Coronary Atherosclerosis and Cardiovascular Risk in Masters Male Marathon Runners

Rationale and Design of the "Marathon Study"

Stefan Möhlenkamp[1], Axel Schmermund[2], Knut Kröger[3], Gert Kerkhoff[4], Martina Bröcker-Preuss[5], Volker Adams[6], Martin Hensel[1], David Kiefer[1], Nils Lehmann[7], Susanne Moebus[7], Kirsten Leineweber[8], Sigrid Elsenbruch[9], Jörg Barkhausen[10], Martin Halle[11], Rainer Hambrecht[12], Johannes Siegrist[13], Klaus Mann[5], Thomas Budde[4], Karl-Heinz Jöckel[7], Raimund Erbel[1]

[1] Department of Cardiology, West German Heart Center Essen, University Hospital Essen, Germany,
[2] Cardiologic Center Bethanien, Frankfurt/Main, Germany,
[3] Department of Angiology, University Hospital Essen, Germany,
[4] Department of Internal Medicine and Cardiology, Alfried Krupp Hospital, Essen, Germany,
[5] Division of Clinical Chemistry and Laboratory Medicine and Department of Endocrinology, University Hospital Essen, Germany,
[6] Department of Cardiology, University of Leipzig, Heart Center Leipzig, Germany
[7] Institute of Medical Informatics, Biometry and Epidemiology, University Hospital Essen, Germany,
[8] Institute of Pathophysiology, University Hospital Essen, Germany,
[9] Department of Medical Sociology, University Hospital Essen, Germany,
[10] Department of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, Germany,
[11] Department of Preventive and Rehabilitative Sports Medicine, Technical University of Munich, Germany,
[12] Department of Cardiology, Klinikum Links der Weser, Bremen, Germany,
[13] Institute of Medical Sociology, University of Düsseldorf, Germany.

Abstract

Background: Regular physical exercise is recommended to reduce cardiovascular mortality. And yet, atherosclerosis is the main cause of exercise-associated death in persons beyond age 35. The need for risk stratification in marathon runners is under discussion. The predictive value of modern imaging- and non-imaging-based markers of risk that can be used for risk stratification in masters endurance athletes still deserves exploration.

Methods: Male runners > 50 years who have completed at least five marathon races during the preceding 3 years and do not suffer from coronary artery disease, angina nor diabetes mellitus are studied to assess the predictive value of established and modern imaging-based and biochemical cardiovascular risk factors. Laboratory parameters including clinical chemistry, hematology and hormone measurements are determined. Lifestyle-related risk factors, psychosocial and socioeconomic variables are explored using standardized questionnaires. Coronary, carotid, femoral and aortic atherosclerosis is measured using electron-beam computed tomography and ultrasound. In addition, a resting ECG, a bicycle stress test and heart rate variability are performed Myocardial morphology and function are assessed using echocardiography and magnetic resonance imaging. Participants are invited to compete in a marathon race to quantify the association of coronary atherosclerosis with marathon-related changes of cardiac troponin levels and the extent of marathon-induced inflammation. At the cellular level, the effect on the amount of circulating progenitor cells (EPCs) is determined by FACS analysis. Changes in laboratory parameters and hormone levels are also studied. Annual long-term follow-up including hospital records and death certificates is performed. Data are compared with those from a general unselected cohort from the Heinz Nixdorf Recall Study.

Conclusion: This study should contribute to cardiovascular risk assessment in the growing number of masters marathon runners with a focus on assessing the predictive value of modern imaging techniques and biochemical markers for comprehensive risk stratification.

Key Words:

Marathon · Atherosclerosis · Risk factors · Electron-beam CT · Coronary artery disease · Cardiovascular screening

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Arteriosklerose und kardiovaskuläre Risikofaktoren bei älteren männlichen Marathonläufern. Grundlage und Design der „Marathon-Studie"

Zusammenfassung

Hintergrund: Regelmäßige körperliche Aktivität eignet sich zur Prävention der Arteriosklerose und kardiovaskulärer Ereignisse. Und dennoch ist die Arteriosklerose die Hauptursache sportassoziierter Todesfälle jenseits des 35. Lebensjahrs. Der prädiktive Nutzen moderner bildgebender Verfahren und biochemischer Marker, die für eine Risikostratifizierung in Frage kommen, wurde bei älteren Ausdauersportlern bislang nicht hinreichend untersucht.

Methodik: Es werden Männer > 50 Jahre untersucht, die in den vergangenen 3 Jahren mindestens fünf Marathonläufe absolviert haben und keine bekannte Herzkrankheit oder Angina pectoris und keinen Diabetes mellitus aufweisen. Etablierte Risikofaktoren sowie moderne bildgebende und biochemische Risikomarker werden gemessen. Lebensstilassoziierte, psychosoziale und sozioökonomische Risikofaktoren werden mit standardisierten Fragebögen erhoben. Die Arteriosklerose der Koronararterien, der Karotiden, der Femoralarterien und der Aorta wird mittels Elektronenstrahltomographie und Ultraschall quantifiziert. Zusätzlich werden ein Ruhe-EKG, eine Fahrradergometrie und eine Messung der Herzfrequenzvariabilität durchgeführt. Morphologie und Funktion des linken Ventrikels werden echokardiographisch und magnetresonanzto-

Schlüsselwörter:
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mographisch erfasst. Die Teilnehmer wurden gebeten, an einem Marathonwettkampf teilzunehmen, um die Assoziation von Koronarsklerose und dem marathoninduzierten Anstieg von kardialem Troponin in Abhängigkeit von der erwarteten Entzündungsreaktion zu untersuchen. Auf zellulärer Ebene wird der Effekt auf die Anzahl zirkulierender endothelialer Vorläuferzellen (EPCs) mittels FACS-Analyse bestimmt. Die Ereignisrate im Verlauf wird jährlich erfragt. Es werden auch Krankenhausdokumente und Sterbeunterlagen ausgewertet. Die Daten können im Vergleich zur Allgemeinbevölkerung aus der Heinz Nixdorf Recall Studie analysiert werden.

Schlussfolgerung: Diese Studie kann einen Beitrag zur kardiovaskulären Risikostratifikation in der wachsenden Gruppe älterer Marathonläufer leisten. Der prädiktive Wert der bildgebenden und biochemischen Marker für kardiovaskuläre Ereignisse wird untersucht.

Introduction

Regular physical exercise is a recommended strategy to reduce cardiovascular mortality [7, 87]. And yet, coronary atherosclerosis is the main cause of exercise-related death among adult marathon runners [63, 88], with annual death rates ranging between 0.3/100,000 among high-school and college athletes [45, 89], 2/100,000 in a general cohort of marathon participants [46], and 7/100,000 among elderly joggers [79].

Over the past decades, the numbers of marathon runners has constantly risen. In 1980, approximately 120,000 persons were estimated to have participated in US marathons rising continually to > 430,000 in 2005 [65]. During the same period, the median age of marathon finishers increased from 34 years in 1980 (26% males being > 40 years) to 40 years in 2005 (44% males being > 40 years) [65]. This age trend is likely to continue as the "baby boomers" of the 1960s and 1970s, who grew up in the jogging era, soon approach their 6th decade in life.

Identification of persons at risk of cardiovascular events among those that intend to participate in competitive endurance exercise remains difficult and its need remains a matter of debate. Maron et al. suggested that the risk for sudden cardiac death associated with marathon running is too small to recommend routine screening for cardiovascular disease (CVD) [46]. Roberts & Maron even reported a decreasing trend in mortality among marathon race participants [63], largely attributable to the expanded access to external defibrillators on many marathon courses. However, reported survival data were not adjusted for demographics or other variables, and were not intended to represent precise estimates of changing risk [63]. Therefore, as acknowledged by current guidelines [43], the rate of fatal and nonfatal coronary events in masters marathon runners during or shortly after a marathon competition may nonetheless be substantially higher than previously estimated.

Stratification of marathon runners at risk for cardiovascular events particular during the race is scarce. Several studies have been performed to assess myocardial cell damage by measuring changes of cardiac troponin levels associated with a marathon race. However, the change in cardiac troponin levels seems independent of age, cardiovascular risk factors, race finishing time, systolic and diastolic left ventricular function, antioxidative capacity and reactive oxygen species, or NT-proBNP [21, 27, 36, 68, 77, 94].

In order to improve identification of runners at risk, new and comprehensive approaches to risk stratification including state-of-the-art imaging techniques to visualize and quantify atherosclerosis and novel biochemical markers of cardiovascular risk will have to be applied in older marathon runners. In this study, we report the rationale and design of a large and unique study on comprehensive risk assessment in advanced-age male marathon runners.

Aims of the Study

It is our aim to determine the prevalence and extent of coronary and peripheral atherosclerosis in relation to cardiovascular risk factors in nonprofessional asymptomatic healthy male marathon runners aged > 50 years in comparison to a matched cohort from an unselected general population. We further seek to determine the association of coronary plaque burden with the extent of myocardial cell damage during and after a marathon race as evidenced by increases in cardiac troponin levels. Finally, long-term follow-up will determine the rate of cardiovascular events in relation to the extent of coronary plaque burden, extracoronary atherosclerosis and cardiovascular risk factors in comparison to matched non-marathon-running individuals from the general population.

Participants

Participants for the Marathon Study were recruited in three ways: by (1) an advertisement in a German marathon journal ("Runners World"), (2) a press conference at inauguration of the study, and (3) acceptance of colleagues and friends of participants, if inclusion criteria were met. This study was limited to males for three reasons: (1) up to the age of 60, the

50th percentile of coronary artery calcium (CAC) in women from the general population is 0 [72], which likely limits the usefulness of CAC quantification in healthy athletic women, (2) more males than females are active marathon runners at age > 50, and (3) electron-beam computed tomography (EBCT) is associated with a low but measurable radiation exposure, i.e., < 1 mSv [9]. Therefore, for our research purposes involving the breast, the study was limited to males. All participants requesting participation answered a questionnaire to specify inclusion criteria. All subjects gave written informed consent including evaluation of death certificates. The study was approved by the local ethics committee and by the German board of radiation safety.

Inclusion and Exclusion Criteria

Male runners were eligible if they were > 50 years of age and had completed at least five full-distance marathon races (42.195 km) during the preceding 3 years. Exclusion criteria comprised history of established heart disease, diabetes mellitus, angina pectoris, severe renal failure predisposing to coronary calcification, muscular-skeletal disease at inclusion preventing future regular marathon running, psychiatric disease, and unwillingness to give informed consent.

Methods

All questionnaires, interviews and diagnostic test protocols including algorithms and equipment used in this study are identical or very similar to the Heinz Nixdorf Recall Study [74] to allow comparison of the two cohorts.

Questionnaires

Behavioral risk factors (such as smoking, nutrition habits, and physical activity), medical history (such as a family history of ischemic heart disease), regular intake of cardiovascular and noncardiovascular medication including hormones, vitamins and nutritional supplements, and also sociodemographic and psychosocial variables are assessed. A physician-based interview and the Rose angina questionnaire are used to identify angina pectoris.

Cardiovascular Risk Factors

Blood pressure is measured with an automated oscillometric blood pressure device (Omron 705-CP, OMRON, Mannheim, Germany). The mean value of the second and third of three measurements taken at least 3 min apart is computed. Blood pressure is classified according to JNC-VII [30] threshold values.

Table 1. Diagnostic tests used in the Marathon Study.
Tabelle 1. Diagnostische Tests, die in der Marathonstudie verwendet werden.

- Questionnaires for lifestyle, health, nutrition, exercise, psychosocial and socioeconomic risk factors
- Blood pressure measurements
- Twelve-lead resting ECG
- Bicycle stress test
- Heart rate variability
- Electron-beam computed tomography
- Ankle-brachial index
- Ultrasound of femoral arteries and aorta
- Carotid intima-media thickness/carotid plaques
- Echocardiography
- Magnetic resonance tomography

Body mass index (BMI [kg/m^2]) is calculated from standardized measurements of height and weight. Current smoking is defined as a history of cigarette smoking during the past year. Participants are considered diabetic if they either report a physician diagnosis of diabetes, if they are taking antidiabetic medication, or if their fasting glucose level is > 126 mg/dl.

Biochemical and Hematologic Tests

General health including liver and kidney function and hematologic analyses is evaluated by a number of tests (Table 2). At baseline, blood samples are drawn at fasting state. All samples are analyzed within 1 h. Serum and plasma samples are separated by centrifugation at 2,500´g for 10 min. In addition to samples for immediate analyses, multiple aliquots of serum, plasma and urine are stored frozen at –80 °C.

Various hormone values of marathon runners and control persons are determined (Table 2). Chronic changes of hormone regulation are determined by comparison to control persons of the Heinz Nixdorf Recall Study [74].

Quantification of Coronary and Extracardial Atherosclerosis

EBCT scans (C-150 scanner, GE Imatron, South San Francisco, CA, USA) for the Marathon Study are performed at the Alfried Krupp Hospital Essen, Germany, using the same protocol as in the Heinz Nixdorf Study [74].

Extracardial atherosclerosis is determined by ultrasound (7.5-MHz transducer, Elegra, Siemens, Erlangen, Germany) in the internal, external, and common carotid arteries, bilaterally, as well as in the infrarenal aorta, iliac arteries and common femoral and superficial femoral arteries of both legs. Characteristics

Table 2. Laboratory tests in basic screening. APTT: activated partial thromboplastin time; FSH: follicle-stimulating hormone; LH: luteinizing hormone; PT: prothrombin time; SHBG: sex hormone-binding globulin; T_3: triiodothyronine; T_4: thyroxine; TSH: thyroid-stimulating hormone.

Tabelle 2. Laborwerte, die für die Basisuntersuchung bestimmt werden. APTT: aktivierte partielle Thromboplastinzeit; FSH: follikelstimulierendes Hormon; LH: luteinisierendes Hormon; PT: Prothrombinzeit; SHBG: sexualhormonbindendes Globulin; T_3: Trijodthyronin; T_4: Thyroxin; TSH: thyroideastimulierendes Hormon.

General health
- Blood cell count
- Hematocrit, hemoglobin
- Serum electrolytes
- Liver enzymes
- Serum total protein and albumin
- Lactate dehydrogenase
- Creatine kinase
- Myoglobin
- Serum creatinine, urea and uric acid

Coagulation parameters
- Basic coagulation tests (PT, APTT)
- D-dimer
- Plasminogen activator inhibitor-1 (PAI-1)

Causal risk factors
- Total cholesterol and subfractions with direct measurement of low- and high-density lipoprotein cholesterol, apolipoproteins A and B
- Blood glucose and hemoglobin A1c

Conditional risk factors
- Lipoprotein (a)
- Triglycerides
- Fibrinogen
- Homocysteine

Markers of inflammatory activity
- high sensitive C-reactive protein (hs CRP)

Urinalyses
- Urine status
- Albumin

Hormones
- Thyroid gland: TSH, free T4, total T3, total T4
- Testes: testosterone, SHBG
- Pituitary gland: LH, FSH, prolactin
- Adrenal gland: cortisol

of each vessel are documented as follows: (1) diameter, (2) presence of plaques, (3) percentage of stenosis produced by the plaques, (4) echographic structure of plaques. Intima-media thickness (IMT) is determined at the far wall of the left and right common carotid arteries and in the infrarenal aorta, iliac arteries as well as in common femoral and superficial femoral arteries.

The ankle-brachial index (ABI) is calculated per leg as the ratio of the highest systolic brachial pressure measured in the right and left arm and the highest ankle artery pressure measured either in the posterior tibial or the dorsalis pedis artery [37]. Measurements are performed after 15 min rest for each subject according to a standard protocol always following the same order: left foot, right foot, right arm, and left arm.

Resting ECG

A standardized digital twelve-lead resting surface ECG is recorded on an MAC 5000® ECG recorder (GE Healthcare Technologies, Freiburg, Germany). ECGs are interpreted automatically using the integrated 12SL-Code® [80].

Stress ECG

All participants undergo a standardized upright twelve-lead bicycle ergometry using standard equipment (CASE 8000, GE Healthcare Technologies, Freiburg, Germany). We use bicycle ergometry and not a treadmill protocol to allow comparison with the general population from the Heinz Nixdorf Recall Study [74].

Heart Rate Variability (HRV)

HRV is measured over a period of 15 min: 5 min supine, 5 min upright, 5 min supine (VarCor PF5, Pantalus, Rheinmünster, Germany). Data are analyzed using standard variables of the time and frequency domain [29, 42, 83].

Assessment of Ventricular Morphology and Function

A standard echocardiogram is performed in all subjects including two-dimensional and M-mode ultrasound, continuous- and pulsed-wave Doppler analysis, and color flow assessment of cardiac chambers and valves (Vivid 7, GE Healthcare Technologies, Freiburg, Germany) [92]. In addition, MRI (magnetic resonance imaging) examinations are performed on a 1.5-T MR scanner (Magnetom Avanto, Siemens, Erlangen, Germany) including assessment of myocardial function and additional administration of gadolinium-DTPA (Schering AG, Berlin, Germany) to detect delayed contrast enhancement.

The Marathon Competition

All participants are invited to compete in the 2006 Metro Group Marathon Düsseldorf, Germany (Figure 2). They are equipped with a heart rate monitor during the race (Polar S810-I, Polar Electro GmbH Deutschland, Büttelborn, Germany). In all participants, a resting ECG is recorded (MAC 5000®), body weight is measured, and blood is drawn before, immediately after the race, and the following morning. This is accom-

plished at ten medical stations operating with two-staff personnel each to allow for rapid evaluation of all participants. Strictly every 30 min, plasma and serum aliquots are driven with special emergency permits to the clinical chemistry laboratory at the University Hospital Essen, Germany, for rapid analysis (Table 3). Samples are analyzed no later than 1 h after sampling from participants. Acute endocrine regulation is measured in samples before, immediately after the run, and the following morning. Blood samples for adhesion molecules, cytokines, adrenocorticotropic hormone (ACTH), homocysteine, metanephrine and normetanephrine are immediately centrifuged locally, allocated to aliquots, snap-frozen in liquid nitrogen and stored in a 35-l liquid nitrogen tank, until they are stored within cryotube boxes at –80 °C for further use. Levels of CD34/KDR double positive cells in the marathon runners are measured using FACS analysis before and immediately after the race.

Only participants, their relatives and study personnel have access to the study center, which is located immediately adjacent to the starting area. There is no strict recommendation regarding food or fluid intake. After the race, participants are immediately accompanied from the finish zone to the study center, which is located approximately 600 m away from the finish area. After the race, participants receive medical attention and physiotherapy, when needed. All participants are asked to return to the Department of Cardiology at the University Hospital Essen, Germany, the following morning. Again, no recommendation is given as to food and fluid intake.

Figure 1. Logo of the "Marathon Study". It is adapted from the logo of the Heinz Nixdorf Study. Further details on these trials are available at *www.marathon-studie.de* and *www.recall-studie.de*.

Abbildung 1. Logo der „Marathon-Studie". Es ist adaptiert von dem Logo der Heinz Nixdorf Recall Studie. Weitere Details zu den Studien finden Sie unter *„www.marathon-studie.de* und *www.recall-studie.de*.

Long-Term Follow-Up

In future, participants are asked annually to respond to a questionnaire including assessment of cardiovascular fitness, changes in cardiovascular and noncardiovascular medication, and cardiovascular events. Permission to review hospital records and death certificates is requested.

Discussion

Exercise and physical exertion is associated with a severalfold increased risk for plaque rupture and cardiovascular events [3, 10, 23, 47, 96], with most events occurring within 1 h after initiation of exercise [47]. The risk seems highest in sedentary males with multiple risk factors [23] and the underlying mechanism is most often plaque rupture [10]. Even trained mara-

Figure 2. Participants in the Marathon Study joining the Metro Group Marathon 2006 in Düsseldorf (© RAG Aktiengesellschaft).

Abbildung 2. Teilnehmer der Marathonstudie, die am Metro Group Marathon 2006 in Düsseldorf teilgenommen haben (© RAG Aktiengesellschaft).

thon runners have a fivefold increased risk of experiencing a cardiovascular event during exercise [76].

Cardiovascular risk assessment in masters marathon runners includes personal and family history as well as a physical examination and blood pressure measurements [43]. Persons considered to be at moderate-to-high cardiovascular risk based on conventional risk assessment who wish to enter vigorous competitive situations are recommended to undergo exercise testing [43]. If coronary artery disease is detected, participation in high-intensity competitive exercise is not advised [43]. In recognition of the potential risk associated with undetected atherosclerotic disease, medical clearance is frequently required prior to marathon race participation, which creates medical and legal issues for risk stratification [57].

At present, it is unclear, which diagnostic test or combination of tests reliably identifies or rules out coronary artery disease. It has been suggested that "… mild atherosclerotic disease … may increase the risk of an acute event" [43] and implications of such finding are advised to be discussed individually. Yet, specific criteria and tests to define "mild atherosclerotic disease" as well as thresholds for intervention are missing. The potential value of modern imaging techniques to quantify subclinical atherosclerosis is not mentioned in the current guidelines or scientific recommendations on preparticipation screening in masters athletes [43, 44].

Critical Appraisal of the Role of Established Cardiovascular Risk Factors

The established strategy for determining CVD risk includes screening for traditional cardiovascular risk factors as well as incorporating that information into conventional "office-based" risk prediction tools, e.g., Framingham Score [97], PROCAM Score [5] or EURO Score [18], to estimate "global risk". Regular physical exercise beneficially affects the individuals' cardiovascular risk profile [87]. Even at the high-end spectrum of cardiovascular fitness in middle-aged marathon runners, the degree of fitness remains related to risk factor burden [32].

Despite the measurable beneficial effect of exercise on the risk factor profile and the apparent success of risk stratification tools in risk detection and prevention in populations, there are several limitations to risk factor assessment as a screening tool in marathon runners. The Framingham Score, as the most widely used risk prediction tool, is only moderately accurate for predicting short-term risk (< 10 years) of acute coronary events in healthy asymptomatic individuals [53]. It does not take lifestyle factors such as diet, exercise, BMI, family history of CVD events, or autonomic function into account, that all may have a potential independent effect on risk prediction beyond traditional risk factors. Risk factors other than atherosclerotic plaque burden such as chronic inflammation, blood thrombogeneity and fibrinolytic activity, as well as myocardial propensity to develop life-threatening arrhythmia are not included in conventional risk assessment. Finally, regular cardiovascular exercise may have already modified the individual risk factor profile at the time of presentation, concealing a previously much higher risk. It is unclear, if and when such a change in risk factor burden translates into stabilization of preexisting plaque.

The Potential Role of Atherosclerosis Imaging

In view of these limitations, current guidelines acknowledge the value of additional atherosclerosis imaging as part of a comprehensive approach to risk stratification in subjects that plan to start vigorous exercise programs [54]. Greenland et al. [24, 25] noted three tests of atherosclerosis imaging that may be of value: CAC scanning, the ABI, and carotid ultrasound. These markers of atherosclerotic burden are attractive tools for risk stratification in marathon runners, as they may better reflect the sequelae of lifelong risk factor exposure rather than measuring the risk factor burden attributable to a particular fitness level.

The presence of CAC evidences the presence of coronary atherosclerosis. CAC quantities are closely correlated to overall plaque burden both in histological [67] and intravascular ultrasound-(IVUS-)based [70] studies. It is a measure of coronary atherosclerotic disease activity and hence an index for the likelihood of future coronary events [50, 73]. There is a growing body of evidence suggesting that quantification of CAC burden allows prediction of cardiovascular events above and beyond conventional risk factors [4, 38, 51, 61,75, 91].

Carotid IMT is another reliable marker for atherosclerotic vascular injury [24]. Large observational studies established that carotid IMT correlates with levels of cardiovascular risk factors and clinical CVD [84]. The predictive power of carotid IMT for future incident cardiovascular events has been demonstrated in multiple epidemiologic studies to be graded and independent of other risk factors [8, 11, 12, 20, 28, 56]. However, intraindividual variation in the presence and extent of CAC burden and IMT is high [48], which deserves exploration in different cohorts. ABI values < 0.9 are quite sensitive and specific for the presence of peripheral arterial disease [24]. However, it is not clear to which degree alterations in lower limb artery wall morphology represent atherosclerosis or an adaptation to continuous strain.

In addition to identifying presence and quantities of subclinical plaque burden, the relationship of plaque

localization with different concomitant cardiovascular risk factors and with events is still under discussion [14]. Plaques in the carotid artery were found to be related to cardiovascular death or nonfatal myocardial infarction, whereas plaques in the femoral artery were related to revascularization [26]. The interaction of endurance exercise and individual sites of atherosclerosis is also not well examined.

Stress ECG and Heart Rate Variability (HRV) Testing

Recent AHA/ACC (American Heart Association/ American College of Cardiology) and U.S. Preventive Services Task Force guidelines have discouraged the use of exercise testing as a screening modality for routine use (class III indication), particularly in low-risk subjects [19, 22, 95]. While in men > 45 years and women > 55 years who plan to start vigorous exercise programs, exercise testing may have a beneficial role (class IIb indication), its value in persons already undergoing regular exercise is not established. During the past years, emerging evidence suggests that measures other than those directly related to myocardial ischemia are strong predictors of mortality in cardiovascular risk. These include exercise capacity, chronotropic response, heart rate recovery, and ventricular ectopy [39] which are related to cardiovascular fitness and/or autonomic tone. We could recently demonstrate that a poor heart rate recovery is associated with advanced plaque burden in persons without overt coronary artery disease independent of age and gender [49].

HRV represents a marker of autonomic activity and provides useful information on autonomic failure and cardiovascular risk [13]. It is influenced by factors such as age, gender, respiration, and cardiorespiratory fitness. There is evidence for an association between HRV and propensity for lethal arrhythmias in subjects with coronary artery disease. In recent years, time and frequency domain indices of HRV also gained increasing interest in sports sciences. A detailed review is provided in this issue of HERZ [29]. In healthy subjects and cardiovascular patients including those at advanced age, regular endurance exercise results in improved HRV parameters with a shift in favor of enhanced vagal modulation of cardiac rhythm [29].

Assessing Ventricular Morphology and Function in Masters Athletes

Echocardiography is fundamental in differentiating athlete's heart from structural cardiac disease [52, 59, 60]. Extreme variations in left ventricular morphology can be observed among athletes participating in endurance versus resistance training [41]. More importantly for this study, acute and long-term effects of prolonged exertion including systolic and diastolic function as well as appearance of regional wall motion abnormalities have been studied in younger but not in older marathon runners [16,31, 55].

MRI-based evaluation of cardiac volumes, myocardial mass as well as right and left ventricular function may be used to detect athlete's heart [69]. To the best of our knowledge, there is no study that has assessed the presence of myocardial late enhancement in relation to risk factor profile in advanced-age marathon runners.

The Role of Markers of Inflammation and Cytokines

Atherosclerosis is nowadays recognized as a chronic inflammatory disease of the large arteries [64]. A marker of inflammation is high sensitive C-reactive protein (hsCRP), that has been shown to be a strong predictor of cardiovascular events [62]. Intense regular physical exercise does not only influence the risk factor profile but also suppresses circulating CRP levels [86]. Exhaustive exercise, however, induces pro-inflammatory cytokine production, such as interleukin-6, and promotes release of reactive oxygen species [33, 58, 82]. This is consistent with the observation that CRP levels and acute-phase reactants substantially rise after a marathon race [78], which may be accompanied by a prothrombotic/fibrinolytic dysbalance [6, 78]. In the presence of atherosclerotic plaque, acute bouts of inflammation may result in acute coronary syndromes as inflammation is crucially determinant in precipitating plaque rupture and some forms of superficial erosion [15, 34, 85, 90].

Biochemical and Hematologic Tests

Marathon running has profound effects on many laboratory parameters and hormones [35, 36]. Changes in laboratory parameters are often inconsistent in the literature and depend on the cohort studied, cardiovascular fitness levels, the type of exercise, weather conditions, times of measurement, and also the essays and the technology used for analysis. Kratz et al. provided a table of modified reference values (or better: expected values) of biochemical, cardiac and hematologic laboratory parameters in marathon runners [36]. However, previous studies often comprise less than 50 participants and include both men and women. Fitness levels, age ranges, and other confounders vary among studies. The Marathon Study might be helpful in providing baseline and pre- and post-race laboratory parameters in older runners that can be used for interpretation of observed changes and clinical problems.

Table 3. Laboratory tests before and after the marathon race. ACTH: adrenocorticotropic hormone; EPCs: endothelial progenitor cells; TPO: tryptophan peroxidase. For other abbrevations see Table 2.

Tabelle 3. Laborwerte, die vor und nach dem Marathonwettkampf gemessen wurden. ACTH: Kortikotropin; EPCs: endotheliale Vorläuferzellen; TPO: Tryptophanperoxidase. Übrige Abkürzungen s. Tabelle 2.

General health
- Blood cell count with differential leukocyte counts
- Hematocrit, hemoglobin
- Serum electrolytes
- Liver enzymes
- Serum total protein and albumin
- Lactat dehydrogenase
- Serum creatinine, urea and uric acid
- Creatine kinase
- Myoglobin

Coagulation parameters
- Basic coagulation tests (PT, APTT)
- D-dimer
- Coagulation factor VIII
- Von Willebrand factor antigen and ristocetin cofactor

Cardiac markers
- Troponin I
- NT-pro BNP (brain natriuretic peptide)

Causal risk factors
- Total cholesterol and subfractions with direct measurement of low- and high-density lipoprotein cholesterol, apolipoproteins A and B
- Blood glucose and hemoglobin A1c

Conditional risk factors
- Lipoprotein (a)
- Triglycerides
- Fibrinogen
- Homocysteine

Markers of inflammatory activity
- high sensitive C-reactive protein (hsCRP)

Urinalyses
- Urine status
- Albumin

Hormones
- Thyroid gland: TSH, free T4, total T3, total T4, anti-TPO antibodies
- Testes: testosterone, SHBG
- Pituitary gland: LH, FSH, prolactin, ACTH, growth hormone
- Adrenal gland: cortisol, metanephrine, normetanephrine
- Leptin, adiponectin

Circulating EPCs
- Level of CD34/KDR double positive cells in the peripheral blood

In a recently published report, Werner et al. described that the level of circulating endothelial progenitor cells (EPCs), defined as CD34/KDR double positive cells, predicts the occurrence of cardiovascular events and death from cardiovascular causes, and therefore may help to identify patients at increased cardiovascular risk [93]. Furthermore, exercise training in patients with coronary artery disease has an influence on the amount and physiological function of EPCs [1, 40, 66, 81]. The influence of regular exercise in healthy athletes on EPCs and the effect of a marathon race on EPCs has not been studied.

Conclusion

Regular cardiovascular exercise provides effective protection against cardiovascular events. Persons at all ages should be encouraged to engage in physical activity, including those with established coronary heart disease [2, 33]. However, in advanced-age persons determined to participate in highly competitive strenuous exercise, risk stratification may be warranted. Current risk stratification strategies in masters athletes may underestimate the extent of atherosclerotic plaque burden and hence the true cardiovascular risk. Exercise stress testing may be of limited value [17]. The burst of inflammation caused by marathon running may trigger plaque rupture and acute coronary syndromes in the presence of an increased but yet preclinical plaque burden.

Our Marathon Study provides prevalence data on atherosclerotic burden in asymptomatic advanced-age male marathon runners. It addresses the association of established and novel risk factors with coronary, carotid, femoral and aortic atherosclerotic plaque burden. It also evaluates the impact of atherosclerosis burden on marathon-induced changes in cardiac troponin levels. Finally, the prognostic value of risk factors and markers of atherosclerosis burden in advanced-age marathon runners is determined. The study is unique in that all findings and outcome data can be directly compared with matched controls from the unselected general population of the ongoing Heinz Nixdorf Recall Study.

The Marathon Study should help to define biochemical markers and imaging techniques that may be useful for comprehensive risk assessment in the increasing number of advanced-age marathon runners.

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Address for Correspondence
PD Dr. Stefan Möhlenkamp
Department of Cardiology
West German Heart Center Essen
University Hospital Duisburg-Essen
Hufelandstraße 55
45122 Essen
Germany
Phone (+49/201) 723-4803, Fax -5401
e-mail: stefan.moehlenkamp@uk-essen.de