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EDITORIAL COMMENT

Imaging of Arterial Inflammation

Keeping Our Cool on a Hot Topic*

Connie W. Tsao, MD,†‡ Ramachandran S. Vasan, MD‡§
Boston and Framingham, Massachusetts

Despite advances in treatment of cardiovascular disease (CVD) over the past several decades, its burden remains high (1). Appropriately, contemporary investigations have focused on the identification of patients at greatest risk for CVD. Although the central role of inflammation within the atherosclerotic plaque in the pathogenesis of CVD events has been recognized (2), serologic biomarkers such as C-reactive protein have not necessarily improved CVD risk prediction (3). Alternatively, noninvasive imaging may provide direct characterization and quantitation of inflammation within the atherosclerotic plaque, suggesting a role for an imaging biomarker to improve CVD risk prediction incrementally over standard risk factors.

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To this end, the investigation by Figueroa et al. (4) in this issue of *iJACC* delivers great promise of the power of positron emission tomography (PET) to identify vascular inflammation. In this study of patients referred for evaluation of suspected malignancy, the investigators examined the relationship of the fluorine-2-deoxy-D-glucose (FDG)-PET signal, indicative of inflammation, in the ascending aorta to the development of a CVD event on follow-up. In a retrospective review of 513 patients who underwent FDG-PET imaging, 44 patients developed CVD, defined as a composite of acute coronary syndrome, revascularization, new-onset angina, peripheral arterial disease, heart failure, stroke, transient ischemic attack, or CVD death. The degree of signal intensity was measured as the ratio of the mean aortic to blood pool standardized FDG uptake value, termed target-to-background ratio (TBR). TBR was associated positively with incident CVD even after adjustment for confounding clinical variables, including the coronary artery calcification score, and was inversely related to the time to incident CVD. Furthermore, the investigators observed that addition of TBR to models improved discrimination (the C statistic improved from 0.62 ± 0.03 [for a model without TBR] to 0.66 ± 0.03 upon addition of TBR) as well as the net reclassification index (NRI) of subjects (improvement of 27.5% and 22.3% for 10% and 6% intermediate-risk cut points). Thus, the investigators concluded that FDG-PET identification of arterial inflammation may be helpful to assist in risk stratification of participants at risk for CVD in the sample studied.

Atherosclerosis is characterized by slow progression with a long clinically latent stage. However, because plaque rupture results in arterial occlusion, leading to acute coronary syndrome or stroke (5), identification of active plaques before their rupture offers opportunities for therapeutic intervention. The "vulnerable plaque" is thought to consist of a lipid-rich core and a thin fibrous cap, with inflammatory cells including macrophages (6). Increasing evidence implicates a strong relationship between atherosclerotic inflammation and CVD events (2). Computed tomography, cardiac magnetic resonance, and vascular ultrasonography, including echocardiography, are able to detect the presence, quantity, and characteristics of atherosclerotic plaques. However, this armamentarium of noninvasive imaging

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From the †Department of Medicine, Cardiovascular Division, Beth Israel Deaconess Medical Center, Boston, Massachusetts; ‡Framingham Heart Study, Framingham, Massachusetts; and the §Sections of Cardiology and Preventative Medicine, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts. The authors have reported that they have no relationships relevant to the content of this paper to disclose.

modalities largely is unable to capture inflammatory activity within the plaque other than in experimental settings. Thus, the ability to detect the inflammatory component of atherosclerosis is attractive for gaining insight into the potential vulnerability of plaques.

In the past decade, FDG-PET has emerged as a noninvasive tool that provides this missing element of functional atherosclerotic imaging in humans (7,8), and now the present study extends its role into the avenue of CVD risk prediction. A prior study investigated FDG-PET uptake in multiple regions along the length of the aorta and showed that FDG-PET was a strong predictor of CVD events in a model additionally including age, sex, arterial calcification, and at least 1 other traditional CVD risk factor (9). However, the limitations of that study included the small number of incident CVD events and limited statistical modeling. Both studies quantified the intensity of the signal on FDG-PET imaging by TBR. The current investigation extends prior knowledge by broadening the spectrum of CVD events evaluated, including transient ischemic attacks, angina, peripheral arterial disease, heart failure, and CVD death. Furthermore, the current study investigated the addition of TBR to traditional CVD risk assessment and extended the findings to cancer-free individuals. Moreover, the investigators observed an inverse association of TBR with the timing of CVD, with greater TBR associated with earlier CVD during the follow-up period. To the extent that TBR may identify vulnerable plaques with higher levels of active inflammation, the findings are provocative and suggest the need for prospective investigation of this imaging technique in larger multiethnic cohorts.

However, several caveats must be considered, which rein in enthusiasm for the implementation of FDG-PET for routine imaging of atherosclerotic plaques at this time. As acknowledged by the investigators, a retrospective study based on review of a clinical tertiary care hospital database and available medical records is subject to errors and bias in classification of exposures, clinical characteristics (disease spectrum bias), and outcomes. In addition, although the present study accrued more CVD events relative to prior studies, the 44 composite events still constrain statistical power for adequate assessment of the performance of FDG-PET in prediction of CVD. This point is further emphasized by consideration of only the hard events (21 cases of acute coronary syndrome, 2 cases of ischemic stroke, 4 cases of peripheral arterial disease, and 2 CVD deaths). Greater numbers of CVD events would allow differentiation of the ability of FDG-PET to predict CVD risk in groups of subjects with varied demographic characteristics (such as young vs. old, men vs. women, low risk vs. higher risk, etc.) and by CVD subtype (stroke vs. coronary events). Furthermore, the patients in this investigation were all referred to a tertiary care medical center for suspected malignancy, thus limiting the generalizability of these findings. Another important concern is for patient safety. Whereas FDG-PET is appropriate for oncologic applications, it imparts substantial exposure to ionizing radiation and has been associated with risk of cancer (10). Further advances in imaging techniques and the limitations of the field of imaging may serve to decrease the radiation exposure. Nevertheless, the risk-benefit ratio must be weighed carefully if we are to consider extending this technique to standard imaging of arterial inflammation in the future.

In addition to the previously described limitations, consideration of the incremental value of FDG-PET for CVD risk prediction in this study should give us further pause. First, it must be kept in mind that attenuation correction scans have lower sensitivity for the detection of coronary artery calcification. Thus, the improvement of TBR to a model including coronary artery calcification as a covariate must be interpreted with caution. Next, it has been noted in large cohorts that the C statistic for models with traditional risk factors to predict CVD and coronary disease is 0.76 (11). In the current study, the C statistic in the model with conventional risk factors was only 0.62 ± 0.03. An improvement of the C statistic with any new biomarker is more often observed when the baseline model without the biomarker itself has a low C statistic (as in the current study). Thus, we must consider the improvement in model discrimination in this investigation with this understanding. In the context of a moderately high baseline C statistic with standard risk factors, the addition of novel biomarkers such as C-reactive protein and brain natriuretic peptide often does not significantly improve risk discrimination (11). Figueroa et al. (4) were not able to include blood C-reactive protein concentrations or other serum inflammatory biomarkers associated with CVD in models due to lack of available data. Because well-validated serum biomarkers are simpler blood tests that do not expose a subject to the potential risks and costs of FDG-PET, a pertinent question is whether there would be added utility of FDG-PET imaging in models that incorporate these additional serum biomarkers. Finally, the NRI is derived from

improved reclassification of both those with CVD and without events when the additional variable of interest is included in the model. In this study, the 27.5% improvement in NRI at the 10% risk cutoff point was to a greater extent driven by reclassification of those who did not experience a CVD event (14.8%) than those who developed new-onset CVD (12.7%). The identification of patients who will develop CVD (upgrading of risk reclassification) is critical because an intervention may alter their natural course toward morbidity or mortality. On the other hand, downgrading of risk reclassification of those who will not develop CVD does not directly offer potential for therapeutic benefit. Thus, while the NRI improved significantly in this study in a statistical sense, the derivation of benefit from FDG-PET is somewhat less compelling, considering all the other limitations of this study and its potential side effects and costs.

The outlined caveats should not detract from what is an important, hypothesis-generating study that highlights both the ability to capture functional arterial imaging in humans and the association of arterial inflammation with CVD events. Rather, in addition to validation of these findings in larger, prospective studies in the future, this investigation opens the field of noninvasive imaging and biomarker research to approach further questions, including opportunities for the use of FDG-PET to evaluate imaging response to anti-inflammatory treatment and the extent to which any changes on serial imaging tests correlate with improvement in clinical outcomes. Eventually, for FDG-PET to become a routine test in the clinical care of at-risk patients, it will have to meet several of the criteria for informative CVD biomarkers proposed by experts (12), including evidence related to its impact on patient management and outcomes and cost-effectiveness. While we must continue to "keep our cool" when surveying the evidence for imaging of arterial inflammation, the present study may be only the tip of the iceberg in a "hot" area of promising investigation.

Reprint requests and correspondence: Dr. Connie W. Tsao, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, RW-453, Boston, Massachusetts 02215. *E-mail:* *ctsao1@bidmc.harvard.edu*.

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