Review of cardiovascular imaging in The Journal of Nuclear Cardiology in 2014: Part 1 of 2: Positron emission tomography, computed tomography, and neuronal imaging

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The year 2014 has been an exciting year for the cardiovascular imaging community with significant advances in the realm of nuclear and multimodality cardiac imaging. In this new feature of the *Journal of Nuclear Cardiology,* we will summarize some of the breakthroughs that were published in the *Journal* in 2014 in 2 sister articles. This first article will concentrate on publications dealing with cardiac positron emission tomography (PET), computed tomography (CT), and neuronal imaging.

Key Words: Positron emission tomography • neuronal imaging • computed tomography • MIBG • atherosclerosis • sarcoidosis • regadenoson

ATHEROSCLEROTIC PLAQUE IMAGING

The COURAGE[1] and BARI2D trials[2] failed to show advantage from revascularization as opposed to optimal medical therapy in preventing cardiac death or myocardial infarction, except in a limited subset of patients. The ineffectiveness of revascularization in stable coronary artery disease (CAD) is perhaps due to the fact the current strategies have focused on the treatment of stenotic rather than vulnerable lesions.

The non-invasive identification of a vulnerable plaque is considered the holy gray of cardiovascular imaging research. For years, scientists have been trying to optimize the techniques, identify new tracers and hybrid imaging tools to identify plaques with propensity for rupture or erosion. In a recent state-of-the-art review in the *Journal*, Tavakoli et al discuss in depth the molecular imaging of vulnerable plaques,[3] and summarize the potential processes that lead to atherosclerosis with the proposed representative tracers for identification and quantification. This complex mechanism includes cell apoptosis (imaged by 99m-Tc labeled annexin), neo-revascularization (increased VEGF expression measured by 89-Zr-bevacizumab), active calcification (F18-NaF), lipid accumulation (oxidized LDL-targeted micelle detected by cardiac magnetic resonance imaging), inflammation (111-In-oxine labeled monocytes, ultrasmall supermagnetic iron oxide, iodinated nanoparticles), matrix remodeling (99mTc-labeled MMP inhibitor), and several others.[3] Furthermore, Su el al[4] identified a novel integrin tracer 18F-Flotegatide that selectively binds to integrin $\alpha v\beta 3$, that is a protein expressed by macrophages and neovascular endothelium. In an ApoE knockout mouse model of atherosclerosis, 18F-Flotegatide was preferentially bound to aortic plaque (Figure 1) and

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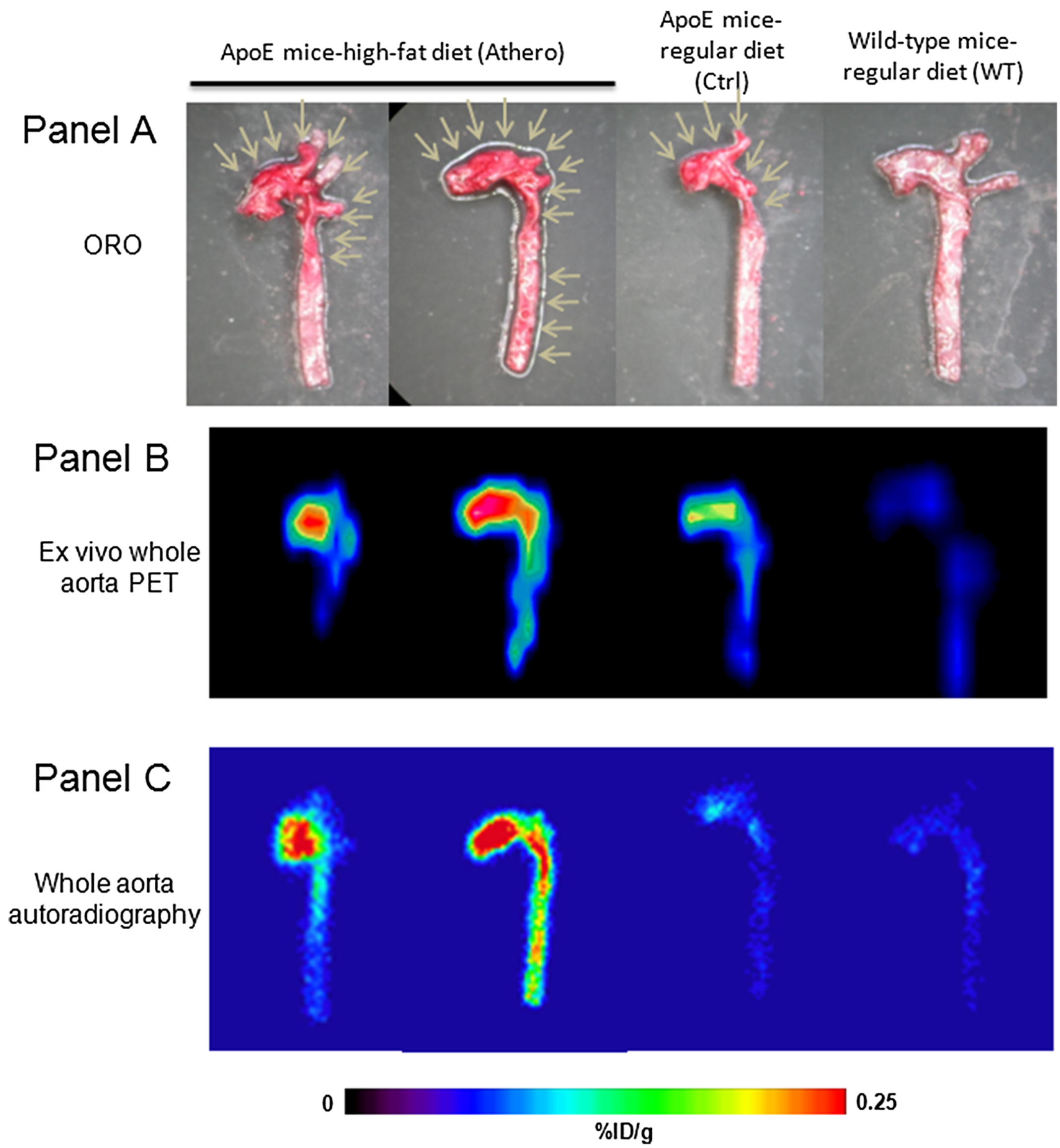

Figure 1. Flotegatide uptake by atherosclerotic plaque in whole aorta in ApoE targeted mutation mice-high fat diet (atheroma model: Athero), ApoE mice-regular diet (control: Ctrl), and wild-type mice (WT). (**A**) The aorta was excised and the lumen was exposed. ORO staining of Athero, WT, and control mice is shown. *Arrows* point to focal areas enriched for plaque in the aortic arch. (**B**) Aorta explanted from Athero, WT, and control mice was subjected to ex vivo PET 1 hour after injection of 18F-Flotegatide. The signal intensity is a reflection of tracer uptake (areas of high uptake appear *red*). (**C**) Aorta explanted from Athero, WT, and control mice was subjected to autoradiography 1 hour after injection of 18F-Flotegatide. 18F-Flotegatide uptake correlated well with ORO staining. Reproduced with permission from Su et al J Nucl Cardiol 2014;21:553-562.

strongly correlated with histological markers of macrophage infiltration and inflammation, and to a lesser extent neovascularization.[4] The clinical application of molecular imaging of plaque inflammation was tested in 40 subjects that were administered 18FDG and were imaged by hybrid PET/CT to detect plaque glycolysis, a surrogate marker of inflammation and hypoxia.[5] Delayed 18FDG PET/CT imaging at 180 minutes improved quantification of atherosclerotic plaque imaging in the thoracic aorta and the carotid arteries.[5] The clinical application of 18FDG PET/CT was tested in patients with active vasculitis (Takayasu arteritis) and was able to detect active disease in 100% of patients (17/17), and showed high sensitivity, specificity, positive- and negative-predictive values (83%, 90%, 77%, and 93%, respectively) to detect residual disease while on immunosuppression.[6]

The assessment of coronary plaque in vivo, however, remains a challenge because of the size of the coronary arteries as compared to the carotids and aorta. The best practical and used clinical imaging modality to date remains detection of coronary artery calcification (CAC) by cardiac CT. With the increased use of cardiac CT, a significant number of non-obstructive plaques have been identified. The clinical implications of these findings have been recently evaluated in a multicenter retrospective study which showed that non-obstructive CAD compared with no apparent CAD was associated with increased 1-year risk of myocardial infarction and death, and with incremental increase with the number of vessels involved.[7] Shah et al assessed the prognostic value of CAC score in 7200 symptomatic patients with non-obstructive CAD enrolled in the Coronary Computed Tomography Angiography Evaluation For Clinical Outcomes multicenter registry.[8] The 4-year mortality ranged from 0.8% (CAC score 0) to 9.8% (CAC score $\geq$400), with a hazard ratio of 6.0 (CAC score 100-399) and 13.3 (CAC score $\geq$400) ($P < .001$ for all). CAC score remained an independent predictor of death or myocardial infarction after multivariate adjustment.[8]

The evaluation of CAC score has greatly added value to risk stratification of patients. The Framingham risk score often classify young patients as low risk despite the presence of uncontrollable risk factors, taking into account short-term risk only. In a recent paper, Hulten et al stratified 1,863 patients at ''low'' Framingham risk score into low- and high-lifetime risk based on clinical risk factors.[9] Those that were reclassified into high lifetime risk had significantly more CAD burden on CT angiography and higher CAC score.[9]

CARDIAC SARCOIDOSIS

Cardiac sarcoidosis is a frequent cause of arrhythmia and cardiac death.[10] Cardiac magnetic resonance imaging, using late gadolinium enhancement, has proven to be a powerful non-invasive method to detect and quantify myocardial scar in patients with cardiac sarcoidosis, which carries prognostic value.[10] Recently, PET imaging has proven itself an alternative complimentary method to image cardiac sarcoidosis, particularly the acute inflammatory nodules before scaring and granuloma formation. Ahmadian et al sought to develop and validate a clinically helpful quantitative method to measure FDG uptake in patients with cardiac sarcoidosis with hybrid PET/CT imaging, and test its prognostic value in predicting cardiovascular endpoints.[11] Between 2011 and 2013, 38 patients with cardiac sarcoidosis undergoing FDG PET/CT were compared to 10 controls. Cardiac metabolic activity using standard uptake values was measured and showed high sensitivity and specificity to detect disease, and decreased in parallel with immunosuppressive therapy. Furthermore, it was the only independent predictor of events (odds ratio 2.6 [1.09-6.22].[11] Therefore, quantification of total volume and intensity of FDG update in patients with cardiac sarcoidosis might prove to be a useful reproducible technique with improved diagnostic interpretation that can be used to monitor response to therapy and has potential prognostic value.[11]

Follow-up imaging of patients with cardiac sarcoidosis is important to assess response to therapy. The acute inflammatory phase that is readily seen as high FDG uptake on PET/CT imaging can often regress if treated early on with immunosuppressive therapy. Osborne et al studied 23 patients with cardiac sarcoidosis that had 90 PET scans (median time between tests 2 years), and showed significant inverse correlation between decrease in standard uptake values of FDG and improvement in baseline ejection fraction.[12] Hence, serial imaging might play a role in guiding therapy, particularly the intensity and duration of immunosuppressive treatment, in patients with cardiac sarcoidosis in conjunction with monitoring and predicting improvement in left ventricular systolic function (Figure 2).

123I-MIBG IMAGING

The role of cardiac sympathetic nerve activity in patients with heart disease has been previously described.[13] The ability to non-invasively assess sympathetic neuronal integrity using 123I-metaiodobenzylguanidine (123I-mIBG), an analog of norepinephrine, has provided insights about the role of sympathetic activity in regulating arrhythmias. In patients with heart failure, the traditional tools that risk stratify for sudden cardiac death such as left ventricular ejection fraction have proven suboptimal, emphasizing a non-uniform distribution of risk among patients.[14] The presence of autonomic dysfunction has been associated with serious arrhythmia. Badarin et al identified 778 patients with left ventricular ejection fraction (LVEF) <35% and heart failure symptoms from the ADMIRE-HF study.[15] Arrhythmic events occurred in 7% of patients after a median follow-up time of 17 months; a decreased cardiac sympathetic activity (heart to mediastinum ratio <1.6) was an independent predictor of arrhythmia (HR 3.5, 95% CI [1.5-8] (Figure 3), and resulted in a significant 45% improvement in discriminatory ability of the model.[15] The origin of ventricular arrhythmia in patients with cardiomyopathy has been proposed to originate not only from the scar area, but also from the ''gray zone'' or border zone, a heterogeneous area of viable and non-viable tissue which is a highly susceptible arrhythmogenic focus. In a recent study, Zhou et al

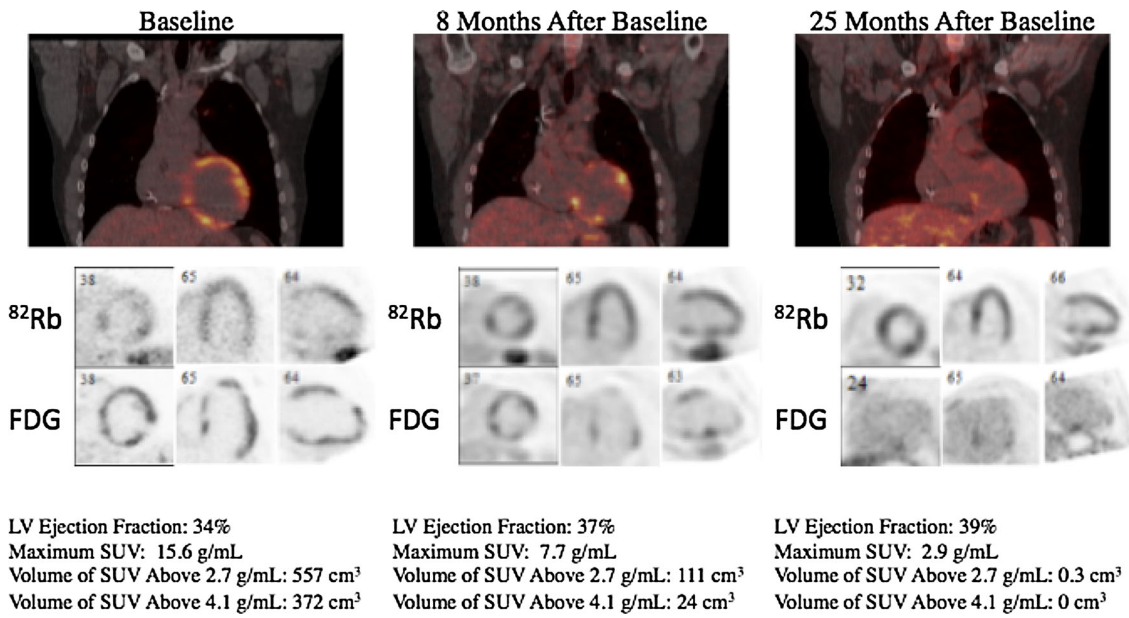

Figure 2. Serial FDG PET exams showing change in inflammation. The results of three serial studies over 25 months from a 46-year-old man with cardiac sarcoidosis treated with corticosteroids are shown. The *color* maps demonstrate the intensity of FDG uptake in a coronal view. The *grayscale* images demonstrate serial perfusion images using 82-rubidium (*top*) and metabolism images using FDG (*bottom*) in three distinct axes at approximately the same location. For each scan, the measurements of LV ejection fraction, SUV maximum, and SUV volumes are displayed. There was significant decrease of tracer uptake and inflammation with corresponding improvement in LV ejection fraction on serial examination. Reproduced with permission from Osborne et al J Nucl Cardiol 2014;21:166-74.

showed that patients with positive electrophysiology study have similar scar burden to those with negative study, but had significantly larger border zone and less mIBG uptake signifying more sympathetic denervation.[16] Adding mIBG imaging to the model results in improvement of model prediction of arrhythmia.[16] Therefore, mIBG imaging of the border zone has potential role in further risk stratifying patients and guiding therapy.

The role of the autonomic system is not only important in arrhythmia control, but also in regulating coronary flow. Indeed, sympathetic denervation has been proposed as one of the key mechanisms in coronary vasospasms, in addition to endothelial dysfunction. Honda et al recently investigated the role of sympathetic denervation in detecting patients with coronary spastic angina, and showed a significant decrease in mIBG uptake in this group as compared to those with chest pain but without spasm and controls.[17] Furthermore, adding mIBG to flow-mediated dilation testing resulted in improved diagnostic accuracy and achieved the highest sensitivity and specificity to distinguish patients with coronary spasm among those with chest pain at rest.[17]

Autonomic dysfunction can be indirectly assessed by quantifying chronotropic incompetence or abnormal heart rate reserve. Recently, the relationship between impaired heart rate reserve and outcomes in patients undergoing pharmacological stress testing has been brought to light.[18] This simple tool that is defined as peak minus resting heart rate was recently shown in a large cohort of 2,398 patients undergoing pharmacological stress PET to be an independent predictor of mortality beyond traditional imaging parameters.[19]

NEW IN PET IMAGING

The role of PET imaging in patients with hibernating myocardium and guiding revascularization is well established.[20] However, in patients with ischemic cardiomyopathy and significant LV remodeling, particularly in those with LV aneurysm, the accuracy of PET and SPECT imaging as compared to cardiac MRI in quantifying volumes and ejection fraction is not well determined. In a study evaluating 96 patients with LV aneurysms undergoing SPECT, PET, and cardiac MRI, Wei et al showed good correlation, with some variation between the measured parameters, between the different imaging modalities. The accuracy of LVEF by PET or SPECT, as opposed to cardiac MRI, was affected mainly by the number of akinetic/dyskinetic segments with

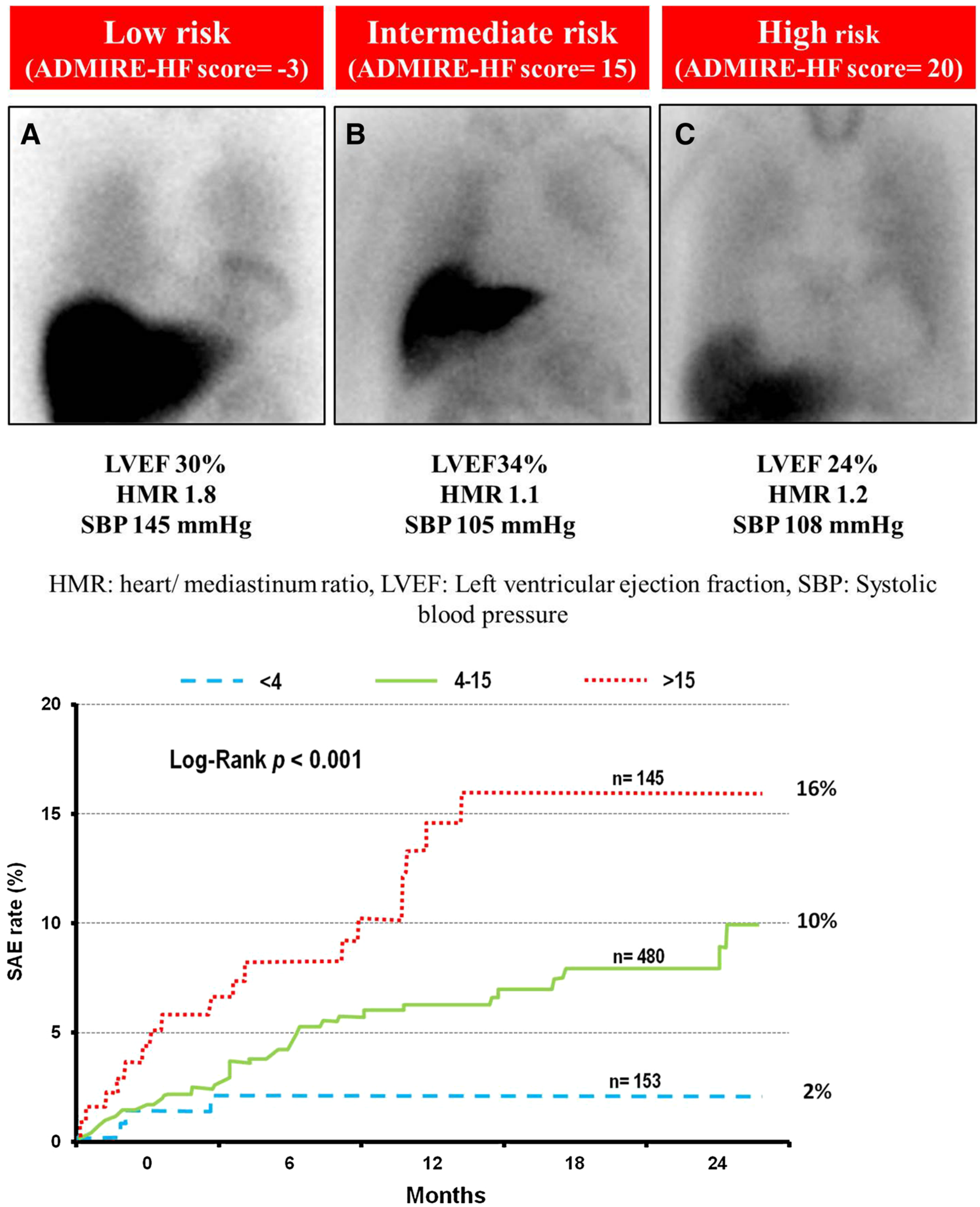

Figure 3. Planar mIBG imaging for patients with LVEF <35% and heart failure symptoms. Heart to mediastinum ratio (HMR) of mIBG uptake was calculated (abnormal HMR is <1.6). Patients were stratified into low, intermediate and high-risk groups according to tertiles of the ADMIRE-HF score (*top panel*). Patients with low HMR and hence higher ADMIRE-HF scores had significant increase in serious arrhythmogenic events (*bottom panel*). Reproduced with permission from Badarin et al J Nucl Cardiol 2014;21:756-62.

absent wall thickening. This is an important study that highlights that despite a good correlation between modalities, the measurements cannot be used interchangeably. One of the limitations of PET and SPECT imaging is attenuation artifact. This is particularly important in patients with hibernating myocardium with areas of decreased perfusion uptake. Retrospective attenuation correction using internal or external CT scans has been shown to be useful with comparable results. However, on a patient by patient basis, the amount of viable or hibernating myocardium can vary and lead to change in management in up to 10% of patients.[21]

The safety of regadenoson stress PET imaging in severe aortic stenosis has been recently studied in a cohort of 50 patients undergoing evaluation for transcatheter valve replacement. Although the guidelines has discouraged stress testing in severe valvular heart disease, Cremer et al showed no major adverse events with regadenoson, and 16% transient hypotension.[22] Furthermore, PET correctly identified jeopardized myocardium that was revascularized appropriately in 91% of patients.[22] The potential role of PET in guiding therapy in patients undergoing transcatheter valve replacement should be further studied prospectively.

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