therapy, improving the success of radiation therapy and minimizing adverse effects, and providing "1-stop shopping" for simulation and diagnostics. Approaching radiation oncologists for enhanced use of imaging is not without its challenges. The field of molecular imaging, as a number of presenters at this summit have emphasized, is still short on validation (e.g., outcomes data). We have additional challenges in target motion, reproducible patient positioning, and more accurate quantification. We are still waiting, too, for new radiopharmaceuticals that can address many of the most pressing of radiation oncology imaging questions.

Effective collaboration and partnership with radiation oncologists may help to stave off the phenomenon of radiation oncologists purchasing their own scanners and farming out reads, keeping the technical component of reimbursement.

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Cardiovascular Molecular Imaging: Promoting Utilization and Outreach

Imaging of molecular markers and biological pathways can provide important insight into the pathogenesis and progress of cardiovascular diseases and assessment of therapeutic intervention. These include novel imaging strategies for heart failure, thrombosis, apoptosis, atherosclerosis, and angiogenesis. Molecular approaches directed at imaging of these processes will be discussed here, along with opportunities and challenges for advancing cardiovascular molecular imaging. The opportunities to be highlighted include: (1) current availability of metabolic imaging; (2) current availability of receptor imaging; and (3) availability of hybrid imaging systems. The challenges that will be outlined briefly here include: (1) equipment with inadequate sensitivity for imaging small vascular targets and inadequate correction capabilities for cardiac and respiratory motion; (2) lack of commercially available quantitative software for analysis of dynamic images or targeted "hot spot" images; (3) current investment in SPECT imaging on an outpatient basis by many cardiology practices; and (4) limited availability of ^{123}I and the need for more approved ^{99m}Tc-labeled agents.

To promote utilization and outreach in cardiovascular molecular imaging we need to first look at the current state of the art in molecular imaging in relation to current problems in management of cardiovascular disease. Molecular imaging techniques currently allow us to assess cardiac metabolism and neuronal function. We can perform receptor imaging and, in the future, targeted imaging of biological processes, including but not limited to atherosclerosis, vascular remodeling, thrombosis, inflammation, angiogenesis, apoptosis, necrosis, postinfarct remodeling, and heart failure. There is also a clear future role of cardiovascular molecular imaging for the monitoring of genetic or stem cell therapy. However, for the purposes of this discussion, we will focus on imaging in patients following myocardial infarction (MI) with left ventricular (LV) dysfunction at risk for sudden cardiac death and LV remodeling as 2 practical applications. Receptor imaging offers a clinical approach available now, whereas other more specific targeted approaches may be available in the future.

Sudden Cardiac Death After MI

One area in which molecular imaging can have a major clinical impact right now is in assessing the potential for sudden cardiac death after MI and in providing direction for treatment. Patients are currently triaged on the basis of simple parameters such as LV ejection fraction (LVEF), and we know, for example, that an LVEF $<$30% carries with it a much higher risk for sudden cardiac death and that this risk is high in the earlier stages (Solomon et al., *N Engl J Med*. 2005;352:2581–2588). These at risk patients are managed with implantation of automatic internal cardiac defibrillators (AICDs). The current selection criteria for AICD placement are based on the results of a number of large clinical trials, the most prominent of which are the Multicenter Automatic Defibrillator Implantation Trials (MADIT) I and II. The results of MADIT-I suggested that patients who had positive electrophysiologic studies for induced ventricular tachycardia (VT) or even showed nonsustained VT on a Holter monitor might benefit from preventive insertion of an implantable defibrillator. MADIT-II offered amended criteria when participating researchers found a 30% reduction in mortality in patients who were randomized to receive an AICD (in fact, the trial was stopped early so that more participants could benefit from the procedure). Today the recommendation is

that anyone at 1 mo post-MI with an LVEF <30% is a candidate for AICD implant, regardless of whether he or she undergoes Holter monitoring or electrophysiologic studies.

The economic implications of this management strategy are high, because AICDs cost $30,000–$40,000 to implant and last for only 4–5 y. Moreover, only a small percentage of implanted devices ever fire (i.e., are called upon to provide the service for which they were implanted). Based on the MADIT-II recommendations, about 400,000 patients in the United States would qualify annually to receive AICDs. This presents a prohibitive cost challenge to our health care system. A better solution would be to find an approach that could triage patients more effectively than simple measurement of LVEF.

Several imaging approaches have been proposed for better assessing risk in these patients. MR imaging, in particular, is making inroads in this area. Yan et al. (*Circulation.* 2006;114:32–39) demonstrated that characterization of the periinfarct zone by contrast-enhanced cardiac MR imaging is a powerful predictor of post-MI mortality. These investigators found that patients in whom the periinfarct area was >50% of the infarct size had a much lower survival and that "infarct characteristics by cardiac MR may prove to be a unique and valuable noninvasive predictor of post-MI mortality." A subsequent study by Schmidt et al. (*Circulation.* 2007;115:2006–2114) looked at the subset of patients who actually receive defibrillators after MI. These researchers also quantified the heterogeneous infarct periphery and the denser infarct core and defined infarct transmurality. These MR indices were related to inducibility of sustained VT during electrophysiologic or device testing. They concluded that infarct tissue heterogeneity on MR imaging identified enhanced cardiac arrhythmia susceptibility in patients with prior MI and LV dysfunction.

We need to consider whether there are nuclear medicine or targeted molecular approaches that could be used to provide better risk stratification of post-MI patients. We know that neuronal function is impaired after myocardial ischemic injury and that significant denervation is seen after MI. We can already perform presynaptic imaging with either a SPECT tracer (^{123}I-metaiodiobenzylguanidine [^{123}I-MIBG]) or a PET tracer (^{11}C-hydroxyphedrine [^{11}C-HED]). Fortunately, ^{123}I-MIBG is already approved for clinical use, although not for this application. A large body of clinical literature already exists with regard to the role of ^{123}I-MIBG imaging. We know, for example, that if MIBG imaging is used to assess the heart-to-mediastinal ration and that ratio is low, then the patient is at higher risk for cardiac events. Higuchi and Schwaiger (*Heart Failure Clin.* 2006;2:193–204) compiled an impressive survey of literature suggesting the utility of ^{123}I-MIBG neuronal imaging in assessing risk of sudden death in patients with congestive heart failure. This approach, however, is not currently used in routine clinical practice. A large industry-sponsored trial is currently looking at ^{123}I-MIBG imaging as a potential approach for AICD triage in patients at risk for sudden cardiac death (coronary artery disease, LV ejection fraction <35%). A pilot clinical study tried to relate the early heart-to-mediastinal ratio as assessed by ^{123}I-MIBG to heart rate variability as another parameter for identifying those patients who would be most appropriate for AICD implant. This study by Arora et al. (*J Nucl Cardiol.* 2003;10:208–210) reported that patients with an AICD discharge had significantly lower ^{123}I-MIBG heart-to-mediastinal uptake ratios and ^{123}I-MIBG defect scores, as well as more extensive sympathetic denervation. The authors concluded that, "Cardiac autonomic assessment using a combination of myocardial scintigraphic and neurophysiologic techniques may help select patients who would most benefit from an implantable defibrillator by identifying those at increased risk for potentially fatal arrhythmias." The National Institutes of Health (NIH)–sponsored Prediction of ARrhythmic Events with PET (PAREPET) trial at the University of Buffalo is assessing $^{13}NH_3$, ^{18}F-FDG, and ^{11}C-HED PET as alternative approaches for triaging these patients for AICD implantation.

The use of neuronal imaging represents a big opportunity for immediate clinical application of molecular imaging in a large group of patients following MI at risk for sudden cardiac death. The challenge is to identify ways in which the benefits that can be conferred by this molecular imaging approach are recognized and applied by the medical community at large. Perhaps part of the solution will come when the results of the larger ongoing clinical trials are in. A significant amount of education will be required so that patients, referring physicians, and regulators understand the economic and lifesaving benefits that imaging can bring in the setting of sudden cardiac death after MI.

Remodeling

Another area in which molecular imaging is likely to play a key role in the future is in the assessment and prediction of cardiac remodeling after MI. A number of approaches are currently taken to evaluate the dilatation and hypertrophy of the left ventricle that occurs after MI and that is associated with poor outcomes and increased risk of cardiac arrhythmias. These approaches include assessment of LV function and geometry, myocardial ischemia (perfusion, metabolism, hypoxia) or injury (infarction, apoptosis), inflammation, myocardial denervation, angiogenesis, and the extracellular matrix.

Matrix metalloproteinase (MMP) activation is believed to play an important role in tissue remodeling. In the heart, circulating MMPs are released and degrade the matrix and membrane-bound MMPs activate other MMPs. MMPs are regulated both at the transcriptional level and at the protein level, with circulating inhibitors. Spinale (*Physiol Rev.* 2007;87:1285–1342) has provided an excellent and comprehensive review of MMPs and myocardial matrix remodeling. He concluded that "the regulation of matrix protease pathways such as the MMPs and TIMPs [tissue inhibitors of MMPs] will likely yield a new avenue of diagnostic and therapeutic strategies for myocardial remodeling and the progression to heart failure."

Imaging can provide information that goes beyond that provided by serum biomarkers. Clinical data already indicate that changes in serum levels of MMP-9 are predictive of which patients will remodel and have poor outcomes. Webb et al. (*Circulation.* 2006;114:1020–1027) have shown a direct relationship between change in MMP-9 levels and dilatation of the left ventricle.

At Yale, we believe that there is an advantage to targeted cardiac imaging of MMPs that goes beyond the information provided by serum markers. MMPs are activated in other inflammatory processes, such as arthritis, so that the serologic presence of MMPs cannot provide a complete and specific cardiac predictor for remodeling. We began by using hybrid microSPECT/CT with a ^{99m}Tc-labeled MMP-targeted radiotracer (^{99m}Tc-RP805) to look at a murine model of postinfarction remodeling (Su et al. *Circulation.* 2005;112: 3157–3167). We obtained excellent fusion images, with favorable biodistribution and clearance kinetics for the tracer, and concluded that this approach held significant potential for localization of MMP activation and tracking of MMP-mediated post-MI remodeling.

Traditional radiotracer imaging involves evaluation of relative radiotracer uptake patterns. However, accurate assessment of MMP activation with imaging would involve more than simply looking at relative uptake. We would need to establish whether MMPs are activated in the infarct area as well as in the remote areas, because remodeling occurs throughout the left ventricle. Ideally we need to quantify the level of MMP of activation in all regions of the heart. This requires the application of hybrid imaging systems that allow for correction of attenuation and partial volume errors.

To establish in vivo imaging approaches for quantification of MMP activation, we extended our small animal imaging studies to porcine and canine models of either angioplasty occlusion of coronary arteries or surgical ligation of coronary arteries to induce MI. Analysis of hybrid SPECT/CT images with MMP-targeted radiotracers and perfusion agents from these large animal studies indicate that this hybrid imaging approach offers a valid method to noninvasively quantify MMP activation not only in the infarct areas but also in the remote areas. We have been able to quantify regional myocardial uptake of the MMP-targeted radiotracers as a percentage of injected dose, providing a reliable estimate of regional MMP activation, which we have validated by ex vivo immunoblotting and zymography for tissue MMP activity. Ongoing studies are evaluating the potential value of targeted MMP imaging for the prediction of LV remodeling and tracking therapeutic interventions to prevent the adverse post-MI remodeling.

Challenges and Recommendations

We are very close to the routine application of molecular imaging in management of patients with cardiovascular disease. It is clear that we have the capability to perform post-MI neuronal SPECT ^{123}I-MIBG imaging in patients, although this molecular imaging approach has not been widely applied, in part because of problems with the availability of ^{123}I, lack of quantitative tools for analysis of the in vivo images, and limited exposure of the medical community to the value of this approach. It is also clear that the increased availability of various hybrid imaging systems (SPECT/CT and PET/CT) will facilitate quantification of molecular imaging agents like ^{123}I-MIBG or ^{11}C-HED. Unfortunately, the current hybrid systems are not optimally designed for this type of quantitative cardiac molecular imaging.

It is imperative that we pursue the many possibilities that molecular imaging offers for cardiovascular medicine. For example, as outlined here molecular imaging can improve selection of patients after MI for AICD implantation, enhancing outcomes and having a potentially significant impact on reducing health care costs. Molecular imaging of MMP activation or other critical molecular processes after MI may also predict LV remodeling and subsequent development of congestive heart failure, as well as risk for sudden cardiac death. The application of these and other techniques promises to facilitate truly personalized medicine.

A number of challenges stand in the way of realizing these promises. The majority of cardiac imaging today is done with SPECT on an outpatient basis. Most cardiac practices have invested in and actively employ SPECT. Convincing them to turn to hospital-based PET may be a difficult task. Moreover, it is not yet clear whether targeted PET or SPECT imaging will be better for evaluation of patients with cardiovascular disease. Quantification of SPECT images will likely also require more expensive hybrid imaging systems. The limited availability of ^{123}I is another challenge, and we need more ^{99m}Tc-labeled targeted agents. Finally, current nuclear imaging systems have not been optimized for cardiac applications, with inadequate correction for cardiac and respiratory motion and a lack of quantitative software for targeted agents.

From the cardiovascular perspective, I would recommend several actions that SNM and the molecular imaging community could take to increase utilization and adoption of these highly promising molecular imaging techniques:

- Educational efforts should be created for outreach to both basic scientists and clinicians in the cardiovascular community, including outreach to members of the American Heart Association, the American College of Cardiology, and the American Society of Nuclear Cardiology. It is important to remember that cardiologists, unlike oncologists, are still relatively unaware of the potential value of molecular imaging.
- NIH should be encouraged to support funding in cardiovascular molecular imaging. The National Cancer Institute has invested large amounts of money and resources in molecular imaging, but the National Heart, Lung, and Blood Institute has been slow to follow suit, despite the significant health implications.
- The development of hybrid imaging systems for small and large animal translational research in cardiovascular medicine should be encouraged. Translational research in

cardiology is somewhat more challenging than in oncology. Often larger animal models and, therefore, larger research scanners are required.
- Current clinical imaging systems should be optimized to facilitate cardiovascular molecular imaging.
- And, as many individuals at the Molecular Imaging Summit have emphasized, standardization of imaging protocols and quantification schemes is needed to facilitate evidence-based, multicenter clinical studies.

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Utilizing Technological Advances to Grow Molecular Imaging Clinical Services: Industry Perspective

Technology has been a driving force behind the rapid growth of clinical molecular imaging. Advances in scanners, postprocessing, application software, and information technology (IT) integration have been key enablers of growth into broader clinical services and higher productivity in existing service lines. For example, today's PET/CT scanners have broad clinical utility in diagnostic oncology, radiation therapy planning, treatment monitoring, evaluation of myocardial perfusion and viability, and neurodegenerative diseases, as well as a complete diagnostic CT service including peripheral and coronary angiography, stroke, and interventional applications. Only a few years ago, many of these clinical applications were not possible on a single PET/CT system. Today, however, successful PET/CT centers are utilizing their scanners in many or all of these areas. Technology has also driven higher productivity for routine ^{18}F-FDG oncology, which comprises more than 90% of today's PET/CT procedures. Hybrid PET/CT imaging with CT attenuation correction has reduced exam times by half. Higher sensitivity scanners and 3D imaging can deliver shorter patient exam times. Physician productivity has improved through fused PET and CT displays with dedicated application software for faster interpretation and shorter report turnaround times.

The Molecular Imaging Value Stream

The perspective I bring to this session and to the Molecular Imaging Summit is that of industry. The makers of medical devices are as interested as the field's practitioners in determining how to grow clinical utilization and in identifying both drivers and bottlenecks in this process. The engine that drives innovation in medical imaging is powered by market forces: those that bring new devices to market and those that create sustainable markets for these new devices. One of the business improvement methodologies that GE uses to optimize different steps of a market or business process is Lean Six Sigma. Lean Six Sigma combines tools from the Lean Manufacturing and Six Sigma methodologies to focus on speed of development and on quality. A typical (simplified) application of Lean Six Sigma involves identifying the processes most important to delivering customer value, mapping these processes using value stream mapping, identifying the bottlenecks or constraints inherent in the value stream, and finally applying "variation reduction" techniques that can speed development and ensure consistent high quality. Lean Six Sigma allows us to create a framework for goal-directed discussion of growth, simplification, and quality in medical device manufacture and marketing.

The value stream for molecular imaging devices involves multiple viewpoints and elements that drive utilization. One way this value stream can be conceptualized is in a flow representing the stages at which a patient may be imaged, integrating industry, practice, and delivery into a framework for discussion. In the first stage, a patient comes in with a symptom or sign of a disease. The utilization drivers that can lead to imaging at this stage include disease prevalence, clinical indications for use, and cost effectiveness. The primary care physician or specialist then seeks diagnostic imaging based on patient management guidelines, the extent to which he or she as a physician is educated about the benefits of imaging in this specific disease setting, patient awareness of these benefits, and the quality of information the imaging report is likely to yield. If disease is confirmed, the patient then proceeds to treatment and/or monitoring, for which imaging choices are based on (and may be an active part of) clinical trial results and new drug development. Finally, imaging may be used in follow-up studies, where the decision to utilize imaging is driven by known survival and recurrence rates. Reimbursement is a prime utilization driver throughout the value stream.

At the center of this value stream, which includes key handoff points, is the imaging service provider. If we assume,