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Effects of Exercise on Systemic Inflammatory, Coagulatory, and Cardiac Autonomic Parameters in an Inhalational Exposure Study

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Abstract

Background—Intermittent moderate-intensity exercise is used in human inhalational exposure studies to increase the effective dose of air pollutants.

Methods—To investigate the inflammatory, coagulatory, and autonomic effects of intermittent moderate-intensity exercise, we measured hemodynamic, ECG, and inflammatory and coagulatory parameters in peripheral blood of 25 healthy subjects across an exercise protocol that included running on a treadmill or pedaling a cycle-ergometer for 30min of every hour over 4h in a climate-controlled chamber with a target ventilation of 20L/min/m^2 body surface area.

Results—Intermittent moderate-intensity exercise induced a systemic pro-inflammatory response characterized by increases in leukocyte counts, CRP, MCP-1, and IL-6, but did not change coagulation tendency or heart rate variability.

Conclusion—Interpretation of pollutant-induced inflammatory responses in inhalational exposure studies should account for signals and noises caused by exercise, especially when the effect size is small.

INTRODUCTION

Multiple epidemiological studies have demonstrated associations between air pollutant levels and cardiopulmonary morbidity and mortality. Consequently, various agencies have funded controlled human exposure studies in order to help elucidate the mechanisms behind these cardiopulmonary effects. To maximize exposure to pollutants, such studies have often used intermittent moderate-intensity exercise regimens to increase a subject's minute ventilation (V_E)(1). However, a possible problem with the use of exercise is that it may elicit

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significant inflammatory, coagulatory, and cardiac autonomic changes that may interfere with detection of any potential effects of air pollutants.

Although routine exercise has been shown to induce significant long-term effects on inflammatory, coagulatory, and autonomic markers of the cardiovascular system (2–7), the study of the immediate effects of exercise has yielded conflicting results. While multiple studies have reported no significant inflammatory changes (8–11), others have found a systemic “acute-phase” pro-inflammatory response to exercise, characterized by leukocyte redistribution (12, 13) and increased C-reactive protein (CRP)(14), the magnitude and duration of which may depend on the intensity and length of exercise (12–14). Similarly, measurements of effects of exercise on coagulatory and fibrinolytic parameters have yielded conflicting results with some showing a delayed increase in fibrinogen a day after acute intensive exercise (15) and others showing a decrease in fibrinogen and an increase in plasma D-dimer fragments immediately following a long-distance run (16).

Possible explanations for these inconsistent findings may be the differences in the intensity of exercise protocols as well as potential effects of inhalation of outdoor pollutants or ambient temperature and humidity. Many of these studies were performed in the setting of short-duration maximum effort (e.g., “cardiac stress” test protocols) or prolonged endurance exertion (e.g., long-distance running), at the extremes of intensity and/or duration (17). Furthermore, many of these studies were also conducted in non-controlled settings, either outdoors, or indoors but without air filtration or maintenance of temperature and humidity. Overall, no studies have conclusively established the acute cardiovascular effects of intermittent moderate-intensity exercise.

In the present study, we investigated the effects of exercise using a protocol employed in controlled human inhalational exposure studies in a climate-controlled setting with clean filtered air to determine whether the type of intermittent exercise regimen used in controlled exposure studies can cause acute changes in markers of systemic inflammation, coagulation, or autonomic dysfunction. Our hypothesis was that intermittent moderate-intensity exercise would produce changes in these markers that could mask potential pollutant-induced effects.

METHODS

Study Design

This study used a repeated measures design in which subjects performed intermittent moderate-intensity exercise for 4 h in a climate-controlled chamber with clean filtered air. All endpoints were measured immediately before (0-h), immediately after (4-h), and on the following morning (approximately 20 h) after exercise (24-h).

Subjects

Twenty-five subjects were recruited using the following inclusion/exclusion criteria: (1) age between 18–50 years; (2) ability to perform moderate-intensity exercise; (3) healthy with no history of cardiovascular, hematologic, or pulmonary diseases other than mild asthma; (4) non-smoker as defined by having a history of less than ½ pack-year lifetime tobacco use and no history of any tobacco use in the past 6 months; and (5) no history of illicit drug use. The subjects were informed of the risks of the experimental protocol and signed a consent form that had been approved by the UCSF Institutional Review Board.

Experimental Protocol

The exercise sessions lasted 4 h and included alternating 30-min exercise and rest periods. The exercise consisted of running on a treadmill or pedaling a cycle ergometer. The exercise

intensity was adjusted for each subject to achieve a target V_E of 20 L/min/m^2 body surface area, following a previously published protocol(18). During exercise, the V_E was calculated (LabView 6.1; National Instruments) from tidal volume and breathing frequency measured using a pneumotachograph for 1 min at 10-min and 20-min time-points during each 30-min exercise period. Subjects remained inside the chamber for the entire 4-h exercise period. The subject underwent phlebotomy, blood pressure and heart rate measurement, and electrocardiographic (ECG) monitoring for heart-rate variability (HRV) measurement at 0-h, 4-h, and 24-h time-points.

Sample Size and Power Calculations

Human inhalational exposure studies have reported significant changes in blood inflammatory and coagulatory biomarkers with a sample size of 30 subjects (19–21). In addition, statistically significant changes in HRV have been observed with a sample size of five subjects with exposure to a combination of particulate matter and ozone (22). Our sample size was based on the ability to detect a 10% change in concentration of the blood biomarkers of interest with presumed standard deviations twice the magnitude of the effect size. Given the above, sample sizes of 20 and 25 provided statistical power of 81% and 86%, respectively, to observe a minimal change of 10% with a type I error of 5%.

Data Management and Statistical Analysis

All concentrations were adjusted to account for possible changes in blood volume due to exertion, through a correction factor determined from the ratio of each subject's hemoglobin concentration at different 4-h and 24-h time-points compared to baseline (0-h). All concentrations were log-transformed before analysis, and their distributions were examined. Student's *t*-test was used for statistical comparisons. Data are presented as mean±SD, and were analyzed using STATA (STATA 10.0; StataCorp). A p-value of 0.05 was considered to be statistically significant.

RESULTS

Subject Characteristics and Climate-Controlled Chamber Conditions

Subject characteristics are shown in Table 1. The average temperature and relative humidity in the climate-controlled chamber were (mean±SD) 17.4±1.1°C and 54±2.1%, respectively.

Exercise-induced Changes in Peripheral Blood Leukocytes

The concentrations of peripheral blood leukocytes are shown in Table 2. The concentration of total leukocytes significantly increased at 4-h and remained elevated at 24-h (mean increase: $3.1\pm2.11\times10^6$ cells/ml, $p<0.0001$ and $0.85\pm0.9\times10^6$ cells/ml, $p=0.0001$, respectively) compared to 0-h. The concentrations of neutrophils, lymphocytes, and monocytes increased significantly at 4-h, and while the neutrophil concentration returned to baseline by 24-h, the concentrations of lymphocytes and monocytes remained elevated.

Exercise-induced Changes in CRP, ACE, and Cytokines

The concentrations of serum CRP and ACE activity are shown in Table 2. No significant change in CRP level occurred between 0-h and 4-h. However, at 24-h, CRP had significantly increased in the entire group (mean increase: 1.66±2.9 mg/L, p=0.011). ACE activity levels showed a slight but significant decrease at 4-h (mean decrease: 1.8±4.18 U/L, p=0.04) but returned back to baseline by 24-h.

Serum MCP-1 and IL-6 concentrations are also shown in Table 2. MCP increased significantly from a baseline value of 542.4±54.5pg/ml to 726.2±81.9 pg/ml, and IL-6 from

4.6±1.3 pg/ml to 5.8±1.2pg/ml at 4-h (p=0.009 and p=0.03, respectively). No significant changes were observed for any other measured cytokine (data not shown).

Exercise-induced Coagulatory and Fibrinolytic Changes

Plasma fibrinogen did not change after exercise at any time-point. In contrast, PAI-1 level decreased significantly at 4-h (mean decrease: 11.8±19.2IU/ml, p=0.005) but returned back to baseline level by 24-h. The changes in PT and PTT, though significant, were small in magnitude (Table 3).

Exercise-induced Changes in Blood Pressure and Heart Rate

At 4-h, diastolic blood pressure significantly decreased (mean decrease: 3.7±6.6 mmHg, p=0.01). By 24-h, diastolic pressure had returned to baseline. No significant changes in systolic blood pressure were observed (data not shown). Heart rate measurement showed a non-significant increase at 4-h (mean increase: 5.7±10.3 beats/min, p=0.11), and a significant decrease relative to baseline at 24-h (mean decrease: 4.66±6.28 beats/min, p=0.001).

Exercise-induced Changes in Cardiac Autonomic Function

No significant changes in the standard deviation of all R-R intervals (SDNN), the standard deviation of the mean of all intervals (SDANN), or the root mean square of successive differences among normal R-R intervals (RMSSD) were observed for spontaneous breathing. A significant decrease in the mean of all R-R standard deviations (SDNNI) at 4-h was observed for all subjects (mean decrease: 8.16±19.4 ms, p=0.046).

When the subjects underwent timed (metronome) breathing, RMSSD significantly decreased at 4-h (mean decrease: 10.3±21.9 ms, p=0.027). No significant changes were observed in RMSSD at 24-h or for any other index of HRV during timed breathing (Table 4).

Analysis of the normalized frequency domain variables (LF, HF, LF/HF ratio) did not reveal any significant changes across the exercise session (from 0-h to 4-h) (Table 5).

DISCUSSION

In this study, we found that intermittent moderate-intensity exercise as frequently used in human inhalational exposure studies induces a systemic pro-inflammatory response characterized by an immediate post-exercise increase in peripheral blood monocyte, neutrophil, lymphocyte counts; an immediate increase in serum IL-6 and MCP-1 concentrations; and a delayed increase in serum CRP at 24 h post-exercise. No substantial exercise-induced effects on coagulatory parameters were found. Furthermore, while significant decreases in SDNNI during spontaneous breathing and RMSSD during timed breathing were observed, the overall lack of significant changes in the majority of HRV indices suggests that intermittent moderate-intensity exercise does not considerably alter autonomic modulation of the heart if measured 30 min after the end of exercise. Together, these results suggest that the typical intermittent moderate-intensity exercise protocols used in inhalational exposure studies can cause an acute systemic pro-inflammatory response but no substantial coagulatory or cardiac autonomic changes.

Inhalational exposure studies commonly use intermittent exercise regimens in order to increase minute ventilation (V_E) and maximize the “effective dose” of exposure to pollutants while decreasing total exposure time (23, 24). However, when studying the systemic inflammatory, coagulatory, and cardiac autonomic effects of inhaled pollutants, exercise may hamper the ability to measure pollutant-induced changes by decreasing the signal-to-

noise ratio. Our study is the first to explicitly demonstrate that an exercise protocol used in inhalational exposure studies can significantly alter several markers of systemic inflammation. The repeated-measure cross-over design used in many of inhalational exposure studies may control for the confounding effects of exercise; however, the exercise effects may still overwhelm the pollutant signal and make it undetectable.

Several recent controlled human exposure studies that assessed effects of various pollutants on outcomes similar to those we investigated found that exercise during a filtered air exposure did cause significant changes. In a study of the effects of ultrafine particles (UFP) on leukocytes, Frampton et al. found that intermittent exercise for 2 h at a V_E of 20 L/min/m2 body surface area in filtered air increased in peripheral blood monocyte expression of CD54 (ICAM-1) as well as the percent total leukocytes (25). This group later reported the results of another study of UFP in which the same exposure to filtered air with exercise induced a transient decrease in HRV during exercise with a return to near baseline immediately after exercise and a complete return to baseline by 21 h after exercise (26). In contrast, three studies with shorter and somewhat less intense exercise periods found no effects on outcomes that we assessed. Mills et al. reported the results of a study of diesel exhaust in which no effect of intermittent exercise for 1 h in filtered air on t-PA, PAI-1, CRP, or neutrophils was observed in subjects with ischemic heart disease (27). This group also found no effect of exercise in filtered air using the same protocol on t-PA and PAI-1 in a study of NO_2 (28). In a third study, this group reported no effect of the 1-h intermittent exercise protocol on HRV (29). The differences in results among these studies and ours are likely due to differences in subject characteristics and study protocols in terms of exercise level and duration. However, the lack of effect in the filtered-air arms on HRV or PAI-1 after exercise in filtered air in these recent studies is consistent with the results that we report here. At the same time, the possibility of small differences in endpoints due to minor differences in exercise protocols argues for standardization and harmonization of exercise protocols used in controlled human exposure studies as suggested by others (30).

Given the multiple studies that have investigated the effects of exercise on systemic inflammation, peripheral blood coagulatory and fibrinolytic markers, and HRV, it may be useful to summarize the previous literature and place our results in context. A number of studies have reported acute increases in circulating leukocytes within several hours after exercise (12–14). With regard to CRP, only one of the five studies cited above that measured this acute phase reactant (8–11, 14) reported an increase after exercise (14). Compared to the cited studies, our study is notable for a protocol that involved 2 h of moderate exercise over a 4-h period. It also had a larger number of subjects (n=25) than any of the previous studies.

In contrast to the observed systemic inflammation due to intermittent moderate exercise, we did not find this exercise protocol to substantially affect peripheral blood coagulatory and fibrinolytic markers. A review of previous studies suggests that type and intensity of exercise have significant effects on whether or not any coagulatory or fibrinolytic changes are observed (10, 31). Others have suggested that a minimum exercise intensity threshold must be reached to observe fibrinogen degradation products (32). Overall, we conclude that intermittent moderate-intensity exercise does not cause substantial coagulatory changes.

Similarly, our results do not demonstrate any significant changes in the majority of HRV indices with intermittent moderate-intensity exercise, which suggests that this exercise protocol does not induce changes in cardiac autonomic function. It is important to note that the 4-h time-point ECG measurements were performed at the end of the 4-h exercise session, which ends with 30 min of rest period that may have blunted any HRV indices variation due to exercise. Although SDNNI for spontaneous breathing and RMSSD for timed breathing did decrease post-exercise, the lack of corresponding changes in other

indices suggests that cardiac autonomic function is not considerably altered by our specific exercise protocol. While chronic exercise has been shown to increase HRV indices in humans (5–7), the effects of a single exercise session on HRV may be much less pronounced. Yamamoto et al have suggested that indicators of sympathetic nervous system activity would not increase following a single bout of exercise until a minimum ventilatory threshold has been reached (33). If so, the lack of cardiac autonomic changes in our study could be due to sub-threshold exercise intensity.

Several limitations to our study must be noted. Firstly, unlike other studies examining acute cardiovascular effects of exercise, our protocol used target V_E, and not target heart rate, for adjustment of exercise intensity. However, the aim of our study was to investigate the cardiovascular effects of an exercise protocol employed in inhalational exposure studies, and these studies target V_E and not heart rate as a measure of exercise intensity. Secondly, the exercise protocol allowed for use of a treadmill or a cycle ergometer. It is possible, although unlikely, that the different methods of exercise may produce different systemic responses due to muscle mass involvement or mechanical stimulation through movement. We did not analyze our data based on use of treadmill or cycle ergometer.

In conclusion, we demonstrated that an exercise regimen typical of inhalational exposure studies induces systemic inflammatory responses that are sustained at 24-h. Coagulatory markers and heart rate variability were not notably affected by our exercise regimen. The observed systemic inflammatory responses are unlikely to be of clinical significance. However, the interpretation of inflammatory responses induced by ambient pollutants in human inhalational exposure studies should take into account the signals and noises caused by exercise, especially when the effect size is small.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Subject characteristics.

Subject Characteristic	N=25
Age (years)	33.0 ± 7.4
Female Sex [N(%)]	14 (56%)
Height (cm)	169.4 ± 9.45
BMI (kg/m^2)	26.1 ± 6.5
BSA (m^2)	1.87 ± 0.28
V_E ($L/min/m^2$ BSA)	19.98 ± 0.46
Mild Asthmatics [N(%)]	10 (40%)

Data presented as mean±SD unless otherwise noted. BMI: body mass index; BSA: body surface area; V_E: Minute Ventilation.

Table 2

Exercise-induced changes in peripheral blood leukocytes, C-reactive protein (CRP), and angiotensin-converting enzyme activity (ACE).

Inflammatory Indices	Measurement Time Point		
	0-h	4-h	24-h
Leukocytes (×10^6 cells/mL)	5.8 ± 1.6	**8.9 ± 2.6*****	**6.6 ± 1.9*****
Neutrophil (×10^4 cells/mL)	350 ± 131	**621 ± 233*****	361 ± 145
Lymphocyte (×10^4 cells/mL)	162 ± 48	**191 ± 59*****	**222 ± 58*****
Monocyte (×10^4 cells/mL)	30.0 ± 8.5	**41.3 ± 14*****	**38.3 ± 14.5****
Eosinophil (×10^4 cells/mL)	22.3 ± 16	**19.75 ± 15.5***	23.4 ± 13.9
CRP (mg/L)	2.64 ± 4.7	2.77 ± 4.8	**4.30 ± 5.3****
ACE (U/L)	40.1 ± 14.6	**41.9 ± 15.4***	41.5 ± 14.6

Data presented as mean±SD. Measurement time points refer to the time of the sample collection (0-h: immediately before; 4-h: immediately after; 24-h: 24 hours after the start of the exercise). N=25. Statistically significant data are shown in bold.

* : 0.05≥p>0.01;

** : 0.01≥p>0.001;

*** p≤0.001 (vs. the corresponding 0-h).

Table 3

Exercise-induced coagulatory and fibrinolytic changes.

Coagulatory Indices	Measurement Time Point		
	0-h	4-h	24-h
Fibrinogen (mg/dL)	311 ± 117	307 ± 64	304 ± 93
PAI-1 (IU/mL)	13.8 ± 21.6	**2.1 ± 4.3****	17.3 ± 29.8
Platelets (×106 cells/mL)	289.6 ± 73.8	**303 ± 73.3****	281.1 ± 70.4
PT (s)	13.1 ± 0.6	13.2 ± 0.7	**13.4 ± 0.5***
PTT (s)	29.9 ± 3.5	**28.5 ± 3.7****	**30.6 ± 3.5***

Data presented as mean±SD. Statistically significant data are presented in bold. Measurement time points refer to the time of the sample collection (0-h: immediately before; 4-h: immediately after; 24-h: 24 hours after the start of the exercise). N=25.

*: 0.05≥p>0.01;

**: 0.01≥p>0.001;

PAI-1: Plasminogen activator-inhibitor 1 activity; PT: Prothrombin time; PTT: Partial thromboplastin time.

Table 4

Exercise-induced changes in cardiac autonomic function.

HRV Time-Domain Indices (ms)	Measurement Time Point		
	0-h	4-h	24-h
SDNN-spontaneous	53.8 ± 25.8	53.0 ± 35.7	57.9 ± 27.3
SDNN- metronome	55.7 ± 26.5	51.4 ± 30.6	58.7 ± 24.1
SDANN- spontaneous	0.48 ± 2.2	3.4 ± 8.6	3.7 ± 7.4
SDANN- metronome	38.3 ± 31.7	33.2 ± 32.2	38.3 ± 31.7
SDNNI- spontaneous	52.1 ± 23.8	**44.0 ± 28.9***	51.4 ± 30.7
SDNNI- metronome	30.1 ± 15.3	30.2 ± 17.3	31.1 ± 11.0
RMSSD- spontaneous	43.4 ± 31.7	41.2 ± 43.2	45.1 ± 29.8
RMSSD- metronome	45.2 ± 31.4	**34.9 ± 31.3***	47.6 ± 31.0

Data presented as mean±SD. Statistically significant data are shown in bold. Measurement time points refer to the time of the sample collection (0-h: immediately before; 4-h: immediately after; 24-h: 24 hours after the start of the exercise). N=25.

*: $0.05 \geq p > 0.01$ (vs. the corresponding 0-h); SDNN: Standard deviation of all R-R intervals; SDANN: Standard deviation of the mean of all intervals; SDNNI: Mean of all R-R standard deviations; RMSSD: Root mean square of successive differences in normal R-R intervals.

Table 5

Heart rate variability frequency-domain indices with spontaneous breathing.

HRV Frequency-Domain Indices	Measurement Time Point	
	0-h	4-h
LFn (nu)	58.1 ± 16.7	56.2 ± 15.9
HFn (nu)	41.9 ± 16.7	43.8 ± 15.9
LF (ms^2)	799.9 ± 1492.6	625.5 ± 1004.2
HF (ms^2)	751.5 ± 1793.7	618.2 ± 1132.7
LF/HF ratio	1.81 ± 1.3	1.7 ± 1.3

Data presented as mean ± SD. Measurement time points refer to the time of the sample collection (0-h: immediately before; 4-h: immediately after). N=25. LF: low frequency component; HF: high frequency component; LFn: normalized low frequency component; HFn: normalized high frequency component; nu: normalized unit.