

Biology and Pathology

Cardiovascular Disease

Molecular Imaging of Myocardial Ischemia and Remodeling

David E. Sosnovik

Cardiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Learning Objectives:

- Become familiar with the principal molecular processes relevant to myocardial ischemia and remodeling
- Become familiar with the advantages and disadvantages of the various molecular imaging platforms with specific reference to myocardial imaging
- Review the work that has been done to date on the molecular imaging of myocardial ischemia and remodeling

Numerous molecular processes are involved in myocardial ischemia and remodeling and are amenable to molecular imaging.(1, 2) Myocardial ischemia is characterized by cell death. This can be due to apoptosis, necrosis or autophagy. Molecular MRI approaches have been developed to image apoptosis and necrosis in vivo.(3, 4) These processes can also be imaged with SPECT and PET.(5, 6) More recently, a fluorescence based approach was developed to image autophagy in vivo.(7) Cell death in ischemia is followed by inflammation. This can be imaged with iron oxide nanoparticles,(8) Gd loaded liposomes,(9) and fluorine loaded liposomes.(10) The proteolytic enzymes released by these infiltrating macrophages have been imaged with activatable MR and optical imaging agents.(11, 12) Inflammation is followed by myocardial healing during which scar formation and angiogenesis are the principal processes. Radiolabeled RGD has been used to image angiogenesis during the remodeling process.(13, 14) Gd chelates targeted to type-1 collagen and elastin and radiolabeled probes to MMP allow scar formation to be assessed noninvasively.(15-17) The remodeled heart is characterized apoptosis, fibrosis, overactivity of the renin-angiotensin system and an imbalance in cardiac sympathetic activity. Approaches have been developed to image sympathetic activity and angiotensin-II receptors in the heart.(18, 19)

References:

1. Sosnovik DE, Nahrendorf M, Weissleder R. Molecular magnetic resonance imaging in cardiovascular medicine. *Circulation*. 2007;115:2076-2086.
2. Nahrendorf M, Sosnovik DE, French BA, Swirski FK, Bengel F, Sadeghi MM, Lindner JR, Wu JC, Kraitchman DL, Fayad ZA, Sinusas AJ. Multimodality cardiovascular molecular imaging, Part II. *Circ Cardiovasc Imaging*. 2009;2:56-70.
3. Sosnovik DE, Garanger E, Aikawa E, Nahrendorf M, Figueredo JL, Dai G, Reynolds F, Rosenzweig A, Weissleder R, Josephson L. Molecular MRI of cardiomyocyte apoptosis with simultaneous delayed-enhancement MRI distinguishes apoptotic and necrotic myocytes in vivo: potential for midmyocardial salvage in acute ischemia. *Circ Cardiovasc Imaging*. 2009;2:460-467.
4. Huang S, Chen HH, Yuan H, Dai G, Schuhle DT, Mekkaoui C, Ngoy S, Liao R, Caravan P, Josephson L, Sosnovik DE. Molecular MRI of acute necrosis with a novel DNA-binding gadolinium chelate:

kinetics of cell death and clearance in infarcted myocardium. *Circ Cardiovasc Imaging*. 2011;4:729-737.

5. Narula J, Acio ER, Narula N, Samuels LE, Fyfe B, Wood D, Fitzpatrick JM, Raghunath PN, Tomaszewski JE, Kelly C, Steinmetz N, Green A, Tait JF, Leppo J, Blankenberg FG, Jain D, Strauss HW. Annexin-V imaging for noninvasive detection of cardiac allograft rejection. *Nat Med*. 2001;7:1347-1352.
6. Liu Z, Zhao M, Zhu X, Furenli LR, Chen YC, Barrett HH. In vivo dynamic imaging of myocardial cell death using 99mTc-labeled C2A domain of synaptotagmin I in a rat model of ischemia and reperfusion. *Nucl Med Biol*. 2007;34:907-915.
7. Chen HH, Mekkaoui C, Cho H, Ngoy S, Marinelli B, Waterman P, Nahrendorf M, Liao R, Josephson L, Sosnovik DE. Fluorescence tomography of rapamycin-induced autophagy and cardioprotection in vivo. *Circ Cardiovasc Imaging*. 2013;6:441-447.
8. Sosnovik DE, Nahrendorf M, Deliolanis N, Novikov M, Aikawa E, Josephson L, Rosenzweig A, Weissleder R, Ntziachristos V. Fluorescence tomography and magnetic resonance imaging of myocardial macrophage infiltration in infarcted myocardium in vivo. *Circulation*. 2007;115:1384-1391.
9. Naresh NK, Xu Y, Klibanov AL, Vandsburger MH, Meyer CH, Leor J, Kramer CM, French BA, Epstein FH. Monocyte and/or macrophage infiltration of heart after myocardial infarction: MR imaging by using T1-shortening liposomes. *Radiology*. 2012;264:428-435.
10. Flogel U, Ding Z, Hardung H, Jander S, Reichmann G, Jacoby C, Schubert R, Schrader J. In vivo monitoring of inflammation after cardiac and cerebral ischemia by fluorine magnetic resonance imaging. *Circulation*. 2008;118:140-148.
11. Nahrendorf M, Sosnovik D, Chen JW, Panizzi P, Figueiredo JL, Aikawa E, Libby P, Swirski FK, Weissleder R. Activatable magnetic resonance imaging agent reports myeloperoxidase activity in healing infarcts and noninvasively detects the antiinflammatory effects of atorvastatin on ischemia-reperfusion injury. *Circulation*. 2008;117:1153-1160.
12. Nahrendorf M, Sosnovik DE, Waterman P, Swirski FK, Pande AN, Aikawa E, Figueiredo JL, Pittet MJ, Weissleder R. Dual channel optical tomographic imaging of leukocyte recruitment and protease activity in the healing myocardial infarct. *Circ Res*. 2007;100:1218-1225.
13. Meoli DF, Sadeghi MM, Krassilnikova S, Bourke BN, Giordano FJ, Dione DP, Su H, Edwards DS, Liu S, Harris TD, Madri JA, Zaret BL, Sinusas AJ. Noninvasive imaging of myocardial angiogenesis following experimental myocardial infarction. *J Clin Invest*. 2004;113:1684-1691.
14. Sherif HM, Saraste A, Nekolla SG, Weidl E, Reder S, Tapfer A, Rudelius M, Higuchi T, Botnar RM, Wester HJ, Schwaiger M. Molecular imaging of early alphavbeta3 integrin expression predicts long-term left-ventricle remodeling after myocardial infarction in rats. *J Nucl Med*. 2012;53:318-323.
15. Helm PA, Caravan P, French BA, Jacques V, Shen L, Xu Y, Beyers RJ, Roy RJ, Kramer CM, Epstein FH. Postinfarction myocardial scarring in mice: molecular MR imaging with use of a collagen-targeting contrast agent. *Radiology*. 2008;247:788-796.
16. Makowski MR, Wiethoff AJ, Blume U, Cuello F, Warley A, Jansen CH, Nagel E, Razavi R, Onthank DC, Cesati RR, Marber MS, Schaeffter T, Smith A, Robinson SP, Botnar RM. Assessment of atherosclerotic plaque burden with an elastin-specific magnetic resonance contrast agent. *Nat Med*. 2011;17:383-388.
17. Su H, Spinale FG, Dobrucki LW, Song J, Hua J, Sweterlitsch S, Dione DP, Cavaliere P, Chow C, Bourke BN, Hu XY, Azure M, Yalamanchili P, Liu R, Cheesman EH, Robinson S, Edwards DS, Sinusas AJ. Noninvasive targeted imaging of matrix metalloproteinase activation in a murine model of postinfarction remodeling. *Circulation*. 2005;112:3157-3167.

18. Fukushima K, Bravo PE, Higuchi T, Schuleri KH, Lin X, Abraham MR, Xia J, Mathews WB, Dannals RF, Lardo AC, Szabo Z, Bengel FM. Molecular hybrid positron emission tomography/computed tomography imaging of cardiac angiotensin II type 1 receptors. *J Am Coll Cardiol.* 2012;60:2527-2534.
19. Thackeray JT, Bengel FM. Assessment of cardiac autonomic neuronal function using PET imaging. *J Nucl Cardiol.* 2013;20:150-165.

Disclosure of author financial interest or relationships: D.E. Sosnovik, Siemens Medical, Grant/research support.