EDITORIAL

Exercise Intensity and Coronary Plaque Composition: Is Harder, Better, Faster, Stronger?

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The beneficial protection of physical activity from coronary artery disease (CAD) has been known since the 1950s London Bus Study demonstrated that stair climbing bus conductors had half the rate of myocardial infarction when compared with their sedentary bus driving counterparts.[1] A recent meta-analysis showed that exercise-based cardiac rehabilitation substantially reduces mortality for patients hospitalized for CAD.[2] Despite this reported association, the precise mechanism by which physical activity reduces coronary event risk remains incompletely understood—especially at the level of coronary atherosclerotic plaque. Plaque rupture is the most frequent mechanism for acute coronary syndromes. Ruptured plaques have morphological characteristics, which include large lipid pools, thin fibrous caps, macrophage infiltration, microvessels, cholesterol crystal, and positive remodeling.[3] Although exercise favorably associates with reduced CAD risk, a high-resolution answer to how exercise training directly influences coronary plaques remains unclear.

See Article by Vesterbekkmo et al.

To date, invasive coronary angiography, coronary computed tomography angiography, and intravascular ultrasound have been used in clinical studies to understand the influence of exercise on coronary plaque burden and composition. Using coronary angiography, several clinical trials demonstrated that exercise when combined with other lifestyle interventions could either halt or regress angiographic atherosclerosis.[4,5] One study suggested that change in fitness was the best predictor of angiographic change.[4] These studies taught us that exercise and lifestyle could influence coronary plaques but what remained puzzling was how modest changes in angiographic severity were tied to large reductions in clinical events. This highlights the limitations of invasive angiography as it offers only a silhouette of the lumen and does not provide information on plaque burden or composition.

In contrast to invasive angiography, coronary computed tomography angiography allows visualization of the coronary lumen and plaques. Features of vulnerable plaque by computed tomography angiography include low attenuation, positive remodeling, spotty calcification, and the napkin-ring sign.[6,7] Cross-sectional studies using coronary computed tomography angiography have demonstrated that male athletes with CAD have denser and more abundant coronary artery calcification while CAD in sedentary individuals demonstrate more mixed plaque morphologies.[8,9] This has bolstered the hypothesis that exercise may beneficially remodel plaque to generate stable, more calcific lesions that are less likely to destabilize.
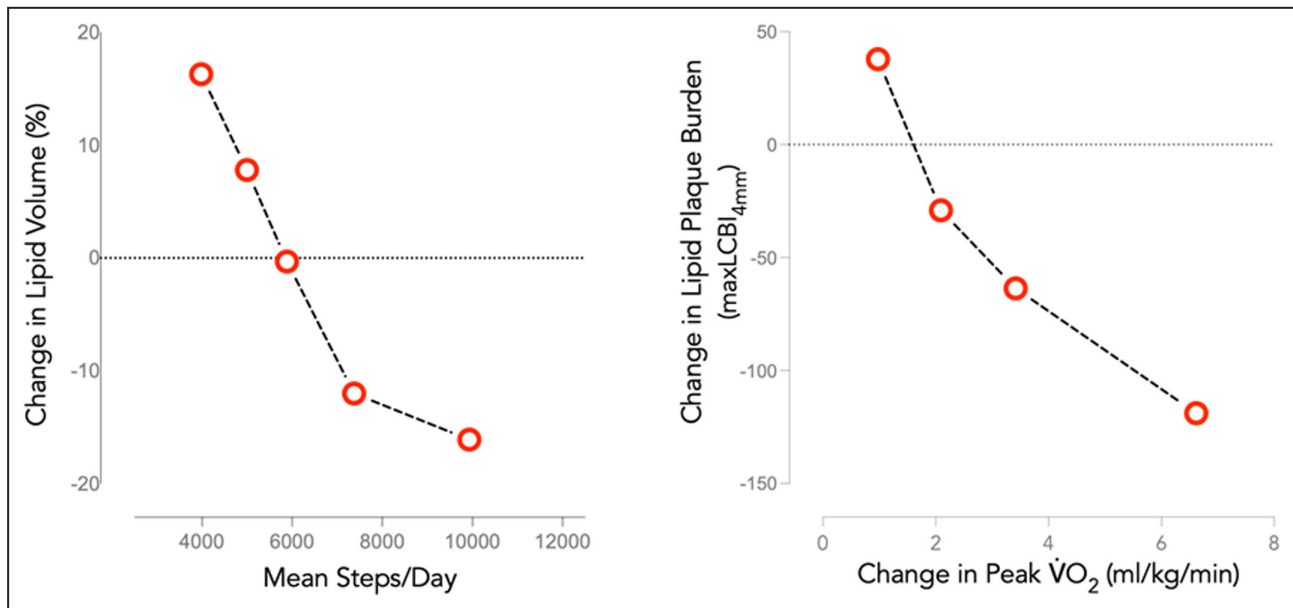

Figure. Influence of exercise and fitness on plaque lipid.
Several studies have shown no significant differences in plaque volume between different exercise programs. However, when the groups are combined (agnostic to type of exercise), secondary analyses reveal statistically significant favorable correlations of decreasing lipid volume with increasing physical activity in steps/day in an ACS population (left panel). In this issue of the *Journal of the American Heart Association* (*JAHA*), Vesterbekkmo and colleagues show decreasing lipid plaque burden with increasing fitness in a stable CAD population (right panel). For clarity, data are binned, with mean changes redrawn from Nishitani-Yokoyama (2018)[11] and Vesterbekkmo (2022).[13] ACS indicates acute coronary syndrome; and CAD, coronary artery disease.

Finally, 2 studies using intravascular ultrasound randomized patients to different exercise interventions. One study reported modest reductions (2%–3%) in the necrotic core by radiofrequency intravascular ultrasound in both arms.[10] A second study showed that greater exercise volume correlated with greater reductions in plaque and lipid volume (Figure).[11] While hypothesis generating, the extent to which these changes are attributable to exercise or background medical therapy remain unclear as high intensity statin therapy is known to reduce atheroma volume.[12]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Vesterbekkmo and colleagues[13] report the findings of the CENIT (Impact of Cardiac Exercise Training on Lipid Content Coronary Atheromatous Plaque Evaluated by Near-Infrared Spectroscopy—A Randomized Trial). The investigators used intracoronary near infrared spectroscopy to examine whether supervised high intensity interval training (HIIT) modified coronary plaque lipid content relative to unsupervised exercise with standard counseling. Lipid plaque content was measured by determining the maximum lipid core burden index at the 4-mm segment ($maxLCBI_{4mm}$).[14] The authors randomized 60 patients with stable CAD into 2 groups: one arm underwent HIIT with relative heart rates of 85% to 95% of peak (n=20). Patients in the other arm were unsupervised and encouraged to pursue endurance exercise according to public health guidance (n=29). After randomization, 11 patients were excluded from the study because of low intracoronary lipid content. Both groups underwent baseline and 6-month near infrared spectroscopy imaging. The primary outcome was change in lipid plaque content ($maxLCBI_{4mm}$) measured by near infrared spectroscopy. All patients received background statin and antiplatelet therapy, and all underwent cardiopulmonary exercise testing with assessment of peak oxygen consumption ($\dot{V}O_{2peak}$).

There were 3 key findings. First, after 6 months, no differences were found between the 2 exercise groups with both groups demonstrating similar reductions (13%–14%) in average $maxLCBI_{4mm}$. Second, exercise in a stable CAD population objectively improves fitness with HIIT resulting in greater fitness gains. In only 6 months, the HIIT arm enjoyed a 3.9 mL/kg per minute (12%) increase in $\dot{V}O_{2peak}$, and the usual care arm had a 1.5 mL/kg per minute (5%) increase in VO_{2peak}. Third, when the 2 exercise arms were combined, a secondary analysis showed a moderate negative correlation between increasing fitness and decreasing $maxLCBI_{4mm}$ ($r_{Spearman's}=-0.44$, $P=0.009$).

The authors should be congratulated because physical activity science is challenging, and those challenges bring limitations. First, the rise in fitness observed in both arms reflects the tendency for individuals who enroll in exercise studies to exercise more

and weakens the scientific ability to isolate physical activity as a variable. Although it weakens causal inference, this is a common challenge in exercise trials, as it would be unethical not to promote physical activity given its benefits.[15] It highlights the importance of tracking physical activity, when possible, inside, and outside of supervised settings. Second, in addition to a small sample size, the study arms became unbalanced after exclusion of patients with little intracoronary lipid content. While most baseline characteristics were comparable, the HIIT group had higher baseline fitness ($\dot{V}O_{2peak}$ 32.3 versus 29.1 mL/kg per minute) which raises concerns surrounding other forms of unmeasured confounding. Third, a major limitation was the lack of female participants. The majority (92%) of participants were male. While plaque composition in males and females with stable CAD may be similar[16] it remains unclear whether plaque responses to exercise are also similar and will require sex inclusive trial designs. Fourth, the study was relatively short (6 months). With statin therapy, we know that benefit accrues with time and thus the findings are likely an underestimate limited to short term exercise and not chronic habitual exercise. Fifth, the population had stable CAD. Prior studies have demonstrated that plaque composition tends to differ by coronary syndrome with stable angina populations having less lipid rich plaque and thicker fibrous caps (Table).[17] Since acute coronary syndrome is a significant predictor of favorable vascular response to statin therapy[18] it is conceivable that exercise in post acute coronary syndrome populations would show greater favorable changes in lipid composition. Finally, since near infrared spectroscopy-intravascular ultrasound was used in this study, other features of plaque vulnerability such as a thin fibrous cap, large lipid pool, macrophage infiltration, cholesterol crystals, and microvessels could not be measured. Currently, the only diagnostic modality to identify these features is optical coherence tomography.

Data derived from this study and others represent important contributions to the understanding of the influence of exercise on CAD. The authors confirmed the ability of exercise and especially HIIT to enhance cardiovascular health with meaningful reductions in body mass index and substantial increases in $\dot{V}O_{2peak}$. As $\dot{V}O_{2peak}$ is itself a potent predictor of future cardiovascular outcomes, a 12% increase in $\dot{V}O_{2peak}$ merits mention. Moreover, while the evidence is secondary and correlative, these data suggest that exercise and specifically increases in fitness may favorably reduce lipid content in only 6 months. This resonates with findings from prior randomized trials using invasive angiography[4,11] (Figure). Importantly, this study showed intracoronary lipid reductions in both exercise arms and thus favorable remodeling is not unique to HIIT. This emphasizes the prevailing wisdom that as it pertains to the benefits of exercise, some activity is better than none and more activity is better than less. Therefore, clinicians should promote exercise that their patients can enjoy and sustain.

This study reminds us of the importance of clinical supervision for patients with CAD who are starting a new or intense exercise regimen. One patient in the HIIT arm developed worsening and severe angina during the study and required surgical coronary artery bypass grafting. High intensity exercise is physiologically and biologically distinct[19] and as seen in this study can come with remarkable improvements in fitness but also risk. We would emphasize that clinical supervision and gradual increases in exercise intensity are critical. Most cardiac rehabilitation programs have proven protocols that should be encouraged and should likely serve as the mainstay for patients with CAD who have been sedentary and are starting to exercise anew.

A considerable portion of the observed benefits from exercise remains unexplained by improvements in conventional cardiovascular risk factors.[20] The data from this study contribute to the hypothesis that exercise may confer some of its cardiovascular benefits through favorable changes in plaque characteristics. As atherosclerosis is a systemic disease, the totality of clinical benefit is likely underestimated. Taken together, despite the negative study, we congratulate Vesterbekkmo and colleagues[13] as well as their patients for reporting these important data. Plaque imaging research and physical activity science are both challenging domains. These data edge us closer to understanding how exercise confers protection from adverse coronary events.

Table. Culprit Plaque Morphologies by Different Clinical Presentations

	AMI	ACS	Stable CAD	*P* value
Lipid-rich plaque, %	90	75	58	0.09
Fibrous cap thickness, μm	47	54	103	0.03
Thin cap fibroatheroma, %	72	50	20	0.01

Data from Jang et al.[17] ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; and CAD, coronary artery disease.

ARTICLE INFORMATION

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Disclosures

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