

Marathon-Induced Cardiac Fatigue

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There is a clear impact of marathon on skeletal muscle and myocardium structure.

Keywords: cardiac fatigue ; cardiac stress ; prevention ; marathon ; recreational athletes

1. Introduction

The beneficial effect of regular physical exercise on heart function is now widely recognized by researchers in the field of physical activity and sport around the world and more generally in society. Among the main beneficial effects are the improvement of the lipid profile, carbohydrate homeostasis, decrease in resting blood pressure, blood coagulation, improvement of myocardial perfusion and an increase in cardiac output ^[1]. While the function of the heart pump is improved by regular exercise of moderate intensity ^[2], it was first shown in 1964 that the function of the left ventricle (LV) was reduced after prolonged physical exercise (PPE) ^[3]. Almost twenty years later, work has shown impaired cardiac function in athletes who have achieved PPE and used the concept of Exercise-Induced Cardiac Fatigue for the first time ^[4]. This phenomenon is defined as a transient decrease in systolic and diastolic ventricular functions and is sometimes associated with an increase in markers of myocardial degradation (i.e., cardiac troponins I) ^[5].

Endurance activities have been very popular since the end of the 1990's. The attraction to life in the great outdoors and the desire to know its limits lead more and more people to practice PPE each year ^[6]. Among these PPE, there are those of moderate duration such as the half-marathon (i.e., between 1–2 h of effort) and the marathon (i.e., 2–4 h), those with long duration such as the semi-triathlon distance “Ironman” (i.e., 5–8 h), and the “Ironman” distance triathlon with its 3.8 km of swimming, 180 km of cycling and 42.195 km of running (i.e., 9–16 h) and those with very long duration such as ultra-marathons or ultra-trails (some events can exceed 24 h). The effect of these PPEs on the cardiac function of participants has been the subject of much scientific research since the end of the 1990's. The general methodology used in these various works includes the evaluation of echocardiographic parameters of the cardiac function before and after PPE under resting conditions.

After a marathon running, the majority of studies have reported a decrease in LV and right ventricular (RV) diastolic function. Interestingly, the decrease in diastolic function was effective after 1 h of exercise ^[7]. More recently, it has been reported that cardiac fatigue is present but with left and right ventricular dysfunction, even more marked than at rest ^[8]. This study underlined the importance of the intensity of exertion during a marathon in the occurrence of cardiac fatigue. In summary, a moderate duration PPE results in a decrease in LV and RV diastolic function associated with a decrease in ventricular relaxation. The results concerning LV and RV systolic function are contradictory and seem to show that the myocardial alterations are rather dependent on the intensity with which the marathon is performed.

2. Biomarkers of Cardiac Fatigue and Cardiac Stress after a Marathon

Sixteen papers were identified in this review and are presented in **Table 1**. All of them were experimental studies and investigated the change in specific biomarkers between pre- and post-marathon runs. At least 32 different biomarkers were identified in the different studies. The majority of them were biomarker of skeletal muscle and myocardium damage ^{[9][10][11][12][13][14][15][16][17]}. In this family, the creatine kinase (CK), the highly sensitive cardiac troponin I and T (hs cTnI; hs cTnT) were mainly measured in the plasma. It was demonstrated that CK and hs cTnT were significantly increased after a marathon run. A second family of biomarkers measured the cardiac injury after marathons ^{[18][11][12][13][15][17][19][20]}. The N-terminal pro brain natriuretic peptide (NT-proBNP) was mainly measured in the plasma and was significantly increased after a marathon. In addition, it was reported that the increment of this biomarker immediately after a marathon exhibited a positive curvilinear relationship ($r^2 = 0.359$, $p = 0.023$) with the running time achieved by the runners ^[20]. A third family of biomarkers measured the systemic inflammation after marathons ^{[17][21][22]}. The interleukin-6 (IL-6) and the tumor necrosis factor-alpha (TNF-alpha) were mainly measured in the plasma. It was demonstrated that both biomarkers were significantly increased after a marathon run.

Table 1. Cardiac fatigue, cardiac stress and marathon.

References	Methods/Parameters	Pre-Marathon	Post-Marathon	p-Value
	Biomarkers Analyses			
Traiperm ^[20]	cTnT (ng/mL)			
	NT-proBNP (pg/mL)		Curvilinear relationship between NT-ProBNP increment and running time ($r^2 = 0.359$)	<0.05
Kaleta-Duss ^[9]	CK (U/l)	148 ± 76.3	411 ± 170	<0.001
	hs-cTnI (ng/mL)	0.01 ± 0.01	0.06 ± 0.09	<0.001
	H-FABP (ng/mL)	2.22 ± 1.18	13.57 ± 9.63	<0.001
	BNP (pg/mL)	79.86 ± 53.11	155.38 ± 156.23	<0.001
	NT-proANP (pg/mL)	469.25 ± 155.44	753.3 ± 176.60	<0.001
	Gal-3 (ng/mL)	8.53 ± 3.04	10.65 ± 2.33	<0.001
	GDF-15 (pg/mL)	50.97 ± 27.61	137.34 ± 85.19	<0.001
Martinez-Navarro ^[10]	hs-cTnT (ng/L)	5.74 ± 5.29	50.4 ± 57.04	<0.001
Sierra ^[21]	IL-6 (pg/mL)	581 ± 1529	87 ± 53	NS
	IL-8 (pg/mL)	3099 ± 6511	1450 ± 6233	NS
	IL-12p40 (pg/mL)	3775 ± 12406	285 ± 131	<0.05
	IL-23 (pg/mL)	3722 ± 12115	1004 ± 254	<0.05
	IL-33 (pg/mL)	412 ± 1546	267 ± 145	<0.05
	TSLP (pg/mL)	387 ± 1974	20 ± 16	<0.05
	eNO (ppb)	20 ± 11	35 ± 19	↑
Wegberger ^[11]	Troponin I (µg/L)	btw 0–0.01	0.03 (0.02–0.05)	0.016
	CK (U/L)	btw 0–250	425 (327–681)	0.001
	Copeptin (pmol/L)	btw 0–20	26.25 (16.29–39.02)	0.078
	NT-proBNP (ng/L)	btw 0–100	132 (64–198)	0.001
	MR-proADM (nmol/L)	btw 0.25–0.60	0.88 (0.55–0.99)	0.023
de Gonzalo-Calvo ^[12]	hs-cTnT (pg/mL)	btw 0–5	btw 0–35	<0.01
	NT-proBNP (pg/mL)	btw 0–25	btw 0–110	<0.05
	CK (U/L)	btw 0–150	btw 0–300	<0.001
	hFABP (ng/mL)	btw 0–3	btw 0–24	<0.01
	Gal-3 (ng/mL)	btw 0–7	btw 0–22	<0.001
Kosowski ^[13]				

References	Methods/Parameters	Pre-Marathon	Post-Marathon	p-Value
Biomarkers Analyses				
	hs-cTnI (pg/mL)	3.67 (1.88–5.38)	22 (9.58–34.56)	<0.001
	NT-proBNP (pg/mL)	50 (33–73)	169 (112–365)	<0.001
	ET-1 (pg/mL)	3.03 (2.5–3.4)	5.22 (4.4–5.89)	<0.001
	Creatinine (mg/dL)	0.85 (0.79–0.98)	1.39 (1.22–1.56)	<0.001
Richardson ^[14]				
	cTnT (ng/L)	5.60 ± 3.27	74.52 ± 30.39	<0.001
Sengupta ^[18]				
	NT-proBNP (pg/mL)	86.0 ± 9.5	106.5 ± 24.2	0.001
Clauss ^[19]				
	Chromogranin A (pg/mL)	btw 0–60	btw 0–90	<0.001
	NT-proBNP (ng/mL)	btw 0–30	btw 0–110	<0.001
Roca ^[15]				
	NT-proBNP (ng/L)	70 (70–70)	92 (70–147)	<0.001
	ST2 (ng/mL)	34.2 (24.7–40.9)	54.2 (38.2–72.4)	<0.001
	hs-TnT (ng/L)	2.9 (1.7–7)	46.9 (24.1–91.1)	<0.001
Bekos ^[23]				
	sRAGE (pg/mL)	btw 250–600	btw 400–750	<0.001
	ST2 (pg/mL)	btw 0–250	btw 125–400	<0.001
Niemelä ^[22]				
	suPAR (ng/mL)	btw 0.5–2	btw 1.2–3.5	<0.01
	CD163 (ng/mL)	btw 300–800	btw 500–1100	<0.05
	CRP (mg/L)	btw 0–12	btw 0–22	<0.05
	IL-6 (pg/mL)	btw 0–8	btw 17–25	<0.01
	IL-8 (pg/mL)	btw 5–12	btw 25–42	<0.05
	IL-10 (pg/mL)	btw 0–1	btw 1–3.5	<0.05
	TNF-α (pg/mL)	btw 0–1	btw 1–2.5	NS
	TGF-β (pg/mL)	btw 500–1000	btw 0–1000	NS
Martin ^[16]				
	Creatinine (mg/dL)	0.94 ± 0.12	1.42 ± 0.24	<0.001
	CK (U/L)	133 ± 60	367 ± 167	<0.001
	White blood cells (thousand/ μL)	5.75 ± 1.19	15.77 ± 3.29	<0.001
	Neutrophils (cells/μL)	3420 ± 1049	13580 ± 3019	<0.001
Scherr ^[17]				
	hs-cTnT (ng/L)	3 (3–5)	31 (19–47)	<0.001
	NT-proBNP (ng/L)	27 (14–40)	93 (57–150)	<0.001
	h-FABP (Kg/L)	7 (5–10)	45 (32–64)	<0.001

References	Methods/Parameters	Pre-Marathon	Post-Marathon	p-Value
Biomarkers Analyses				
Baggish ^[24]	hs-CRP (mg/L)	0.52 (0.30–0.93)	0.40 (0.24–0.85)	<0.001
	IL-6 (ng/L)	2.1 (1.9–2.2)	32 (21–41)	<0.001
	IL-10 (ng/L)	5.1 (4.9–5.4)	20 (11–50)	<0.001
	TNF-α (ng/L)	9 (7–10)	10 (9–12)	<0.001
	Cystatin C (mg/L)	0.8 (0.7–0.9)	0.9 (0.9–1.0)	<0.001
	c-miR-1 (fold change)		21.8	0.04
	c-miR-126 (fold change)		1.9	<0.001
	c-miR-133 (fold change)		18.5	0.02
	c-miR-134 (fold change)		1.9	<0.001
	c-miR-146a (fold change)		3.3	<0.001
	hsCRP (fold change)		1.0	1.000
	Echography, HRV & STE analyses			
Lewicka-Potocka ^[25]	LV EF (%)	61.8 ± 4.9	60.5 ± 4.4	0.38
	LV GLS (%)	−19.9 ± 2.3	−19.4 ± 2.1	0.41
	RV 4CSL (%)	−22.0 ± 2.8	−20.80 ± 2.6	<0.05
	TAPSE (mm)	25.0 ± 3.6	24.0 ± 3.7	0.56
	RVd MID (cm)	3.4 ± 0.6	3.7 ± 0.5	<0.01
	RVd BAS (cm)	3.8 ± 0.4	3.8 ± 0.5	0.44
	LVd BAS (cm)	4.8 ± 0.4	4.6 ± 0.3	<0.001
	RVd/LVd BAS	0.77 ± 0.1	0.82 ± 0.1	<0.05
Roeh ^[26]	E/A	1.6 ± 0.5	1.1 ± 0.3	<0.001
	E/e' mean	6.4 ± 1.5	6.5 ± 1.8	0.6
	DT (s)	0.18 ± 0.05	0.20 ± 0.05	<0.001
	V _{min} (mL/m ²)	11.4 ± 3.7	9.9 ± 3.5	<0.01
	V _{max} (mL/m ²)	28.0 ± 6.2	25.0 ± 7.0	<0.01
	Total-SV (mL/m ²)	59.6 ± 7.8	60.7 ± 6.0	0.3
	Total-EF (%)	34.9 ± 8.6	31.33 ± 10.2	<0.01
	ASV (mL/m ²)	16.6 ± 3.8	15.1 ± 4.1	<0.01
	True-EF (%)	6.1 ± 2.4	4.8 ± 2.8	<0.001
Sengupta ^[18]	Heart rate (beats/minute)	74.1 ± 6.4	64.5 ± 7.6	<0.001
	Systolic BP (mmHg)	123 ± 11	120 ± 9	0.214
	Diastolic BP (mmHg)	79 ± 5	79 ± 5	0.675

References	Methods/Parameters	Pre-Marathon	Post-Marathon	p-Value
Biomarkers Analyses				
Mertová ^[27]	IVSd (cm)	0.94 ± 0.16	1.03 ± 0.20	0.005
	LV mass (gm)	0.94 ± 0.16	1.03 ± 0.20	0.005
	LV mass (gm)	120.2 ± 30.0	160.3 ± 43.0	<0.001
	LVEDV (mL)	61.8 ± 16.5	72.8 ± 5.1	<0.001
	LVESV (mL)	21.9 ± 7.5	20.3 ± 3.7	0.191
	LVEF (%)	64.9 ± 5.6	72.0 ± 5.7	<0.001
	Mitral E (cm/s)	89.8 ± 17.1	80.1 ± 17.0	0.001
	Mitral annular e0 (cm/s)	10.4 ± 2.1	10.1 ± 2.2	0.638
	Mitral E/e0	9.1 ± 2.4	8.3 ± 2.7	0.227
	Left atrial volume index (mL/m ²)	23.2 ± 6.1	19.0 ± 6.5	0.01
	LV global longitudinal strain (%)	−19.3 ± 2.71	−16.5 ± 4.6	0.003
	LV global circumferential strain (%)	−17.2 ± 2.41	−15.2 ± 2.6	0.001
	LV global radial strain (%)	31.9 ± 7.4	30.9 ± 1.3	0.422
	Sympathovagal balance	-	Ln LF/HF	↑
	Heart rate (bpm)	-	+30	
Sierra ^[28]	Peak VO ₂ (mL/kg/min)	51 (46–52)	46 (43–49)	<0.05
	Peak VE (L/min)	134 (99–148)	120 (111–147)	NS
	VE/VCO ₂ slope	34 (30–41)	31 (27–39)	<0.05
	HR	62 (60–67)	104 (101–111)	<0.05
	Systolic volume	80 (79–100)	61 (51–68)	<0.05
	Cardiac output	5354(4747–6458)	6234(5238–7433)	NS
	LVEDD	51(49–52)	51 (45–58)	NS
	LVESD	32 (29–32)	32 (28–34)	NS
	EF	67 (66–70)	62 (61–67)	NS
	E wave	0.9 (0.7–1.0)	0.6 (0.5–0.7)	<0.05
	A wave	0.7 (0.5–0.9)	0.9 (0.8–0.9)	NS
	E/A ratio	1.3 (1.1–1.5)	0.7 (0.6–0.8)	<0.05
	s' wave	8.8 (8.2–9.7)	6.7 (5.9–8.0)	<0.05
	e' wave	9.2 (8.4–10.6)	8.5 (6.4–10.4)	NS
	a' wave	8.1 (7.6–9.1)	7.6 (6.6–9.6)	NS
Hanssen ^[29]	E/e' ratio	0.09 (0.08–0.10)	0.08 (0.06–0.09)	NS
	Heart rate (beats/min)	57 ± 7	86 ± 13	<0.001

References	Methods/Parameters	Pre-Marathon	Post-Marathon	p-Value
Biomarkers Analyses				
Chan-Dewar ^[30]	Systolic blood pressure (mmHg)	132 ± 13	121 ± 12	<0.001
	Diastolic blood pressure (mmHg)	86 ± 8	74 ± 7	<0.001
	LVEF (%)	65 ± 4	67 ± 5	0.280
	LV end-diastolic volume (cm ³)	120 ± 25	113 ± 27	0.142
	E (cm/s)	74 ± 14	66 ± 14	0.054
	A (cm/s)	56 ± 13	72 ± 12	<0.001
	E /A ratio	1.4 ± 0.3	0.9 ± 0.2	<0.001
	Septal E' (cm/s)	10 ± 1	8 ± 2	0.001
	Septal A' (cm/s)	10 ± 2	12 ± 3	0.001
	E /E' ratio	8.3 ± 1.6	8.4 ± 3.4	0.871
	Sub-epicardial radial strain (%)	32.6 ± 12.5	20.3 ± 9.6%	<0.01
	Sub-endocardial circumferential strain (%)	-26.9 ± 3.6	-23.7 ± 4.1	<0.01
	EF	63 ± 5	62 ± 7	NS
	E/A	1.8 ± 0.7	1.1 ± 0.2	<0.01

4CSL: four-chamber longitudinal strain = global strain; ASV: atrial stroke volume; BNP: B-type natriuretic peptide; BP: blood pressure; Bpm: beats per minutes; Btw: between; CK: creatine kinase; DT: deceleration time; E: early diastolic mitral inflow velocity; E/e': ratio of early diastolic mitral inflow to mitral annular velocity; e': early diastolic mitral annular velocity; EDD: end-diastolic diameter; EF: ejection fraction; eNo: exhaled nitric oxide; ESD: end-systolic diameter; ESV: end-systolic volume; FAC: fractional area change; Gal-3: galectin 3; GDF-15: growth differentiation factor 15; GLS: global longitudinal strain; H-FABP: heart-type fatty acid binding protein; HRV: heart rate variability; hs-cTnI: high sensitivity cardiac troponin I; IL: interleukin; IVSd: diastolic interventricular septum thickness; LF/HF: low-frequency power/high-frequency power; LV: left ventricle; LVd BAS: LV basal end-diastolic diameter; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVESV: left ventricular end-systolic volume; NT-proANP: N-terminal proatrial natriuretic peptide; PWd: posterior wall in diastole; PWS: posterior wall in systole; RV: right ventricle; RVd BAS: RV basal end-diastolic diameter; RVd MID: RV mid-cavity end-diastolic dimension; RVd/LVd BAS: basal RV to LV end-diastolic diameter ratio; S: peak systolic pulmonary venous flow velocity; STE: speckle tracking echography; SV: stroke volume; TAPSE: tricuspid annular plane systolic excursion; Total-EF: total ejection fraction; Total-SV: total stroke volume; True-EF: true ejection fraction. Data are expressed as means, medians and interquartile ranges (25th percentile; 75th percentile) and R-squared.

4CSL: four-chamber longitudinal strain = global strain; ASV: atrial stroke volume; BNP: B-type natriuretic peptide; BP: blood pressure; Bpm: beats per minutes; Btw: between; CK: creatine kinase; DT: deceleration time; E: early diastolic mitral inflow velocity; E/e': ratio of early diastolic mitral inflow to mitral annular velocity; e': early diastolic mitral annular velocity; EDD: end-diastolic diameter; EF: ejection fraction; eNo: exhaled nitric oxide; ESD: end-systolic diameter; ESV: end-systolic volume; FAC: fractional area change; Gal-3: galectin 3; GDF-15: growth differentiation factor 15; GLS: global longitudinal strain; H-FABP: heart-type fatty acid binding protein; HRV: heart rate variability; hs-cTnI: high sensitivity cardiac troponin I; IL: interleukin; IVSd: diastolic interventricular septum thickness; LF/HF: low-frequency power/high-frequency power; LV: left ventricle; LVd BAS: LV basal end-diastolic diameter; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVESV: left ventricular end-systolic volume; NT-proANP: N-terminal proatrial natriuretic peptide; PWd: posterior wall in diastole; PWS: posterior wall in systole; RV: right ventricle; RVd BAS: RV basal end-diastolic diameter; RVd MID: RV mid-cavity end-diastolic dimension; RVd/LVd BAS: basal RV to LV end-diastolic diameter ratio; S: peak systolic pulmonary venous flow velocity; STE: speckle tracking echography; SV: stroke volume; TAPSE: tricuspid annular

plane systolic excursion; Total-EF: total ejection fraction; Total-SV: total stroke volume; True-EF: true ejection fraction. Data are expressed as means, medians and interquartile ranges (25th percentile; 75th percentile) and R-squared.

Three of the selected studies measured the heart-type fatty acid binding protein (H-FABP) (i.e., mainly found inside cardiomyocytes) after a marathon [9][12][17]. Despite an important variability between the studies, H-FABP was significantly increased after a marathon run in three studies.

In addition, two studies measured the galactin-3 (gal-3) which is a protein involved in various biological activities in different organs, including apoptotic regulation, inflammation and fibrosis [9][12]. After a marathon, this protein was significantly increased in both studies. Another two studies measured the suppression of tumorigenicity 2 (ST2) [15][23] after a marathon. They both reported a significant increase of ST2 after running. Technical issues and determination of a diagnostic threshold have to be done to fully recognize the specificity of these biomarkers.

Finally, only one study investigated the potential of circulating short nonprotein coding RNA (c-miRNA) to explore the impact of a marathon run [24]. In this study, which was conducted with 21 healthy male marathon runners, the authors demonstrated that all plasma levels of the selected c-miRNA (i.e., enriched in muscle: c-miR-1; c-miR-133a; c-miR-499-5p; enriched in myocardium: c-miR-208a; enriched in vascular endothelium: c-miR-126; marker of inflammation: c-miR-146a) were significantly increased when compared to pre-marathon. The authors also stated that these c-miRNAs might represent real-time and tissue-specific adaptation biomarkers of a marathon run.

3. Cardiovascular Function after Marathon

Seven papers were identified in this review and are presented in **Table 1**. All of them were experimental studies and assessed the cardiovascular function before and after a marathon run. The majority of the selected studies used echocardiography alone [18][25][26][28][30]. The majority of these studies reported a decreased E wave and/or an E/A ratio after a marathon. They also all reported no significant difference of the LV EF values between pre- and post-marathon. Three of these studies used the speckle tracking imaging technique to evaluate LV and RV strains [18][25][30]. For LV function, Sengupta et al. reported a significant decrease of the global longitudinal ($\approx -3\%$ in average) and circumferential (-2% in average) strains but not in the radial plane after a marathon in recreational runners with a mean age of 41 ± 8 years [18]. In their study, Chan-Dewar et al. reported a significant decrease of the LV subepicardial radial strain (-12.3% in average) sub-endocardial circumferential strain (-3.2% in average) in male non-elite marathon runners with a mean age of 32 ± 10 years [30]. On the contrary, Lewika-Potocka et al. did not report any difference for the LV global strain between pre- and post-marathon in amateur marathon runners with a mean age of 40 ± 8 years [25]. However, these authors also analyzed the RV function and they reported a significant decrease of the RV four chambers longitudinal strain after a marathon (-1.2% in average).

Moreover, one study used the heart rate variability to assess the cardiac autonomous nervous system [27] and one study assessed cardiac function with cardiac magnetic resonance and echocardiography [29], pre- and post-marathon. In the first study, the authors reported a significant increase of the cardiac sympathetic activity (+30 min) and of the heart rate in supine position (+30 bpm) after a skyrunning marathon (i.e., 42 km distance with an ascent distance of 3.15 km and a descent distance of 2.85 km) in healthy male amateurs with a mean age of 37 ± 9 years. In the second study, the authors demonstrated a significant decrease of the LV E/A ratio and of the LV septal E' and A' waves after a marathon with male amateur runners with a mean age of 41 ± 5 years. In addition, they demonstrated no difference between pre- and post-marathon for the LV radial shortening and the circumferential and longitudinal strains assessed by MRI. However, the analysis revealed an increase in LV torsion and maximal torsion velocity after a marathon.

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