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Coronary artery calcification: More than meets the eye

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As the clinical world moves closer toward personalized medicine, we learn once again that the devil is in the details. If we take a one-fits-all perspective, we can perhaps miss nuances that can explain why all the pieces of the puzzle do not fit perfectly for every patient. In this issue of the journal, Hsu et al[1] use computed tomographic (CT) and ^{18}F-NaF positron emission tomographic (PET) imaging to unravel the mystery of why athletes have a high burden of coronary artery calcium (CAC), a strong predictor of cardiovascular morbidity and mortality, but have better survival than more sedentary persons. In their study, they found that "active" Apolipoprotein E deficient mice (Apo $E^{-/-}$) have similar burdens of aortic CAC on microCT after 9 weeks of consuming a Western diet despite varying levels of activity, suggesting that exercise training did not alter plaque structure and may not modify risk. Taking their analysis a step further, however, they used ^{18}F-NaF PET imaging to examine the micro-architecture of the calcified plaque of "active" compared to "sedentary" mice. Interestingly, the mice randomized to exercise had a lower ^{18}F-NaF signal density, defined as ^{18}F uptake normalized to injected dose per deposit volume, and each individual calcium deposit in the aorta had decreased mineral surface area index, calculated as the perimeter divided by the cross-sectional area by histology. Taken together, these findings suggest that exercise reduces the amount of exposed surface area per unit bone volume, a measure that has been associated with plaque vulnerability. Based on the findings of Hsu et al[1] ^{18}F-NaF PET imaging may be a promising technology to better risk stratify patients and serially monitor the effectiveness of lifestyle modifications, such as exercise, or new pharmacological therapy designed to stabilize plaque.

CORONARY ARTERY CALCIFICATION AS A MEASURE OF CARDIOVASCULAR RISK

Coronary artery calcium (CAC) is a prominent feature of atherosclerosis, considered a form of ectopic bone formation.[2] Now routinely measured using multidetector CT scanners, CAC has emerged as a widely available, consistent, and reproducible measure

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of cardiovascular risk. CAC is present in both men and women, both young and old, and across multiple ethnicities (e.g., whites, Asians, blacks, and Hispanics),[3,4] representing a robust marker of atherosclerotic burden. Study after study has shown that CAC predicts cardiovascular risk beyond traditional risk factors,[5–7] estimating the likelihood of suffering a cardiac event better than risk calculators such as the Framingham Risk Score, ACC/AHA ASCVD risk estimator,[8] original MESA Risk Score Calculator,[8] and Reynolds Risk Score.[9] With such mounting evidence, not surprisingly, the American College of Cardiology has recently recommended that physicians use CAC to help reclassify patients with borderline to intermediate risk (10-year risk between 5% and 20%) to guide the initiation of pharmacological therapy.[10]

For most of the patients, CAC has been shown to be a strong predictor of cardiovascular risk. A CAC score alone, however, may have limitations. Recent studies have shown that some patients who are more physically fit, including marathon runners[11] and athletes[12,13] have higher levels of CAC than age-matched controls, but do not have increased cardiovascular morbidity and mortality.[14] This clinical paradox suggest that measuring plaque burden alone is not enough to risk stratify all patients.

In their article, Hsu et al[1] address this issue by randomizing Apo $E^{-/-}$ mouse, which develop aortic plaque after being fed a Western diet, to control vs an exercise training program with a rodent treadmill. After 9 weeks, they did not find a significant difference in coronary calcium burden between the two groups. Although these findings are consistent with clinical observations that plaque burden seems to be present whether you are active or sedentary, the lack of effect may result from an exercise regimen that was not intense enough or long enough to see these changes. Alternatively, their model may be sufficient, but we may need to look beyond overall plaque volume to determine how exercise can modify risk.

IMAGING MORE THAN THE CAC VOLUME

Multi-detector CTs can provide information not only on the total volume of calcium deposits in the coronary arteries to yield the CAC score, but also on calcium density, defined as the concentration of calcium present in a given atherosclerotic plaque. Interestingly, in contrast to CAC volume, a higher CAC density score, which is dependent on the highest Hounsfield units found in the plaque per given area, has been shown to be inversely associated with incident coronary heart disease for any CAC volume.[15] Conversely, spotty calcification on CT is associated with > 2-fold increase risk in plaque rupture (HR 2.25; 95% CI 1.26–4.04; $P = 0.006$).[16] Similarly, analysis of plaque vulnerability by intravascular ultrasound has revealed that patients with stable angina have fewer and larger contiguous plaques compared to those who present with acute coronary syndrome, who have a greater number of small calcium deposits.[17] Taken together, these findings suggest that calcification may have a biphasic effect on plaque stability with early spotty deposition increasing plaque vulnerability and denser calcium deposition that group together into large areas stabilizing plaque (Figure 1).

It is likely that plaque rupture is caused by the failure to withstand the effects of fluid and mechanical stress, which occurs at the interface between materials of different stiffness.

Specifically, at the interface between calcified and non-calcified plaque where the difference between stiffness can be as high as 4- to 5-fold, the plaque may be most vulnerable to longitudinal, circumferential and radial stress caused by pulsatile blood coursing through the arteries.[18] Based on the principals of biomechanics, it appears that how and where calcium deposits interface with other components of plaque are important determinants of plaque vulnerability. In other words, the degree of plaque vulnerability is proportional to the interface area between calcified and non-calcified plaque, which decreases as the calcification areas continue to form, grow, and coalesce. Taking this into account, perhaps a more valuable measure for predicting plaque vulnerability may be to measure the interface surface area between calcified and non-calcified plaque rather than the overall calcium burden, as measured by the CAC score. Although calcium density can approximate areas where calcium deposits are tightly grouped together, it does not reflect the surface area between calcified and soft plaque that is exposed to stressors that can lead to rupture. Another measure, thus, may be warranted.

First introduced as a tracer for imaging skeletal disorders in 1962 and FDA approved since 1972, ^{18}F-sodum fluoride (^{18}F-NaF) has emerged as a promising vascular imaging agent that can directly image active calcification and quantify areas of microcalcification. In bone, ^{18}F-NaF incorporates into exposed areas of hydroxyapatite, and, thus, may be able to image active bone remodeling. In the vasculature, ^{18}F-NaF binds to micro-calcifications and to the outer surface, but not inner surfaces of macrocalcifications, suggesting it may be a good measure of the interface between calcified plaque and non-calcified plaque.[19,20] Importantly, a prospective clinical trial showed that increased ^{18}F-NaF uptake was associated with vulnerable plaques, which was verified by histology ex vivo in the case of carotid plaques and by intravascular ultrasound in vivo with respect to coronary plaques.[21]

To complement their findings on CT and to examine the plaque micro-architecture, Hsu et al[1] used ^{18}F-NaF PET imaging to measure the exposed surface area of calcium deposits before and after exercise training. They found that the PET signal density (percent injected dose of tracer per deposit volume) but not the total surface area (percent injected dose) was significantly reduced after exercise. Because ^{18}F-NaF also binds to the surface of macrocalcifications, which may actually increase with exercise and improve plaque stability, these results are not surprising. Using histology to verify their ^{18}F-NaF PET findings, they also found that the mineral area surface index, the total perimeter divided by the total cross-sectional area, measured per histological section, decreased with exercise, which is consistent with the changes in signal density on PET imaging. By imaging more than CAC volume, Hsu et al[1] have presented a plausible mechanism by which athletes can have high levels of CAC but have a low incidence of cardiovascular events. Based on their model, the overall burden of plaque may be dependent on the Western diet, but how and where plaques develop, either as a few, discrete dense plaques or spotty, micro-calcifications, is likely shaped by physical activity levels.

TRANSLATIONAL IMPLICATIONS

Accurately assessing cardiovascular risk has been the holy grail of preventative cardiology. While risk estimate calculators, all of which are based on pooled cohorts including

information on age, sex, race, and traditional risk factors, have proven invaluable in guiding preventative care, they have over- and under-estimated risk in certain subpopulations including patients with a family history of premature cardiovascular disease, women, South Asians, and other Asians.[22] To address this limitation, some risk calculators have added a measure of inflammation and the CAC score, which have resulted in improved accuracy.[23,24] An assessment of physical fitness and physical activity, however, is still missing despite ample evidence that these "vital signs" are better predictors of cardiovascular morbidity and mortality than traditional risk factors.[25–28]

This brings us to the following question: How can we accurately assess the risk of an active individual or elite athlete who has a CAC score > 400? Placing the patient on high intensity statin may be an option but this can expose these patients to the risk of statin-related myopathy, hepatotoxicity, glucose intolerance, and potentially memory loss. Depending on the location of the calcifications, the patient may have anxiety about these findings and wonder if he/she should have a cardiac CT angiography or stress imaging to evaluate whether they need a diagnostic cardiac catheterization. Lesions located in the left main or proximal left anterior descending artery can create even more consternation. Despite the presence of calcium deposits, which can often cause a blooming artifact on CT and make lesions appear larger than they are, the likelihood is low that the patient has significant obstruction warranting an intervention if he is physically active, fit, and asymptomatic. Based on recent findings from the International compariSon of comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial, revascularization will also not reduce the risk of morbidity and mortality if the patient does not have angina or an anginal-equivalent.

The physically fit person with a high plaque burden based on their CAC score, however, may benefit from further characterization of their plaque micro-architecture. Although not ready for prime time, ^{18}F-NaF PET imaging can potentially help risk stratify these patients.[29] The absence of ^{18}F-NaF PET signal in calcified lesions likely indicates stable plaque. Further validation with large multi-center randomized trials, however, are needed to determine the negative predictive value of ^{18}F-NaF PET imaging. While the presence of ^{18}F-NaF PET uptake may indicate plaque vulnerability, it would be important to correlate the amount of signal density with the degree of risk in different patient populations and in patients with varying levels of plaque burden. Importantly, it seems that ^{18}F-NaF PET imaging is sensitive enough to pick up changes after lifestyle interventions like exercise, but its accuracy and reproducibility need further study. Finally, the mechanisms by which calcium deposits in atherosclerotic plaque take up ^{18}F-NaF should be investigated to refine this technology. Although our current risk stratification tools are still imperfect because of our reliance on epidemiological data, we continue to make strides in our ability to image the vulnerable plaque, so that one day we can deliver more personalized approaches to preventative care (Figure 2).

Calcification may have a biphasic effect on plaque stability. Early spotty deposition will increase the surface area between calcified and non-calcified plaque, which increases exposure to mechanical stress and, thus, making the plaque vulnerable to rupture. As the calcification deposits grows, becomes denser, and coalesces, the interface between calcified

plaque and non-calcified plaque decreases and the plaque becomes more stable. It remains unclear how traditional risk factors affect this process although exercise appears to decrease the surface area to volume ratio.

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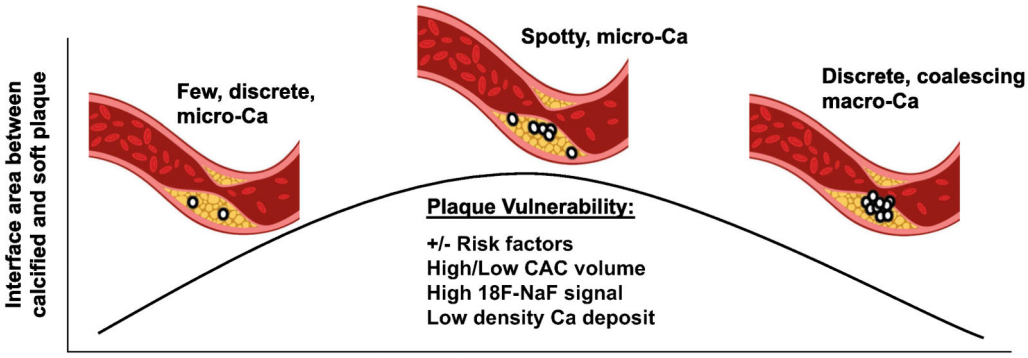

Figure 1.

Schematic of the relationship between interface area and plaque vulnerability. Plaque vulnerability is difficult to predict. Patients with and without traditional risk factors suffer heart attacks. The relationship between coronary artery calcification (CAC) volume is also unreliable. Recent data suggests that 18F-NaF PET imaging and measurements of calcium (Ca) density may be more reflective of plaque vulnerability because they measure the interface area between hard and soft plaque. Thus, plaques with spotty micro-calcification, which have high 18F-NaF signal and low density calcium may be most vulnerable to rupture.

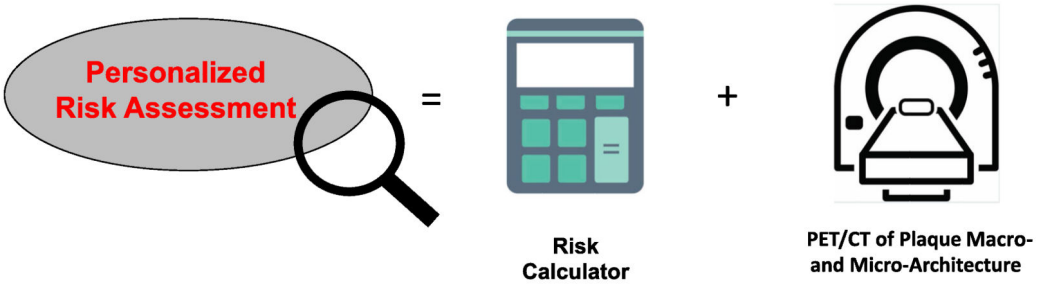

Figure 2.

Schematic of how to improve risk stratification. To deliver a more personalized approach toward risk stratification, we need to incorporate risk calculators that are sex- and race-specific and include measures of physical activity and fitness. Moreover, the addition of imaging to closely evaluate the macro- and micro-architecture would help to identify the most vulnerable patients.