2013 SNMMI Highlights Lecture: Cardiovascular Sciences

From the Newsline Editor: The Highlights Lecture, presented at the closing session of each SNMMI Annual Meeting, was originated and presented for more than 33 years by Henry N. Wagner, Jr., MD. Beginning in 2010, the duties of summarizing selected significant presentations at the meeting were divided annually among 4 distinguished nuclear and molecular medicine subject matter experts. The 2013 Highlights Lectures were delivered on June 12 at the SNMMI Annual Meeting in Vancouver, British Columbia. The second presentation is included here (the first appeared in the September Newsline, the third follows in this issue, and the last will appear in the November issue). Frank M. Bengel, MD, spoke on highlights from cardiovascular imaging. Note that in the following presentation summary, numerals in brackets represent abstract numbers as published in The Journal of Nuclear Medicine *(2013;55[suppl 2]).*

The SNMMI Annual Meeting Highlights lectures provide the opportunity to look into the past, analyze the present, and come up with some conclusions about where we might go in the future. Mark Twain said, "Plan for the future because that's where you are going to spend the rest of your life."

The number of abstract submissions in the cardiovascular sciences at the SNMMI meeting increased slightly from 2012 to 2013. The number of submissions in the basic cardiovascular sciences category also rose in 2013. I concluded my Highlights lecture on this topic last year with 3 major trends that emerged from presentations at the 2012 meeting. It was clear that cardiovascular imaging was taking a lead role in: (1) clinical implementation of absolute quantification; (2) implementation of solid-state detector SPECT; and (3) comprehensive, pathway-driven implementation of molecular imaging (e.g., in inflammation, infarct, and atherosclerosis). These trends have continued in 2013 and were in evidence at the meeting. Cardiovascular-related abstract submissions for the 2013 Annual Meeting included increasing numbers of submissions on molecular imaging (49%) and new hardware/software (32%) and declining numbers of submissions on perfusion imaging (19%). Another continuing trend is toward high-end technology. This year 61% of cardiovascular submissions were related to PET (6% PET/MR) and only 39% were SPECT-related (6% solid-state cadmium-zinc-telluride [CZT]–detector technologies).

de Haan et al. from VU University Medical Center (Amsterdam, The Netherlands) reported that "PET/CT-assessed myocardial innervation and perfusion mismatch correlates with heterogenic scar size assessed with cardiac MR" [26]. The authors, who received the Cardiovascular Council Clinical Young Investigator Award, used PET/CT to quantify myocardial innervation and perfusion to identify a mismatch between innervation and perfusion in the border zone of myocardial infarction. They used MR imaging to look at the infarct area and its border zone, implementing it with PET innervation and perfusion imaging to look at the respective defects (Fig. 1). They reported on correlation between the 2 techniques. This is an innovative approach for multimodality characterization of the infarct border zone that could be used to identify individuals who are at higher risk for arrhythmia or progression of heart failure.

Thackeray et al. from the Hannover Medical School (Germany) reported on "Phenotyping of myocardial metabolism in a transgenic mouse model of catecholamine-induced heart failure" [23]. The authors, who received the Cardiovascular Council Basic Science Young Investigator Award, used quantitative PET methodology to phenotype myocardial metabolism. With a quantitative ^{18}F-FDG technique, the group was able to show an exaggerated increase in glucose utilization in response to isoproterenol, a catecholamine, in a transgenic mouse model (Fig. 2). This was observed before the animals developed overt heart failure. Of note, the metabolic impairment identified here using quantitative imaging preceded the development of heart failure and may be used to predict disease progression.

Frank M. Bengel, MD

The most important award presented each year at the SNMMI Annual Meeting by the Cardiovascular Council is the Hermann Blumgart Award, given to a distinguished expert in the field. This year the awardee was Rob Beanlands, MD, a professor at the University of Ottawa and director of Canada's National Cardiac PET Centre. He spoke about cardiovascular PET, identifying 5 key contemporary trends: (1) improved perfusion and flow quantification, including efforts to better understand the microvasculature and the clinical roles of ^{82}Rb flow quantification and of ^{18}F-flurpiridaz; (2) better characterization of vascular and myocardial inflammation; (3) more efficient translation of molecular imaging to clinical research/care; (4) an enhanced focus on value-based

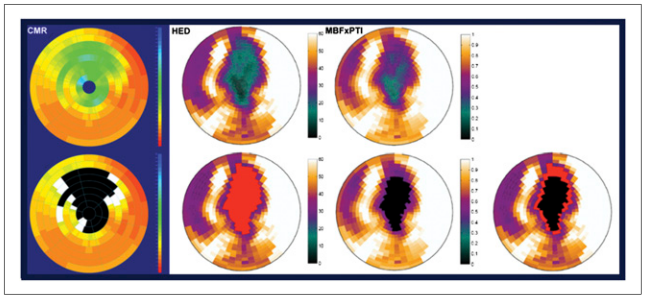

FIGURE 1. Bullseye maps of cardiac MR (CMR), ^{11}C-hydroxephedrine PET/CT (HED), myocardial blood flow/perfusable tissue index (MBF/PTI), and (far right) correlation between HED and MBF, which provides multimodality characterization of infarct border zone.

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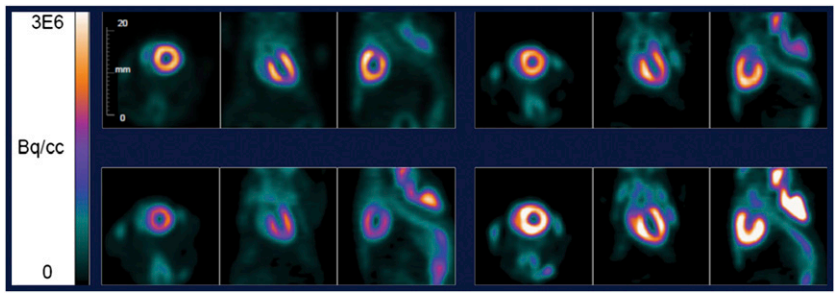

FIGURE 2. Metabolic impairment preceding heart failure. Transaxial, coronal, and sagittal ^{18}F-FDG PET images in (top) wild-type mice injected with saline (left 3 images) and isoproterenol (right 3 images); and (bottom) transgenic mouse model injected with saline (left 3 images) and isoproterenol (right 3 images). Exaggerated responses to increased glucose utilization with isoproterenol were observed before animals developed overt heart failure.

imaging and higher quality evidence, including: appropriate use criteria, standards, multicenter registries, randomized controlled trials, network collaborations, comparative and cost effectiveness research, and the creation of studies sufficiently powered to answer key questions about effects on outcomes, quality of life, and cost; and (5) the importance of multimodality approaches in which training and practice include the use of different technologies that document both structure and function and in which multimodality teams and networks collaborate to characterize the heart.

SPECT and Solid-State Detector Cameras

In SPECT we are seeing increasing use of solid-state detector cameras, which are quite sensitive. Miyagawa et al. from the Ehime University School of Medicine (Japan) and Fujifilm RI Firma Co., Ltd., reported on "Estimation of myocardial flow reserve using CZT SPECT in patients with multivessel coronary artery disease (CAD)" [517]. With their novel and sensitive system, the researchers were able to create dynamic images of myocardial ^{99m}Tc-MIBI kinetics. They measured time/activity curves for the myocardium and blood pool and were able to look at quantitative myocardial blood flow and myocardial flow reserve in subjects with CAD (Fig. 3). Global myocardial flow reserve was lower in subjects with multivessel CAD than in those with single-vessel disease. Future research will demonstrate the ways in which this quantitative metric can be used to augment the diagnostic potential of SPECT with solid-state detector cameras.

Another advantage of these cameras is that they have a very high energy resolution, so that they can be used for simultaneous imaging of multiple radioisotopes. Rouzet et al. from GH Bichat-Claude Bernard (Paris), Université Paris Diderot (France), and Cyclopharma (Saint-Bauzire, France) reported on "Clinical evaluation of simultaneous ^{123}I-MIBG/^{201}Tl imaging with cardiac CZT camera" [518]. Their aim was to compare a simultaneous myocardial innervation and perfusion imaging technique with sequential imaging using a conventional camera in 32 patients with familial amyloid neuropathy or heart failure (Fig. 4). Overall examination time was greatly reduced with CZT-based imaging, and substitution of ^{201}Tl for a ^{99m}Tc-labeled tracer is expected to result in dose reduction with no downscatter from the ^{123}I window. The researchers showed that quantitative parameters with both approaches were in agreement. Resulting images with CZT were of good quality and had the advantage of showing areas of myocardial innervation that were normally perfused. This is a novel way to look at molecular signals from damaged myocardium that may be important in predicting cardiac events such as arrhythmia or heart failure progression.

PET/MR

PET/MR is also increasingly used for characterization of cardiovascular disease. Lau et al. from Washington University in St. Louis (MO) and Siemens Medical Solutions (Malvern, PA) reported on "Feasibility of MRI attenuation correction in cardiac FDG PET" [27]. This research was recognized with selection for the Cardiovascular Council Young Investigator competition. The group compared myocardial standardized uptake values (SUVs) obtained with PET/MR with those obtained with PET/CT in the same patients and found excellent correlation (Fig. 5). They demonstrated several possible applications of clinical PET/MR, including myocardial viability assessment using simultaneous gated ^{18}F-FDG PET and delayed contrast-enhanced MR.

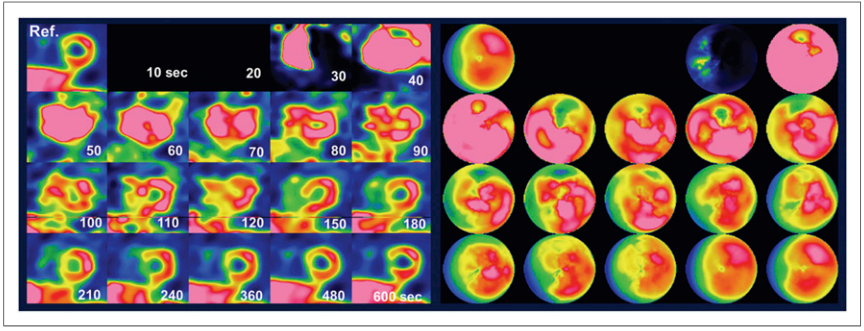

FIGURE 3. Dynamic ^{99m}Tc-MIBI imaging (left block) with a solid-state CZT detector camera and dynamic bullseye mapping (right) were used in patients with multivessel coronary artery disease to quantify global myocardial flow reserve.

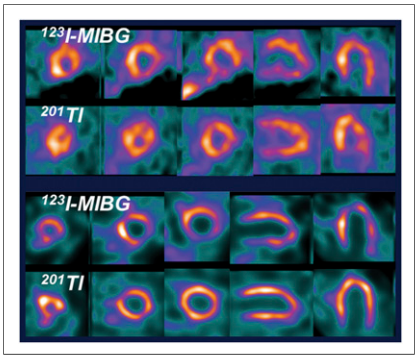

FIGURE 4. ^{123}I-MIBG/^{201}Tl imaging with: (top 2 rows) conventional camera and sequential radioisotope imaging; and (bottom block) CZT-based simultaneous imaging. In addition to significantly reducing examination time, CZT imaging showed areas of myocardial innervation that were normally perfused.

Ripa et al. from the Rigshospitalet, University of Copenhagen (Denmark), and Hvidovre University Hospital (Denmark) reported on the "Feasibility of simultaneous PET/MR of the carotid artery: first clinical experience and comparison to PET/CT" [181]. They characterized the carotid arteries with MR and obtained PET parameters for uptake of ^{18}F-FDG in all of the carotid arteries (Fig. 6). They also found correlations between PET/CT and PET/MR parameters in this setting, suggesting that we can also use PET/MR to look at vascular biology and morphology.

Novel Radiotracers

New tracers were introduced at this meeting, with the majority intended for PET imaging. Higuchi et al. from the Technical University of Munich (Wurzburg, Garching, and Munich, Germany) and Lantheus Medical Imaging (Billerica, MA) reported on "Myocardial kinetics of novel F-18 sympathetic nerve tracer LMI1195 in the isolated working rabbit heart" [130]. This tracer is already in use in humans in phase 1 clinical studies. The team showed that pretreatment with the blocker desipramine abolishes uptake of the tracer, so that it is a specific marker of nerve terminals in the heart. They were also able to use electrical stimulation to obtain washout of the tracer from the heart, suggesting that it may be not only a marker of the integrity of nerves but of sympathetic nerve tone and activity.

Liu et al. from Washington University (St. Louis, MO) and the University of California, Santa Barbara reported on

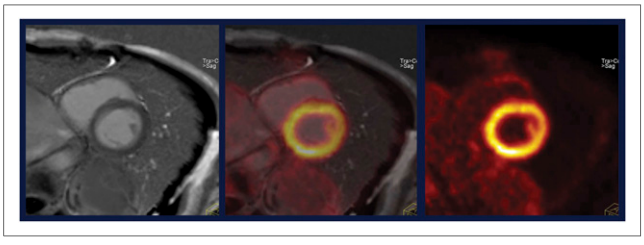

FIGURE 5. Simultaneous ^{18}F-FDG PET and delayed contrast-enhanced (DCE) MR for myocardial viability assessment. DCE MR (left), fused PET-MR (middle), and PET (right). PET data were acquired in list mode and binned, and DCE MR images were acquired in diastole.

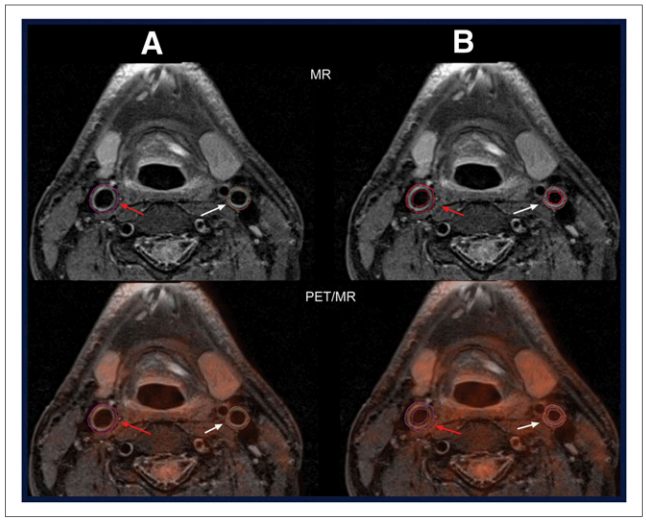

FIGURE 6. Transverse MR (top) and fused ^{18}F-FDG PET/MR (bottom) imaging at level with right common carotid artery (red arrows) and left internal carotid artery (white arrows). ROI including both vessel wall and lumen is drawn in column A, and ROI including only vessel wall is drawn in column B.

"Assessment of natriuretic peptide clearance receptor–targeted nonparticle for PET atherosclerosis translational research" [466]. Using a ^{64}Cu-labeled tracer they were able to show specific uptake in sites of vascular injury (Fig. 7). I particularly liked what this group described as their "Roadmap to PET atherosclerosis translational research." Mileposts of this roadmap as it is followed at Washington University include completion of: in vitro cell binding assay, in vivo biodistribution profile, in vivo target identification (including immunohistochemistry identification, Western blot characterization, and reverse transcriptase-polymerase chain reaction), in vivo PET imaging, animal dosimetry, animal toxicity, Good Manufacturing Practice (GMP) production (driven by standard operating procedures in a GMP facility), and Investigational New Drug application. This is an excellent model for all of us as we work to translate novel molecular imaging tracers to the clinic more rapidly and more robustly in the future.

Changing Perspectives: A Focus on Inflammation

Major trends in cardiovascular nuclear medicine noted last year in this lecture, then, are clearly continuing. As we

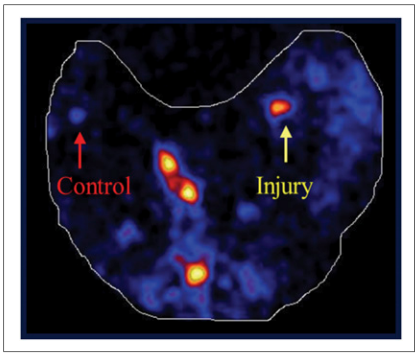

FIGURE 7. ^{64}Cu-C-atrial natriuretic factor PET imaging of natriuretic peptide clearance receptor in rabbit model of atherosclerosis shows specific uptake in sites of vascular injury.

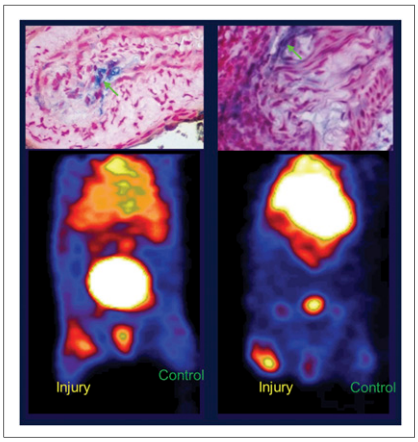

FIGURE 8. PET/CT and chemokine signaling in rat model of hindlimb injury. Left: CCR5 receptor immunohistochemistry and ^{64}Cu-DOTA-DAPTA PET/CT targeting CCR5. Right: CXCR4 receptor immunohistochemistry and ^{64}Cu-AMD-3100 PET/CT targeting CXCR4.

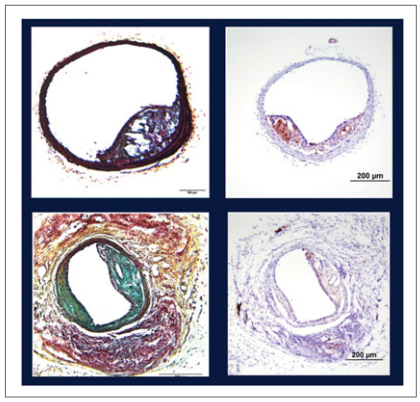

FIGURE 10. ^{117m}Sn-DOTA-annexin targeting and therapy of vulnerable plaque in APO-E mice. Left: controls. Right: mice administered low doses of ^{117m}Sn-labeled pharmaceutical. Histology showed reduced macrophage and increased smooth muscle cell expression at low-to-intermediate doses.

have seen at the 2013 meeting, PET is continuing to thrive. Solid-state detectors are changing the SPECT field. Quantification is desired for improved accuracy. Cardiovascular applications of PET/MR are growing. New (mostly PET) probes are moving toward clinical applications. Last year I concluded the cardiovascular highlights lecture with a wish list for SNMMI 2013. This list included the hope that we would: (1) focus more on multimodality integrative imaging; (2) tackle the many translational challenges with renewed vigor; and (3) think (and act) beyond traditional organ boundaries to look at the molecular mechanisms that play a variety of roles in different diseases. We have seen advances in the first 2 areas, and I would like to briefly focus on the third wish.

Perspectives in cardiovascular disease are changing. In the old view, cardiovascular disease was a degenerative condition, with imaging targets that included atherosclerosis, perfusion defects, infarct scar, and pump failure. The new view, as evidenced by many presentations at this meeting, is that cardiovascular disease is an inflammatory condition, with molecular imaging targets that include (but are not limited to) immune signaling, cell trafficking, tissue remodeling, and tissue regeneration.

Ogawa et al. from Hamamatsu University School of Medicine (Japan) and Takeda Pharmaceutical Company, Ltd. (Fujisawa, Japan) reported that "Macrophage polarization in atherosclerotic plaque affects FDG uptake" [78]. Macrophages are a key component of the inflammatory reaction in vulnerable plaques. We know that macrophages can have different polarization and can be proinflammatory (M1 macrophages) or anti-inflammatory (M2 macrophages). The researchers showed that ^{18}F-FDG uptake ex vivo preferentially accumulated in the proatherogenic M1 macrophages, whereas ultra-small superparamagnetic iron oxide particles preferentially accumulated in the M2 macrophages. The signal from ^{18}F-FDG, then, is specific for the proinflammatory reaction and is not the same as the information received from MR imaging. The 2 can be integrated to achieve a more accurate and informative picture of what is going on in vascular lesions.

Razavian et al. from Yale University (New Haven, CT), the Veterans Affairs CT Healthcare System (West Haven, CT), and Lantheus Medical Imaging (North Billerica, CT) reported on "Molecular imaging of matrix metalloproteinase (MMP) activation in abdominal aortic aneurysm" [77]. In a mouse model of aneurysms, they found that MMPs are expressed very strongly in animals that develop aortic aneurysms and in which the aneurysms progress as compared to those animals that do not develop aneurysms. This suggests that RP805, the marker used in this study (which is also an inflammation marker), may have potential for predicting whether aneurysms progress or even rupture.

Liu et al. from Washington University (St. Louis, MO) and the University of California, Santa Barbara looked at chemokine signaling, a different component of inflammation, and reported on "PET/CT of chemokine receptors CCR5 and CXCR4 in vascular injury and atherosclerosis" [131]. The researchers developed different ^{64}Cu-labeled

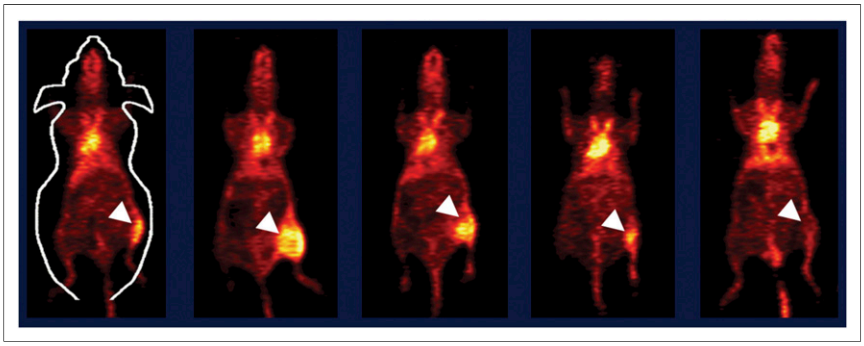

FIGURE 9. ^{64}Cu-NOTA-TRC105 PET imaging of angiogenesis in murine hindlimb ischemia at (left to right) days 1, 3, 10, 17, and 24. Signal preceded reestablishment of normal perfusion in damaged area (arrows).

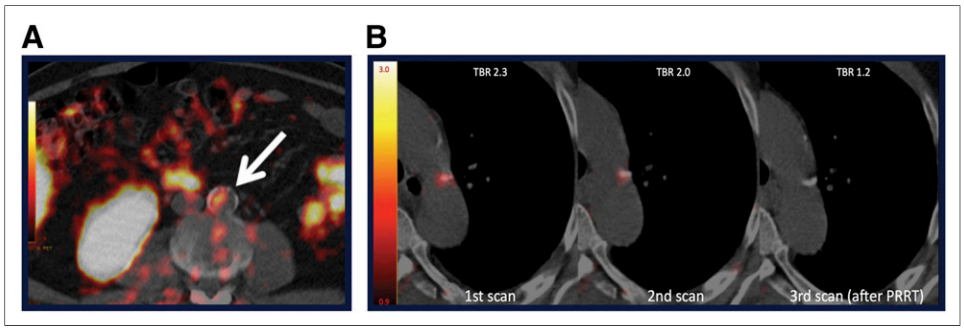

FIGURE 11. Peptide receptor radionuclide therapy (PRRT) and inflammation in atherosclerotic plaques. ^{68}Ga-DOTATATE PET/CT showed focal uptake in vessel wall lesions in oncologic patients, correlating with atherosclerotic risk factors. (A) Focal uptake (arrow). (B) Serial images in patient with neuroendocrine tumor show reproducibility of PRRT imaging (scans 1 and 2) before therapy and reduction in uptake (scan 3) after therapy.

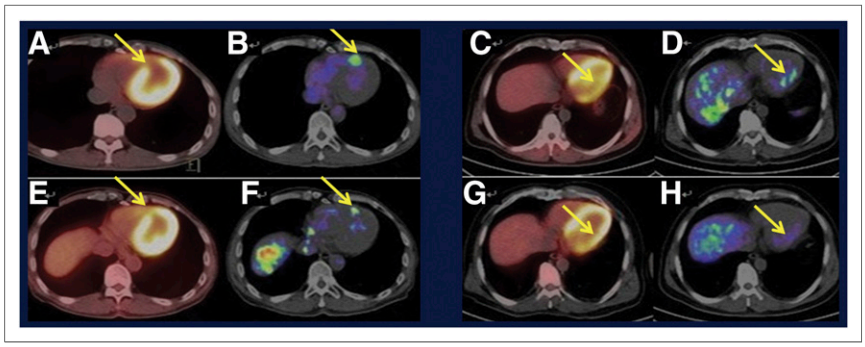

FIGURE 12. Integrin receptor imaging of postmyocardial infarction repair using ^{68}Ga-PRGD2 PET/CT. Left: images acquired in patient with chest pain. Right: Images in same patient without chest pain.

markers for different chemokine receptors and tested them in a rat model of hindlimb injury. They showed specific uptake at injury sites compared with sites in controls, indicating that these new markers might be used to develop novel molecular insights into the inflammatory process in the vessels (Fig. 8).

Orbay et al. from the University of Wisconsin, Madison and TRACON Pharmaceuticals (San Diego, CA) reported on "PET imaging of angiogenesis in murine hindlimb ischemia with a ^{64}Cu-labeled anti-CD105 antibody" [22]. This work was selected by the Cardiovascular Council for inclusion in the Young Investigator competition. With their novel marker, the researchers were able to acquire an early signal coming from the damaged hindlimb. The signal preceded reestablishment of normal perfusion in the damaged area (Fig. 9). This marker, then, may allow new insights into the repair process following vascular damage.

Srivastava et al. from Brookhaven National Laboratory (Upton, NY), Memorial Sloan–Kettering Cancer Center (New York, NY), Mount Sinai Hospital (New York, NY), CVPath Institute (Gaithersburg, MD), and Clear Vascular, Inc. (New York, NY) reported on the "Theragnostic potential of Sn-117m-DOTA-annexin for the molecular targeting and therapy of vulnerable plaque" [461]. ^{117m}Sn-annexin binds to apoptotic cells, including inflammatory apoptotic cells. In a preliminary apolipoprotein E mouse study, the researchers showed that systemic administration of ^{117m}Sn-DOTA-annexin targets and treats vulnerable plaque inflammation in the necrotic core without damage to surrounding tissue (Fig. 10). This indicates the potential for theragnostic use involving simultaneous SPECT/CT imaging and treatment of the vulnerable plaque.

Schatka et al. from the Hannover Medical School (Germany) asked "Does peptide receptor radionuclide therapy (PRRT) alter inflammation in atherosclerotic plaques?" [183]. The researchers looked at patients with neuroendocrine tumors who underwent PRRT. The patients had vascular lesions in which the somatostatin receptor was overexpressed, a hallmark of inflammation. After PRRT, they showed a reduction of uptake of the somatostatin receptor ligand in the vascular region, suggesting that this is another way that we may be able to modulate atherosclerotic plaque biology (Fig. 11).

Researchers are looking beyond vascular lesions with molecular imaging techniques and are reporting on studies involving the myocardium and inflammation within the myocardium. Sun from Peking Union Medical College Hospital (Beijing, China) and the National Institute of Biomedical Imaging and Bioengineering (Bethesda, MD) reported on: "Integrin receptor imaging of postmyocardial infarction repair using ^{68}Ga-PRGD2 PET/CT: a pilot clinical study" [80]. The researchers were able to identify a specific signal from the damaged site (Fig. 12). If the signal persisted over time, patients were more likely to have persistent chest pain. Thus, the SUV_{max} of RGD peptide uptake might be useful for predicting recovery and monitoring the repair process.

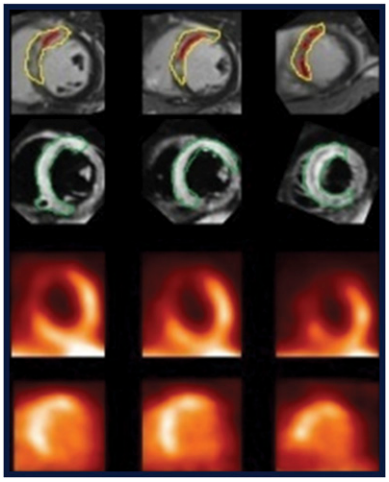

FIGURE 13. Multimodality imaging of inflamed acutely infarcted myocardium. Top 2 rows: MR imaging of infarct (top) and edema (bottom). Bottom 2 rows: ^{18}F-FDG PET imaging of perfusion (top) and inflammation (bottom).

Wollenweber et al. from Hannover Medical School (Germany) reported on "Characterization of inflamed, acutely infarcted myocardial tissue by combined clinical FDG PET and cardiac MR" [185]. In this approach, heparin pretreatment is used to suppress the uptake of ^{18}F-FDG in healthy myocytes. This results in a specific signal from the transmurally infarcted region and may be another way in which we can secure a specific inflammation signal that can be used to monitor novel therapies for myocardial repair and recovery (Fig. 13).

Conclusion

We have seen many presentations at this meeting that suggest that most cardiovascular disease, including atherosclerosis, CAD, myocardial infarction, and even heart failure, is inflammatory disease. Inflammation is also a cross-disciplinary key mechanism. In the other Highlights Lectures at this meeting the roles of neuroinflammation in neurodegenerative disease, of the immune system in cancer progression and therapy, and of inflammation in other organ disease will be highlighted.

We have seen, too, that cardiovascular technology in our field is advancing rapidly. Moreover, the broad scope and diversity of molecular imaging is changing our collective point of view. My wish for the future is for continued development beyond traditional organ boundaries, such as heart, brain and tumor, toward a more pathway-based imaging and therapy approach.

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Erratum

In the article "2013 SNMMI Highlights Lecture: Neuroscience" in the September issue of Newsline (2013;54[9]:15N), the lead author of the presentation "Retest imaging of nociceptin/orphanin FQ peptide (NOP) receptors using a new PET radioligand [11C]NOP-1A in healthy human brain" should have been identified as Talakad Lohith, MD, PhD. This error was made during editorial preparation of the publication and was not the result of an error on the part of the Highlights lecturer.