Inflammatory activation biomarker profile after marathon running and its impact on cardiovascular stress in amateur middle-aged male runners

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Abstract

Background. Cardiovascular safety of marathon running middle-aged amateurs remains unclear. We previously hypothesized that transient release of cardiac troponin I (cTnI) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), in addition to an acute inflammatory response to exercise, may be the cause.

Objectives. To evaluate the effects of running a marathon on inflammatory biomarkers, and its impact on cardiovascular function.

Materials and methods. Thirty-three healthy male amateur runners aged ≥50 (mean age: 57 ±7 years) were enrolled in the study. Venous blood samples were obtained before the marathon, just after the race, and 2–4 days and 7 days after the marathon. Using novel single molecule counting (SMC) technology, we measured plasma concentrations of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). White blood cell (WBC) count was measured using a certified hematology analyzer. The results were related to previous analyses on cardiovascular stress and endothelial function biomarkers. Transthoracic echocardiography (TTE) and cardiac magnetic resonance (CMR) were used to determine myocardial function.

Results. We observed a sharp rise of all studied biomarkers after the race, which subsequently normalized after 2–4 days and stayed within the normal range 7 days after the race. We found no correlation between inflammatory and cardiovascular stress biomarkers. Transthoracic echocardiography and CMR did not show ischemic or inflammatory myocardial damage.

Conclusions. Marathon running is associated with a sharp and significant rise in inflammatory and cardiovascular stress biomarkers. We found no connection between immune activation and cardiac biomarker release. Cardiovascular imaging showed no myocardial damage due to ischemia or inflammation.

Key words: inflammation, marathon, cardiovascular biomarkers, cardiovascular imaging, novel methods

Background

Exercise and physical activity have been proven to minimize cardiovascular risk. Regular aerobic activity triggers physiological adaptations that improve cardiorespiratory fitness, prevent the development of coronary artery disease and alleviate symptoms of already diagnosed cardiovascular disease. There is also evidence that suggests a reduction in the risk of other chronic diseases, including arterial hypertension, type 2 diabetes, depression, and some types of cancer.[1,2] However, the intensity of activity to achieve beneficial effects remains controversial. Some studies have shown that there may be a U-shaped relationship between exercise intensity, cardiovascular disease and mortality. Very intensive endurance activity may be associated with worse survival compared with low and moderate physical activity.[3–6]

The authors have already presented an evaluation of cardiovascular stress biomarkers in marathon running middle-aged amateurs – a group at potential risk of cardiovascular disease.[7] The race was associated with a sharp and significant, yet transient, rise in the levels of cardiac stress (cardiac troponin I (cTnI) and N-terminal pro-B-type natriuretic peptide (NT-proBNP)) and vascular (endothelin-1 (ET-1)) function biomarkers. The cause of these changes remains unclear and has been extensively investigated.

The fatigue induced by endurance exercise has been studied in terms of inflammation and immunological consequences.[8,9] An acute inflammatory response involving cytokine release has been observed after strenuous exercise, including marathon running.[10–12] Systemic inflammation has an established role in the atherosclerotic process and has been linked to myocardial and endothelial injury.[13–15]

Cardiovascular imaging studies, including cardiac magnetic resonance (CMR), show exercise- and inflammation-related features of myocardial dysfunction and a possible association between inflammatory mediators release and myocardial fibrosis.[16–18]

Objectives

In this study, we aimed to evaluate the inflammatory response to marathon running and possible correlations with cardiovascular stress biomarkers release and myocardial function, assessed with multimodality imaging (transthoracic echocardiography (TTE) and CMR).

Materials and methods

Study design and participants

The project was a prospective, observational study enrolling male recreational long-distance runners. The inclusion criteria were: age ≥50 years, male sex, completion of at least one full-distance (42.195 km) marathon, and regular physical activity. Any known cardiovascular disease (diagnosis and current treatment) was an exclusion criterion. The detailed protocol has been previously published.[7]

Venous blood samples drawn from the antecubital vein were obtained at the screening phase (V1), immediately after the run (V2), 72–96 h after the run (subgroup of 12 runners who underwent CMR study; V3), and 7 days after the marathon (V4). Plasma samples after centrifugation in ethylenediaminetetraacetic acid (EDTA) were aliquoted and stored at –80°C until the analyses were done. Complete and white blood cell (WBC) counts were performed immediately after the blood draw using standardized hospital methods.

All the participants were asked to refrain from endurance training for at least 2 days before V1, V3 and V4 blood draw.

To evaluate inflammatory activation, we chose to analyze WBC, interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), biomarkers that have been extensively studied in terms of myocardial damage pathophysiology. We have previously analyzed data on cardiovascular stress biomarkers (cTnI, NT-proBNP and ET-1).[7]

Plasma concentrations of IL-6 and TNF-α were measured using a novel single molecule counting (SMC) technology (Erenna Immunoassay; Singulex, Inc., Alameda, USA). The assay was proven to be up to 2 orders of magnitude more sensitive than assays available commercially.

The 99th percentile upper reference limit (URL) was 7.2 pg/mL and 4.2 pg/mL for IL-6 and TNF-α, respectively. The URLs were evaluated against age- and sex-matched groups by the producer. White blood cell count was measured using a certified hematology analyzer. The 99th percentile URL for males aged ≥50 years was 10.0 × 10^3/μL.

Transthoracic echocardiography was performed using a commercially available ultrasound system (Vivid S6; GE Healthcare, Milwaukee, USA) at baseline (screening phase) and immediately after the run. The cardiac morphology and function measurements were carried out according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommendations. Left ventricular (LV) longitudinal strain was assessed using 2-dimensional speckle-tracking technique.

Heart rate (HR) during the entire run was recorded in 1-minute intervals using chest band pulse meters. Training distances were self-reported by participants.

The group of 12 randomly chosen participants underwent CMR between the 2nd and 4th day after the marathon using Siemens Magnetom Aera 1.5 T scanner (Siemens AG, Munich, Germany). Late gadolinium enhancement (LGE) modality was used for the detection of myocardial scar formation and fibrosis. Cardiac edema was assessed using the short tau inversion recovery (STIR) method. Cardiac magnetic resonance follow-up was scheduled 3 months after the run.

Statistical analyses

Continuous variables with normal distribution were reported as mean ± standard deviation (M ±SD), and variables with skewed distribution were reported as median with interquartile range. Depending on the distribution type, the intergroup differences were compared using paired Student's t-test, Mann–Whitney U test or Wilcoxon test. Analysis of variance (ANOVA) was used to analyze the differences among group means. The Spearman's rank correlation test was used to calculate correlations. Factors determining biomarker level dynamics were defined using linear and logistic regression models. Statistica v. 10.0 (StatSoft Inc., Tulsa, USA) software was used to perform all analyses.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. The Bioethics Committee of Wroclaw Medical University, Poland, reviewed and accepted the protocol of the study (approval No. KB-412/2014). All participants gave written informed consent for participation in the project.

Results

Participants

Initially, we have invited 50 Marathon Academy (Wrocław, Poland) initiative affiliates willing to participate in the 32nd Wroclaw Marathon (September 14, 2014) to be enrolled in the study. The number of subjects was limited to 50 in order to complete the whole protocol (as described above).

After the screening phase (physical examination, TTE and initial blood draw, 4–8 weeks before the run), we included 37 runners without cardiovascular disease. One subject was rejected due to moderate aortic regurgitation (bicuspid aortic valve) and 1 due to untreated hypothyroidism. Another 2 participants stated that they could not undergo all study procedures due to personal matters. Eventually, 33 healthy subjects (mean age: 57 ±7 years) were included.

The baseline parameters are presented in Table 1.

Table 1. Baseline characteristics

Parameter	Results (n = 33)
Age [years], M ±SD, min–max	57 ±7, 50–74
BMI [kg/m^2]	23.6 (21.9–25.7)
Resting HR [1/min]	57 (53–63)
Resting SBP [mm Hg]	120 (115–125)
Resting DBP [mm Hg]	73 (68–80)
Training and marathon run parameters	
Training intensity [km/month]	169 (74–201)
Long distance running experience [years]	6 (5–10)
Marathon total time [min]	250 (225–269)
Marathon mean HR [1/min]	149 (143–157)
Marathon maximum HR [1/min]	161 (157–172)

M ±SD – mean ± standard deviation; BMI – body mass index; HR – heart rate; SBP – systolic blood pressure; DBP – diastolic blood pressure.

Biomarkers

We observed a significant increase of the concentrations of all studied biomarkers (WBC, IL-6 and TNF-α) immediately after the marathon (all $p < 0.01$), which subsequently normalized (Fig. 1).

The IL-6 concentration was elevated immediately after the run above URL in all subjects. Peak IL-6 levels and absolute post-race increase correlated positively with peak WBC and TNF-α concentrations, as well as with their absolute increase.

The TNF-α levels were elevated above URL after the race in 19 (58%) subjects. The TNF-α levels after the run and absolute increase positively correlated with the other biomarkers.

White blood cell count was elevated above URL post-race in 30 (91%) subjects. Peak WBC count and absolute increase positively correlated with IL-6 and TNF-α.

Peak IL-6 concentration, WBC count, and absolute increase in IL-6 and TNF-α inversely correlated with finishing time.

Neither peak biomarker concentrations after the marathon nor their absolute increases were related to any cardiovascular stress biomarker level or any index of HR.

No specific parameter was found to determine the increase or peak level of any biomarker (logistic and linear regression models).

The analysis of the 12 selected participants in the CMR subgroup showed normalized biomarker concentration within 24–48 h after the marathon.

None of the participants reported any symptoms of infection or injury which could have contributed to increased biomarker concentrations.

All of the values of biomarker plasma concentrations, rates of abnormal biomarker levels and biomarker correlations are presented in Table 2–4.

Echocardiography and cardiac magnetic resonance

Both left and right ventricular size, and left ventricular global longitudinal strain (LVGLS) remained unchanged after the run and stayed within normal limits. We did not observe abnormal right ventricular function indices – tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular plane systolic velocity (s'). A decrease in the left atrial

Table 2. Biomarker levels

Parameter					p-value						
n	V1	V2	V3	V4	V1 vs V2	V1 vs V3	V1 vs V4	V2 vs V3	V2 vs V4	V3 vs V4	ANOVA
IL-6 [pg/mL]											
n = 33	1.55 (1.3–2.11)	63.25 (39.72–75.03)	–	1.64 (1.3–2.02)	**<0.001**	–	0.734	–	**<0.001**	–	**<0.001**
n = 12	1.94 (1.33–2.12)	60.49 (44.14–82.89)	1.83 (1.31–2.87)	1.65 (1.29–1.80)	**0.002**	0.530	0.388	**0.002**	**0.003**	0.131	**<0.001**
TNF-α [pg/mL]											
n = 33	3.20 (2.85–3.78)	4.43 (3.80–5.49)	–	3.44 (2.80–3.88)	**<0.001**	–	0.514	–	**<0.001**	–	**<0.001**
n = 12	3.18 (2.84–3.90)	4.97 (3.83–5.50)	3.37 (2.83–4.34)	3.87 (3.20–4.02)	**0.009**	0.528	0.308	**0.034**	0.084	0.530	0.127
WBC [10^3/μL]											
n = 33	5.03 (4.47–6.15)	14.5 (12.21–16.71)	–	5.15 (4.38–6.15)	**<0.001**	–	0.492	–	**<0.001**	–	**<0.001**
n = 12	5.15 (4.27–6.32)	12.65 (11.57–15.51)	5.15 (4.82–5.54)	4.45 (4.32–6.18)	**0.002**	0.695	0.991	**0.002**	**0.023**	0.937	**<0.001**

Values in bold are statistically significant. V1 – baseline; V2 – marathon finish; V3 – 3–4 days after the marathon (n = 12); V4 – 7 days after the marathon; IL-6 – interleukin-6; TNF-α – tumor necrosis factor alpha; WBC – white blood cells. Data presented as median with interquartile range (Wilcoxon test and Friedman non-parametric analysis of variance (ANOVA) test).

Table 3. Rates of abnormal (above upper reference limit) biomarker levels

Parameter	V1 (n = 33)	V2 (n = 33)	V3 (n = 12)	V4 (n = 33)
hs-cTnI, n (%)	7 (21)	29 (88)	5 (42)	7 (21)
NT-proBNP, n (%)	3 (9)	22 (67)	3 (25)	3 (9)
ET-1, n (%)	5 (15)	31 (94)	4 (33)	4 (12)
TNF-α, n (%)	4 (12)	19 (58)	4 (33)	2 (6)
IL-6, n (%)	0	33 (100)	1 (8)	1 (3)
WBC, n (%)	0	30 (91)	0	0

V1 – baseline; V2 – marathon finish; V3 – 3–4 days after the marathon; V4 – 7 days after the marathon; hs-cTnI – high-sensitivity cardiac troponin I; NT-proBNP – N-terminal pro-B-type natriuretic peptide; ET-1 – endothelin-1; TNF-α – tumor necrosis factor alpha; IL-6 – interleukin-6; WBC – white blood cells.

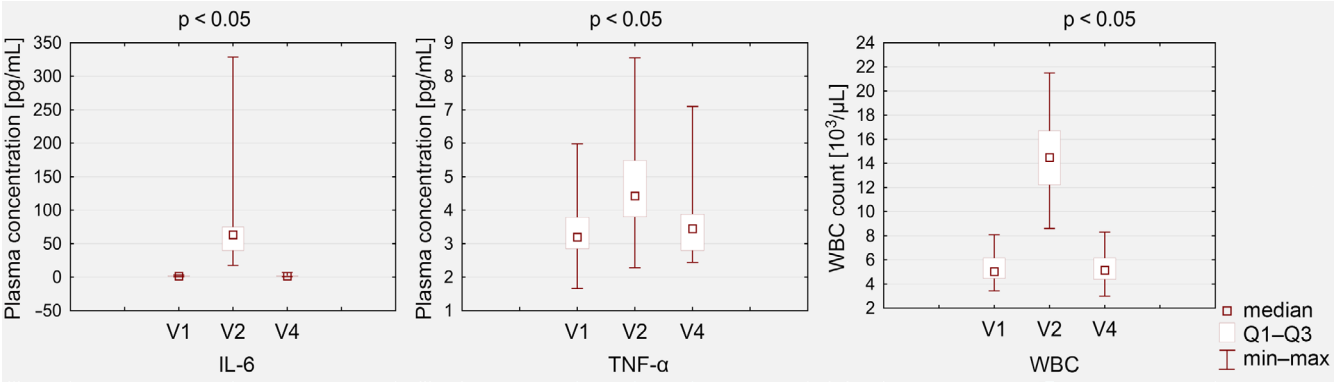

Fig. 1. Interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and white blood cell (WBC) concentrations measured before the marathon run (V1), immediately after (V2), and 7 days after (V4) in the whole studied group (n = 33). Data presented as median with interquartile (Q1–Q3) range and minimum–maximum values

volume index (LAVI) and an increase in the maximal right atrial volumes were found. A post-run reduction in peak velocity flow in early diastole (the E wave), peak velocity flow in late diastole caused by atrial contraction (the A wave) ratio and early diastolic mitral annular velocity (e') suggesting the deterioration of LV diastolic function were shown. However, E/e' septal and lateral ratios remained unaltered. We failed to demonstrate any correlations between echocardiographic parameters and inflammatory biomarker values. Echocardiographic data are presented in Table 5.

Both the CMR study carried out between the 2nd and 4th day after the marathon, and the follow-up study

Table 4. Spearman's rank correlation: post-race cardiovascular, inflammatory biomarker concentrations and total marathon time

Parameter	Peak hs-cTnI	Δhs-cTnI (V2–V1)	Peak NT-proBNP	ΔNT-proBNP (V2–V1)	Peak ET-1	ΔET-1 (V2–V1)	Peak TNF-α	ΔTNF-α (V2–V1)	Peak IL-6	ΔIL-6 (V2–V1)	Peak WBC	ΔWBC (V2–V1)	Total time
peak hs-cTnI	–	**0.92**	0.28	0.27	0.31	0.14	0.14	−0.03	0.26	0.26	−0.12	−0.09	0.24
Δhs-cTnI (V2–V1)	**0.92**	–	0.28	0.27	0.21	0.11	0.15	−0.07	0.24	0.24	−0.01	0.01	0.25
peak NT-proBNP	0.28	0.28	–	**0.97**	0.28	−0.03	0.23	0.02	0.18	0.19	0.06	0.12	0.26
ΔNT-proBNP (V2–V1)	0.27	0.27	**0.97**	–	0.27	−0.06	0.19	−0.02	0.16	0.17	0.01	0.10	0.23
peak ET-1	0.31	0.21	0.28	0.27	–	**0.72**	0.03	−0.12	0.02	0.02	−0.23	−0.13	0.19
ΔET-1 (V2–V1)	0.14	0.11	−0.03	−0.06	**0.72**	–	0.01	−0.22	−0.15	−0.16	−0.17	−0.11	0.29
peak TNF-α	0.14	0.15	0.23	0.19	0.03	0.01	–	**0.68**	**0.49**	**0.49**	**0.50**	**0.45**	−0.24
ΔTNF-α (V2–V1)	−0.03	−0.07	0.02	−0.02	−0.12	−0.22	**0.68**	–	0.33	**0.34**	**0.39**	**0.39**	**−0.35**
peak IL-6	0.26	0.24	0.18	0.16	0.02	−0.15	**0.49**	0.33	–	**1.00**	**0.44**	**0.39**	**−0.40**
ΔIL-6 (V2–V1)	0.26	0.24	0.19	0.17	0.02	−0.16	**0.49**	**0.34**	**1.00**	–	**0.43**	**0.39**	**−0.41**
peak WBC	−0.12	−0.01	0.06	0.01	−0.23	−0.17	**0.50**	**0.39**	**0.44**	**0.43**	–	**0.93**	**−0.35**
ΔWBC (V2–V1)	−0.09	0.01	0.12	0.10	−0.13	−0.11	**0.45**	**0.39**	**0.39**	**0.39**	**0.93**	–	−0.32
Total time	0.24	0.25	0.26	0.23	0.19	0.29	−0.24	**−0.35**	**−0.40**	**−0.41**	**−0.35**	−0.32	–

Values in bold are statistically significant with $p < 0.05$. hs-cTnI – high-sensitivity cardiac troponin I; NT-proBNP – N-terminal pro-B-type natriuretic peptide; ET-1 – endothelin-1; TNF-α – tumor necrosis factor alpha; IL-6 – interleukin-6; WBC – white blood cells; V1 – baseline; V2 – marathon finish.

conducted 3 months after the run did not reveal any abnormalities in cardiac dimensions or function. The STIR heart to skeletal muscle signal ratios were 1.74 (1.54–1.81) and 1.66 (1.58–1.73), respectively, for the initial and follow-up scan excluding myocardial edema. No myocardial fibrosis reflected by LGE was detected in any study.

Discussion

Our previous research using novel ultrasensitive laboratory assays showed a sharp but transient increase in cTnI, NT-proBNP and ET-1 levels in the setting of a marathon run.[7] The impact of this phenomenon on the circulatory system, as well as the cause and mechanism of cardiovascular stress biomarker release, remain unclear. Growing evidence linking immune response to strenuous exercise, a known effect of systemic inflammation on atherosclerosis and possible cardiac fibrosis, warranted further analyses.[8,9,13–15,17,18] This paper focused on studying the dynamics of inflammatory biomarker release, possible correlations with cardiovascular stress biomarkers and establishing whether marathon running provokes myocardial damage as assessed by imaging (TTE and CMR).

In 1902, Larrabee reported one of the first observations of exercise-induced increase in blood neutrophils among athletes who participated in the 1901 Boston Marathon.[19] The cytokine response to exercise was documented for the first time by Cannon and Kluger in the study where blood obtained from human subjects after exercise was injected into rats and caused an inflammatory response.[20]

Strenuous physical activity may trigger the same response as physical stress. The immunological response seen in the setting of trauma, sepsis, burn, etc., has a similar pattern to that caused by exercise. Local muscle damage due to prolonged exercise and systemic stress promotes cytokine production, originally released at the site of inflammation. Laboratory models show that the injection of TNF-α, IL-6 and IL-1 into laboratory animals induces an acute phase response. These cytokines are usually referred to as pro-inflammatory cytokines. The infusion of IL-6 alone can induce fever, but not shock, and cannot upregulate other inflammatory mediators.[21]

Since IL-6 and TNF-α release leads to hepatic production of C-reactive protein (CRP), which has established a role as a marker of increased cardiovascular risk, many studies have focused on the relationship between inflammation and cardiovascular response. Arterial inflammation in response to certain factors such as cholesterol, toxins, shear stress, and reactive oxygen species (ROS) causes endothelial dysfunction and thrombosis.[22] Rhabdomyolysis due to exertion triggers the release of von Willebrand factor from endothelium which, together with distention of vascular bed and reduced plasma volume, may provoke an imbalance between thrombosis and fibrinolysis.[23] Animal models, followed by case reports of athletes who died suddenly, showed interstitial fibrosis due to myocardial inflammation caused by endurance exercise.[13,24,25]

Table 5. Echocardiography

Parameter (n = 33)	Baseline	Post-race	p-value
Transthoracic echocardiography			
LVEDD [mm]	50 ±5	48 ±4	0.712
LVESD [mm]	31 ±4	30 ±4	0.386
RVEDD [mm]	27 ±4	27 ±3	0.523
IVS [mm]	12 ±2	12 ±1	0.142
PW [mm]	11 ±1	11 ±1	0.937
IVC [mm]	21 ±3	21 ±4	0.489
LVEF (%)	66 ±5	67 ±6	0.317
LVGLS (%)	−20.1 ±1.4	−19.9 ±1.5	0.721
TAPSE [mm]	24 ±4	24 ±5	0.722
TV s' [cm/s]	29.5 ±6.7	29.9 ±6.0	0.643
LA [mm]	37 ±3	35 ±4	**0.009**
LAVI [mL/m^2]	22 ±6	17 ±7	**<0.001**
LA min. volume [mL]	25 ±9	19 ±10	**<0.001**
LA max. volume [mL]	58 ±17	45 ±18	**<0.001**
RA min. volume [mL]	29 ±11	30 ±11	0.432
RA max. volume [mL]	49 ±12	53 ±12	**0.025**
E [m/s]	0.71 ±0.16	0.53 ±0.12	**<0.001**
A [m/s]	0.64 ±0.15	0.70 ±0.11	0.078
E/A	1.1 ±0.3	0.8 ±0.3	**<0.001**
e' septal [m/s]	0.09 ±0.03	0.07 ±0.02	**<0.001**
e' lateral [m/s]	0.12 ±0.04	0.10 ±0.03	**<0.001**
E/e' septal	8.0 ±2.5	8.1 ±2.6	0.837
E/e' lateral	5.8 ±1.6	5.3 ±1.3	0.134
Average E/e'	6.7 ±1.8	6.4 ±1.7	0.418

Values in bold are statistically significant. LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; RVEDD – right ventricular end-diastolic diameter; IVS – intraventricular septum; PW – posterior wall; IVC – inferior vena cava; LVEF – left ventricular ejection fraction; LVGLS – left ventricular global longitudinal strain; TAPSE – tricuspid annular plane systolic excursion; TV s' – tricuspid annular plane systolic velocity; LA – left atrium; LAVI – left atrial volume index; RA – right atrium; E – peak velocity flow in early diastole (the E wave); A – peak velocity flow in late diastole caused by atrial contraction (the A wave); e' – early diastolic mitral annular velocity. Data presented as mean ± standard deviation (paired Student's t-test).

The release of TNF-α was well-described after physical activity and has been linked to a risk of cardiac dysfunction.[26–28] On the other hand, some studies emphasize the regulatory role of IL-6, which no longer should be considered a pro-inflammatory cytokine only. Despite reports suggesting a key role of IL-6 in destabilizing atherosclerotic plaques, this cytokine may also have anti-inflammatory properties and has been linked to exercise-related positive metabolic changes, adaptation to training, protection against ischemic myocardial injury, or even a reduced prevalence of arrhythmias among marathon runners.[29–31]

Papers on exercise-induced release of cardiovascular stress biomarkers were inconclusive in terms of the relationship between cardiovascular damage and acute immune response.[32–34] Our data show that the release of inflammatory, cardiovascular stress and endothelial function biomarkers after marathon running was rapid and sharp but transient. Despite potential BNP (and NT-proBNP) gene modulation via cytokine pathways, we did not observe any relationship between an increase of NT-proBNP and levels of WBC, IL-6 or TNF-α. Increased post-race cTnI levels, reflecting potential myocardial damage, were also independent of any inflammatory biomarker. Peak IL-6 concentration, WBC count and absolute increase in IL-6 and TNF-α inversely correlated with finishing time, suggesting that the intensity of exercise plays a role in inflammatory response. The same suggestions come from data obtained during the Copenhagen Marathon (1996–1998).[21] Table 6 depicts selected publications on exercise-induced inflammatory biomarker release.

Post-race echocardiography did not show any evidence for LV and right ventricular (RV) systolic dysfunction. These findings are in line with the majority of publications on this topic.[35–38] Nevertheless, some authors have reported transient RV systolic function impairment and increased estimated pulmonary vascular resistance following strenuous exercise.[39–41]

The interpretation of post-race changes in LV diastolic function should be made with caution, given the load

Table 6. Summary of selected publications on exercise-induced inflammatory biomarker release

Authors	Year	Findings
Ostrowski et al.[27]	1999	increase in plasma levels of TNF-α, IL-1 and IL-6 after a marathon (n = 10)
Nieman et al.[10]	2001	increase in plasma levels of IL-10, IL-1 receptor antagonist, IL-6, IL-8, and TNF-α after a marathon (n = 98)
Siegel et al.[23]	2001	increase in plasma levels of CRP and WBC count after a marathon (n = 55)
Jee and Jin[28]	2012	increase in plasma levels of CRP, TNF-α, soluble vascular cell adhesion molecule-1, serum E-selectin, and WBC after a 308-kilometer ultramarathon (n = 24)
Scherr et al.[32]	2011	increase in plasma levels of high-sensitivity cardiac troponin T, NT-proBNP, IL-6, and high-sensitivity CRP after a marathon with a normalization within 72 h (n = 102)
Santos et al.[34]	2016	increase in plasma levels of WBC, creatinine kinase, lactate dehydrogenase, IL-6, IL-10, IL-8, IL-12, CRP, and TNF-α after a marathon (n = 23)

TNF-α – tumor necrosis factor alpha; IL – interleukin; WBC – white blood cells; NT-proBNP – N-terminal pro-B-type natriuretic peptide; CRP – C-reactive protein.

dependence of diastolic parameters.[35–38,42] Since the duration of diastole is affected by HR, LV preload is altered by dehydration and redistribution of blood flow, and blood pressure changes modify LV afterload, the finding of a post-run decrease in E/A ratio and e' may not reflect the actual effort-induced impairment in LV filling, especially as it was not accompanied by corresponding changes in E/e' ratio.

Repeated CMR in a subgroup of 12 subjects did not confirm any abnormalties suggestive of ischemia- or inflammation-associated myocardial damage that could be linked with the race.

This is consistent with other authors' findings.[17,18]

Limitations

First, this was a single-center study that enrolled a relatively small but homogenous population, yet represented a group at potential risk of developing exercise-related adverse events. Second, the small sample size might have led to the underestimation of some statistical associations, as well as the inability to conduct parametric tests on all data and provide causality analysis. Third, post-race echocardiography was performed in the early recovery period and might not have reflected the exact cardiac response to exercise. Fourth, although widely accepted, the use of load-dependent methods could not adequately assess the effect of effort on LV ventricular diastolic function. Finally, due to the small random sample of 12 subjects who underwent a repeated CMR study, the generalizability of findings by this technique is limited.

Conclusions

Strenuous exercise, such as marathon running, is associated with a transient but significant increase in plasma concentrations of inflammatory and cardiovascular stress biomarkers. No correlation between immune activation, cardiac biomarker release or cardiac dysfunction was found. Cardiovascular imaging showed no permanent myocardial damage due to ischemia or inflammation. Given the growing number of recreational runners, further studies on the pathophysiology and clinical importance of these findings are warranted.

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