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Research paper

Relationship of exercise to coronary artery disease extent, severity and plaque type: A coronary computed tomography angiography study

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A B S T R A C T

Background: While exercise has been associated with favorable coronary artery disease (CAD) outcomes, the relationship between endurance exercise levels and CAD findings has not been well explored.

Purpose: To evaluate the relationship of endurance exercise to CAD findings by coronary computed tomographic angiography (CCTA).

Methods: We evaluated consecutive patients referred to CCTA who filled out a survey instrument between 2015 and 2017, and who graded their level of weekly endurance exercise as: none, low (1–2 times per week), moderate (3–5 times per week) or high (5–7 times per week); along with the number of hours per week engaged in exercise as: low (< 30 min), moderate (1 h) or high (> 1–3 h).

CCTA: analysis included measurement of maximum per-patient, per-vessel and per-segment stenosis severity, which was judged as minimal (< 25%), mild (< 50%), moderate (50–70%), and severe (> 70%). CAD extent and severity was also summated CADRADS score, plaque burden by segment involvement score (SIS), and non-calcified plaque score (G-score). High-risk plaque (HRP), as defined by the presence of low attenuation plaque, positive arterial remodelling, spotty calcifications and napkin ring signs, was assessed. Finally, coronary artery calcium scores (CCS), as determined by Agatston units, were quantified.

Results: The study cohort comprised 252 patients (55.3y ± 10.1, 39.7% females) with 97 inactives, 87 with low and 68 with moderate-to-high recreational endurance exercise levels (> =3x/week ≥ 1 h) included.

Prevalence of subclinical CAD was 57.4%. Prevalence of > 50% stenosis was with 13.2% lower at moderate-to-high exercise levels as compared to inactives (p = 0.04). Stenosis severity score (p = 0.04), total (p = 0.036) non-calcified plaque burden were lower (p = 0.026) in athletes, and in the absence of confounding risk factors, the effect strenghtened (SIS and G-score, p = 0.012 and 0.008). There was no difference in the CCS. High-risk plaque prevalence was higher in controls as compared to athletes with moderate-to-high exercise levels (13.4% vs 0%, p = 0.002), and HDL was lower (p < 0.001), respectively. MACE rate was 0%, and ICA rate of > 50% stenosis 3.5% at 1 year follow-up.

Conclusion: Regular moderate-to-high endurance exercise results in lower total and non-calcified plaque burden and less high-risk plaque.

1. Introduction

While about half of sudden cardiac death (SCD) occurring in the age group of less than 45 years[1] are caused by CAD, the incidence rises up to 93% in those > 45 years,[1] mainly affecting males.[2–4] In younger athletes, however, other causes of SCD, such as anomalous coronary arteries, hypertrophic cardiomyopathy and myocarditis, are more common. The number of marathon runners, especially leisure–time athletes, has doubled over the last decade.[1]

The European Society of Cardiology (ESC) recommends ECG treadmill-stress exercise testing in athletes > 35 years,[5] due to the 10-fold increased risk of SCD. The ECG treadmill has a moderate sensitivity and specificity of 67–75%,[6] especially in athletes due to high vasodilatory capacity and coronary flow reserve.

There is scarce data on CTA findings in recreational endurance athletes at low-to intermediate CAD risk.

Coronary CTA is a non-invasive imaging modality for evaluation of CAD[7,8] which allows for quantification of global plaque burden,[9,10] characterization of plaque components (non-calcified low attenuation plaque (LAP) versus calcified),[11] and the quantification of "high-risk plaque" criteria,[12–14] novel imaging risk markers for major cardiac events (MACE). Hence, CTA adds incremental value to CAD risk stratification[15,16] and would qualify as an ideal screening tool. Data utilizing CTA in endurance athletes are rare.[17–21] Although prior studies have observed a positive association of excercise on cardiovascular mortality,[17] numerous questions remain regarding the effects of

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exercise on the presence, extent, severity and type of coronary artery disease (CAD). While the favorable prognosis of individuals who engage in regular exercise is well proven in epidemiologic studies, limited imaging studies have identified higher burden of calcified plaque in the coronary vasculature of high-performing endurance athletes. These limited data, however, have raised concerns that prodigious amounts of exercise may be associated with the acceleration of atherosclerosis,[22–24] and aggregate plaque volume relates with adverse outcome.[25] Statin treatment in patients undergoing CCTA has been associated with retardation of non-calcified plaque progression and acceleration of calcified plaque progression, and newer medications such as PCSK9-inhibitors may enhance this effect.[26]

Therefore, the primary aim of this present study was to determine the association of exercise levels with CAD presence, extent, severity and type in patients referred for CCTA, and to assess the usefulness of CTA as screening modality for coronary artery disease in low-to-intermediate risk recreational endurance athletes.

2. Methods

2.1. Study design and population

This prospective single site study was approved by the institutional review board (IRB). Consecutive patients referred to coronary CTA with suspected coronary artery disease (CAD) [9] were approached to complete exercise assessment as determined by a survey instrument between 12/2015 and 12/2018. Inclusion criteria were: (1) Adult patients ≥21 years of age; (2) Low-to-intermediate risk of CAD according to ASCVD.[27] Exclusion criteria included: (1) previous percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), (2) previous myocardial infarction, (3) previous heart valve surgery; (4) significant valvular disease > moderate severity; (5) renal dysfunction (serum GFR < 45 ml/min/1.73 m^2), (6) pregnancy.

Eligible patients completed a lifestyle questionnaire prior to CCTA exam wherein they were asked if they exercised “regularly” or “occasionally.” Further, patients were queried as to whether they participated in formal exercise competitions, which defined them as being recreational or professional athletes. Patients also completed questions related to the frequency of exercise per week, which was graded as low (1–2 times per week), moderate (3–5 times per week) or high (> 5 times per week). Patients recorded the average time engaged per exercise episode, which was rated as low (< 30 min per episode), moderate (≥1 h per episode) or high (≥3 h per episode). Years of continual regular exercise prior to CCTA were also recorded as ≤1 years; 1–3 years, 3–5 years, 5–10 years, > 10 years. Patients reported the type of exercise, which was then defined as either endurance or non-endurance (e.g., strength or others), with non-endurance exercisers excluded from the current analysis. Endurance exercise comprised cycling, running, cross-country skiing, triathlon training and mountaineering. Strength exercise included ballsports (e.g., tennis, golf) and those requiring isometric conditioning (e.g., bodybuilding, boxing). Furthermore, the years of training was recorded and stratified as low ≤1 years; 1–3 years, 3–5 years, 5–10 years and high > 10 years).

From the above criteria, we categorized patients into one of 3 cohorts: inactive, low endurance exercisers and moderate-high endurance exercisers. Inactive patients were defined as those who did not participate in any physical activities. Low endurance exercisers were defined by either low frequency (1–2 times per week) or short duration per episode (< 30 min), or a “low” label in combination with moderate or high in any other category. Moderate-high exercisers were defined by having engaged in regular exercise for > 1 year for ≥3 times per week of at least 1 h per episode. The metabolic equivalent of task (MET) was calculated according to the standardized MET formula and the conversion factor of the activity. For MET calculation, the objective measure of the energy expended by an individual while performing some specific physical activity is compared to a reference, set by convention at 3.5 ml of oxygen per kilogram per minute.[28]

In addition to the survey instrument, we prospectively ascertained CAD risk factors according to standardized criteria as follows: arterial hypertension (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg),[33] dyslipidemia[34] (total cholesterol > 200 mg/dl or HDL < 40 mg/dl), family history (prior myocardial infarction or sudden cardiac death in an immediate male relative < 55 years of age or female relative < 65 years of age), smoker (current or quit wthin the last 6 months) and diabetes. From these measurements, the Framingham Risk Score was calculated.[29]

Outcome data: Patients were followed up to 12 months for the occurrence of major adverse cardiac events (MACE), which was defined by the composite of non-fatal or fatal myocardial infarction, unstable angina or cardiac death. Additionally, we ascertained whether individuals underwent invasive coronary angiography. Event adjudication was performed by review of our hospital charts visits, with invasive coronary angiograms (ICA) reviewed to confirm chart findings.

2.2. Coronary computed tomography angiography (CCTA)

Non-contrast ECG-gated coronary calcium score with standardized scan parameters (detector collimation 64 × 1.5 mm; 120 kV) was performed. Coronary artery calcium score (CACS) was calculated by the method of Agatston.[30] CCTA was performed with a 128-slice dual source CTA (Definition FLASH, Siemens Healthineers, Erlangen, Germany) with a detector collimation of 2 × 64 × 0.6 mm and a z-flying spot and a rotation time of 0.28s, respectively. Prospective ECG-triggering was employed for patients with regular heart rates < 65 beats per minutes (bpm) using diastolic padding and image acquisition at 70% of the R-R interval, with retrospective ECG helical gating reserved for patients with heart rates > 65 bpm. Iodinated contrast agent (Iopromide, Ultravist 370™, Bayer Healthcare, Berlin, Germany) was injected intravenously at a flow rate 4–6 ml/s with a 40 cc saline chaser, and with image acquisition initiated by a bolus tracking technique when the ascending aorta Hounsfield unit (HU) density exceeded a threshold of 100. Contrast volume ranged between 65 and 120 cc according to the individual patient characteristics. Axial images were reconstructed with 0.75 mm slice width at a slice increment 0.4 mm using medium-smooth kernel B26f during the best diastolic and/or systolic phase when required.

2.3. Coronary CTA image analysis

Curved multiplanar reformations (cMPR) and oblique interactive MPR of all coronary vessels was performed using dedicated 3D post-processing software (SyngoVia™, Siemens Healthineers, Erlangen, German). Coronary arteries were evaluated for the following:

1) Coronary stenosis severity was scored for each coronary segment emplying a modified American Heart Association 16-segment model,[30] with maximum diameter stenosis reported as < 25%, 25–49%, 50–69% or ≥70% in accordance with the CADRADS designations.[10]
2) Atherosclerotic plaque composition was judged on a per-segment basis as: calcified, mixed predominantly calcified, mixed predominantly non-calcified, or noncalcified for each coronary segment. Calcified and non-calcified plaque were defined as hyper- and hypoattenuating lesions with HU values HU > and < 150, respectively.[11]
3) Coronary artery disease extent was calculated using the segment involvement score (SIS) score,[15] and the G-score (=Sum of Plaque types 1–4 for each segment) (Fig. 1)[41]; as marker for an increasing non-calcifying vs calcified plaque burden, per-coronary segment (AHA-modified-16-segment classification).[31]
4) High-risk plaque (HRP) features were identified, and defined by the following criteria[12–14]: Low attenuation plaque (LAP) were defined

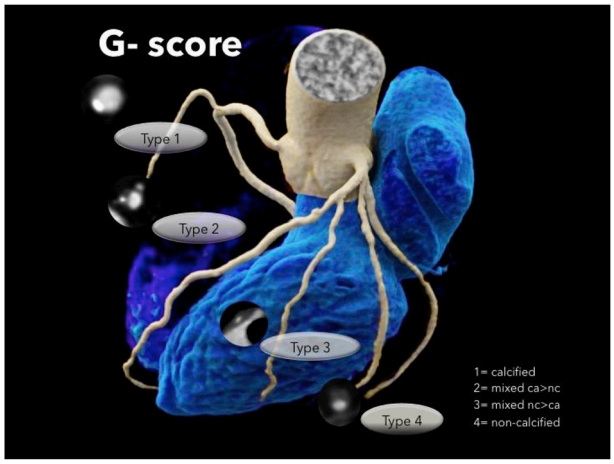


Fig. 1. G-score, describes total mixed increasing non-calcified (nc) plaque burden. An easy visual estimation scale. G-score = Sum of type 1–4 per AHA 16 segment classification. Nc = non-calcified Ca = calcified plaque.

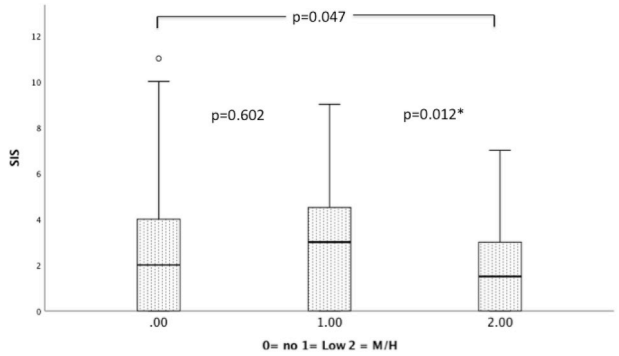


Fig. 2. a. **Total plaque burden (segment involvement score, SIS)** was lower for group 2 M/H (moderate/high) exercise levels as compared to the group with L (low) levels of exercise, and inactive (0) controls.
b. Mixed increasing non-calcified plaque burden **(G-score)** was lower in the moderate-to-high (M/H) endurance sport group (*, Mann Whitney U) as compared to the low group (both groups were balanced for risk factors), and controls (0). Controls were older, had a higher prevalence of arterial hypertension, smoking, diabetes and BMI.
c. **Coronary Calcium Score (CCS)** was not different among all groups (0 = controls, L = low and M/H = moderate-to-high training), while a minor trend towards higher scores in the latter (p = 0.095) was present (U-shape) due to outliers in the high[2] group.

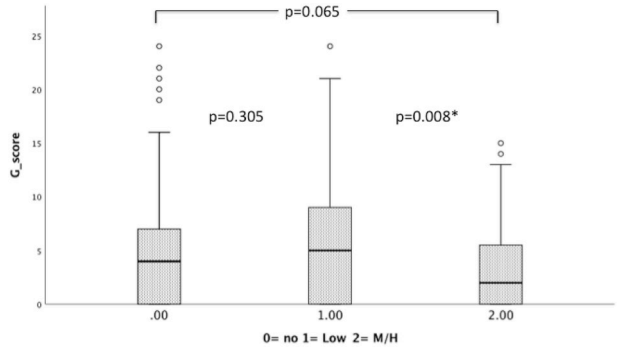
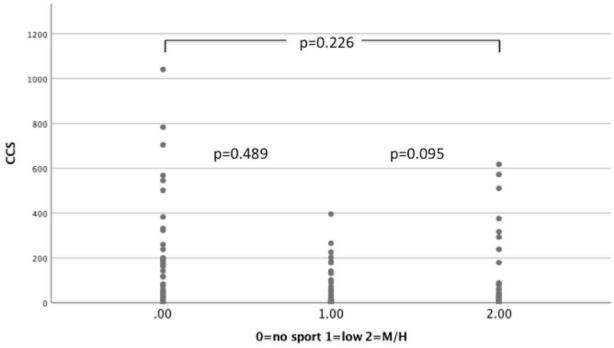


Fig. 2. (*continued*)

as hypodense lesions compared to vessel lumen with a HU < 150.[11] CT-density was screened by utilizing "pixel-lens",[32] and the minimal HU within a coronary lesion was recorded. Then, an area-ROI was placed into the lowest density plaque area, drawn as large as possible, while sparing areas affected by artifacts from motion, streaks or beam hardening/partial volume artifacts adjacent to calcifications, and a mean HU was recorded. Napkin Ring Sign was defined[12] as a LAP when a hyperdense rim („half-moon-sign") was present, as depicted in Fig. 3a. Spotty calcifications were considered present when an intraplaque calcification of < 3 mm size was observed. The remodelling index (RI) was calculated as the ratio of the maximal cross-sectional vessel diameter including the plaque and and the lumen, and its closest proximal (or distal in the case of ostial lesions) normal reference vessel lumen diameter. If a patient had multiple lesions, all lesions were quantified separately. A high-risk plaque was defined if ≥ 2 aforementioned criteria were present, in accordance with the „V"-label of the CADRADS score.[10] CCTA image analysis was performed by one SCCT level III with > 10 years experience and one level II experienced reader, with consensus obtained for any discordance.



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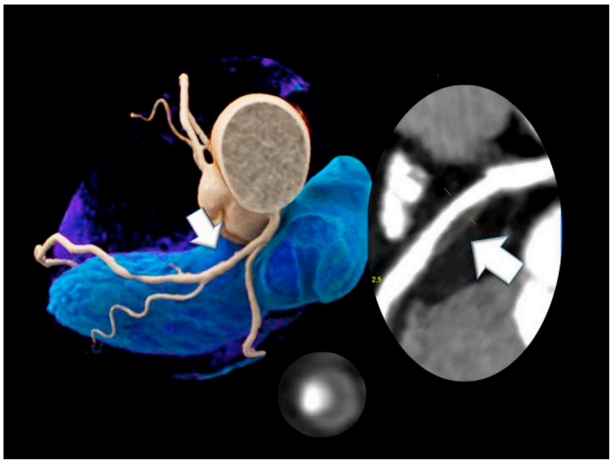
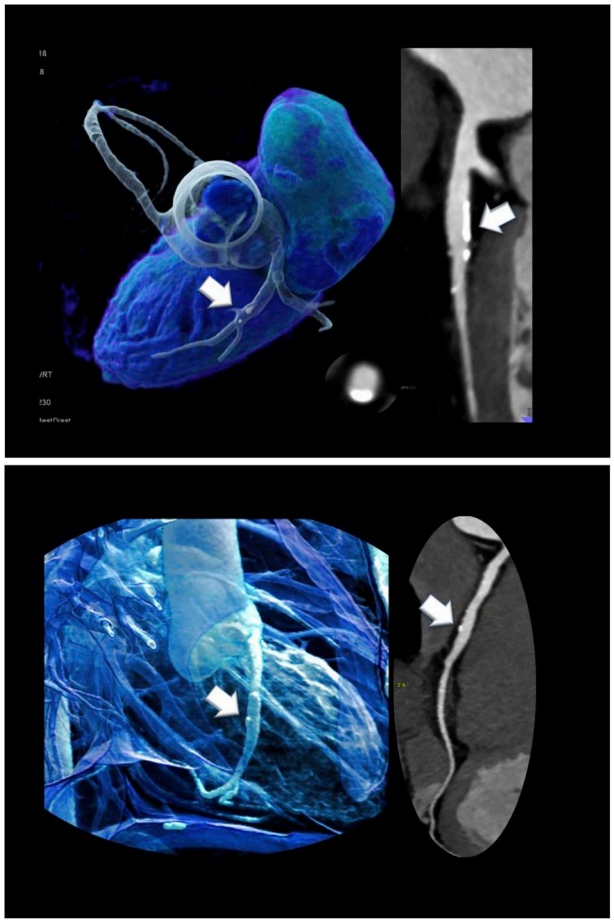


Fig. 3. a. 67 YOM, inactive, BMI 27, 2 risk factors, atypical chest pain, Calcium Score zero, SIS 2, G-score 8. **CTA:** Non-calcified (Type 4) high-risk plaque (HRP) LAD proximal with 3 criteria (low attenuation fibrofatty plaque with lipid-necrotic core (4 HU), Napkin Ring Sign, RI 1.5).
b. 62 YOM, positive family history, high exercise level (running, skitouring and cycling). **CTA** showed calcified plaque (Type 1) in the proximal LAD and RCA with mild < 50% stenosis.
Coronary Calcium Score was 137.3 AU, SIS 5 and G-score low with 5.
c. 63 YOM, BMI 22, 2 RF (art HT, pos FA), moderate-to-high exercise, asymptomatic but during treadmill ECG abnormal multiple complex VES and VT.
CTA: LAD mixed dominantly calcified plaque prox LAD (Type 2) 40% stenosis. Coronary calcium score 38.4, SIS 2, G-score 2.

2.4. Statistical analysis

Statistical analysis was performed using IBM SSPS™ software (V25.0, IBM Corporation, Armonk, NY; USA). Quantitative variables



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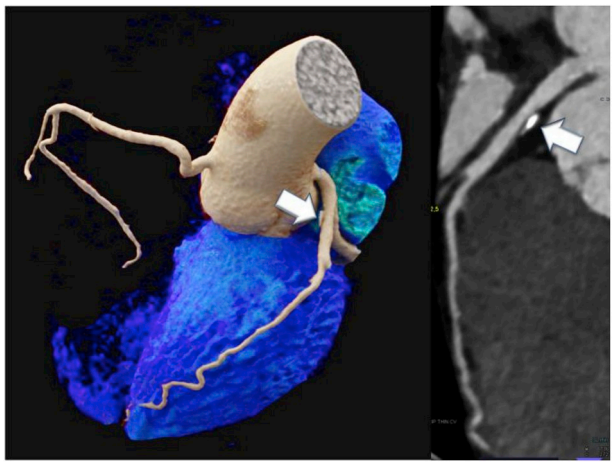

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are expressed as means ± standard deviation (SD), categorical variables as absolute values and percentages, and as median/interquartile range (IQR) for non-normally distributed data. A *p*-value of less than 0.05 was considered significant. Normal distribution was tested with Kolomogorow' test and Histogramm. Among the 3 groups, the Chi-Square for categorical or the ANOVA test for parametric normally-distributed variables were employed, while the Kruskal-Wallis test for rank scale data was applied to non-normally distributed data. If significant differences were present, post-hoc tests among groups and the exercise levels were performed in a stepwise fashion. Post-hoc mean differences in parametric data among 2 groups were tested by using the independent *t*-test or Mann–Whitney test for normally or non-normally-distributed data, respectively, according to their distribution (*t*-test for normally, and Mann Whitney U for non-normally distributed and rank-scale data). Differences in categorial data were determined with Chi-Square, or Fisher's exact test if $n \leq 5$ per group. Multivariate linear regression analysis was performed to associate plaque burden (SIS and G-score) and the Framingham Risk Score with the exercise level defined by MET (metabolic equivalent of training), as dependent variable.

3. Results

Out of 2345 patients screened, patients with incomplete health information data, strength sport type and others were excluded (211), and finally 290 pooled. 38 individuals were further excluded for prior known coronary artery disease. Finally 252 were included in the study population, which comprised 97 inactive patients, 87 low endurance exercisers and 68 moderate-high exercisers. Age of the study was median 55.0 (IQR 15) years, and 91 were women (39.7%).

Amongst patients in whom years of exercise participation was available (n = 139, 45.2%), 101 (72.7%) reported > 10 years, 15 (10.8%) > 5 years and in 16.5% less than 5 years, with a total of 83.5% participating in exercise for more than 5 years.

Inactive subjects were older, more often females, had a higher BMI and a higher % of arterial hypertension, smoking, and diabetes as compared to recreational endurance athletes, while risk factors were balanced between the low and moderate-to-high exercise group. Still, HDL was significantly higher in the moderate-to-high group as compared to inactives, but no difference between the low and moderate-to-high group was found. There was not difference in LDL-c and total cholesterol.

Mean Framingham Risk Score (FRS) was 6.4 ± 6.4% and there was no difference (p = 0.791, ANOVA) among the 3 groups (post-hoc p = 0.968, p = 0.602, p = 0.561). Mean FRS was 6.9 ± 5.6% in controls, 6.8 ± 6.4% in the low exercisers and 6.2 ± 8.1% in the moderate-to-high exercisers. There was an inverse trend and weak correlation of decreasing exercise intensity (MET) and non-calcified plaque burden (G-score, r = −0.14, p = 0.08, Spearman). FRS was not correlated inversely with MET (r = 0.129, p = 0.106, Spearman). On multivariate linear regression analysis, the G-score was associated with the exercise intensity defined by metabolic equivalent of training (MET) (p = 0.039; HR-0.33; 95% CI: -41.4 to −1.13 while FRS was not associated (p = 0.122; 95% CI: -0.15– 1.288), and SIS was not correlated as well (p = 0.133).

Table 1 describes the study population stratified by exercise levels, along with the CCTA findings. Prevalence of any CAD defined as any atherosclerotic plaque was with 57.4% lower in the moderate-high exercisers as compared to inactive controls, as well as compared to the low training group (p = 0.04). Prevalence of stenosis > 50% was 13.2% and lower as compated to in those who reported moderate-to-high exercise levels, respectively (p = 0.02). Lower stenosis severity (CADRADS) and plaque burden scores (SIS and G-score) were observed with increasing exercise level.

Stenosis severity was lower (p = 0.008) in the moderate-to-high exercisers as compared to inactive patients and low exercisers, and the effects strenghtened when comparing the moderate-to-high with the inactive group alone (head-to-head).

Total and noncalcified plaque burden (SIS, G-score) (Fig. 2a, b) and high-risk plaque prevalence were significantly lower in the moderate-to-high exercisers (Table 1b), with a pronounced effect as compared to inactives. Coronary artery calcium score did not differ between groups, although some abnormal high calcium scores were observed in the high level of exercise group (H) (n = 14) when compared to the inactive patients (p = 0.09) (Fig. 2c).

At 1-year follow-up, no MACE was observed in the entire cohort. Overall, 30 patients underwent invasive coronary angiography, with a lower absolute number of inactive patients (n = 11) undergoing

Table 1a
Study cohort (n = 252): coronary artery disease profile by CTA: stenosis severity, plaque burden, high risk plaque.

	No N = 97	Low N = 87	M/H N = 68	3 groups p-value	No vs M/H p-value	No vs L p-value	L vs M/H p-value
CAD n (%)	69 (71.1%)	64 (73.6%)	39 (57.4%)		0.04	ns	0.034
stenosis	15	18	4		0.04	ns	0.034
50%–70%	12	13	5				
> 70%	27 (27.8%)	25 (28.7%)	9 (13.2%)				
total > 50%							
CAD RADS	1.71 ± 1.4	1.9 ± 1.46	1.32 ± 1.2	0.04	0.08	0.360	0.064
SIS	2.63 ± 2.7	2.72 ± 2.4	1.75 ± 1.9	0.036	0.047	0.602	0.012
G-score	4.98 ± 5.6	5.64 ± 5.6	3.29 ± 4.0	0.026	0.065	0.305	0.008
CCS	45.5 ± 90	57.1 ± 116	27.7 ± 85	0.230	0.226	0.489	0.095
High Risk Plaque	13 (13.4%)	12 (13.7%)	0 (0%)		0.002	0.938	< 0.001

Abb: No = no sport, L = low, M/H = moderate/high level of exercise (> 3x/week > =1 h). CAD = coronary artery disease defined as "any plaque".CCS = Coronary Calcium Score (Agatston Units). SIS = segment involvement score (total plaque burden). G-score = sum of segments (plaque type1-4) = mixed plaque type score.CADRADS stenosis severity score.
ns = nonsignificant.

angiography than in the low exercisers (n = 15) and moderate to high exercisers (n = 4). A total of 4 patients in the inactive, 4 in the low and 1 in the moderate-to high group had > 50% stenosis by ICA.

4. Discussion

In this prospective single site survey study, we observed a higher prevalence, extent and severity of coronary artery disease in patients who reported lower levels of exercises volume in terms of frequency of training/week and time per unit. More specifically, in recreational endurance athletes we observed a lower total and non-calcified plaque burden, fewer high risk plaques and lower overall stenosis severity, when exercise was performed at a moderate-to-high exercise level compared to inactives or those with lower exercise levels. Notably, our definition of moderate-to-high exercise volume was defined as the participation in an endurance sport activity (running, cycling or others) ≥3 times per week for ≥1 h per unit.

The novelty of our study comprises the comprehensive phenotypic quantification and characterization of total and non-calcified atherosclerotic plaque burden (G-score), as well as the semi-quantitative designations of high-risk plaques.[12–14] High risk plaque by CCTA[12] represents novel risk biomarkers for MACE, with an up to 9.8 fold increased risk. In the present study, high-risk plaque were less frequently found in those who exercised regularly at moderate-to-high intensity, as compared to inactives and those with low exercise participation.

Furthermore, total atherosclerotic plaque burden has been associated with increased risk of both MACE[26] and ischemia.[33] Similarly, low attenuation plaque with a lipid-rich necrotic core component (< 30HU) has been associated with ischemia in lesions with non-severe stenosis.[34] We observed these plaque features to be inversely proportional to the frequency and duration of exercise in patients undergoing clinically-indicated CCTA.

Recently, machine-learning tools have revealed a further sharpening of CAD risk prediction by outperforming conventional risk scores, and it remains possible that the addition of lifestyle factors such as frequency, duration and years of participation of endurance exercise to CCTA findings may enhance risk prediction.

Interestingly, we observed a high prevalence of subclinical CAD (57.4%) and a modest prevalence of coronary artery lesions demonstrating a > 50% diameter stenosis in recreational endurance exercisers who reported participation at moderate-to-high levels. Our findings are in accordance with those reported by Merghani et al.,[18] who examined 152 male veteran athletes with a long (> 25 years) running competition history, observing the presence of predominantly calcific lesions (72.7%) in athletes while predominantly mixed were found in inactive persons. Our present study is distinct compared to those by Merghani in that we specifically enrolled recreational endurance athletes, which resulted in a population with a higher % of females, only a few professionals, and a shorter overall time period of training (83.5% participants reported training of > 5–10 years).

We observed no difference in coronary artery calcium score amongst groups, but a slight increase in coronary artery calcium score in patients reporting the highest levels of exercise frequency of > 5 times per week. This increase was driven mainly by 14 patient outliers who reported very high levels of exercise, a phenomenon that has been previously reported as the „U-shape" association between excercise and coronary calcium[18]: endothelial damage from increased shear stress during exercise and increased mechanical bending during vigorous

Table 1b
Risk factors among the different exercise level groups.

	Non N = 97	Low N = 87	M/H N = 68	3 groupsp-value	No vs M/H p-value	Low vs M/H p-value
Age (y)	57.0 (IQR 14)	55.0 (IQR 13)	52 (IQR 15)	0.215	0.089	0.266
Females	49 (50.5)	24 (24.7)	18 (26.4)	< 0.001	< 0.001	0.978
BMI kg/m^2	27.7 ± 7.1	25.1 ± 3.2	24.1 ± 3.1	0.000	0.000	0.054
Art HT	50 (51.5)	35 (40.2)	21 (30.8)	0.028	0.013	0.303
Smoking	47 (48.8)	15 (17.2)	12 (17.6)	< 0.001	< 0.001	0.883
Pos FH	51 (52.6)	44 (50.6)	26 (38.2)	0.162	0.097	0.171
Dyslipid.	45 (46.4)	46 (52.9)	29 (42.6)	0.428	0.751	–
Diabetes	14 (14.4)	3 (3.4)	0 (0)	< 0.001	< 0.001	0.348
Chol mg/dL	199.1 ± 51	210.8 ± 51	212.8 ± 32	0.403	0.183	0.844
LDL-c mg/dL	121.7 ± 46	135.4 ± 46	129.3 ± 31	0.490	0.481	0.581
HDL mg/dL	49.3 ± 16	64.2 ± 16	70.6 ± 19.4	p < 0.001	p < 0.001	0.202
FRS	49 (IQR 88.5)	56 (IQR 82)	41.5 (IQR 67)	< 0.001	< 0.001	0.054

Abb.Pos. FH = positive family history, FRS = Framingham Risk Score, HT = arterial hypertension, N = counts (%) and means ± SD for normally and for non-normally distributed data, median (IQR) are shown.
n.s. = not significant. BMI = body mass index (kg/m^2). Chol = total cholesterol. For HDL, the „no-sport" compared to low group testing was significant as well (p < 0.001).M = moderate; H = high levels.

Table 2
Endurance sport types in the moderate-to-high exercise group (n = 68).

Running	35 (51.5)	Halfmarathon n = 8 Marathon n = 2 Running + cycling n = 2
Mountain-endurance[a]	17 (25)	
Cycling	14 (20.5)	
Swimming	2 (2.9)	

[a] „Skitouring" is defined by a minimum of 1.5h–3 h ski hiking upwards the mountains (mountainbiking ± race-cycling summer).

contraction may enhance the development of coronary calcification, despite greater vasodilator capacity in endurance athletes.[35] Additionally, adverse mechanism may comprise exercise-induced coronary artery spasm during nonlaminar flow, rise in blood pressure, and the generation of oxidative free radicals[36] or systemic inflammatory response from multiple units of high intensive training.[37] Furthermore, increased parathyroid hormone levels after high-intensity training may stimulate calcifications.[38]

Interestingly, although coronary artery disease risk factors were balanced between the low and moderate-to-high exercisers, total and mixed-non-calcified plaque burden, stenosis severity, and high risk plaque prevalence was inversely proportional to exercise, with the lowest prevalences observed in the moderate-to-high exercisers. This finding suggests beneficial effects of excercise on atherosclerosis,[9] even at low levels acting exclusively over risk factor modulation. After stepwise downtesting all levels of training strata levels, the positive effect of exercise on atherosclerotic plaque burden emerged at moderate levels, with a major effect on non-calcified plaque burden and most prominently, on high-risk plaque, but not coronary calcium score. While the mechanism of the effects of exercise on plaque are at present unknown, one interesting possibility may relate to lipid-plaque interactions, as the HDL was higher in the moderate-to-high exercisers as compared to inactive patients, but not as compared to the low exercise group.

The data reported herein should be approached with caution, but it represents new information related to the relationship of exercise to coronary artery disease that is both concordant as well as additive to the present literature which is often ostensibly contradictory in nature. Merghani et al.[18] reported low prevalence of > 50% stenosis in 7.5% of endurance athletes,[18] with years of exercise training as the only independent variable associated with increased risk of CAC > 70th percentile or stenosis ≥50% ($p = 0.016$).[18] Conversely, higher coronary artery calcium scores in 50 veteran marathon runners were associated with risk factors (e.g., smoking history) rather than the years of competition.[39] The clinical significance of these findings were indirectly confirmed by a recent study which observed coronary artery calcium score and the number of marathons run as independent predictors of late gadolinium enhancement on MRI.[19]

Similar to our cohort, a high prevalence of subclinical CAD by CTA was observed in other studies[21,40] enrolling 318 asymptomatic recreational sportsmen following a normal medical exam (with normal resting and exercise ECG),[21] and 50 marathon runners (age 52 years)[29] (prevalence 63.2%: any plaque or CACS > 0 and low prevalence of 2.5% > 75% stenosis). Another study[20] investigated 50 male marathon runners (> 25 years competition, 59.4y) with lower BMI, less hypertension and diabetes and higher HDL than controls, and found increased total plaque volume ($p < 0.01$), calcified plaque volume ($p < 0.0001$), and non-calcified plaque volume ($p = 0.04$); which recently raised major concerns in terms of adverse effects of high-levels of endurance sports. No adverse effect on CAD burden was seen in our cohort, which consisted of recreational athletes with > 5 years of training (83.5%).

These studies demonstrate the complex relationship between atherosclerosis and coronary artery stenosis to lifestyle exercise regimens and coronary artery disease risk factors. Given the generally small study samples that have been previously reported, the clinical significance of the atherosclerosis observed is based upon indirect comparisons to study cohorts in which exercise participation is unknown. In our present study, we observed no MACE events during the 1-year follow-up period. While this is ostensibly reassuring, it should be remembered that our cohort reflects the typical lifestyle-related leisure time recreational endurance athlete, and the present results cannot be applied to professional athletes. Furthermore, we specifically examined endurance athletes wherein the majority were runners (51.1%), cyclists (race or mountain biking) or mountain-related endurance athletes, and the potential relationship of other types of exercise such as strength-sport types to atherosclerosis cannot be known from the present study (Table 2).

5. Conclusion

In this present prospective single-site study of recreational endurance exercisers, frequency and duration of exercise is inversely proportional to coronary atherosclerosis plaque burden, stenosis severity and high-risk plaque features. Regular moderate-to-high endurance exercise results in lower total and non-calcified plaque burden and less high-risk plaque.

Our study advocates CTA for detection of occult coronary artery disease in low-to-intermediate risk recreational endurance athletes.

Conflict of interest

No financial support was received. There is no conflict of interest. There are no disclosures for all authors.

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