MAYO CLINIC PROCEEDINGS

Innovations, Quality & Outcomes

Extreme Physical Activity May Increase Coronary Calcification, But Fitness Still Prevails

Considerable data have emphasized the powerful impact of sedentary behavior, physical inactivity, and low levels of physical activity (PA) that result in poor levels of cardiorespiratory fitness (CRF) on overall and cardiovascular health.[1-5] In fact, low PA and CRF may be the greatest threat to health in the 21st century. Therefore, greater efforts are needed throughout the health care system and at the government level to promote PA that improves CRF and contributes to reduced cardiovascular disease (CVD) and total mortality worldwide.[1-7]

Nevertheless, there is also considerable data and attention directed at the possible adverse effects of extreme endurance exercise (EEE) on CVD end points, pointing out potential U-shaped relationships with some CVD end points.[1-3,8] For instance, regular EEE increases cardiac troponin and brain natriuretic peptide release and normally leads to transient right ventricular dilation that sometimes is linked to right ventricular dysfunction and dysfunction of the ventricular septum. Furthermore, strenuous PA and EEE have also been reported to promote coronary artery calcification (CAC), leading to coining of the phrase "hearts of stone" among heavy endurance athletes.[9-11] This issue has raised concerns about the safety of such exercise in athletes with very high CAC.

In this issue of *Mayo Clinic Proceedings: Innovations, Quality & Outcomes*, 2 landmark studies address the association of EEE in marathon runners and patients with high levels of CRF with levels of CAC.[12,13] Jafar et al[12] studied 85 runners and compared those who had performed many EEE events during the past 10 years compared with those who had completed only shorter races during this time and compared CAC levels between these groups. They found that those with a constant high participation in EEE had higher percentages of CAC scores greater than 0 (73.3% vs 23.1%), rankings above the 50th percentile per age and sex (70% vs 19.2%), and more CAC scores greater than 100 (33% vs 11.5%) compared with those who had completed only shorter races. Although the risk of having a CAC score greater than 100 among the EEE group was not significantly different than that for the short distance runners after controlling for age, sex, and years running (P=.12), the EEE athletes were 10 times and 9 times more likely to have CAC at the 50th percentile or greater and scores greater than 0 compared with the lower distance runners after controlling for the covariates.

In the second study, Kermott et al[13] analyzed almost 3000 participants from the Mayo Clinic Executive Health Program who had assessment of CAC and CVD risk factors from January 1, 1995, through December 31, 2008, although they did not quantify levels of PA or exercise training in this cohort. Not surprisingly, known CVD risk factor profiles

and high-risk calculations tended to uniformly improve with higher levels of CRF. Surprisingly, however, a U-shaped relationship occurred with CRF and CAC. Those with above average CRF levels had lower levels of CAC, whereas CAC scores were increased with highest levels of CRF despite the fact that this group had better levels of CVD risk factors.

These 2 studies certainly add to the current literature regarding the potential for EEE and now high levels of CRF to be associated with high levels of CAC.[9-13] However, one of these studies assessed EEE but did not measure CRF,[12] whereas the Mayo study assessed CRF but not PA.[13] A recent study found that very high CRF levels (approaching 20 estimated metabolic equivalents on treadmill testing) continued to be associated with lower mortality, and they made the case that this vindicated high levels of PA and exercise for increasing CVD risk.[14] However, Arena and Lavie[15] pointed out that their study only assessed CRF and not PA, which are different, and although the main determinant of CRF is PA, there is a genetic or nonexercise component of CRF. Clearly, high CRF is associated with low risk of CVD-associated and all-cause mortality in large studies, and even in patients with chronic conditions such as diabetes, dyslipidemia, and obesity, those with high CRF generally have a better prognosis than their counterparts with low levels of CRF.[1-5] Another issue is that all of these studies are retrospective with implicit bias, and none are true outcome studies. The number of participants in the ultramarathon study was quite small,[12] causing the authors to combine this group with the marathon group. Finally, an issue with the entire exercise CAC literature is that PA, exercise, and now CRF classifications differ considerably from study to study. If the hypothesis exists that PA/EEE/CRF above a certain level promote acceleration of atherogenesis, these levels should be relatively consistent between studies, rather than at the highest level in each particular study.

A major issue is how clinicians should interpret the emerging data on EEE and CRF and CAC. Does high PA and EEE increase the risk of having CAC and "hearts of stone" and how should clinicians react to this evidence?

First, the constellation of data supports the fact that high PA/EEE, and now possibly high CRF, is associated with higher levels of CAC. A recent large study found that those with the highest level of PA from marathon running often have CAC levels greater than 100 and even averages over 800.[10] However, despite this finding, the highest levels of PA/exercise were associated with low rates of CVD-associated and all-cause mortality and show that exercise is safe even at high levels of CAC.[10,11] Quite possibly, as with high-intensity statin therapy,[16] high-intensity PA/EEE may promote more calcific coronary atherosclerosis that may be more stable than soft, noncalcified plaque, which is less likely to rupture and cause acute, morbid CVD events.[9-11,16] Certainly, considerable evidence supports that high levels of CRF are associated with low all-cause and CVD mortality[1-5,8] even if CAC presumably is present.

Finally, does this mean that CAC levels are worthless in those patients with high PA/EEE? In fact, Defina et al[10] recently reported that high CAC retained its ability to predict risk with high volumes of PA, as high CAC scores were still associated with higher risk at any given PA level. Clearly, CAC scores are useful to predict risk and potential need for greater prevention and lipid treatment for the primary and secondary prevention of CVD.[17-19] We would still advocate consideration of CAC testing in those with high PA/EEE who have intermediate coronary risk profiles, with plans to intensify risk factor modification and statin therapy in those with high CAC scores and consideration for stress testing in those with very high CAC scores, at least to assess for severe ischemia and malignant arrhythmias.[11] However, as Lavie et al[11,20] recently explained, high levels of PA and CRF are extremely protective against CVD events and mortality, making it possible for individuals to perform high doses of running and exercise safely even with high CAC and "hearts of stone."

Carl J. Lavie, MD
Department of Cardiovascular Diseases
John Ochsner, Heart and Vascular Institute
Ochsner Clinical School - University of Queensland
School of Medicine
New Orleans, LA, USA

Harvey F. Hecht, MD
Department of Cardiology
Icahn School of Medicine at Mount Sinai
Mount Sinai St. Luke's Medical Center
New York, NY, USA

Ulrik Wisloff, PhD
Cardiac Exercise Research Group
Department of Circulation and Medical Imaging
Faculty of Medicine and Health Sciences
Norwegian University of Science and Technology
Trondheim, Norway

Correspondence: Address to Carl J. Lavie, MD, Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School - University of Queensland School of Medicine, New Orleans, LA (clavie@ochsner.org).

REFERENCES

1. Lavie CJ, Ozemek C, Carbone S, Katzmarzyk PT, Blair SN. Sedentary behavior, exercise, and cardiovascular health. *Circ Res.* 2019;124(5):799-815.
2. Fletcher GF, Landolfo C, Niebauer J, Ozemek C, Arena R, Lavie CJ. Promoting physical activity and exercise: *JACC* Health Promotion Series. *J Am Coll Cardiol.* 2018;72(14): 1622-1639.
3. Ozemek C, Laddu DR, Lavie CJ, et al. An update on the role of cardiorespiratory fitness, structured exercise and lifestyle physical activity in preventing cardiovascular disease and health risk. *Prog Cardiovasc Dis.* 2018;61(5-6):484-490.
4. Katzmarzyk PT, Lee IM, Martin CK, Blair SN. Epidemiology of physical activity and exercise training in the United States. *Prog Cardiovasc Dis.* 2017;60(1):3-10.
5. Harber MP, Kaminsky LA, Arena R, et al. Impact of cardiorespiratory fitness on all-cause and disease-specific mortality: advances since 2009. *Prog Cardiovasc Dis.* 2017;60(1):11-20.
6. Ozemek C, Lavie CJ, Rognmo Ø. Global physical activity levels—need for intervention. *Prog Cardiovasc Dis.* 2019;62(2): 102-107.
7. Giroir BP, Wright D. Physical activity guidelines for health and prosperity in the United States. *JAMA.* 2018;320(19):1971-1972.
8. Zubin Maslov P, Schulman A, Lavie CJ, Narula J. Personalized exercise dose prescription. *Eur Heart J.* 2018;39(25):2346-2355.
9. Baggish AL, Levine BD. Coronary artery calcification among endurance athletes: "hearts of stone" [editorial]. *Circulation.* 2017;136(2):149-151.
10. DeFina LF, Radford NB, Barlow CE, et al. Association of all-cause and cardiovascular mortality with high levels of physical activity and concurrent coronary artery calcification. *JAMA Cardiol.* 2019;4(2):174-181.
11. Lavie CJ, Wisløff U, Blumenthal RS. Extreme physical activity and coronary artery calcification—running heavily and safely with "hearts of stone. *JAMA Cardiol.* 2019;4(2):182-183.
12. Jafar O, Friedman J, Bogdanovicz I, et al. Assessment of coronary atherosclerosis using calcium scores in short and long distance runners. *Mayo Clin Proc Innov Qual Outcomes.* 2019;3(2): 116-121.
13. Kermott CA, Schroeder DR, Kopecky SL, Behrenbeck TR. Cardiorespiratory fitness and coronary artery calcification in a primary prevention population. *Mayo Clin Proc Innov Qual Outcomes.* 2019;3(2):122-130.
14. Mandsager K, Harb S, Cremer P, Phelan D, Nissen SE, Jaber W. Association of cardiorespiratory fitness with long-term mortality among adults undergoing exercise treadmill testing. *JAMA Netw Open.* 2018;1(6):e183605.
15. Arena R, Lavie CJ. Cardiorespiratory fitness and physical activity: two important but distinct clinical measures with different degrees of precision - a commentary. *Prog Cardiovasc Dis.* 2019; 62(1):74-75.
16. Puri R, Nicholls SJ, Shao M, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. *J Am Coll Cardiol.* 2015;65(13):1273-1282.
17. Hecht HS, Blaha MJ, Kazerooni EA, et al. CAC-DRS: Coronary Artery Calcium Data and Reporting System. An expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT). *J Cardiovasc Comput Tomogr.* 2018;12(3):185-191.
18. Hecht HS, Cronin P, Blaha MJ, et al. 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: a report of the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology. *J Thorac Imaging.* 2017;32(5):W54-W66.
19. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/ AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/ PCNA Guideline on the Management of Blood Cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published online ahead of print November 8, 2018]. *J Am Coll Cardiol.* https://doi.org/10.1016/j.jacc.2018.11.003.
20. Lavie CJ, Kokkinos P, Ortega FB. Survival of the fittest: promoting fitness throughout the life span [editorial]. *Mayo Clin Proc.* 2017;92(12):1743-1745.