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On the paradox of exercise: coronary atherosclerosis in an apparently healthy marathon runner

Stefan Möhlenkamp*, Dirk Böse, Amir Abbas Mahabadi, Gerd Heusch and Raimund Erbel

SUMMARY

Background An asymptomatic and apparently healthy 64-year-old marathon runner underwent comprehensive cardiovascular risk assessment as part of a prospective study on calcified coronary plaque burden in master marathon runners. His profile suggested a low 10-year cardiovascular risk.

Investigations Conventional risk-factor assessment, coronary artery calcium quantification, bicycle stress test, echocardiography, coronary angiography, intravascular ultrasonography, including virtual histology, and intracoronary Doppler ultrasonography.

Diagnosis Severe coronary atherosclerosis of the left anterior descending, mid left circumflex, and left main arteries.

Management Stenting of the left anterior descending artery, CABG surgery, and intensive risk-factor modification. The patient was also advised against participating in future marathon competitions.

KEYWORDS atherosclerosis, exercise, marathon running, microvascular function, risk stratification

CME

S Möhlenkamp is Associate Professor of Medicine and Cardiology, D Böse is a Fellow of Cardiology, and R Erbel is Professor of Medicine and Cardiology and Head of the Department of Cardiology, all at the West-German Heart Center Essen, and AA Mahabadi is a fourth-year student at the Medical School, and G Heusch is Professor of Medicine and Pathophysiology and Head of the Institute of Pathophysiology, at the University Clinic Duisburg-Essen, Essen, Germany.

Correspondence
*West German Heart Center Essen, Clinic of Cardiology, University Clinic Duisburg-Essen, Hufelandstrasse 55, 45122 Essen, Germany
stefan.moehlenkamp@uk-essen.de

Received 28 November 2006 **Accepted** 22 March 2007
www.nature.com/clinicalpractice
doi:10.1038/ncpcardio0926

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THE CASE

A 64-year-old male participated in a prospective study on the prevalence of coronary atherosclerosis in master marathon runners.[1] He trained 4–6 times per week throughout the year, averaging a weekly distance of 60–90 km, and had completed 22 marathon competitions over the past 27 years. He had played soccer for 25 years before taking up regular running, and also engaged in swimming and cycling. He had arterial hypertension, which was well controlled with an angiotensin-converting enzyme-inhibitor (5 mg ramipril once daily), and a positive family history for myocardial infarction (his father and brother experienced fatal events, both at the age of 65). No angina pectoris or dyspnea was reported on exertion or at rest. His dietary habits were common, but he paid no particular attention to eating heart-healthy foods. Uric acid and homocysteine levels were slightly elevated, whereas HDL cholesterol was normal. His cardiovascular risk profile indicated a low (7%) 10-year risk of experiencing a coronary event.[2] For more information on the patient's profile at presentation, see Table 1.

In the bicycle stress test he achieved 250 W without signs of ischemia, complained of no dyspnea, had no ectopic beats, and no relevant ST-segment changes. Heart rate recovery and exercise capacity were normal. The echocardiography-based ejection fraction was 54% with no regional wall motion abnormalities and a muscle mass index of 137.2 g/m^2. He had mild stenosis of the bicuspid aortic valve with a mean pressure gradient of 12 mmHg (aortic valve area 1.88 cm^2) and mild to moderate aortic regurgitation (a narrow jet reaching just beyond the left ventricular outflow tract, with a deceleration time of 1,575 ms).

The ankle–brachial index was 1. On ultrasonography, there was no relevant plaque in the femoral arteries and the intima media thickness

of the common carotid artery was 0.8 mm, which is normal for a man of his age. An electron-beam CT study revealed a coronary artery calcium (CAC; Agatston) score of 472, which is above the 75th percentile.[3]

The patient was admitted for further investigation, beyond that detailed by the protocol of the prospective study. Invasive coronary angiography revealed diffuse coronary atherosclerosis with clinically significant lesions (>75%) in the mid left anterior descending artery (LAD) and mid left circumflex artery (LCX; Figure 1). The right coronary artery (RCA) showed no stenosis.

Flow-wire measurements (using the FloWire® Doppler Guide Wire, Volcano, Rancho Cordova, CA) were performed in the distal LAD. The nonstenosed RCA was used as the reference vessel. Coronary flow reserve, induced by selective injection of 30 μg adenosine, was 2.8 in the distal LAD (normal 3.0 ± 0.8)[4] and 5.1 in the RCA, resulting in a fractional flow reserve of 0.55 (normal >0.75). During flow-wire pullback across the lesion, flow increased from 12 to 69 cm/s (Figure 2).

Intravascular ultrasound (IVUS) of the LAD was performed using a 2.9 F, 20 MHz catheter (Eagle-Eye® Gold, Volcano, Rancho Cordova, CA). Automated pullback was performed at 0.5 mm/s, beginning in the distal LAD. Lumen area in the distal LAD lesion was 2.6 cm^2 at the minimal lumen site, corresponding to a 73% area stenosis.

Radiofrequency data analysis of the IVUS signal was used for virtual histology assessment. Of the total plaque burden found in the LAD, 59% was fibrous plaque, 17% was fibro–fatty, 16% was lipid-rich (necrotic), and 8% was calcified (example plaque shown in Figure 3). Three nonculprit thin-cap fibroatheroma (TCFA) lesions (defined as having a lipid-rich core >10% and plaque volume ≥40%)[5] were identified in the LAD, and four in the LCX.

Initially, the LAD was revascularized using a 3.5 × 13 mm sirolimus-coated stent (Cypher®, Cordis Corporation, Miami Lakes, FL). Immediately after stent deployment, the patient developed sustained ventricular tachycardia, which was rapidly converted to sinus rhythm with 360 J. After revascularization, coronary flow reserve in the distal LAD increased to 4.5 with a peak flow almost identical to that in the RCA (Figure 4). The patient was discharged 2 days later.

The patient returned for IVUS assessment and intended stenting of the LCX 8 weeks later. As the narrow calcified lesion was crossed with the IVUS catheter, he again experienced a brief episode of rapid ectopic beats, which resolved immediately after pullback of the IVUS catheter. IVUS

Table 1 Profile of the asymptomatic marathon runner at presentation.

Characteristic	Patient's value	Normal values/ranges
Age	64	NA
Blood pressure (mmHg)	105/67[a]	<120/80
BMI (kg/m^2)	24.6	<25
Smoking status	Never	NA
Family history	Brother and father experienced fatal myocardial infarctions	NA
Total cholesterol (mmol/l[b])	5.2	<4.1
HDL cholesterol (mmol/l[b])	1.6	>1.0
LDL cholesterol (mmol/l[b])	3.0	<3.4
Triglycerides (mmol/l[c])	0.8	<1.7
Apolipoprotein A1 (g/l)	1.43	0.79–1.87
Apolipoprotein B (g/l)	0.97	0.46–1.74
Lipoprotein (a) (μmol/l[d])	0.6	<1.1
Homocysteine (μmol/l)	17.6	<12
Uric acid (μmol/l[e])	553.2	208.2–428.3
Fasting glucose (mmol/l[f])	5.8	<5.55
High-sensitivity CRP (mg/l)	2.94	<1
Framingham risk score	7% in 10 years	NA

[a]When receiving 5 mg ramipril once daily. [b]For conversion to mg/dl divide by 0.0259. [c]For conversion to mg/dl divide by 0.0113. [d]For conversion to mg/dl divide by 0.0357. [e]For conversion to mg/dl divide by 59.48. [f]For conversion to mg/dl divide by 0.0555. Abbreviations: CRP, C-reactive protein; NA, not applicable.

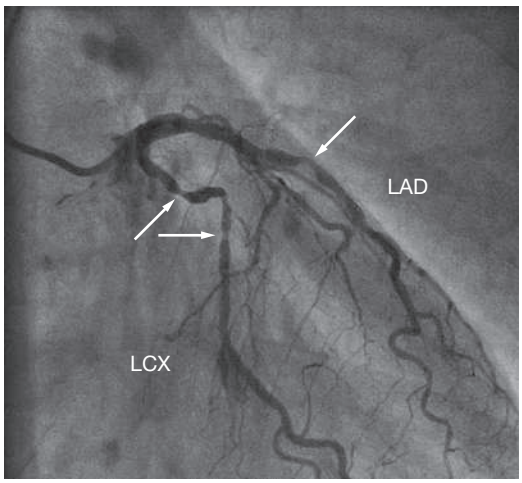


Figure 1 Coronary angiogram demonstrating marked lumen reduction in the mid LAD and mid LCX (arrows). The right coronary artery showed no stenosis (not shown). Abbreviations: LAD, left anterior descending artery; LCX, left circumflex artery.

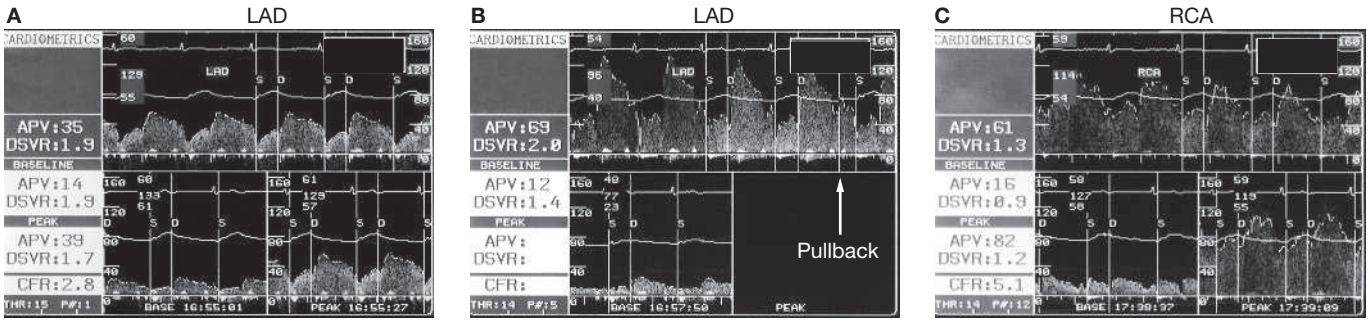
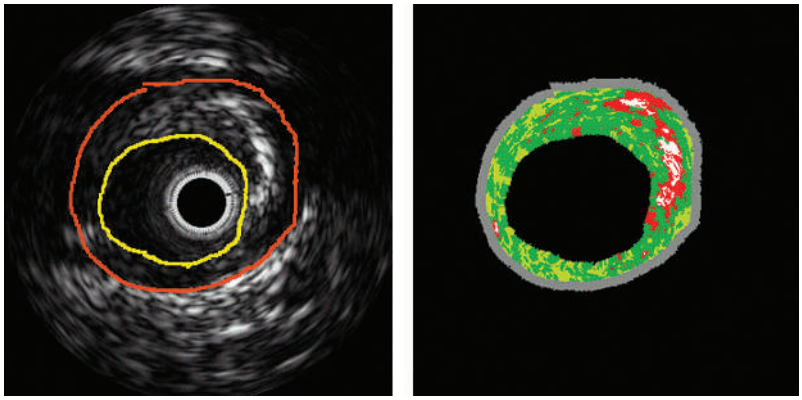


Figure 2 Intracoronary Doppler ultrasound scans demonstrating blood flow in the stenosed LAD and the non-stenosed RCA. (**A**) On injection of 30 μg adenosine, coronary blood flow in the LAD increased from 14 to 39 cm/s, corresponding to a CFR of 2.8. (**B**) During pullback in the LAD, coronary blood flow across the lesion increased 5.75-fold, from 12 to 69 cm/s. (**C**) In comparison, adenosine induced a blood flow increase from 16 to 82 cm/s in the RCA, equivalent to a CFR of 5.1. The fractional flow reserve of the LAD was, therefore, 0.55 (normal >0.75). A series of patients with normal coronary arteries documented that fewer than 1% of subjects had a CFR greater than 5 and a flow greater than 80 cm/s.[4] Abbreviations: APV, average peak velocity; CFR, coronary flow reserve; DSVR, diastolic/systolic velocity ratio; LAD, left anterior descending artery; RCA, right coronary artery.



Lumen area	9.5 mm^2	
EEL area	25.1 mm^2	
Plaque area	15.6 mm^2	
% Plaque burden	62%	
Fibrous area	7.0 mm^2	61%
Fibro–fatty area	2.4 mm^2	21%
Dense calcium area	0.5 mm^2	4%
Necrotic core area	1.6 mm^2	14%

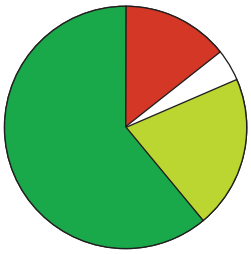


Figure 3 Intravascular ultrasound virtual histology image of a single plaque in the left anterior descending artery, demonstrating a relatively high amount of necrotic core plaque component (14%), as marked in red. Fibrous tissue is marked in dark green (61%), fibro–fatty tissue (21%) in light green and calcified plaque in white (4%). The total plaque area at this nonculprit lesion site is 62%. Abbreviation: EEL, external elastic lamina.

of the left main artery demonstrated advanced plaque burden with a residual left main lumen area of 6.4 mm^2. In light of these observations, stenting of the LCX was not performed. Again, the patient recovered well from the procedure and was discharged on 100 mg aspirin and 40 mg atorvastatin once daily, and his ramipril dosage was increased to 5 mg twice daily. The patient was recommended for CABG surgery. He underwent uneventful revascularization of the LAD using an internal mammary artery graft, with a venous graft used for the marginal branch. Six months later he is fit and well, and has recommenced regular running. He continues taking the same medication. He was advised, however, to no longer participate in marathon competitions.

DISCUSSION OF DIAGNOSIS

Vigorous physical exertion increases the short-term risk of sudden cardiac death in all people, yet simultaneously offers protection from this risk in those who exercise regularly, while they are both active and sedentary.[6] This so-called 'paradox of exercise'[7] is also seen in marathon runners, as first reported by Noakes *et al*,[8] yet the rate of acute coronary syndromes (ACSs) associated with marathon running is considered too small to justify routine screening for coronary atherosclerosis among master athletes.[9] In fact, a decreasing trend in mortality among marathon race participants has recently been reported,[10] although this was largely attributable to the expanded access to external defibrillators on many marathon courses.

The first step in assessing cardiovascular risk is quantification of risk-factor burden using stratification tools such as the Framingham score, which have generally proved successful in assessing populations. There is unequivocal evidence that regular exercise improves cardiovascular risk-factor burden. The likelihood of

a coronary event in the present case, however, seems higher than that anticipated from conventional risk-factor analysis. The Framingham score does not take into account lifestyle factors such as diet, exercise and BMI. Neither does the score reflect a positive family history of cardiovascular disease nor a personal history of elevated blood pressure, both of which were evident in the present case. Atherosclerotic plaque burden, autonomic function, chronic inflammation, lipoprotein subfractions, blood thrombogeneity and myocardial propensity to develop life-threatening arrhythmia are also not part of conventional risk assessment. The patient's C-reactive protein levels were at the upper limit of normal values. There was no history of a thrombotic event or arrhythmia. The patient only began running regularly in his 30s, and the subsequent years of exercise could have conferred benefits that improved his overall risk-factor profile. It is possible that his profile would have shown him to be at greater risk had assessment been carried out earlier in his life.

The CAC burden, obtained in this case as part of the prospective study, is a measure of the extent of coronary atherosclerosis. A CAC score greater than 400 is associated with an increased risk of coronary artery disease,[11] and there is strong evidence from various patient and population cohorts that a high CAC burden is a strong predictor of future cardiovascular events independent of established risk factors. Accordingly, during the 36th annual Bethesda Conference, which was dedicated to eligibility recommendations for competitive athletes, it was speculated that an advanced CAC burden might warrant a cautious approach to exhaustive exercise.[12] Although the presence of CAC alone provides no information as to the stability of existing plaques,[11] it indicates an increased chance of there being an unstable plaque somewhere in the coronary tree. IVUS-virtual histology was, therefore, used for *in vivo* analysis of the patient's total coronary plaque burden, enabling identification and quantification of fibrous, fibro–fatty, lipid-rich necrotic and calcium components.[5] The number of rupture-prone TCFA lesions and the high proportion of lipid-rich plaques found were comparable with those previously observed in patients with ACS,[5,13] indicating that the patient was at an increased risk of having a coronary event. Furthermore, the left main artery contained plaque with a residual

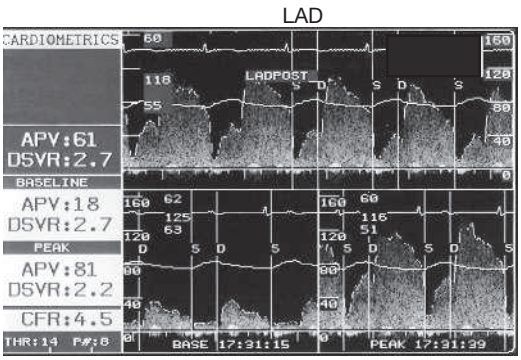


Figure 4 Intracoronary Doppler ultrasound scan of the distal LAD after stent deployment. The CFR increased from 2.8 (see Figure 2A) to 4.5, with a peak flow of 81 cm/s—almost identical to the peak flow in the reference vessel (see Figure 2C). The CFR in the revascularized LAD was slightly lower than in the right coronary artery (4.5 vs 5.1), which is attributable to the increased baseline flow in the LAD, probably caused by procedure-related microembolization. Abbreviations: APV, average peak velocity; CFR, coronary flow reserve; DSVR, diastolic/systolic velocity ratio; LAD, left anterior descending artery.

lumen area of less than 7.5 mm^2, a value shown to be of prognostic relevance.[14]

If and when an exercise-induced change in risk-factor burden translates into stabilization of pre-existing atherosclerotic plaque is unclear. The DNA Polymorphism and Carotid Atherosclerosis (DNASCO) study documented an attenuation of intima media thickness progression following 6 years of low to moderate intensity aerobic physical exercise in men who were not taking statins.[15] Physical activity has also been shown to be inversely associated with CAC burden.[16] These findings are consistent with experimental evidence demonstrating the anti-atherosclerotic effects of exercise on epicardial arteries.[17]

In addition, regular exercise also improves microvascular function,[17] as shown in this case by intracoronary Doppler ultrasonography. Injection of adenosine increased the cross sectional area of the resistance vessels, which led to an unusually large increase in flow across the lesion. These findings suggest that regular exercise could improve coronary microvascular function to the point at which it can compensate for severe epicardial plaque burden, 'concealing' the true extent of atherosclerosis. This concept could explain why the patient seems to be at increased risk of developing an ACS, yet remains asymptomatic.

To reduce the risk in athletes, it is crucial to identify the mechanisms by which exhaustive exercise might be responsible for ACS. Marathon running induces a burst of inflammation, with proinflammatory cytokine production, the release of reactive oxygen species, and increases in the levels of C-reactive protein and acute phase reactants.[18,19] These processes can be accompanied by an imbalance of prothrombotic/fibrinolytic factors. In the presence of vulnerable atherosclerotic plaques, such repetitive bursts of inflammation during competitive marathon racing and intensive training could contribute to the triggering of an ACS, resulting in the clinical manifestation of the paradox of exercise. Recently, premarathon training mileage was shown to be inversely related to increases in N-terminal pro-brain natriuretic peptide, a marker of myocardial strain, and troponin T, a marker of myocardial cell damage.[20] The mechanisms underlying this effect, the role of inflammation, and whether these changes have any role in the development of ACS is thus far unknown. Finally, endothelial shear stress, frequently elevated during training and marathon competitions, could also have a role in plaque growth, plaque rupture or plaque erosion.

For appropriately selected asymptomatic subjects at intermediate risk, current guidelines acknowledge the potential value of more comprehensive assessment beyond measuring established risk factors.[2,11] We believe that some master marathon runners are appropriate candidates for additional testing, as demonstrated by this case. At present, however, it is unclear which of the available tests—including cardiac CT scanning, MRI, stress echocardiography, nuclear stress testing or endothelial function assessment—best predicts future coronary events in endurance athletes. This case demonstrates that ischemia testing alone can fail to detect a considerable plaque burden.

TREATMENT AND MANAGEMENT

Treatment options were discussed in detail with the patient. In addition to intensive risk factor modification, CABG surgery was recommended on the basis of several observations: the prognostically relevant left main artery plaque burden; the high number of rupture-prone TCFA lesions; the development of ventricular tachycardia during stenting (suggesting vulnerable myocardium); and the positive family history of myocardial infarction. In addition to surgery and stenting, which served to restore unrestricted blood flow to the myocardium, atorvastatin was prescribed to lower LDL cholesterol levels to a target of less than 1.8 mmol/l (70 mg/dl). Aspirin was prescribed to inhibit platelet aggregation and ramipril was continued to control blood pressure. Continuous regular exercise was recommended, but he was advised against participating in future marathon competitions, owing to the potential for plaque rupture on vigorous exertion.

It must be acknowledged, however, that this master marathon runner might never experience an ACS, and absolute numbers of marathon-related cardiovascular events are low. Furthermore, there is no hard evidence that revascularization will reduce long-term morbidity and mortality from coronary artery disease in this asymptomatic low-risk subject. We believe, however, that sufficient evidence was gathered to justify the clinical decisions taken in this case, which will hopefully improve the patient's long-term prognosis.

CONCLUSIONS

This case illustrates the challenge of cardiovascular risk stratification in master marathon runners. These athletes can have greater than 75% stenoses and potentially vulnerable coronary atherosclerosis, despite a low Framingham risk score, a long standing history of vigorous exercise and the absence of symptoms. Noninvasive quantification of coronary plaque burden can help to identify athletes at a higher than anticipated risk. Further studies are required to determine the prevalence, functional consequence and prognostic value of coronary atherosclerosis in master marathon runners.

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Competing interests
The authors declared they have no competing interests.