = 0.04$; $\Delta R^2 = .036$).

In the present investigation, we included 16 subjects with moderate obesity (class I obesity, BMI 30.0–34.9). Considering i) the strong relationship between BMI and CD₂₅, ii) the potentially confounding role of BMI on the relationship between CD₂₅ and inflammation, and iii) our intention to study a potential relationship between in vivo β -adrenergic receptor function and inflammation under non-pathological conditions, an exploratory model excluding these obese participants ($N = 16$, 10.8 %) was run. Results for step 1 indicated that this model significantly accounted for variance in CRP ($P = 0.02$; $R^2 = .259$) with BMI ($\beta = 0.300$, $P = 0.03$) being a significant predictor of CRP but not age ($\beta = 0.251$, $P = 0.06$), sex ($\beta = -0.019$, $P = 0.87$), ethnicity ($\beta = 0.027$, $P = 0.84$), smoking status ($\beta = -0.038$, $P = 0.75$), LTE ($\beta = -0.102$, $P = 0.44$), MAP ($\beta = 0.111$, $P = 0.39$) and HR ($\beta = -0.036$, $P = 0.77$). Results for step 2 again indicated that the inclusion of CD₂₅ significantly accounted for additional variance in CRP (β for CD₂₅ = 0.288, $P = 0.02$; $\Delta R^2 = .062$). The exclusion of moderately obese participants thus strengthened the relationship between CD₂₅ and CRP.

Although CD₂₅ was not related to other inflammatory measures in the bivariate correlations, the same procedure (determining confounders followed by hierarchical analyses) was conducted for IL-6 and sTNF-R1. Using this approach, there were no significant associations of CD₂₅ with IL-6 or with sTNF-R1 (results not shown).

DISCUSSION

This study investigated the association of β -adrenergic receptor function with plasma levels of inflammatory markers in a sample of healthy unmedicated adults. β -adrenergic receptors mediate several catecholamine-induced effects. A decreased sensitivity of these receptors is considered a physiological component of chronic stress (3, 11, 20) and an overactive sympathetic nervous system (49, 50). While prior findings in animals as well as human in vitro studies suggest that prolonged β -adrenergic receptor over-activation may facilitate inflammation (42–44), this study is the first study to include CD₂₅, an in vivo marker of β -adrenergic receptor sensitivity. Our main finding is that higher CD₂₅ values (reflecting decreased β -adrenergic receptor sensitivity) are related to higher circulating levels of the acute phase protein CRP. This association remained significant even after taking into account for several socio-demographic and health variables which may theoretically be confounded with CD₂₅ and inflammation respectively.

The observed link between β -adrenergic receptor function and CRP is in line with previous research. First of all, catecholamines such as epinephrine increase the production of CRP in isolated hepatocytes in the presence or absence of IL-6 (81). In young mice, chronic β -adrenergic receptor stimulation with isoproterenol was sufficient to increase circulating CRP, whereas chronic treatment with β -adrenergic antagonists resulted in reduced CRP concentrations in aging mice (82, 83). The latter findings are quite interesting because chronic isoproterenol application in animal models may resemble prolonged catecholamine-induced β -adrenergic receptor over-activation in humans. Our findings also seem to be compatible with studies focusing on anti-inflammatory effects of β -adrenergic antagonists in clinical samples. For example, treatment of CVD patients with β -adrenergic antagonists has been shown to reduce circulating CRP concentrations (46, 47). A cross-sectional study among 2340 participants taking antihypertensive medications found lower serum CRP level among participants taking a β -blocker than among those not taking a β -blocker (84). Last but not least, CRP secretion is substantially heritable and plasma CRP concentrations in twins were predicted by multiple, common genetic variants in the catecholaminergic/ β -adrenergic pathway (48).

Although the exact pathways by which β -adrenergic receptors may affect CRP are not clear, there are some potential mechanisms to be considered. First of all, a prolonged sympathetic over-activation may increase CRP production via pro-inflammatory cytokines. Especially, the secretion of IL-6 but also of TNF- α and IL-1 by the liver and adipose tissue has been proposed to increase hepatic CRP production (25, 85–91). Such a pathway would be in line with in vitro findings showing that pro-inflammatory responses in human monocytes are mediated by β -adrenergic receptor activation (42) and with animal studies demonstrating that chronic β -adrenergic stimulation increases pro-inflammatory cytokine expression (43, 44).

Curiously, in the present study no relationship between CD₂₅ and IL-6 was observed. Assuming that CRP is induced by IL-6 in the liver, the observed association between CD₂₅ and CRP may simply reflect the fact that CRP is a more integrative, stable and reliable marker for inflammation than IL-6. The latter may be supported by a higher average correlation coefficient for CRP (av.r = .878) than for IL-6 (av.r = .496) (average correlation coefficients were calculated from Z-transformed correlation coefficients of the three measures for each of the three inflammatory markers). Longitudinal analyses have found that CRP is stable during long-term follow-up, as long as it is not measured within 2 weeks of an acute infection (92, 93). Unlike CRP, the half-life of IL-6 is short and serum levels of IL-6 reflect only unbound IL-6. Moreover, CRP is less sensitive to minor health changes than IL-6 (70, 94–97).

As mentioned above, epinephrine, as well as glucagon, increases the production of CRP in isolated human hepatocytes even in the absence of IL-6 (81). In addition, exercise decreases CRP irrespective of any significant changes in IL-1, IL-6 and TNF- α in patients with fibromyalgia (98). Therefore, it may be possible that β -adrenergic receptor function is also related to CRP via pathways that are currently not known and that do not involve mechanisms involving pro-inflammatory cytokines such as IL-6 or TNF- α . The latter might also explain why sTNF-R1, which has similar stability as CRP (av.r = .932), was not related to CD₂₅.

Although our data and the findings of previous studies suggest an association between β -adrenergic receptor function and CRP, it remains unclear what mechanism underlies that association. We suggest that a prolonged over-activation of β -adrenergic receptors may be related to a wide range of inflammatory alterations which might be better reflected by CRP, as an integrated and reliable inflammatory marker, than by specific pro-inflammatory cytokines. Features which have been related to reduced in vivo or vitro β -adrenergic receptor sensitivity (i.e. anxiety, perceived stress, hostility and depression) have also been linked to increased levels of inflammatory markers (12–15, 17, 31, 33, 56–59, 99, 100). The observation that psychological stress is important for almost all of these features may be interesting in view that β -adrenergic receptors are involved in stressor-induced pro-inflammatory alterations in animals (101, 102), and that α - and β -adrenergic receptor antagonists are sufficient to block stressor-induced increases in innate immunity (43, 103). Therefore, our finding of a robust relationship between inflammation and in vivo β -adrenergic receptor function in humans implicates that in vivo assessment of β -adrenergic receptor function may be promising in stress-related clinical states and conditions which have been linked to both sympathetic nervous system abnormalities and inflammation. Finally, our findings are interesting in light of the fact that previous human in vitro research has suggested an impact of β -adrenergic receptor function on the cardiovascular system by mediating the procoagulant response to acute stressors (16). Assuming the observed link between CD₂₅ and CRP, and the association of elevated CRP with an increased risk for CVD (21–24), interesting results may arise from longitudinal studies which focus on CD₂₅ as an additional predictor for pathological alterations in the cardiovascular system.

A number of limitations should be considered when interpreting our results. First of all, it may be important to consider alternative explanations of the observed relationship between CD₂₅ and CRP. For example, β -AR function decreases with age (63, 63) and increased inflammatory markers such as CRP have also been related to higher age (66). Although we control for numerical age, we cannot exclude that the CD₂₅-CRP relationship may be partially confounded by physiologic age since physiologic age may not always match numerical age. We also cannot exclude that the relationship between CD₂₅ and CRP is due to confounding variables, which were not assessed in this study, although the impact of the most probable covariates was carefully examined. Secondly, a more complete understanding of the association between β -adrenergic receptor function and inflammation may arise from studies that assess immunological function more comprehensively. Finally, because of the cross-sectional design, causality in the relation between CD₂₅ and CRP cannot be determined.

In conclusion, our findings suggest that decreased β -adrenergic receptor sensitivity (i.e., higher chronotropic 25 dose values) predicts CRP in a sample of healthy adults. To our knowledge, this study is the first to demonstrate a link between inflammation and β -adrenergic receptor function using an in vivo method in humans. Future studies which focus on CD₂₅ and inflammation in clinical samples may be promising.

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List of Abbreviations

BMI	Body Mass Index
cAMP	cyclic Adenosine Monophosphate
CD₂₅	Chronotropic 25 Dose
CRP	C-Reactive Protein
CVD	Cardio Vascular Diseases
HR	Heart Rate
LTE	Leisure-time Exercise
IL	Interleukin
MAP	Mean Arterial Blood Pressure
sTNF-R1	Soluble Tumor Necrosis Factor Receptor 1

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Figure 1.

Table 1

Characteristics of the study group (N = 93).

Age, years	35.1 (9.7)
Body mass index, kg/m ²	26.3 (3.6)
Women, N (%)	39 (41.9)
African Americans, N (%)	43 (46.2)
White, N (%)	50 (53.8)
Current smoker, N (%)	10 (10.7)
Leisure-time exercise ^I	77.9 (121.3)
Baseline heart rate, bpm	65.1 (10.1)
Mean arterial blood pressure, mmHg	91.5 (12.0)
Chronotropic 25 dose, µg	1.4 (0.8)
C-reactive protein, mg/L ^I	0.9 (1.0)
Interleukin 6, pg/mL ^I	3.6 (2.5)
Soluble tumor necrosis factor receptor 1, pg/mL ^I	888.2 (420.5)

Notes: Values shown as mean (SD) unless otherwise noted.

^I = untransformed data are displayed, statistical analyses based on log-transformed data

Table 2

Pearson's correlations between metric study variables.

Variable	Age	BMI	HR	MAP	LTE ^I	CD ₂₅	CRP ^I	IL-6 ^I	sTNF-R1 ^I
Age	–	.521***	.027	–.001	–.173	.235*	.445***	.106*	.003
BMI		–	.194*	.303**	–.216*	.189*	.535***	.321**	.077
HR			–	.201*	–.240*	.080	.110	.220	.219
MAP				–	.042	–.103	.169	.060	.129
LTE ^I					–	–.017	–.206	–.001	–.109
CD ₂₅						–	.326**	–.033	–.170
CRP ^I							–	.159	–.005
IL-6 ^I								–	.188
sTNF-R1 ^I									–

Notes: BMI = body mass index; CD₂₅ = chronotropic 25 dose; CRP = C-reactive protein; HR = baseline heart rate; IL-6 = interleukin 6; LTE = leisure-time exercise; MAP = baseline mean arterial blood pressure; sTNF-R1 = soluble tumor necrosis factor alpha receptor 1.

^I = based on log-transformed data.

* $P < 0.05$;

** $P < .01$,

*** $P < .001$.