European Journal of Applied Physiology
https://doi.org/10.1007/s00421-024-05599-9

ORIGINAL ARTICLE

Acute exercise-induced inflammatory and thrombotic response in hypertensive patients

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Received: 9 March 2024 / Accepted: 24 August 2024

Abstract

Purpose Vigorous physical activity may acutely trigger the onset of an acute coronary syndrome especially in sedentary persons with established cardiovascular risk factors such as arterial hypertension. The rupture of an inflamed coronary plaque and the activation of the coagulation cascade are the main underlying mechanisms. The present study aimed to determine the effect of acute exercise on the inflammatory and thrombotic response in patients with arterial hypertension as compared to normotensive peers.

Methods After excluding patients with any inflammatory or/and coronary artery disease, a total of 60 non-treated hypertensive patients and 65 normotensive individuals underwent a maximal treadmill exercise testing. Blood samples were drawn at rest and immediately after peak exercise. High-sensitivity C-reactive protein (hsCRP), serum amyloid A (SAA), white blood cell (WBC), interleukin-6 (IL-6), and total fibrinogen (TF) levels, as well as plasminogen activator inhibitor-1 (PAI-1) activity, were measured.

Results All biomarkers increased with exercise, except PAI-1, which decreased ($P < 0.05$ for the change between resting and peak exercise for all biomarkers). After adjusting for relevant confounders (duration of exercise, metabolic equivalents, systolic BP, and rate-pressure product achieved at peak exercise), the normotensive group had less marked ($P < 0.05$) exercise-induced changes than the hypertensive group in hsCRP (7.7 vs. 8.6%), SAA (5.6 vs. 11.9%), WBC (45.0 vs. 51.7%), and PAI-1 (−17.3 vs. -20.1%) and a similar ($P =$ NS) change in IL-6 (23.8 vs. 23.0%) and TF (8.5 vs. 8.5%).

Conclusion In conclusion, the acute exercise-induced inflammatory and thrombotic response seems to be more pronounced in non-treated hypertensive patients than in normotensive controls. Possible clinical implications of this finding merit further examination.

Keywords Acute-phase response · Arterial hypertension · Biomarkers · Exercise · Inflammatory response · Thrombotic response

Abbreviations

BP	Blood pressure
CAD	Coronary artery disease
CRP	C-reactive protein
CV	Cardiovascular
EDTA	Ethylenediaminetetraacetic acid
HR	Heart rate
HsCRP	High-sensitivity C-reactive protein
IL	Interleukin
MANCOVA	Multivariate analysis of covariance
PAI-1	Plasminogen activator inhibitor-1
SAA	Serum amyloid A
TF	Total fibrinogen
WBC	White blood cell

Communicated by Fabio Fischetti.

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Published online: 09 September 2024

Introduction

Habitual aerobic physical activity is reasonably considered as an important preventive measure associated with beneficial long-term health outcomes and especially cardiovascular (CV) protection over time (Warburton and Bredin 2017; Thompson et al. 2007). There is consistent evidence that a physically active lifestyle plays role in the prevention of arterial hypertension and reduction of elevated blood pressure (BP) and also prevents the development of CV disease, irrespective of BP levels (Mancia et al. 2023; Kraus et al. 2019; Joseph et al. 2019).

On the other hand, vigorous exercise may acutely and transiently increase CV risk and trigger the onset of an acute coronary event in asymptomatic adults (Thompson et al. 2007). This is especially true in sedentary individuals with established CV risk factors such as arterial hypertension who engage in high-intensity exercise but are unaccustomed to this mode of exercise (Thompson et al. 2007). The underlying mechanisms for the exercise-associated acute cardiac events are not well defined. Nevertheless, the most plausible scenario is that the increased vascular wall stress from the increased BP and heart rate (HR) leads to the rupture or erosion of a small inflamed, mildly fissured, vulnerable atherosclerotic coronary plaque, followed by platelet aggregation, coagulation cascade activation, clot formation, and finally acute thrombotic occlusion (Thompson et al. 2007).

Moreover, subclinical inflammation and thrombosis as well as endothelial dysfunction have been shown to constitute a common pathway implicated in the pathophysiology of both arterial hypertension and coronary artery disease (CAD) (Medina-Leyte et al. 2021). Research on inflammatory and prothrombotic biomolecules, such as acute-phase proteins and cytokines, and their clinical application as potential novel CV risk factors has grown exponentially over the last decades. Among several studied circulating biomarkers, C-reactive protein (CRP), serum amyloid A (SAA), white blood cell (WBC) count, interleukin-6 (IL-6), fibrinogen, and plasminogen activator inhibitor-1 (PAI-1) have emerged as predictors of hypertension, atherosclerosis, plaque instability, and serious CV events (Medina-Leyte et al. 2021; Sesso et al. 2007; Bautista et al. 2005; Lip and Beevers 1994; Kumric et al. 2021; Koenig and Khuseyinova 2007; Suzuki et al. 2006; Catena et al. 2005; Pai et al. 2004; Johnson et al. 2004; Danesh et al. 1998; Juhan-Vague and Alessi 1993).

The acute effects of exercise on circulating inflammatory and prothrombotic biomarkers' levels have mostly been explored several hours post-exercise in young, trained athletes performing exhaustive long-duration exercise, e.g., a marathon race (Kasapis and Thompson 2005; Cox et al 2009; Suzuki et al. 2002; Ostrowski et al. 2000, 1998; Antunes et al. 2019). The early acute response of these biomarkers during short-term, vigorous aerobic exercise, e.g., jogging (Thompson et al. 2007) in older, untrained individuals with morbidities such as hypertension, is less well studied (Mendham et al. 2011; Dorneles et al. 2016; Tartibian et al. 2009; Plaisance et al. 2007; Andreozzi et al. 2007; DeSouza et al. 1997; Gavriilaki et al. 2014). Generally, the acute exercise-induced inflammatory/coagulative reaction seems to be related with the mode and the intensity of the activity, the muscle injury, and the physical fitness of the participant (Kasapis and Thompson 2005; Antunes et al. 2019; Mendham et al. 2011; Dorneles et al. 2016). Consequently, it is unclear whether short-duration exercise, such as a treadmill (graded) exercise testing, an exam commonly performed in patients with one or more CV risk factors, such as arterial hypertension, causes rapid systemic cytokine release.

Based on the aforementioned data, we conducted a case–control study to comparatively evaluate the effect of short bouts of exercise-induced physical stress, via a graded treadmill exercise testing, on a variety of mediators of inflammation and coagulation in hypertensive patients in contrast to normotensive peers. Although the scenario of performing aerobic physical exercise is common both in daily physicians' clinical practice and in daily humans' life, previous studies and the number of participants in this setting are very limited and the results are not unanimous. Given its potential clinical implications in terms of hard end-points such as triggering an acute coronary event, we consider that merits further evaluation.

Materials and methods

Population and design

This non-interventional, observational study enrolled 30–65-year-old normotensive individuals and patients with untreated, uncomplicated, grade 1–2 arterial hypertension. Patients with secondary hypertension, CAD, heart failure, cerebrovascular events, any inflammatory disease, malignancy, diabetes mellitus, renal or liver dysfunction, atrial fibrillation, conduction disturbances, pre-excitation syndromes, inability to walk on treadmill, current anti-inflammatory medication, including aspirin, or lipid-lowering treatment and pregnant females were excluded from this study.

All candidates, for this study, were screened at our institution's hypertension unit to define which of them met the inclusion or/and exclusion criteria. The evaluation included a thorough medical history, repeated

BP measurements, physical examination, resting electrocardiogram, echocardiogram, and full laboratory exams. After examination of 186 individuals, 70 hypertensive patients and 72 normotensive controls were eligible and accepted to participate in this study (Fig. 1). Written informed consent was obtained from all. This study was conducted in accordance with the Declaration of Helsinki recommendations and was approved by our institution's ethics committee (Reference number: 36153/2005).

The participants underwent maximal treadmill exercise testing. The test was indicated due to a 10-year CV risk score consistent with at least a moderate risk for cardiac events, non-typical angina, intention to initiate systematic strenuous exercise, or occupations in which acute CV events may have direct impact on public safety (Gibbons et al. 2002). Levels of high-sensitivity CRP (hsCRP), SAA, WBC, IL-6, and total fibrinogen (TF), as well as PAI-1 activity, were measured in blood samples drawn before and immediately after peak exercise. In a minority of participants (10 normotensive and 12 hypertensive individuals) they were also measured in blood samples drawn 3 h after peak exercise in order to roughly estimate the dynamics of biomarkers over time in the two groups. Blood samples' analyses and biomarkers' measurements were performed by biochemists blinded to the origin (hypertensive or normotensive participant) and the status (before or after exercise) of each sample. Participants with inconclusive or submaximal exercise testing were excluded from this analysis, whereas individuals with positive exercise testing underwent a stress echocardiography or a thallium-201 scintigraphy. The absence of wall motion abnormalities or perfusion defects, respectively, ruled out obstructive CAD. Coronary angiography was performed in patients with positive stress imaging results. Individuals with ≥ 50% coronary stenosis were not used in the analysis because this study targeted non-CAD subjects. Finally, 60 patients and 65 controls were included in this analysis (Fig. 1).

Grade 1 and 2 arterial hypertension definition

In accordance with the 2018 European Society of Hypertension guidelines, arterial hypertension was diagnosed as office systolic BP ≥ 140 mmHg or/and diastolic BP ≥ 90 mmHg, at repeat office visits (Williams et al. 2018). An office BP 140–159/90–99 mmHg was defined as grade 1, whereas 160–179/100–109 mmHg was defined as grade 2 hypertension. The office BP was recorded as the average of the last 2 out of 3 consecutive BP measurements taken with 1–2 min intervals and the patient seated comfortably

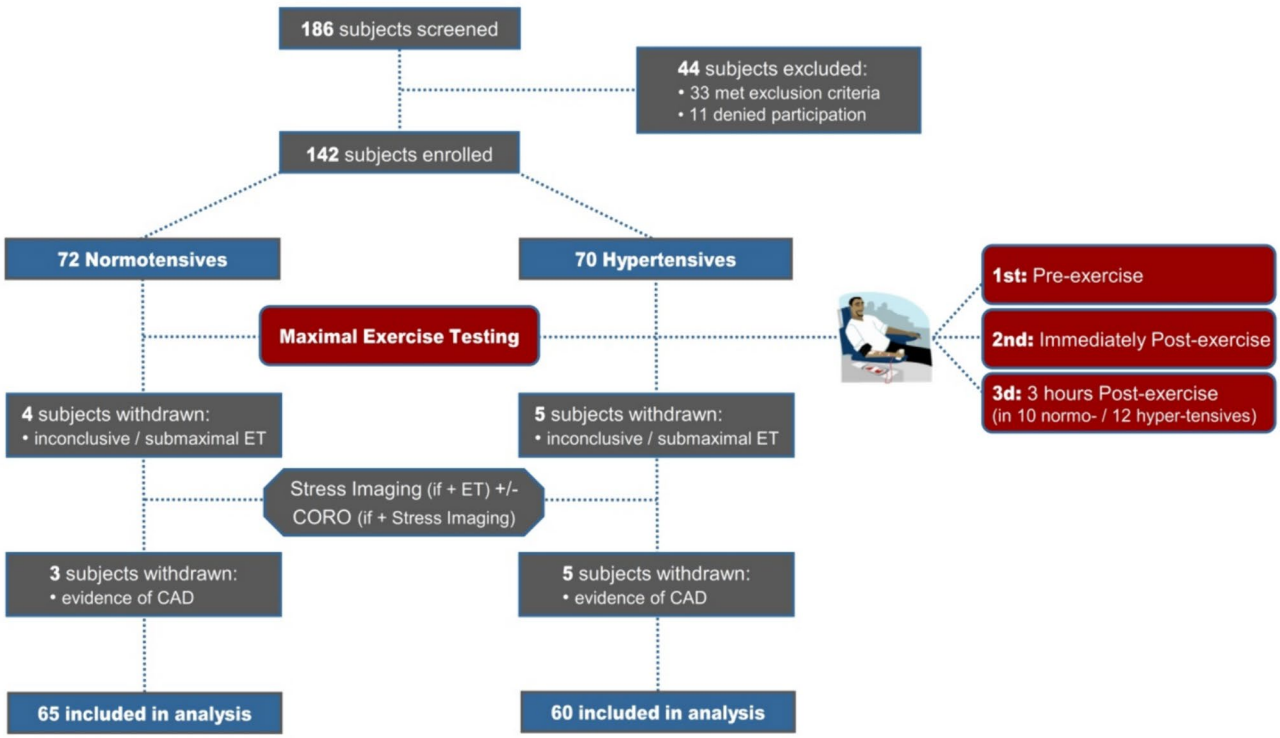

Fig. 1 Study design. Flowchart of participants' screening, enrollment, and performed exams. *CAD* coronary artery disease, *CORO* coronary angiography, *ET* exercise testing

in a quiet environment for 5 min before beginning BP measurements. Out-of-office BP measurements, using a certified 24-h ambulatory BP monitoring device (Spacelabs 90207, Redmond, WA, USA), was performed in participants with a borderline office BP or a home BP not corresponding to the office BP. The diagnostic threshold for hypertension, based on 24-h ambulatory recordings, was ≥ 130/80 mmHg over 24 h, ≥ 135/85 mmHg for the day-time BP average, and ≥ 120/70 for the night-time BP average, all equivalent to office BP ≥ 140/90 mmHg.

CV risk estimation

The underlying 10-year CV risk of the participants was estimated using the Framingham Risk Score and the Hellenic version of the HeartScore. The equations for the calculation of these scores are based on established CV risk factors: age, sex, systolic BP, total cholesterol, high-density lipoprotein, presence of smoking, presence of diabetes mellitus, and presence of BP-lowering medication (D'Agostino et al. 2008; Conroy et al. 2003). The Framingham Risk Score refers to the risk for fatal and non-fatal CV events and is considered low if < 10%, intermediate if 10–20%, and high if > 20% (D'Agostino et al. 2008). The HeartScore refers to the risk for fatal CV events and is considered low if < 1%, intermediate if 1–5%, high if 5–10%, and very high if > 10% (Conroy et al. 2003).

Physical activity evaluation

The physical activity of the participants was assessed using a translated version of the validated International Physical Activity Questionnaire (Craig et al. 2003). Participants reported all kinds of their activity during a usual week over the past year: time spent walking as well as in moderate- and vigorous-intensity exercise. Both continuous score (in metabolic equivalents times minutes of exercise per week) and categorical score (as low, moderate, or high level of activity) were calculated. The criteria for grouping in the categorical score have been previously described (Kavouras et al. 2007).

Exercise testing

A graded maximal exercise testing, defined as achieved HR > 90% of the maximal predicted HR (220 beats per min minus age in years), according to the Bruce protocol, was performed to all the participants. The test was performed between 07:30 and 08:30 a.m., after a 12-h overnight fast, on a 15-lead electrocardiogram analysis, treadmill system (GE CaseT-2000 Series, Milwaukee, WI, USA). The electrocardiogram was recorded continuously and the BP was measured at rest, at the 2nd min of each stage of exercise and during the recovery. The exam was terminated when the target HR was reached. An ischemic ST-segment response was defined according to the standard ST deviation criteria (Gibbons et al. 2002). Tests achieving a HR < 85% of the maximal predicted HR without ischemic ST-segment changes were considered inconclusive.

Blood samples analyses – biomarkers measurements

Routine laboratory exams were performed at all participants. Blood samples were collected between 07:30 and 08:30 a.m., after a 12-h overnight fast, and were analyzed in the central laboratory of our institution using the standard equipment and certified methods.

Blood samples were also drawn immediately pre- and post-exercise, between 07:30 and 08:30 a.m. for measurement of the studied biomolecules. A 12-h overnight fast preceded, to avoid the diurnal variation in the measured biomarkers. As previously reported, an extra blood sample was drawn from 22 fasting participants 3 h post-exercise.

Blood samples intended for hsCRP, SAA, and IL-6 measurement were collected in Serum separator tubes with micronized silica particles which help clot the blood before centrifugation, and a gel at the bottom of the tube which separates whole blood cells from serum. Blood intended for TF and PAI-1 measurement was collected in Citrate tubes. Blood intended for WBC measurement was collected in EthyleneDiamineTetraacetic Acid (EDTA) tubes.

Each sample was labeled with an anonymous barcode. Thus, the analysts were not aware of the origin and the status of the samples. The WBC count was measured on the same day from whole-blood specimens in a CelltacMEK-6410 automatic hematology analyzer (Nihon Kohden, Rosbach v.d.H., Germany). The blood samples intended for measurement of all the other biomarkers were immediately placed on ice and before they freeze were centrifuged at 1500 g, at 4 °C for 10 min. The supernatants were stored in 1-ml aliquots at −80 °C until further analyses. The analyses were performed with no more than 1 freeze–thaw cycle, were made in duplicate, and the reported results are the mean of the duplicate measurements. Serum hsCRP and SAA concentrations were measured with particle-enhanced immunonephelometry using the BNII system (Siemens Healthcare Diagnostics, Marburg, Germany). Serum levels of IL-6 were determined with a high-sensitivity, enzyme-linked immunosorbent assay according to the manufacturer's instructions (R&D Systems Europe, Abingdon, UK) in a ELX-800™ Universal Microplate Reader (Biotek® Instruments Inc., Winooski, Vermont 05404–0998 USA). TF was measured using a modified Clauss method on a BCS coagulation system (Siemens Healthcare Diagnostics). PAI-1 activity was determined with an amidolytic method using a

synthetic chromogenic substrate (Diagnostica Stago S.A.S., Asnières sur Seine, France). The intra-assay coefficients of variation of the aforementioned analyses ranged between 2.2 and 4.2%. All samples from a single participant were analyzed in the same assay in order to eliminate inter-assay variability.

Statistical analysis

The analysis of the data was performed with the IBM SPSS Statistics 23 software (2013, IBM, Route 100 Somers, NY, USA). Continuous variables are presented as mean ± standard deviation and categorical variables as observed number (*n*) and percentage (%). Differences in continuous variables were evaluated with the student's t-test, paired or two sample, as appropriate, once distribution normality was demonstrated with the Kolmogorov–Smirnov test. Otherwise, the Wilcoxon or Mann–Whitney non-parametric test, respectively, was used. Chi-square test, or Fisher's exact test, if applicable, was used to assess differences in categorical variables. Differences in the exercise-induced inflammatory and thrombotic response between the groups were adjusted for the effects of relevant confounders (that is, duration of exercise, metabolic equivalents, systolic BP, and rate-pressure product achieved at peak exercise) using multivariate analysis of covariance (MANCOVA). Differences were considered significant for a two-sided $P < 0.05$.

Results

A total of 60 hypertensive patients (65.0% males) and 65 normotensive controls (60.0% males) were included in this analysis. For the two groups, respectively, the mean age of the participants was 46.9 and 45.2 years; the mean office BP was 141/94 and 117/75 mm Hg; the mean office HR was 79 and 76 beats per min; the mean Framingham Risk Score was 13.0% and 7.1%; and the mean HeartScore was 1.47% and 0.82% (Table 1). The 2 groups were comparable (P = NS) with regard to clinical and biochemical parameters, with the exception of office BP and CV risk scores (Table 1). Maximal achieved HR at peak exercise did not differ between the two groups (P = NS) (Table 2). None of the participants complained about angina-like symptoms during exercise.

Resting values of the studied biomarkers were higher in hypertensives compared to controls with the exception of TF (Table 3). However, these differences were not statistically significant (P = NS for all). At peak exercise, all inflammatory and prothrombotic biomolecules significantly increased in both groups, except PAI-1, which notably decreased ($P < 0.05$ for all) (Table 3). However, the normotensive individuals compared with the hypertensive patients had a less marked ($P < 0.05$) exercise-induced percentage change in hsCRP (7.7 ± 0.8% vs. 8.6 ± 1.0%), SAA (5.6 ± 1.3% vs. 11.9 ± 1.6%), WBC (45.0 ± 2.9% vs. 51.7 ± 3.2%), and PAI-1 (−17.3 ± 1.3% vs. −20.1 ± 1.5%) and a similar (P = NS) percentage change in IL-6 (23.8 ± 2.5% vs. 23.0 ± 2.7%) and TF (8.5 ± 1.4% vs. 8.5 ± 1.5%) (Fig. 2). The differences between the two groups remained significant ($P < 0.05$) after adjusting for exercise parameters (duration and maximal achieved metabolic equivalents, systolic BP, and rate-pressure product).

In regard to the duration of the acute exercise-induced inflammatory/thrombotic response, available data from a small subgroup of participants of the present study show that 3 h post-exercise most of the studied biomarkers tend to return to pre-exercise or even lower levels both in normotensive and hypertensive individuals, except PAI-1 that continues to decrease (Table 4).

Discussion

The favorable effects of systematic physical exercise on the subclinical inflammation and the underlying CV risk in the long-term have been well documented. These appear to be mediated through reduced cytokine production in skeletal muscle, adipose tissue, mononuclear and endothelial cells; improved endothelial function; decreased insulin resistance; and an antioxidant effect (Kasapis and Thompson 2005; Pitsavos et al. 2003).

On the other hand, the acute exercise-induced inflammatory and prothrombotic response and the factors involved are more difficult to be examined, and thus, they are still only poorly clarified. Given the variety of inflammatory/thrombotic biomarkers, the variety of mode, intensity, and duration of physical activities, the variety of the time intervals after peak exercise at which biomarkers could be measured, and the variety of age, physical performance, and comorbidities (treated or untreated) of the participants, there are too many combination scenarios that could be studied. All of these scenarios are certainly understudied. Data have mainly been derived from professional athletes after strenuous prolonged exercise (for example, a marathon race) (Kasapis and Thompson 2005; Cox et al 2009; Suzuki et al. 2002; Ostrowski et al. 2000, 1998; Antunes et al. 2019).

The present study was undertaken in middle-aged, untrained patients with untreated arterial hypertension without CAD or/and other major comorbidities undergoing short-term vigorous aerobic exercise via a treadmill exercise testing. As far as we know, there is no other study with this number of participants, this variety of measured biomarkers, in these time intervals, in this specific group of patients, and performing this type of exercise. Thus, it is currently

Table 1 Participants' baseline characteristics

	Normotensives ($n = 65$)	Hypertensives ($n = 60$)	P value
Clinical parameters			
Age (years)	45.2 ± 12.4	46.9 ± 9.2	0.321
Male sex, *n* (%)	39 (60.0)	39 (65.0)	0.532
Office systolic blood pressure (mmHg)	117.1 ± 12.6	141.4 ± 11.3	< 0.001
Office diastolic blood pressure (mmHg)	74.5 ± 10.0	94.0 ± 7.5	< 0.001
Office heart rate (beats/min)	76.2 ± 8.7	78.8 ± 9.0	0.088
Obesity markers: body mass index (kg/m^2)	27.1 ± 3.4	27.5 ± 3.9	0.157
Waist to hip ratio	0.901 ± 0.068	0.918 ± 0.075	0.053
Smoking: current smokers, *n* (%)	28 (43.1)	29 (48.3)	0.192
Pack-years (in smokers)	30.2 ± 18.1	32.7 ± 20.0	0.165
Physical activity: low, *n* (%)	15 (23.1)	18 (30.0)	0.332
Moderate, n (%)	32 (49.2)	26 (43.3)	0.354
High, n (%)	18 (27.7)	16 (26.7)	0.875
MET-min/week	1839 ± 1187	1726 ± 1589	0.650
10-year CV risk: Framingham risk score (%)	7.1 ± 4.6	13.0 ± 9.6	< 0.001
Heart score (%)	0.82 ± 1.02	1.47 ± 1.75	< 0.001
Laboratory parameters			
Fasting plasma glucose (Ref. range: 70–110 mg/dl)	92.8 ± 9.9	95.2 ± 8.6	0.243
HBA_1c (Ref. range: 4.0–5.6%)	5.3 ± 0.4	5.4 ± 0.5	0.362
Serum creatinine (Ref. range: 0.7–1.3 mg/dl)	0.95 ± 0.16	0.94 ± 0.15	0.937
eGFR (Ref. range: > 90 ml/min/1.73 m^2)	104.9 ± 25.9	111.1 ± 30.3	0.179
Total cholesterol (Ref. range: < 190 mg/dl)	203.8 ± 36.4	214.4 ± 39.8	0.065
Triglycerides (Ref. ranges < 150 mg/dl)	121.3 ± 58.2	124.3 ± 64.7	0.567
HDL cholesterol (Ref. range: > 40 or 50 mg/dl)*	50.1 ± 11.7	48.3 ± 13.8	0.374
LDL cholesterol (Ref. range: < 116 or 100 mg/dl)**	129. 4 ± 31.4	134.3 ± 40.3	0.151
Echocardiographic parameters			
Ejection fraction (%)	68.5 ± 4.2	65.9 ± 5.0	0.001
Normal left ventricular geometry, *n* (%)	58 (89.2)	31 (51.6)	< 0.001
Transmitral early to late velocity ratio	1.15 ± 0.25	1.02 ± 0.28	0.004

Continuous variables are presented as mean ± standard deviation

* > 40 mg/dl in males, > 50 mg/dl in females; ** < 116 mg/dl in low CV risk, < 100 mg/dl in intermediate CV risk

CV cardiovascular, *eGFR* estimated glomerular filtration rate, *F* females, *HbA$_1$c* glycated hemoglobin, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *M* males, *MET* metabolic equivalent (3.5 ml O_2/kg/min), *n* number of patients, *Ref.* reference

Table 2 Exercise parameters in the two groups

	Normotensives ($n = 65$)	Hypertensives ($n = 60$)	P value
Exercise parameters			
Duration (sec)	649.5 ± 138.6	596.5 ± 114.1	0.023
METs	12.8 ± 2.5	11.7 ± 2.1	0.015
Achieved heart rate (% of target)	98.7 ± 5.9	98.6 ± 6.0	0.919
Maximal heart rate (beats/min)	173.4 ± 15.5	171.5 ± 13.2	0.460
Maximal systolic blood pressure (mmHg)	169.0 ± 20.2	198.4 ± 22.8	< 0.001
Rate-pressure product (beats/min x mmHg)	29,325 ± 4451	33,990 ± 4441	< 0.001
Pseudo-ischemic ST-segment response, *n* (%)	11 (16.9)	22 (36.7)	0.025

Continuous variables are presented as mean ± standard deviation

MET metabolic equivalent (3.5 ml O_2/kg/min), *n* number of patients.

Table 3 Exercise-induced changes in inflammatory and thrombotic biomarkers

	Pre-exercise	Post-exercise	*P* value
Normotensives ($n=65$)			
hsCRP (mg/l)	1.56 ± 1.33	1.68 ± 1.43	< 0.001
SAA (mg/l)	3.19 ± 2.63	3.37 ± 2.72	< 0.001
WBC (μl^{-1})	7018 ± 2034	10,177 ± 2512	< 0.001
IL-6 (pg/ml)	1.05 ± 0.71	1.30 ± 0.97	< 0.001
TF (mg/l)	363.9 ± 78.3	394.8 ± 82.9	< 0.001
PAI-1 (AU/ml)	14.94 ± 12.27	12.36 ± 13.31	< 0.001
Hypertensives ($n=60$)			
hsCRP (mg/l)	1.71 ± 1.45	1.85 ± 1.56	< 0.001
SAA (mg/l)	3.85 ± 2.54	4.31 ± 3.03	0.006
WBC (μl^{-1})	6415 ± 1739	9733 ± 2868	< 0.001
IL-6 (pg/ml)	1.22 ± 0.85	1.50 ± 1.13	< 0.001
TF (mg/l)	362.4 ± 89.8	392.6 ± 91.4	< 0.001
PAI-1 (AU/ml)	16.09 ± 10.70	12.85 ± 9.84	< 0.001

Continuous variables are presented as mean ± standard deviation

hsCRP high-sensitivity C-reactive protein, *IL-6* interleukin-6, *n* number of patients, *PAI-1* plasminogen activator inhibitor-1, *SAA* serum amyloid A, *TF* total fibrinogen, *WBC* white blood cells

unclear whether short-duration exercise, such as a treadmill exercise testing, causes rapid systemic cytokine release in this specific setting. According to our study, serum levels of most of the acute-phase inflammatory markers (hsCRP, SAA and WBC), cytokines (IL-6), and prothrombotic factors (TF) acutely increase within few minutes after exercise initiation, whereas, at the same time, PAI-1 activity decreases. Therefore, the acute thrombotic reaction is accompanied by a concomitant "protective" anti-thrombotic counter-regulation that is also part of the acute response to exercise. Whether the systemic inflammatory stress is also counter-regulated by "protective" anti-inflammatory cytokines released into the circulation was not examined in this study. The acute exercise-induced inflammatory and thrombotic response described above seems to be a "normal" human reaction as it is present in the apparently healthy group of our study, as well. However, the present study interestingly indicates that this "normal" acute exercise-induced inflammatory and thrombotic response is more intense in hypertensive patients as compared to apparently healthy normotensive individuals.

The main findings of the present study seem to be in line with the limited previously published data. A study by Mendham et al. (2011) sought to compare the respective effects of resistance or aerobic exercise of higher or lower intensities on the acute plasma IL-6, CRP, and WBC response in a population of 12 sedentary, overweight, middle-aged, disease-free participants. They found an acute, exercise-induced elevation in all 3 inflammatory biomarkers and also that the exercise modality did not seem to influence this inflammatory response. The main determinant of the IL-6 response was exercise intensity; the highest IL-6 response was evident in the moderate–vigorous-intensity protocol immediately post-exercise. Similarly, Dorneles et al. (2016) compared the effects of two interval exercises with different intensities on acute inflammatory response in 10 lean and 12 overweight-obese males, concluding that the acute inflammatory response (IL-6 increase) to interval exercise is intensity dependent. Moreover, Tartibian et al. (2009) showed that plasma inflammatory biomarkers IL-6,

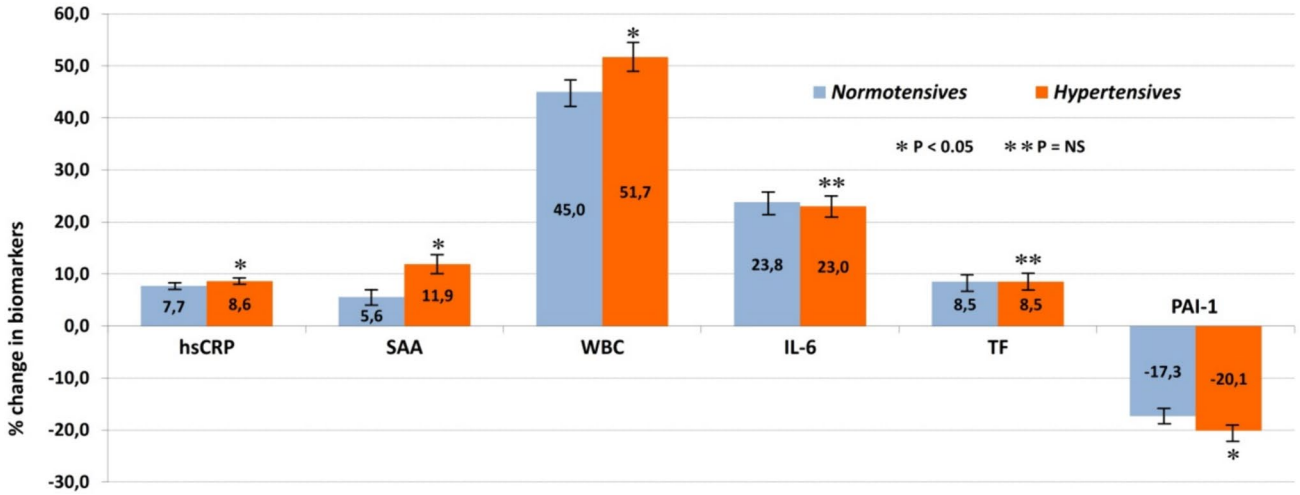

Fig. 2 Exercise-induced percentage changes (± standard deviation) in circulating biomarkers. *hsCRP* high-sensitivity C-reactive protein, *IL-6* interleukin-6, *PAI-1* plasminogen activator inhibitor-1, *SAA* serum amyloid A, *TF* total fibrinogen, *WBC* white blood cells. *$P < 0.05$, **$P = NS$ vs. normotensive group (after adjusting for exercise duration and maximal achieved metabolic equivalents, systolic BP, and rate-pressure product)

Table 4 Biomarkers' levels pre-, immediately post-, and 3 h post-exercise

	Pre-exercise	Immediately post-exercise	3 h post-exercise	P_1 value	P_2 value	P_3 value
Normotensives ($n=10$)						
hsCRP (mg/l)	1.55 ± 1.54	1.61 ± 1.58	1.48 ± 1.39	0.041	0.068	0.247
SAA (mg/l)	4.72 ± 4.83	4.79 ± 4.94	4.34 ± 4.90	0.428	0.039	0.043
WBC (μl^{-1})	7440 ± 2077	10,580 ± 3110	8300 ± 1785	< 0.001	0.008	0.094
IL-6 (pg/ml)	1.51 ± 0.84	1.95 ± 1.19	1.73 ± 0.99	0.012	0.378	0.296
TF (mg/l)	335.9 ± 70.2	377.5 ± 79.6	326.2 ± 48.5	0.012	0.003	0.351
PAI-1 (AU/ml)	16.79 ± 13.81	15.12 ± 15.85	15.04 ± 14.50	0.380	0.976	0.372
Hypertensives ($n=12$)						
hsCRP (mg/l)	1.39 ± 1.26	1.50 ± 1.37	1.32 ± 1.18	0.006	0.010	0.036
SAA (mg/l)	4.61 ± 3.11	4.88 ± 3.18	4.38 ± 2.90	< 0.001	0.001	0.023
WBC (μl^{-1})	6664 ± 1603	9173 ± 2205	6982 ± 1502	< 0.001	< 0.001	0.194
IL-6 (pg/ml)	1.12 ± 0.59	1.42 ± 0.84	1.73 ± 1.16	0.047	0.139	0.071
TF (mg/l)	352.6 ± 93.8	370.9 ± 102.2	344.7 ± 97.3	0.132	0.079	0.592
PAI-1 (AU/ml)	17.88 ± 9.29	14.24 ± 9.22	12.99 ± 10.48	< 0.001	0.529	0.040

P_1 value: comparison in biomarkers' values between pre- and immediately post-exercise

P_2 value: comparison in biomarkers' values between immediately post- and 3 h post-exercise

P_3 value: comparison in biomarkers' values between pre- and 3 h post-exercise

Continuous variables are presented as mean ± standard deviation

hsCRP high-sensitivity C-reactive protein, *IL-6* interleukin-6, *n* number of patients, *PAI-1* plasminogen activator inhibitor-1, *SAA* serum amyloid A, *TF* total fibrinogen, *WBC* white blood cells

CRP, and WBC increased in 18 young untrained males 30 min after treadmill running. However, according to this study, exercise intensity cannot be considered as the main factor that determines the inflammatory responses. The results of all 3 previous pilot studies are in agreement with the results of the present larger-scale study, regarding the acute exercise-induced inflammatory response. However, only our study compared the acute effects of exercise in subclinical inflammation between hypertensive and normotensive individuals, showing that middle-aged, physically active, untreated hypertensive patients exhibit a more pronounced inflammatory response. Given that a large proportion of hypertensive patients is unaware of the presence of hypertension and remains untreated (Williams et al. 2018), our findings may have significant clinical impact but this warrants further examination. Regarding the thrombotic/fibrinolytic response to acute exercise, Desouza et al. (1997) found that PAI-1 activity significantly decreased immediately after exercise in 12 hypertensive and 11 normotensive older men by 25% and 22%, respectively, and remained lower for at least 1 h in both groups. They also concluded that the acute exercise-induced fibrinolytic response is not impaired in sedentary, older, hypertensive men. Their results are similar with the results of the present study. More recently, Gavriilaki et al. (2014) also aimed to determine thrombotic and fibrinolytic activity during exercise in 30 hypertensive patients, pre- and post-treatment with an angiotensin II receptor blocker, as well as in 15 normotensive individuals. Contrary to both Desouza et al. (1997) as well as our findings, they found that in untreated hypertensive patients PAI-1 levels were significantly increased immediately after peak exercise and decreased 30 min later, as compared with baseline levels. At all time points, untreated hypertensives exhibited significantly higher PAI-1 levels compared with normotensives. No significant changes of PAI-1 levels were observed in normotensives and in patients post-treatment. They concluded that acute high-intensity exercise results in impaired thrombotic and fibrinolytic response in untreated hypertensive patients (Gavriilaki et al. 2014). The differentiation in the results regarding PAI-1 in this study is probably due to the fact that PAI-1 levels cannot assess PAI-1 protein status (active, inactive, or latent) while PAI-1 activity reveals inhibitory capacity of PAI-1 system. This is why it is considered that PAI-1 activity analyses are more appropriate for studying clinical entities with rapid changes simultaneously in multiple different biological systems of the human body (Pavlov et al. 2018), e.g., musculoskeletal, cardiovascular, circulatory, and sympathetic nervous system changes during acute exercise. Previous studies also suggest that anti-inflammatory cytokines (for example, the immunomodulatory cytokine IL-10) and cytokine inhibitors (for example, IL-1 receptor antagonist) are mobilized during strenuous exercise and downgrade the acute inflammatory response to exercise (Kasapis and Thompson 2005; Suzuki et al. 2002; Dorneles et al. 2016).

The effect of arterial hypertension on the exercise-induced acute response of thrombotic mediators has also been reviewed by Braschi (2019). The author highlights the analogies, similarities, and differences between normotensive and hypertensive subjects regarding the acute exercise-induced changes to the hemostatic and fibrinolytic properties, showing what differentiates essential arterial hypertension from physiological status. In accordance to our results, this review concludes that following acute exercise, normotensive and hypertensive subjects both undergo changes in hemostatic and fibrinolytic properties, but the hypertensive patients' response to exercise is exaggerated and prolonged, exposing them to increased CV risk during or immediately after vigorous exercise. The activation of the autonomic sympathetic nervous system is more aggressive in hypertensive patients in a pathological milieu characterized by platelet α2-adrenergic receptors with increased responsiveness to circulating catecholamines, altered platelet profile and function, abnormal hemostatic parameters, impaired fibrinolytic potential, endothelial dysfunction, and vasoconstriction (Braschi 2019). The exercise-induced increase in shear stress activates the endothelium and promotes platelet adhesion to endothelial cells, thus affecting the thrombogenic potential of atherosclerotic plaques, even when they are of relatively small dimensions. This pathophysiology probably predisposes to thrombotic complications. The recovery period is particularly dangerous for triggering adverse cardiovascular events, even in healthy subjects, because the balance between the thrombotic and fibrinolytic systems is temporarily shifted toward increased prothrombotic activity (Braschi 2019).

The underlying mechanisms for this rapid change in circulating levels of the inflammatory cytokines and the thrombotic factors shortly after physical exercise are not clear (Suzuki et al. 2002). They probably involve mobilization, systemic release, functional augmentation and hemoconcentration, concerning the macromolecules, rather than de novo synthesis of neutrophils, cytokines, and hemostatic biomolecules. Hemoconcentration emerges as the most dominant mechanism. It is well known that, regardless the hydration status, exercise can cause a transient hemoconcentration, depending mainly on the intensity of the exercise (Komka et al. 2022). The higher systolic BP achieved at peak exercise in the hypertensive group may have caused larger hemoconcentration in this group and merely explains the differences found in inflammatory/thrombotic responses. However, the differences between the two groups remained significant ($P < 0.05$) even after adjusting for exercise parameters (including maximal achieved systolic BP). Moreover, the reduction of PAI-1 activity with exercise implies that transient exercise hemoconcentration is probably not the only implicated mechanism. A decrease in renal blood flow with exercise (Rocha et al. 2023) probably leads to a drop in PAI-1 activity. Nevertheless, no matter what mechanism is responsible for the acute exercise-induced inflammatory/thrombotic response, this is more or less common in both normotensive and hypertensive individuals and cannot be considered as a definite determinant regarding our study's purpose. Thus, the herein shown differences between the (two) groups in the inflammatory and thrombotic response during exercise appear to be only partially attributable to hemoconcentration or other underlying mechanisms.

Regarding the total duration of the acute exercise-related inflammatory/thrombotic response, preliminary data from the present study indicate that approximately 3 h post-exercise, most of the studied biomarkers more or less return to pre-exercise (or even lower) levels, except PAI-1 that continues decreasing. Our data are in line with them reported by Cipryan et al. (2015) who investigated the recovery pattern of the plasma inflammatory markers IL-6 and CRP after a single-bout maximal exercise in 30 males. They concluded that a relatively short-duration exercise, no matter what intensity and type, does not elicit a significant change in IL-6 and CRP for the 1 h to 5 h period of rest following the exercise. Moreover, PAI-1 activity has been found to remain lower at 60 min post-exercise, than pre-exercise levels, in both hypertensive and normotensive individuals (DeSouza et al. 1997).

There is some evidence for the possible effects of BP-lowering treatment on the acute exercise-induced inflammatory and thrombotic response. In the NOAAH (Effects of Nebivolol in Obese African Americans with Hypertension) study, nebivolol has shown to have beneficial effects on inflammation indicators in obese hypertensive patients exposed to exercise-induced stress (Merchant et al. 2011). Similar favorable effects on vascular markers of inflammation have been reported for perindopril during exercise in patients with metabolic syndrome (Vaccari et al. 2008). A head-to-head comparison trial of our team compared the effect of different antihypertensive drugs on the acute exercise-induced inflammatory/thrombotic response and found that irbesartan is most likely more effective than diltiazem at suppressing the inflammatory and coagulative reaction during exercise. Specifically, the percentage increase in hsCRP, SAA, WBC, TNF-a, and TF levels was lower in the irbesartan group (Liakos et al. 2012).

Regarding treadmill exercise testing, this is a medical tool commonly used in intermediate CV risk individuals in order to detect possible underlying CAD. Moreover, its clinical applications extend to the evaluation of exercise capacity and tolerance, BP response, arrhythmias, valvular diseases, and known CAD. It is generally considered a safe procedure. The incidence of major complications, defined by National Heart, Lung, and Blood Institute as either myocardial infarction or death, has been reported as very low (0.04%)

(Wilkinson et al. 2015). Multiple surveys confirm that as many as 10 myocardial infarctions or/and deaths may be expected per 10,000 tests in patients with CAD (Gordon et al. 1993). A review summarizing eight studies of estimates of sudden cardiac death during exercise testing revealed rates from 0 to 5 per 100,000 tests (Gordon and Kohl 1993). Risk is greater in post-infarction patients and in those being evaluated for malignant ventricular arrhythmias (Fletcher et al. 2001). In hypertensive individuals, risk is merely related to the higher incidence of exaggerated BP response (systolic BP ≥ 210 mmHg in men and ≥ 190 mmHg in women) during the test (Fletcher et al. 2001). Whether the more intense inflammatory and thrombotic response during exercise is also implicated in the underlying risk remains to be elucidated.

Limitations

The findings of this study have to be seen in light of some limitations. The first is the relatively limited number of participants. However, as already reported, previous studies on this topic had even smaller sample size. We consider that this limitation is partially bypassed by the high homogeneity among the participants of the two groups (Table 1). In any case, the results of this study are only suggestive, and not definitive, for the greater exercise-induced acute inflammatory/thrombotic reaction in hypertensives vs. normotensives. The second limitation is that only patients with grade 1 or 2 hypertension were eligible for enrollment, considering that performing a maximal exercise testing in untreated grade 3 hypertensive patients is generally not considered feasible and/or safe. Another limitation is that the exclusion of CAD was mainly based on non-invasive methods, whereas coronary angiography, which remains the gold standard for the diagnosis of CAD, was not performed in the majority of the study population. Nevertheless, angiography is not indicated in subjects without ischemic ST-segment response at the exercise testing, wall motion abnormalities at the stress echocardiogram, or perfusion defects at the thallium-201 scintigraphy. Lastly, data from the present study regarding the total duration of the acute exercise-related inflammatory/thrombotic response derive indicatively only by 10 normotensive controls and 12 hypertensive patients, 3 h post-peak exercise, thus making conclusions unsafe.

Conclusions and future perspectives

The present study adds new data regarding the acute exercise-induced inflammatory/thrombotic response in non-CAD hypertensive patients during short-duration vigorous exercise as compared to normotensive controls. It is evident that inflammatory and thrombotic mechanisms are activated during exercise especially in untreated hypertensive patients. Nevertheless, this activation is, at least in part, limited by a parallel homeostatic fibrinolytic stimulation.

The findings of the present study shall be confirmed by larger-scale studies. The exercise-related changes of inflammatory/prothrombotic biomarkers in other groups of patients with one or more common CV risk factors such as dyslipidemia and diabetes mellitus shall be also investigated. Moreover, the duration of the acute inflammatory/thrombotic response to exercise as well as the effect of the type, intensity, and duration of the physical activity and the effect of exercise training and genetic variability (Brull et al. 2003) on the acute exercise-induced inflammatory/thrombotic response also require more detailed examination. Furthermore, approaches to counteract inflammation at rest and during exercise shall be more widely and systematically evaluated. The effects of different BP-lowering agents and drug categories shall be studied over a wider age spectrum. Whether BP normalization restores the exercise-related acute inflammatory/thrombotic response to normotensives' levels shall be further examined. Appropriately designed future studies should also evaluate the potential clinical implications of the acute exercise-induced inflammatory and thrombotic response in terms of hard end-points, such as exercise-triggered CV events or/and mortality in different at-risk populations.

Acknowledgements The authors thank Andreas P. Michaelides,† George Theodosiades, Marina Toutouza, and Efthimia Pavlou-Kidonaki who have kindly given their time, effort, and expertise to complete this study. Their contributions to our research are gratefully acknowledged.

Author contributions The study conception and design were performed by GPV and CA. The investigation, material preparation, data collection, and analysis were performed by CIL and MIM. The provision of study materials, reagents, instrumentation, and other analysis tools was performed by GPV and CT. The validation of the data was performed by GPV and KPT. The statistical analysis was performed by CIL and KPT. The visualization/data presentation was performed by CA and MIM. The supervision of the study was performed by GPV and CT. The first draft of the manuscript was written by CIL and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics approval This study was performed in line with the principles of the 1964 Helsinki Declaration and its later amendments. Approval was granted by the Ethics Committee of Hippokration General Hospital.

Informed consent Informed consent was obtained from all individual participants included in this study.

References

Andreozzi GM, Martini R, Cordova R, D'Eri A, Salmistraro G, Mussap M, Plebani M (2007) Circulating levels of cytokines (IL-6 and IL-1beta) in patients with intermittent claudication, at rest, after maximal exercise treadmill test and during restore phase. Could they be progression markers of the disease? Int Angiol 26:245–252

Antunes BM, Campos EZ, Dos Santos RVT, Rosa-Neto JC, Franchini E, Bishop NC, Lira FS (2019) Anti-inflammatory response to acute exercise is related with intensity and physical fitness. J Cell Biochem 120:5333–5342. https://doi.org/10.1002/jcb.27810

Bautista LE, Vera LM, Arenas IA, Gamarra G (2005) Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-alpha) and essential hypertension. J Hum Hypertens 19:149–154. https://doi.org/10.1038/sj.jhh.1001785

Braschi A (2019) Acute exercise-induced changes in hemostatic and fibrinolytic properties: analogies, similarities, and differences between normotensive subjects and patients with essential hypertension. Platelets 30:675–689. https://doi.org/10.1080/09537104.2019.1615611

Brull DJ, Serrano N, Zito F, Jones L, Montgomery HE, Rumley A, Sharma P, Lowe GD, World MJ, Humphries SE, Hingorani AD (2003) Human CRP gene polymorphism influences CRP levels: implications for the prediction and pathogenesis of coronary heart disease. Arterioscler Thromb Vasc Biol 23:2063–2069. https://doi.org/10.1161/01.ATV.0000084640.21712.9C

Catena C, Novello M, Lapenna R, Baroselli S, Colussi G, Nadalini E, Favret G, Cavarape A, Soardo G, Sechi LA (2005) New risk factors for atherosclerosis in hypertension: focus on the prothrombotic state and lipoprotein(a). J Hypertens 23:1617–1631. https://doi.org/10.1097/01.hjh.0000178835.33976.e7

Cipryan L, Svagera Z, Vala R (2015) IL-6 and CRP response to maximal exercise intervention. J Sports Med Phys Fitness 55:813–823

Conroy RM, Pyörälä K, Fitzgerald A, Sans S, Menotti A, DeBacker G, DeBacquer D, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM (2003) Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 24:987–1003. https://doi.org/10.1016/s0195-668x(03)00114-3

Cox AJ, Pyne DB, Gleeson M, Callister R (2009) Relationship between C-reactive protein concentration and cytokine responses to exercise in healthy and illness-prone runners. Eur J Appl Physiol 107:611–614. https://doi.org/10.1007/s00421-009-1160-0

Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, Oja P (2003) International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 35:1381–1395. https://doi.org/10.1249/01.MSS.0000078924.61453.FB

D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB (2008) General cardiovascular risk profile for use in primary care: the framingham heart study. Circulation 117:743–753. https://doi.org/10.1161/CIRCULATIONAHA.107.699579

Danesh J, Collins R, Appleby P, Peto R (1998) Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 279:1477–1482. https://doi.org/10.1001/jama.279.18.1477

DeSouza CA, Dengel DR, Rogers MA, Cox K, Macko RF (1997) Fibrinolytic responses to acute physical activity in older hypertensive men. J Appl Physiol 82:1765–1770. https://doi.org/10.1152/jappl.1997.82.6.1765

Dorneles GP, Haddad DO, Fagundes VO, Vargas BK, Kloecker A, Romão PR, Peres A (2016) High intensity interval exercise decreases IL-8 and enhances the immunomodulatory cytokine interleukin-10 in lean and overweight-obese individuals. Cytokine 77:1–9. https://doi.org/10.1016/j.cyto.2015.10.003

Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, Froelicher VF, Leon AS, Piña IL, Rodney R, Simons-Morton DA, Williams MA, Bazzarre T (2001) Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. Circulation 104:1694–1740. https://doi.org/10.1161/hc3901.095960

Gavriilaki E, Gkaliagkousi E, Nikolaidou B, Triantafyllou G, Chatzopoulou F, Douma S (2014) Increased thrombotic and impaired fibrinolytic response to acute exercise in patients with essential hypertension: the effect of treatment with an angiotensin II receptor blocker. J Hum Hypertens 28:606–609. https://doi.org/10.1038/jhh.2014.18

Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL Jr (2002) ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). https://www.herzpraxis-solothurn.ch/wp-herzpraxis/wpcontent/uploads/2019/02/exercise_clean.pdf

Gordon NF, Kohl HW (1993) Exercise testing and sudden cardiac death. J Cardiopulm Rehabil 13:381–386

Johnson BD, Kip KE, Marroquin OC, Ridker PM, Kelsey SF, Shaw LJ, Pepine CJ, Sharaf B, Bairey Merz CN, Sopko G, Olson MB, Reis SE (2004) Serum amyloid A as a predictor of coronary artery disease and cardiovascular outcome in women: the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation 109:726–732. https://doi.org/10.1161/01.CIR.0000115516.54550.B1

Joseph G, Marott JL, Torp-Pedersen C, Biering-Srensen T, Nielsen G, Christensen AE, Johansen MB, Schnohr P, Sogaard P, Mogelvang R (2019) Dose-response association between level of physical activity and mortality in normal, elevated, and high blood pressure. Hypertension 74:1307–1315. https://doi.org/10.1161/HYPERTENSIONAHA.119.13786

Juhan-Vague I, Alessi MC (1993) Plasminogen activator inhibitor 1 and atherothrombosis. Thromb Haemost 70:138–143

Kasapis C, Thompson PD (2005) The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. J Am Coll Cardiol 45:1563–1569. https://doi.org/10.1016/j.jacc.2004.12.077

Kavouras SA, Panagiotakos DB, Pitsavos C, Chrysohoou C, Anastasiou CA, Lentzas Y, Stefanadis C (2007) Physical activity, obesity status, and glycemic control: the ATTICA study. Med Sci Sports Exerc 39:606–611. https://doi.org/10.1249/mss.0b013e31803084eb

Koenig W, Khuseyinova N (2007) Biomarkers of atherosclerotic plaque instability and rupture. Arterioscler Thromb Vasc Biol 27:15–26. https://doi.org/10.1161/01.ATV.0000251503.35795.4f

Komka Z, Szilágyi B, Molnár D, Sipos B, Tóth M, Sonkodi B, Ács P, Elek J, Szász M (2022) Exercise-related hemoconcentration and hemodilution in hydrated and dehydrated athletes: an

observational study of the Hungarian canoeists. PLoS One 17:e0277978. https://doi.org/10.1371/journal.pone.0277978

Kraus WE, Powell KE, Haskell WL, Janz KF, Campbell WW, Jakicic JM, Troiano RP, Sprow K, Torres A, Piercy KL; 2018 Physical activity guidelines advisory committee (2019) physical activity, all-cause and cardiovascular mortality, and cardiovascular disease. Med Sci Sports Exerc 51:1270–1281. https://doi.org/10.1249/MSS.0000000000001939

Kumric M, Borovac JA, Martinovic D, Ticinovic Kurir T, Bozic J (2021) Circulating biomarkers reflecting destabilization mechanisms of coronary artery plaques: are we looking for the impossible? Biomolecules 11:881–899. https://doi.org/10.3390/biom11060881

Liakos CI, Vyssoulis GP, Michaelides AP, Chatzistamatiou EI, Theodosiades G, Toutouza MG, Markou MI, Synetos AG, Kallikazaros IE, Stefanadis CI (2012) The effects of angiotensin receptor blockers vs. calcium channel blockers on the acute exercise-induced inflammatory and thrombotic response. Hypertens Res 35:1193–1200. https://doi.org/10.1038/hr.2012.134

Lip GY, Beevers DG (1994) Abnormalities of rheology and coagulation in hypertension. J Hum Hypertens 8:693–702

Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, Muiesan ML, Tsioufis K, Agabiti-Rosei E, Algharably EAE, Azizi M, Benetos A, Borghi C, Hitij JB, Cifkova R, Coca A, Cornelissen V, Cruickshank JK, Cunha PG, Danser AHJ, Pinho RM, Delles C, Dominiczak AF, Dorobantu M, Doumas M, Fernández-Alfonso MS, Halimi JM, Járai Z, Jelaković B, Jordan J, Kuznetsova T, Laurent S, Lovic D, Lurbe E, Mahfoud F, Manolis A, Miglinas M, Narkiewicz K, Niiranen T, Palatini P, Parati G, Pathak A, Persu A, Polonia J, Redon J, Sarafidis P, Schmieder R, Spronck B, Stabouli S, Stergiou G, Taddei S, Thomopoulos C, Tomaszewski M, Van de Borne P, Wanner C, Weber T, Williams B, Zhang ZY, Kjeldsen SE (2023) 2023 ESH Guidelines for the management of arterial hypertension. J Hypertens 41:1874–2071. https://doi.org/10.1097/HJH.0000000000003480

Medina-Leyte DJ, Zepeda-García O, Domínguez-Pérez M, González-Garrido A, Villarreal-Molina T, Jacobo-Albavera L (2021) Endothelial dysfunction, inflammation and coronary artery disease: potential biomarkers and promising therapeutical approaches. Int J Mol Sci 22:3850. https://doi.org/10.3390/ijms22083850

Mendham AE, Donges CE, Liberts EA, Duffield R (2011) Effects of mode and intensity on the acute exercise-induced IL-6 and CRP responses in a sedentary, overweight population. Eur J Appl Physiol 111:1035–1045. https://doi.org/10.1007/s00421-010-1724-z

Merchant N, Rahman ST, Ferdinand KC, Haque T, Umpierrez GE, Khan BV (2011) Effects of nebivolol in obese African Americans with hypertension (NOAAH): markers of inflammation and obesity in response to exercise-induced stress. J Hum Hypertens 25:196–202. https://doi.org/10.1038/jhh.2010.39

Ostrowski K, Hermann C, Bangash A, Schjerling P, Nielsen JN, Pedersen BK (1998) A trauma-like elevation of plasma cytokines in humans in response to treadmill running. J Physiol 513:889–894. https://doi.org/10.1111/j.1469-7793.1998.889ba.x

Ostrowski K, Schjerling P, Pedersen BK (2000) Physical activity and plasma interleukin-6 in humans:effect of intensity of exercise. Eur J Appl Physiol 83:512–515. https://doi.org/10.1007/s004210000312

Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, Curhan GC, Rifai N, Cannuscio CC, Stampfer MJ, Rimm EB (2004) Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med 351:2599–2610. https://doi.org/10.1056/NEJMoa040967

Pavlov M, Nikolić-Heitzler V, Babić Z, Milošević M, Kordić K, Ćelap I, Degoricija V (2018) Plasminogen activator inhibitor-1 activity and long-term outcome in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention: a prospective cohort study. Croat Med J 59:108–117. https://doi.org/10.3325/cmj.2018.59.108

Pitsavos C, Chrysohoou C, Panagiotakos DB, Skoumas J, Zeimbekis A, Kokkinos P, Stefanadis C, Toutouzas PK (2003) Association of leisure-time physical activity on inflammation markers (C-reactive protein, white cell blood count, serum amyloid A, and fibrinogen) in healthy subjects (from the ATTICA study). Am J Cardiol 91:368–370. https://doi.org/10.1016/s0002-9149(02)03175-2

Plaisance EP, Taylor JK, Alhassan S, Abebe A, Mestek ML, Grandjean PW (2007) Cardiovascular fitness and vascular inflammatory markers after acute aerobic exercise. Int J Sport Nutr Exerc Metab 17:152–162. https://doi.org/10.1123/ijsnem.17.2.152

Rocha MP, Mentetzides SH, Drew RC (2023) Renal blood flow during exercise: understanding its measurement with Doppler ultrasound. J Appl Physiol 134:1004–1010. https://doi.org/10.1152/japplphysiol.00392.2022

Sesso HD, Wang L, Buring JE, Ridker PM, Gaziano JM (2007) Comparison of interleukin-6 and C-reactive protein for the risk of developing hypertension in women. Hypertension 49:304–310. https://doi.org/10.1161/01.HYP.0000252664.24294.ff

Suzuki K, Nakaji S, Yamada M, Totsuka M, Sato K, Sugawara K (2002) Systemic inflammatory response to exhaustive exercise. Cytokine Kinetics Exerc Immunol Rev 8:6–48

Suzuki M, Saito M, Nagai T (2006) Systemic versus coronary levels of inflammation in acute coronary syndromes. Angiology 57:459–463. https://doi.org/10.1177/0003319706290742

Tartibian B, Azadpoor N, Abbasi A (2009) Effects of two different type of treadmill running on human blood leukocyte populations and inflammatory indices in young untrained men. J Sports Med Phys Fitness 49:214–223

Thompson PD, Franklin BA, Balady GJ, Blair SN, Corrado D, Estes NA 3rd, Fulton JE, Gordon NF, Haskell WL, Link MS, Maron BJ, Mittleman MA, Pelliccia A, Wenger NK, Willich SN, Costa F (2007) Exercise and acute cardiovascular events: placing the risks into perspective. A scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology in collaboration with the American College of Sports Medicine. Circulation 115:2358–2368. https://doi.org/10.1161/CIRCULATIONAHA.107.181485

Vaccari CS, Rahman ST, Khan QA, Cheema FA, Khan BV (2008) Effects of angiotensin-converting enzyme inhibitor therapy on levels of inflammatory markers in response to exercise-induced stress: studies in the metabolic syndrome. J Cardiometab Syndr 3:12–17. https://doi.org/10.1111/j.1559-4572.2008.07117.x

Warburton DER, Bredin SSD (2017) Health benefits of physical activity: a systematic review of current systematic reviews. Curr Opin Cardiol 32:541–556. https://doi.org/10.1097/HCO.0000000000000437

Wilkinson J, Jurt U, Brouillard D, Matangi M (2015) Complications of 38,821 exercise stress tests performed in a community cardiology clinic. Can J Cardiol 31:S15. https://doi.org/10.1016/j.cjca.2015.07.046

Williams B, Mancia G, Spiering W, AgabitiRosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins

M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I, ESC Scientific Document Group (2018) 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 39:3021–3104. https://doi.org/10.1093/eurheartj/ehy339