Imaging Systemic Inflammation in Patients With Acute Myocardial Infarction

Matthias Nahrendorf, MD, PhD; Filip K. Swirski, PhD

Despite the impressive decline of acute mortality, myocardial infarction (MI) doggedly occupies the top position in worldwide mortality and therefore remains a research focus in need of clinical progress. Recent studies in mouse models of MI using sophisticated research tools, along with new insights in basic immunology, revealed that myocardial ischemia triggers systems-wide activity of innate immune cells. In particular, neutrophils, monocytes, and macrophages respond abundantly in the infarct and also in remote, nonischemic myocardium in mice. After a quick spike of neutrophil activity, macrophages dominate the myocardial wound in 2 distinct phases. Recruitment of classical monocytes gives rise to inflammatory macrophages first, followed by macrophages with less inflammatory phenotypes that participate in tissue regeneration and resolution of inflammation. During the first inflammatory phase, macrophages remove necrotic cells. During the resolution phase, macrophages orchestrate rebuilding of tissue, for instance, through cross-talk with myofibroblasts and by secreting vascular endothelial growth factor. These 2 phases occur in humans with MI. Experimental studies in mice revealed that a misbalance of these 2 phases, for instance, attributable to expanded systemic supply of inflammatory monocytes, compromises infarct healing and leads to heart failure. It also emerged recently that the inflammatory stimulus of acute MI increases supply of immune cells to nonculprit atherosclerotic plaque and thereby accelerates progression of atherosclerosis. These data potentially explain why reinfarction is common.

Inflammatory innate immune cells such as neutrophils and monocytes are made by hematopoietic stem cells, which predominantly reside in the bone marrow of adult mammals. A splenic monocyte reservoir provides ≈50% of the initial burst of monocytes to acute infarcts in mice. In mice with chronic ischemia triggers systems-wide activity of innate immune cells. In particular, neutrophils, monocytes, and macrophages also produce monocytes, likely after release of hematopoietic stem cells from the bone marrow. These cells then seed splenic niches, and, retained by VCAM-1/VLA-4 interaction, produce myeloid cells in an interleukin-1β– and GM-CSF–dependent manner. Known clinical risk factors of atherosclerosis such as hyperlipidemia and chronic variable stress may activate myelopoiesis in mice by either direct action on hematopoietic stem cells or through modifying the microenvironment in hematopoietic tissues. Data on rapid macrophage turnover, which can be as short as 20 hours in acutely ischemic myocardium in mice, motivate the scrutiny of factors regulating immune cell production and supply. To study the source and function of innate immune cells in cardiovascular disorders may reveal the mechanisms and risk factors for post-MI heart failure and reinfarction.

Mice are not humans, and observations in murine models may differ from the disease processes in patients. For instance, although preliminary histology data suggest that the spleen may be a source of monocytes in humans as well, it is unclear whether or not the spleen is an organ that cardiologists should pay attention to when treating patients with acute MI. Likewise, it is currently unclear to what extent the bone marrow supplies inflammatory immune cells to atherosclerotic plaque and acute infarcts. Thus, clinical studies are needed to answer these questions, but these studies face steep hurdles. Access to solid, deep tissues and correlation of inflammatory activity across organ systems is not feasible to pursue through patient biopsies, and sparse autopsy specimens have obvious limitations for examining in vivo processes. Noninvasive imaging, in particular clinical molecular imaging, is poised to accelerate translation of basic research, demonstrated by 2 recent studies published in Circulation: Cardiovascular Imaging. Both studies rely on 18F-fluorodeoxyglucose (18F-FDG), a positron emission tomography (PET) tracer that is in clinical use for cancer staging. The 18F isotope–labeled imaging agent uses glucose transporters for uptake into cells with high glucose metabolism. Arguably the most successful PET agent to date, it is primarily used clinically to locate malignant cells. The high glucose metabolism of immune cells triggered PET imaging studies correlating 18F-FDG signal in arteries with presence of advanced atherosclerotic plaques that harbor large numbers of inflammatory macrophages. PET imaging of macrophages in metabolically active myocardium is more difficult as the tracer is avidly internalized by myocytes. However, preclinical studies in mice after coronary ligation suggested that suppression of myocardial 18F-FDG uptake allows correlation of PET signal with myeloid cell numbers in the infarct. Translating this strategy from mice to humans, Wollenweber et al, in this issue of Circulation:

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From the Center for Systems Biology, Massachusetts General Hospital, Harvard Medical School, Boston.

Correspondence to Matthias Nahrendorf, MD, PhD, Center for Systems Biology, Massachusetts General Hospital, 185 Cambridge St, Suite 5.210, Boston, MA 02114. E-mail mnahrendorf@mgh.harvard.edu or Filip K. Swirski, PhD, Center for Systems Biology, Massachusetts General Hospital, 185 Cambridge St, Suite 5.210, Boston, MA 02114. E-mail fswirski@mgh.harvard.edu

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Cardiovascular Imaging, elegantly characterized acute inflammation in patients with myocardial ischemia using PET/CT and MRI. In 15 patients with a first myocardial infarct, delayed enhancement MRI and perfusion imaging identified the infarct location and size. Patients were imaged with PET 4 days after MI. The time point was prudently chosen to match the peak macrophage activity in acute infarcts. PET imaging after suppression of myocardial 18F-FDG uptake with heparin treatment revealed an increased infarct signal. Although the study did not directly correlate PET signal with infarct macrophage burden, preclinical studies in mice provide this correlation. The PET data obtained by Wollenweber et al. harmonize with 2 recent molecular MRI studies. Alam et al. and Yilmaz et al. used iron oxide nanoparticles, which are avidly taken up by macrophages, to image patients with acute MI. These studies reported increased infarct MRI contrast and a change of splenic nanoparticle signal. In the current PET study, 18F-FDG infarct uptake positively correlated with signal in the bone marrow (R=0.57) and the spleen (R=0.82) but not muscle or liver. In 5 patients 6.5±3.3 years after MI, infarct signal was lower than in the remote myocardium and did not correlate with signal in hematopoietic organs.

In a separate article published recently in this journal, Kim et al. also used 18F-FDG PET/CT but focused on inflammation in carotid arteries of 32 patients 6 days after acute MI, comparing with 33 patients with chronic stable angina and 25 control subjects without cardiovascular disease. In a blinded fashion, the authors also quantified PET tracer uptake in the spleen and the bone marrow of lumbar vertebrae. When compared with controls and patients with stable angina, acute MI increased the PET signal in carotid arteries, signifying remote, nonculprit vascular inflammation. 18F-FDG uptake was also higher in the spleen and in the bone marrow of patients with acute MI. The target to background signal in carotid arteries correlated positively with bone marrow and spleen signal. Although both clinical PET studies are small, they report significant and rather strong correlation of 18F-FDG signal in cardiovascular and hematopoietic organs. After acute MI, PET signal was increased in the inflamed infarct, in carotid arteries, in the spleen, and in the bone marrow. There was no correlation with PET signal in the liver and skeletal muscle, arguing against global changes of glucose metabolism as the primary reason for the increased 18F-FDG uptake in inflamed myocardial infarcts and arteries. The PET signal increase in the bone marrow and spleen observed in patients parallel preclinical data on accelerated hematopoiesis in cardiovascular disease. It is currently unclear how the increased 18F-FDG uptake in the spleen and the bone marrow comes about. However, it is tempting to speculate that the activation of hematopoietic progenitor cells and increased leukocyte production is an energy-intensive process that leads to higher glucose use and increased 18F-FDG uptake. Taken together with accepted clinical paradigms such as leukocytosis in patients with acute MI, and infiltration of acute infarcts with monocytes, these studies argue for robust activation and a potentially important role for the immune and hematopoietic systems in ischemic heart disease.

Because both studies lack PET scans just before acute infarction, which are difficult to obtain in patients, we are still facing a chicken or egg problem. It is conceivable that the increased activity of the hematopoietic system observed in patients acutely after MI actually preceded the ischemic event. In this hypothetical scenario, increased output of white blood cells by a more active hematopoietic system triggers ischemia by supplying inflammatory immune cells to the culprit lesion. The known kinetics of blood leukocytes after MI argue against this scenario, as do preclinical studies that observed emergency myelopoiesis after MI. Serial PET imaging, starting at a early time point after the ischemic event, may be able to address this question in patients but is logistically difficult. Our unpublished data obtained in mice with coronary ligation suggest that a first baseline scan would have to be done no later than 24 hours after onset of ischemia.

The studies by Kim et al. and Wollenweber et al. provide an exciting glimpse into the transformative power of molecular imaging. The data are clearly preliminary because the studies lack rigorous validation in humans. For instance, the molecular and cellular basis for increased PET signal in hematopoietic organs is unknown. We think that the small size of both studies is not a limitation but rather demonstrates the sensitivity of the employed method and the robustness of the underlying biology. More specific molecular imaging agents will likely surpass 18F-FDG in the near future and bring about a much needed acceleration for clinical discovery and drug development.

Disclosures

None.

References


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