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EDITORIAL COMMENT

Do We Need to Expand Our Field of View for Imaging of Atherosclerosis?*

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Noninvasive imaging plays a central role in the management of the patient with atherosclerosis. It provides key pieces of information regarding disease detection, severity, progression, and regression. Indeed, the importance of noninvasive imaging is highlighted by the continued refinement and amalgamation of various advanced imaging technologies into hybrid devices and the development of novel contrast agents. However, these technical advancements in large part still focus on the enhancement and integration of the detection, localization, and characterization of the atherosclerotic plaque and its downstream sequelae. Yet atherosclerosis is inherently a systemic disease characterized by a dynamic immune-inflammatory process typified by cycles of intense activity and progression followed by intervals of stabilization. Consequently, major contributors to the atherosclerotic process arise from sites upstream from the atherosclerotic plaque. For example, macrophage accumulation in the arterial wall via initial differentiation from circulating monocytes or their subsequent local proliferation is fundamental to atherosclerotic plaque formation (1,2). The circulating monocytes are produced by hematopoietic stem and multipotential progenitor cells in the bone marrow and other extramedullary organs such as the spleen. From a clinical perspective, numerous studies have demonstrated that proinflammatory conditions manifesting as leukocytosis, particularly monocytosis, are associated with an adverse cardiovascular outcome. In patients without pre-existing atherosclerosis, the monocyte count is an independent predictor of future carotid plaque formation at 7 years of follow-up (3). Moreover, in patients with acute coronary syndromes (ACS), it appears leukocytosis and an elevated C-reactive protein level are associated with a worsening 6-month prognosis (4).

Based on the results of pre-clinical studies, a paradigm has been proposed that an acute ischemic event, such as a myocardial infarction (MI), results in increased sympathetic nervous system signaling, which liberates hematopoietic stem and progenitor cells from the bone marrow. These progenitors then travel to the spleen, where they boost monocyte production and activation. The subsequent monocytosis results in atherosclerotic plaque expansion (5). This paradigm has been termed the *cardiosplenic axis*. The paradigm provides an explanation for the monocyte trafficking patterns and their mechanistic basis for the acceleration of atherosclerosis. Recently, the presence of increased arterial inflammation and its association with both bone marrow and spleen metabolic activity were confirmed in humans after MI on the basis of imaging with positron emission tomography/computed tomography with ^{18}F-fluorodeoxyglucose (6).

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The paper in this issue of *iJACC* by Emami et al. (7) attempts to provide greater texture to this concept of a cardiosplenic axis. Their report consists of 2 studies. The goal of the first study was to determine whether metabolic activity of the bone marrow and spleen was associated with systemic inflammation, proinflammatory leukocyte remodeling, and arterial wall inflammation in patients after an ACS event. Positron emission tomography with ^{18}F-fluorodeoxyglucose to measure metabolic activity in the bone marrow and spleen and inflammation in the arterial wall (left and right carotid arteries and aorta) was compared with serum biomarkers for systemic inflammation and proinflammatory gene expression of circulating leukocytes. The measurements were obtained in 22 patients with documented ACS and 22 patients with documented atherosclerosis but without ACS. It was

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observed that bone marrow and splenic ^{18}F-fluorodeoxyglucose activity was higher in ACS patients than in non-ACS patients and directly correlated with arterial ^{18}F-fluorodeoxyglucose uptake and serum levels of C-reactive protein, a marker of systemic inflammation. Bone marrow and splenic ^{18}F-fluorodeoxyglucose uptake also directly correlated with the gene expression of circulating proinflammatory leukocytes, although this correlation was more closely associated with metabolic activity of the spleen.

The goal of the second study was to determine whether the metabolic activity in the bone marrow and spleen independently predicted cardiovascular risk in a more stable atherosclerosis clinical scenario. The study design was retrospective in nature and involved the 6.5-year (median 4 years) follow-up of 464 patients who underwent routine clinical positron emission tomography/computed tomography with ^{18}F-fluorodeoxyglucose for the diagnosis, staging, or post-therapy evaluation of cancer. All patients were either not diagnosed with cancer or were in remission at the time of imaging and throughout the follow-up interval. A broad definition of cardiovascular events was used and included cardiac death; MI; ACS; heart failure; revascularization of a coronary, carotid, or peripheral bed; and stroke or transient ischemic attack. In the entire patient cohort, both bone marrow and splenic metabolic activity correlated with arterial inflammation and with each other. Over the median 4-year interval, 34 patients had a cardiovascular event. A higher bone marrow ^{18}F-fluorodeoxyglucose activity was associated with an increased risk for cardiovascular events; however, this association was no longer significant after adjustment for Framingham Risk Score. In contrast, splenic ^{18}F-fluorodeoxyglucose activity was associated with cardiovascular increased risk, and this association remained significant after corrections were made for various cardiac risk factors, Framingham Risk Score, and key factors related to cancer status, such as type of malignancy, timing of diagnosis, and type of therapy. Moreover, the association remained significant even after adjustment for arterial inflammation.

Integrating the results of the 2 studies, the authors concluded that splenic metabolic activity is increased after ACS and correlates with arterial inflammation, systemic inflammation, and proinflammatory remodeling of circulating leukocytes. Moreover, in a more stable cardiovascular population, splenic activity is an independent predictor of the risk of cardiovascular events. They suggest the existence of this cardiosplenic axis may be clinically relevant in both acute and stable atherosclerotic disease.

The studies are very well done, and the results provide a human correlate to pre-clinical studies and expand on the aforementioned initial human observations. As pointed out by the authors, the conclusions must be tempered by the potential confounding effects of underlying cancer status on splenic ^{18}F-fluorodeoxyglucose activity and the increased incidence of atherosclerosis in cancer survivors such as those whose disease occurs at a younger age or who receive mediastinal radiation. Moreover, the retrospective nature of the study and the lack of an intervention preclude the identification of causality for the presence of the increased splenic ^{18}F-fluorodeoxyglucose for subsequent cardiovascular events.

That being said, the findings from this study are provocative and raise the question of whether our field of view for imaging of atherosclerosis in the clinical setting should be expanded to include hematopoietic and extramedullary sites upstream from the atherosclerotic plaque. Although this requires further study, it may be that the presence of splenic activity is a unique biomarker of increased cardiovascular risk, particularly in certain patient populations, such as the post-MI patient, in which case such information may help identify patients at increased likelihood for recurrent ischemia or adverse left ventricular remodeling. Moreover, the imaging of hematopoietic and extramedullary sites may provide the means to evaluate novel cardiovascular therapeutic agents designed to reduce the proliferation, activation, or release of pro-inflammatory monocytes. However, our field of view will also need to expand at the molecular level. Measurement of metabolic activity in the spleen and bone marrow with ^{18}F-fluorodeoxyglucose is nonspecific, because it reflects the integration of signal arising from cellular proliferation and activation of all metabolically active cells. Given that monocyte subpopulations exhibit diverse functions such as being proinflammatory or enhancing cellular repair and yet are both likely metabolically active, molecular imaging probes will need to be developed that identify both the proliferation and activity of those monocyte subsets that contribute to distinct components of the atherosclerotic process.

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REFERENCES

1. Libby P. Inflammation in atherosclerosis. Nature 2002;420:868–74.

2. Robbins CS, Hilgendorf I, Weber GF, et al. Local proliferation dominates lesional macrophage accumulation in atherosclerosis. Nat Med 2013;19:1166–72.

3. Johnsen SH, Fosse E, Joakimsen O, et al. Monocyte count is a predictor of novel plaque formation: a 7-year follow-up study of 2610 persons without carotid plaque at baseline: the Tromsø Study. Stroke 2005;36:715–9.

4. Sabatine MS, Morrow DA, Cannon CP, et al. Relationship between baseline white blood cell count and degree of coronary artery disease and mortality in patients with acute coronary syndromes: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction 18 trial) substudy. J Am Coll Cardiol 2002;40:1761–8.

5. Dutta P, Courties G, Wei Y, et al. Myocardial infarction accelerates atherosclerosis. Nature 2012;487:325–9.

6. Wollenweber T, Roentgen P, Schäfer A, et al. Characterizing the inflammatory tissue response to acute myocardial infarction by clinical multimodality noninvasive imaging. Circ Cardiovasc Imaging 2014;7:811–8.

7. Emami H, Singh P, MacNabb M, et al. Splenic metabolic activity predicts risk of future cardiovascular events: demonstration of a cardiosplenic axis in humans. J Am Coll Cardiol Img 2015;8:121–30.

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