JACC
VOL. 85, NO. 24, 2025

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Exercise-Induced Troponin Elevation and Coronary Atherosclerosis

Have We Crossed the Finish Line?

Cian P. McCarthy, MB, BCH, BAO, SM,[a,b] Meagan M. Wasfy, MD, MPH[a]

Attainment of guideline-recommended levels of physical activity (PA) is associated with improvements in long-term cardiovascular health and longevity. However, the acute stress of exercise can rarely precipitate sudden cardiac events. Among middle-aged and older adults, these events are most commonly attributed to coronary artery disease (CAD). Paradoxically, male athletes who consistently exceed guideline-recommended levels of PA develop more extensive CAD than individuals who are modestly active.[1] This observation both underscores the importance of risk stratification in highly active populations and raises the question of whether there is an extreme dose of PA that confers more harm than benefit. Unfortunately, existing tools do not adequately identify the small number of individuals at highest risk for exercise-associated cardiac events. In this issue of *JACC*, Janssen et al[2] address whether postexercise elevation of cardiac troponin (cTn) relates to CAD prevalence in the TREAT (cardiac TRoponin concentrations following Exercise and the Association with cardiovascular ouTcomes) study.

SEE PAGE 2370

To place these results in context, almost a half century ago, elevations in creatine kinase-MB (CK-MB) were observed among endurance athletes after exercise. While typically indicative of irreversible cardiomyocyte injury (ie, necrosis), muscle biopsy samples from marathon runners suggested skeletal muscle is a significant source of postexercise CK-MB.[3] However, similar elevation was subsequently observed with increasingly specific cTn assays. Due to their higher sensitivity and precision, these assays, particularly when measured using high-sensitivity cTn (hs-cTn), are more likely to detect both irreversible cardiomyocyte injury (eg, necrosis) *and* reversible forms of myocardial injury. Favoring the latter non-necrotic, potentially more benign mechanisms, postexercise cTn elevations are very common, occurring in more than one-half of endurance athletes.[4] However, this notion of benignity has been challenged by recent data demonstrating an association between elevated postexercise cTn and subsequent cardiovascular disease (CVD) events.[5] Accordingly, a better understanding of the mechanisms of exercise-induced cTn elevation may inform both opportunities to mitigate CVD risk and interpretation of these values in clinical practice.

> *"…postexercise cTn elevations are very common, occurring in more than one-half of endurance athletes."*

Janssen et al[2] address this gap by evaluating whether the prevalence of subclinical CAD differed in 2 groups with the highest and lowest concentrations of postexercise hs-cTn, selected from a larger cohort in the TREAT study. The TREAT study prospectively enrolled middle-aged recreational athletes partaking in walking (≥30 km), cycling (≥100 km), or running (≥15 km) events. Pre-exercise and postexercise hs-cTn measurements were obtained using 2 different assays (Roche hs-cTnT and Abbott hs-cTnI). From all

From the [a]Heart and Vascular Institute, Massachusetts General Brigham, and Harvard Medical School, Boston, Massachusetts, USA; and the [b]Baim Institute for Clinical Research, Brookline, Massachusetts, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2025.05.028

participants, 10% (two-thirds with the highest hs-cTn concentrations: "high responders"; one-third with the lowest hs-cTn concentrations: "low responders") underwent coronary computed tomography angiography (CCTA). The prevalence and amount of CAD were compared between these 2 groups, which were matched by age, sex, sport type, and exercise distance.

The investigators report several important findings. First, among the larger cohort (n = 1,011 participants), postexercise elevation in hs-cTn was common but more frequent with hs-cTnT (51%) than hs-cTnI (15.9%).[2] These results help to define expected hs-cTn levels after similar exercise efforts. Second, in the smaller cohorts who underwent CCTA, the investigators found no significant difference in the prevalence of CAD (67.6% vs 50.0%; $P = 0.18$), obstructive CAD (11.8% vs 8.8%; $P = 0.75$), and hemodynamically significant stenosis by computed tomography-fractional flow reserve (11.8% vs. 5.9%; $P = 0.88$) in high vs low hs-cTn responders.[2] Because these 2 cohorts were well matched for other potential contributors, this result suggests that obstructive CAD is not the predominant driver of postexercise hs-cTn elevation. Conversely, lower postexericse hs-cTn was not adequately reassuring because a sizable proportion of low responders had obstructive CAD (9%).

Does this result exclude CAD as a contributor to postexercise hs-cTn elevation? Not completely, because without a formal sample size calculation, the study was not adequately powered for all CCTA endpoints. Notably, high responders had a numerically higher prevalence of CAD than low responders. Indeed, when the authors shifted from comparing between high and low responder groups to evaluating cTn on a continuum, they found that pre-exercise to postexercise change in hs-cTnT and hs-cTnI still correlated with Coronary Artery Disease-Reporting and Data System (CAD-RADs) classification: $R^2 = 0.042$ ($P = 0.046$) and $R^2 = 0.058$ ($P = 0.022$), respectively.[2] While these results could be viewed as contrasting with the group-based comparison, the small amount of variance in exercise-induced cTn elevation ascribable to epicardial CAD (4%-8%) affirms that the vast majority of postexercise cTn rise is related to other factors.

These results in athletes complement those from a prior analysis of a very different cohort. In the ORBITA (Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina) trial published in *JACC*,[6] investigators observed no association between baseline exercise-induced hs-cTnI increment and ischemia or stenosis severity. Furthermore, despite effective percutaneous coronary intervention, no change in exercise-induced hs-cTnI increment was observed from pretreatment to posttreatment. In both the TREAT and ORBITA cohorts, more data are needed to determine alternate mechanisms other than epicardial CAD to explain hs-cTn elevation.

If CAD and ischemia are not the predominant determinants of exercise-induced cTn elevation, what is? As mentioned above, cTn may be released by both irreversible and reversible mechanisms. The most notable mechanism of irreversible injury, myocardial necrosis, occurs when prolonged ischemia leads to cell death and release of intracellular proteins including cTn. Apoptosis (programmed cell death) results in briefer and smaller quantities of cTn release in response to short episodes of ischemia and increased myocardial stretch or strain.[7] Additional mechanisms of reversible cTn release include increased cell permeability and extracellular vesicle release.[7]

The current results by Janssen et al[2] align with prior histologic and imaging studies that suggest postexercise cTn elevation reflects processes other than cardiomyocyte necrosis.[4,8] Prolonged endurance exercise can result in a transient cardiac dysfunction evident on imaging,[4] and in animal studies this has been associated with cardiomyocyte apoptosis.[9] Elevations in cTn postexercise also correlate with a transient increase in myocardial tissue water diffusivity suggestive of an increase in cell permeability and increased cellular leakage of cTn.[10] Beyond cardiomyocyte release, exercise also perturbs noncardiac organ systems. Despite improved specificity of assays over time, postexercise cTn elevations may occur due to skeletal muscle injury and cross-reactivity of cardiac and skeletal muscle cTn. Increased cTn may also result from exercise-induced reductions in renal perfusion and cTn clearance.[7] Both cross-reactivity of assays and cTn elevation related to reduced renal clearance have been observed more frequently with hs-cTnT than hs-cTnI, which could help explain the differences in cTn elevation prevalence by assay type in this study.[7]

Overall, this work by Janssen et al[2] demonstrates that postexericse cTn elevation is common and not well explained by epicardial CAD. Other mechanisms for postexercise cTn rise include those that may be benign, reflecting transient perturbations in physiology that return to normal without consequence.

Alternately, higher elevation in cTn in response to repetitive, large exercise doses may still help identify those susceptible to cumulative negative effects, such as arrhythmias and myocardial fibrosis that are also more common in male endurance athletes. While the current results do not advance our understanding about whether exercise-induced cTn is prognostic, the TREAT investigators intend to follow participants longitudinally for cardiac events, which will better inform this question.

ACKNOWLEDGEMENT The authors thank Paul D. Thompson, MD, Chief of Cardiology, Emeritus, Hartford Hospital, for his excellent insights on this topic.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr McCarthy is supported by a National Heart, Lung, And Blood Institute Career Development Award (K23HL167659); and has received consulting fees/honorarium from Roche Diagnostic, Abbott Laboratories, NewAmsterdam Pharma, and HeartFlow, Inc. Dr Wasfy has reported that she has no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Cian P. McCarthy, Cardiology Division, Massachusetts General Hospital and Baim Institute for Clinical Research, 55 Fruit Street, Boston, Massachusetts 02114, USA. E-mail: cmccarthy37@mgb.org. X handle: @CianPMcCarthy.

REFERENCES

1. De Bosscher R, Dausin C, Claus P, et al. Lifelong endurance exercise and its relation with coronary atherosclerosis. *Eur Heart J*. 2023;44:2388–2399.

2. Janssen SLJE, van Everdingen WM, Saalmink WBJ, et al. Relationship between exercise-induced cardiac troponin elevations and occult coronary atherosclerosis in middle-aged athletes. *J Am Coll Cardiol*. 2025;85(24):2370–2382.

3. Siegel AJ, Silverman LM, Evans WJ. Elevated skeletal muscle creatine kinase MB isoenzyme levels in marathon runners. *JAMA*. 1983;250:2835–2837.

4. Ghekiere O, Herbots L, Peters B, et al. Exercise-induced myocardial T1 increase and right ventricular dysfunction in recreational cyclists: a CMR study. *Eur J Appl Physiol*. 2023;123:2107–2117.

5. Aengevaeren VL, Hopman MTE, Thompson PD, et al. Exercise-induced cardiac troponin I increase and incident mortality and cardiovascular events. *Circulation*. 2019;140:804–814.

6. Rajkumar CA, Wereski R, Parsonage W, et al. Association between high-sensitivity cardiac troponin, myocardial ischemia, and revascularization in stable coronary artery disease. *J Am Coll Cardiol*. 2022;79:2185–2187.

7. Hammarsten O, Mair J, Möckel M, Lindahl B, Jaffe AS. Possible mechanisms behind cardiac troponin elevations. *Biomarkers*. 2018;23:725–734.

8. Nie J, George K, Duan F, Tong TK, Tian Y. Histological evidence for reversible cardiomyocyte changes and serum cardiac troponin T elevation after exercise in rats. *Physiol Rep*. 2016;4:e13083.

9. Weil BR, Suzuki G, Young RF, Iyer V, Canty JM Jr. Troponin release and reversible left ventricular dysfunction after transient pressure overload. *J Am Coll Cardiol*. 2018;71:2906–2916.

10. Aengevaeren VL, Froeling M, Hooijmans MT, et al. Myocardial injury and compromised cardiomyocyte integrity following a marathon run. *JACC Cardiovasc Imaging*. 2020;13:1445–1447.

KEY WORDS athletes, biomarkers, cardiovascular diseases, computed tomography, coronary artery disease, exercise, radiology