Marathon run: cardiovascular adaptation and cardiovascular risk

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The first marathon run as an athletic event took place in the context of the Olympic Games in 1896 in Athens, Greece. Today, participation in a ‘marathon run’ has become a global phenomenon attracting young professional athletes as well as millions of mainly middle-aged amateur athletes worldwide each year. One of the main motives for these amateur marathon runners is the expectation that endurance exercise (EE) delivers profound beneficial health effects. However, with respect to the cardiovascular system, a controversial debate has emerged whether the marathon run itself is healthy or potentially harmful to the cardiovascular system, especially in middle-aged non-elite male amateur runners. In this cohort, exercise-induced increases in cardiac biomarkers—troponin and brain natriuretic peptide—and acute functional cardiac alterations have been observed and interpreted as potential cardiac damage. Furthermore, in the cohort of 40- to 65-year-old males engaged in intensive EE, a significant risk for the development of atrial fibrillation has been identified. Fortunately, recent studies demonstrated a normalization of the cardiac biomarkers and the functional alterations within a short time frame. Therefore, these alterations may be perceived as physiological myocardial reactions to the strenuous exercise and the term ‘cardiac fatigue’ has been coined. This interpretation is supported by a recent analysis of 10.9 million marathon runners demonstrating that there was no significantly increased overall risk of cardiac arrest during long-distance running races. In conclusion, intensive and long-lasting EE, e.g. running a full-distance Marathon, results in high cardiovascular strain whose clinical relevance especially for middle-aged and older athletes is unclear and remains a matter of controversy. Furthermore, there is a need for evidence-based recommendations with respect to medical screening and training strategies especially in male amateur runners over the age of 35 years engaged in regular and intensive EE.

Keywords
Marathon run • Endurance exercise • Middle-aged athletes • Cardiovascular adaptation

Introduction

Inspired by the ancient run from Marathon to Athens 490 BC, the idea to revive this long-distance run was born in the context of the first modern Olympic Games in 1896 taking place in Athens, Greece. While this first marathon run of modern times had a distance of ~40 km today’s official distance of 42.195 km was established with the marathon run of the Olympic Games in London 1908 (Table 1). In recent decades, participation in a ‘marathon run’ has become increasingly attractive for millions of non-professional endurance athletes worldwide each year. Regarding the cohort of athletes participating in city-marathon events, there are only a small number of high-performance professional athletes aged between 18 and 35 years. These athletes are generally healthy, continuously medically supervised, and supported by experienced trainers. In contrast, the number of non-elite recreational marathon runners, including individuals of all age groups, is continuously rising. Indeed, the athletic and demographical characteristics of marathon runners are rapidly changing. According to a demographical analysis of these amateur athletes, the majority are middle-aged male amateur runners competing at amazing performance levels. For example, the winning time of the marathon run of the Olympic Games in 1936 was matched by the running time of the best M55 amateur runner of the 2012 Berlin marathon. These aspects are of special importance since several studies revealed that middle-aged amateur runners frequently exhibit a cardiovascular risk profile, which is typical for their age group.

Meanwhile, it is well known and widely accepted that regular and moderate physical activity (PA) has beneficial effects on nearly all biological structures and functions of the human body, including the cardiopulmonary system (Table 2). With respect to the ideal dose of endurance PA, the Harvard Alumni Study demonstrated an optimal cardiovascular health effect by an additional energy consumption of 2000–3000 kcal/week or 300–400 kcal/day. Even moderate
amounts of regular PA (≏ 15 min per day) are associated with significant preventive effects towards a variety of diseases, e.g. diabetes, cancer, and cardiovascular events, but also prolonging life expectancy. However, concerning beneficial health effects, it is difficult to define the optimal individual amount of endurance exercise (EE) as well as the upper ‘dose-limit’ on the basis of currently available studies. Nevertheless, regarding certain cardiovascular diseases, such as atrial fibrillation (AF), there are indications about potential ‘overdoses’ of EE. In this context, in a case–control study, Elosua et al. identified a threshold of more than 1500 lifetime hours of exercising. Furthermore, Möhlenkamp et al. observed a relatively high coronary artery calcification (CAC) burden in presumably healthy male athletes (> 55 years old) who had performed at least five marathon runs during the previous 3 years. Taking these considerations into account, regular EE at moderate doses and intensities is recommended for the prevention of cardiovascular diseases by international guidelines (Figure 1).

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<tr>
<th>Table 1</th>
<th>History of the ‘Marathon’ run</th>
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<tr>
<td>490 BC</td>
<td>First ‘Marathon’ (Marathon—Athens ~40 km) Pheidippides: 3–4 h</td>
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<tr>
<td>1896</td>
<td>First modern Olympics Marathon Athens, Greece [40.0 km (24.85 miles)] Spyridon Louis: 2:58:50 h</td>
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<td>1921</td>
<td>International Amateur Athletic Federation (IAAF) setting 42.195 km (26.22 miles) as the standard distance</td>
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<td>2013</td>
<td>Current World record for men: Patrick Makau: 2:03:38 h (Berlin 2011)</td>
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<table>
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<tr>
<th>Table 2</th>
<th>Cardiovascular benefits of regular endurance training</th>
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<td>Endothelial function</td>
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<td>Coronary flow reserve</td>
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<td>Tolerance of myocardial ischaemia</td>
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<td>Myocardial capillary density</td>
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<td>Ventricular fibrillation thresholds</td>
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<td>Arterial blood pressure</td>
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<td>Arterial stiffness</td>
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A controversial debate has emerged whether preparation for and participation in a marathon run is beneficial or harmful to the human health. Thus, the following review will critically analyse the available information on the acute and chronic effects of marathon running on the cardiovascular system focusing on middle-aged amateur marathon runners.

### Myocardial adaptations to endurance exercise

Intensive and long-lasting EE is characterized by a significant increase in skeletal muscle oxygen demand met by a marked elevation of pulmonary oxygen uptake and transport of the oxygen-enriched blood to the working skeletal muscles. Under physiological conditions, the acute cardiopulmonary adaptation to EE encompasses increases in pulmonary ventilation, heart rate, stroke volume, and cardiac output accompanied by a moderate increase in systolic blood pressure, peripheral vasoconstriction, and vasodilatation. On the aerobic exercise level, these acute cardiac adaptation processes can be maintained over several hours by the endurance-trained heart. In high-performance endurance athletes, these adaptations may lead to the development of the so-called athlete’s heart, which is morphologically characterized by harmonically increased left ventricular (LV) and right ventricular (RV) volumes, increased LV wall thickness, and myocardial mass and functionally by a five- to sixfold increased cardiac output and reduced resting heart rate. It must be stressed, however, that the development of an athlete’s heart requires intensive endurance training. Whether the development of the athlete’s heart in middle-aged and older amateur endurance athletes follows the same patterns than in young endurance athletes is not entirely clear and needs further investigations.

### Potential functional and structural myocardial abnormalities in marathon runners

The adaptation processes leading to the athlete’s heart must be strongly differentiated from pathological structural myocardial adaptations occurring in the context of hypertensive heart disease or other conditions.
hypertrophic cardiomyopathy. However, even since its first description by Hensen in 1899, the athlete’s heart has provoked controversial discussions with respect to its health-related consequences. Although professional young athletes may also experience serious cardiovascular maladaptations and/or complications, the available data do not suggest that these adverse cardiovascular events are generally related to the functional and structural adaptations associated with the development of an athlete’s heart. In accordance with this view, long-term studies in professional endurance athletes do not point towards an increased cardiovascular event rate in this cohort. A recently published study on Tour de France participants even revealed a significantly lower cardiovascular event rate and a prolonged life expectancy when compared with age-matched ‘ordinary’ French men.

The situation may be different in middle-aged amateur marathon runners frequently performing on a level that was previously reserved to professional and young athletes. In this cohort, high training volumes and intensities as well as exercising during the marathon run are requiring cardiac outputs of 20–25 L/min over periods of several hours. It is evident that this workload imposes a high degree of stress to all myocardial structures including the coronary vessels and the electrical conduction system which may potentially lead to functional and structural maladaptations and/or myocardial injury and fibrosis at least in a subgroup of prone middle-aged individuals (Figure 2).

With the development of advanced and mobile Doppler echocardiography, it became possible to perform detailed non-invasive functional and structural measurements of the heart of highly endurance-trained athletes under resting and exercising conditions. Many working groups have utilized 2D and Doppler techniques before and after marathon runs in order to evaluate the morphological and functional myocardial status. Already in 1987, Douglas et al. described abnormalities in LV systolic and diastolic function after the Hawaii Ironman Triathlon. Neilan et al. observed increased troponin levels related to training volumes and interpreted these findings as myocardial injury. This interpretation sparked an intensive debate about the potential negative health consequences of marathon running especially for the cohort of inadequately trained middle-aged male runners. Recent advances in echocardiographic and magnetic resonance tomography (MRT) imaging, tissue Doppler imaging, and strain rate imaging, including tools for the quantitative assessment of segmental ventricular function, have enabled investigators to collect more detailed information concerning the functional and structural status of the marathon runners heart. With respect to LV systolic function, the findings are quite controversial. A recent meta-analyses based on 294 individuals performing EE (60–1440 min) revealed a small but significant transient reduction of LV systolic function with signs of LV strain and twist.

The evaluation of diastolic functional parameters related to EE provided more consistent findings. In general, EE leads to an increased early diastolic LV filling, suggesting that diastolic function is superior in highly trained endurance athletes when compared with untrained controls. The findings of suppressed diastolic function directly after the marathon run especially in untrained non-elite amateur runners was opposed by further echocardiographic studies demonstrating a complete normalization of these functional alterations generally within 24 h after the marathon run. Therefore, such a transient exercise-induced reduction in ventricular systolic and/or diastolic function is often interpreted as physiological ‘cardiac fatigue’.

Focus on the right heart

The introduction of innovative imaging techniques allowing to investigate the right ventricle revealed signs of potential structural and functional abnormalities affecting the right ventricle occurring in young professional as well as in middle-aged amateur athletes engaged in intensive EE. In most studies, these abnormalities returned to normal within a short time frame. Especially, long-term intensive EE may cause dilation of the right atrium and ventricle also showing signs of potential myocardial scarring and/or myocardial fibrosis in prone individuals. However, the available data are inconsistent and at present many issues related to the effects of endurance training on the right heart remain unclear. The long-term clinical significance of these alterations requires further investigations.

In summary, based on our current knowledge, the alterations of systolic and diastolic myocardial function associated with marathon running may be interpreted as a phenomenon within the physiological range at least in the majority of endurance athletes. A small subgroup of prone runners may develop functional and/or structural abnormalities with clinical significance. Further studies, using modern imaging techniques such as MRT are necessary to further clarify the effect of marathon running on myocardial structure and function and to identify athletes at risk for maladaptation.
Marathon and myocardial injury

Numerous studies have reported clinically significant increases in serological markers potentially indicating myocardial damage during and/or directly after a marathon.\textsuperscript{31,42–46} Recent findings, however, demonstrated that the elevated cardiac biomarkers regressed to normal values within a period of 24–48 h and, therefore, may be the result of transient and reversible alterations of the cardiac myocytes without negative clinical consequences.\textsuperscript{35,47,48} This interpretation is supported by a recent study of Hanssen et al.\textsuperscript{49} who combined measurements of cardiac biomarkers with cardiac magnetic resonance, including late gadolinium enhancement, demonstrating an absence of detectable myocardial necrosis despite a transient increase in cardiac biomarkers.

Nevertheless, taking into account the complexity of myocardial troponin and brain natriuretic peptide release, further experimental studies are warranted to elucidate the biochemical mechanisms and the clinical dignity of the increases in these cardiac biomarkers.

Marathon and the vascular system

There is sufficient evidence that long-term EE induces beneficial functional and structural adaptations of the vascular system, including positive effects on arterial vascular stiffness.\textsuperscript{50,51} In a recent meta-analysis relating to high-performance endurance athletes, Green et al.\textsuperscript{52} came to the conclusion that endurance athletes possess enlarged arteries with a decrease in arterial wall thickness. With respect to peripheral resistance arteries, middle-aged endurance trained athletes exhibited improved acetylcholine-mediated vasodilatation suggesting—according to the authors—that athletic training may retard the effects of ageing on the vasculature. On the other hand, there is limited evidence for improved arterial responsiveness to exercise-induced stimulation in athletes. In conclusion, the majority of the available data suggests that there is an improved function of peripheral resistance vessels in high-performance athletes.\textsuperscript{52}

The effects of acute and chronic EE on blood pressure and heart rate are well documented, demonstrating a significant decrease in peripheral blood pressure, peripheral arterial resistance, and heart rate, which is especially pronounced in hypertensive patients.\textsuperscript{53} However, no sufficient data are available on the effects of EE on central blood pressure.\textsuperscript{54,55} In contrast, in strength-trained athletes, an increase in arterial stiffness was observed.\textsuperscript{55,56}

In a recent study in 49 regularly trained middle-aged marathon runners, a slight increase of blood pressure and pulse wave velocity was observed when compared with age-matched controls. Directly after the marathon run, a significant fall in wave reflections in the presence of an unchanged pulse wave velocity was detected. The authors hypothesized that long lasting extremely vigorous and competitive exercise like marathon running may result in an inverted U-shaped relation with arterial stiffness.\textsuperscript{57} Again, further studies are warranted to clarify this issue.

A further interesting field of research is the status of the blood clotting system during and after prolonged EE. Acute and intensive exercise results in a transient hypercoagulability state, especially pronounced in untrained individuals mostly due to increased thrombin generation, platelet hyperreactivity, and increased activity of several coagulation factors. In contrast, regularly endurance trained subjects reveal a significant increase in the fibrinolysis activity. These potentially adaptive changes might offer protection against the risks of thrombotic events.\textsuperscript{58,59} The precise clinical relevance of these findings is unclear, however.

In summary, functional and structural responses of the arterial vasculature and the blood clotting system to acute and chronic intensive EE are very complex and await further investigation.

Coronary arteries and marathon running

In recent years, evidence has accumulated that regular PA is protective with respect to coronary artery disease (CAD). A large number of studies have shown that regular PA over longer time periods is associated with a marked reduction in CAD and all-cause mortality. These protective effects were especially observed in subjects exercising in mild and moderate exercise intensities when compared with sedentary individuals. These beneficial effects are mainly mediated through improvements of risk factors for CAD, positive effects on endothelial function, autonomic balance, and the blood coagulation system.\textsuperscript{16,60,61} In contrast to these beneficial findings, Möhlenkamp et al.\textsuperscript{5} found CAC scores in 108 middle-aged male marathon runners who have completed five marathon runs during previous 3 years exceeding the CAC scores of controls matched for age and Framingham risk score. The authors offered several potential explanations for these somewhat unexpected findings: a rise in vascular oxidative stress due to exercise-induced high blood flow,\textsuperscript{62} inflammatory cytokines induced by intensive EE such as marathon running.\textsuperscript{63}

Potential proarrhythmic effects of marathon running

There is a general consensus that elite endurance athletes commonly present several electrophysiological alterations frequently in combination with atrial and ventricular ectopy (VE), which have been perceived as functional adaptations not predisposing to serious arrhythmogenic events or sudden cardiac death (SCD).\textsuperscript{54–66} However, at least in a subgroup of middle-aged male endurance athletes, a significant, five-fold, increase in the prevalence of AF has been observed.\textsuperscript{67–69} Although clear evidence about the underlying causes and the pathophysiological mechanisms is lacking, the following hypothesis among others are being discussed: alterations in the autonomic system, fluid shifts, and electrolyte abnormalities potential chronic systemic inflammation, fibrosis of myocardial structures, and even the potential intake of illicit drugs (Figure 3). Clinically, AF associated with EE occurs usually paroxysmal and frequently at night in the beginning, often progressing to persistent AF. Despite the high prevalence, AF in athletes is perceived as abnormal and clinical relevant and requires intensive diagnostic procedures by cardiovascular and sports-medical experts including a thorough sport anamnesis.\textsuperscript{11,70} The natural course and long-term prognosis of lone AF has not been intensively documented in endurance athletes. In a
prospective study with 9-year follow-up in 30 male endurance athletes with paroxysmal AF, Hoogsteen et al. observed that paroxysmal AF remained stable in 50% and the progression to permanent AF occurred only in 17% of the athletes.

Treatment of AF in endurance-trained athletes as well as estimating the prognosis is difficult because large-scale prospective, randomized clinical trials and guidelines focusing directly on the endurance-trained athletes are lacking. Nevertheless, the current guidelines for the management of AF may be helpful and also apply to middle-aged and older endurance athletes. The therapeutic options include restriction of dose and intensity of EE, direct-current cardioversion, and ablation strategies. The value and indication of pharmacotherapy is controversial especially with respect to thromboembolic prophylaxis.

Complex ventricular ectopy and sudden cardiac death associated with endurance exercise

Complex VE, including ventricular tachycardia, is also well documented in endurance-trained athletes; they typically originate from a mildly dysfunctional RV and/or the interventricular septum. The severity and clinical significance of the VEs are very variable and subject of controversial discussions. Serious VEs leading to cardiac arrest mainly result from underlying heart disease, such as cardiomyopathies or coronary abnormalities as well as inflammatory and fibrosing processes.

Fortunately, SCD among marathon runners is very rare. In this context, Kim et al. investigated the incidence and outcome of cardiac arrests during marathon and half-marathon races in the USA and Canada during the period from 2000 to 2010. In the 10.9 million runners examined, 59 cases of cardiac arrests occurred in association with a marathon run. Men were significantly more likely to experience cardiac arrest and SCD than women. These findings are consistent with other reports.

The event rates were significantly correlated with the age of the runners and significantly more frequent in ‘full’ marathon runs (42.195 km) than in ‘half’ marathon runs. Indeed, the final mile (1.6 km), representing <5% of the whole marathon distance, accounts for almost 50% of the SCDs.

Risk stratification in endurance athletes

There is general acceptance for the need of regular medical screenings of endurance athletes. The European Society of Cardiology (ESC) has published recommendations for an athlete’s screening. However, there is a controversy about the detailed diagnostic procedures in order to effectively detect potential pathologic conditions predisposing to exercise-related cardiovascular events. This refers especially to the value of the electrocardiography (ECG) as a diagnostic tool. For instance, in high-performance athlete’s screening, the European guidelines differ from the US recommendations. While the European guidelines suggest a routine ECG, the US recommendations are principally limited to physical examination and anamnesis. Currently, the controversy regarding the role of a routine ECG screening remains unsettled. Considering the serious consequences of exercise-induced cardiovascular events on one side and the large number of athletes to be screened on the other side, it is strongly necessary to evaluate the diagnostic sensitivity of all components of the proposed screening procedures, including the ECG, and to develop effective diagnostic strategies that are highly sensitive in detecting athletes at increased risk for such events. In addition, the clinical value of further diagnostic tools, such as cardiac biomarkers, echocardiography, and/or advanced imaging techniques remains to be clarified.

Referring to the cohort of middle-aged and older endurance athletes, the appraisal concerning the role of the ECG is different. There is general consensus that in this cohort, an exercise ECG especially in the presence of CV risk factors is recommendable. The European Association of Cardiovascular Prevention and Rehabilitation has recently published a comprehensive position stand for the cardiovascular evaluation of middle-aged/senior individuals engaged in leisure-time sport activities. The authors state that these recommendations ‘rely on existing scientific evidence, and in the absence of such, on expert consensus’. For the screening of this very large cohort, self-assessment of the habitual PA level and of the cardiovascular risk profile based on systematic coronary risk evaluation (SCORE) are recommended. In individuals at increased risk and those who intend to exercise at moderate and high intensity, the medical
screening should include anamnesis including family history, physical examination, and a 12-lead resting ECG. Because the sensitivity of the resting ECG with respect to CAD is rather low, in middle-aged/older individuals, an additional exercise test with ECG is recommended in order to detect potential CAD by ST-segment depression and also to evaluate the functional capacity.

Despite the absence of strong evidence for these recommendations, we strongly suggest applying these recommendations in middle aged and older endurance athletes, especially in those with increased global risk score.

**Conclusion**

Running a full-distance Marathon is a great challenge for the entire human organism. Though there is evidence that EE delivers beneficial health effects and a significant increase in life expectancy, the strain imposed on the cardiopulmonary system is extremely high. Long-term excessive EE may cause adverse functional and morphological cardiac adaptations, especially in the continuously growing cohort of middle-aged amateur runners. These athletes who exercise at extremely high doses and intensities should, therefore, be aware that there is a potentially increased risk for cardiovascular complications. However, further investigations to identify the optimal individual dose and intensity of long-term EE are warranted. Presently, regarding the large number of middle-aged male amateur marathon runners, the recommendations of the current ESC guidelines for Physical Activity and Public Health should be observed. Thorough medical screening—including ECG—of the cardiovascular system in association with professional analysis and planning of the training is essential to avoid acute and long-term cardiovascular complications in young elite as well as in middle-aged and older endurance athletes. For the detection of CAD in the cohort of the middle-aged and older endurance athletes, an additional exercise test with ECG should be performed. Further studies are warranted to profoundly understand the acute and long-term effects of intensive EE, such as marathon running, on the cardiovascular system in order to identify individuals at risk and to develop individualized training recommendations. Finally, it seems to be prudent to advise the middle-aged or older endurance athlete to content himself with a ‘half-marathon’ performed with ‘full pleasure’. Such an approach will offer the best perspective for experiencing the fascination of marathon running and simultaneously delivering positive health effects to the cardiovascular system and the entire human body.

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