Strategies for defining an optimal risk-benefit ratio for stress myocardial perfusion SPECT

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INTRODUCTION

Tremendous growth in medical imaging has prompted a re-focusing on the appropriateness of testing and the rationale for exposure to ionizing radiation for large segments of the adult population at intermediate to high likelihood for coronary artery disease (CAD).[1-9] Part I of this series addressed the technical or methodological approaches to measuring radiation exposure and laboratory approaches to reducing exposure including the clinical utility of stress only imaging.[10] In the current statement, we present a clinical approach for defining the risk:benefit ratio of myocardial perfusion imaging (MPI) focusing on the appropriate use of single photon-emission computed tomography (SPECT) or positron emission tomography (PET) MPI. We also review the concept of ''patient-centered imaging'' and discuss methods for effectively addressing patient concerns regarding procedural risk.

THE PUBLIC'S AND PAYER'S SAFETY CONCERNS

Several recent high profile reports have highlighted the expansive growth in medical imaging using ionizing radiation.[5,6,11-13] The Congressionally chartered National Council on Radiation Protection and Measurements (NCRP) evaluated all sources of ionizing radiation to the US population in 2006.[12] They reported a 6-fold increase in radiation exposure from medical imaging between 1980 and 2006, with computed tomography (CT) and nuclear imaging accounting for most of this growth. Two other recent reports have used insurance claims data from a single large payer (UnitedHealthcare) to further study this question. In one study that assessed all imaging procedures involving ionizing radiation within a large cohort of non-elderly adults, cardiac imaging contributed over 29% of all radiation exposure from medical imaging and MPI alone accounted for 22%.[6] In this study, 1.9% of the population received annual effective doses of $\geq$20 mSv from medical imaging, projecting that over 3 million Americans received these doses each year. A second study reported that 9.5% of individuals underwent at least 1 cardiac imaging procedure in a 3-year time period, including 3.5% undergoing MPI. In a more recent cohort study of 1,097 consecutive patients undergoing MPI, $\sim$39% of patients underwent multiple MPI procedures resulting in a cumulative effective dose of >100 mSv in most of these patients.[14]

Not surprisingly, these reports have prompted considerable controversy within the medical community as well as captured the attention of the media and patients regarding the impact of imaging utilization on cancer risk. Earlier this year, Congress held hearings to investigate the need to regulate radiation exposure in the clinical setting. In at least one instance, these reports have been cited by a third-party payer as justification for instituting a requirement for prior authorization of MPI.[15]

In an effort to guide this discourse, we attempt to provide a rational, evidence-based approach to evaluating the relative risks and benefits of MPI in this statement. Although the relationship between low-dose (<100 mSv) radiation exposure and cancer risk cannot be causally established from existing data, there is a reasonable chain of evidence to suggest that such a link exists.[16-18] As such, this document serves to focus clinicians on how to approach the public's concerns respectfully and seize the opportunity to educate patients

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and payers about the concept of appropriate indications and that the benefits of CAD detection far outweigh radiation exposure risk when applied to targeted, appropriate patients.

RADIATION EXPOSURE FROM MPI

Direct evidence is not available demonstrating causality between low-dose (<100 mSv) radiation exposure from a cardiac imaging procedure, and in particular the radiopharmaceuticals used for MPI, and an increased risk of cancer. Concern relating to cancer risk from cardiac imaging is derived from associations between other sources of ionizing radiation, often at higher radiation doses than those typical for any single cardiac imaging procedure, and increased cancer risk.[15-17] Thus, any estimate of cancer risk from cardiac imaging is a projection and is subject to multiple sources of uncertainty. Nevertheless, current US and worldwide expert consensus, based on extensive review of the biophysical and epidemiologic data, states that there is *no* dose of ionizing radiation below which there is *not* an expected increased risk of cancer. Moreover, cancer risk increases proportionally with radiation dose, forming the basis for the linear no-threshold hypothesis.[16,19,20]

A first step in assessing the risk is to understand how it is estimated and its limitations. There are several challenges to estimating the lifetime attributable risk (LAR) of cancer incidence from MPI. First, the overall (whole-body) LAR of cancer incidence from a given exposure is calculated by summing the organ-specific LARs as defined in Table 12D-1 in the National Academies' Biological Effects of Ionizing Radiation 7th Report (BEIR-VII Phase 2). In the case of MPI, the hepatobiliary excretion of Tc-99m leads to high organ doses to the gall bladder. However, due to paucity of data, BEIR-VII does not include an organ-specific LAR for the gall bladder and using LAR estimates listed under the ''other'' category in this table is subject to significant uncertainty. Second, BEIR-VII risk estimates were developed for the average US population and are applicable to individuals with a normal life expectancy. This assumption may be reasonable for patients with a low risk for CAD; yet these patients are largely not appropriate MPI candidates. However, in patients with decreased life expectancy (e.g., those with CAD or in symptomatic populations), the BEIR-VII model overestimates cancer risk because patients may not survive long enough to develop a radiation-attributable cancer. Finally, the organ doses that are typically used are not patient-specific, but rather assume the anatomy and radiopharmaceutical kinetics of a sex-averaged reference subject. Thus, predictions made on population-based or gender-averaged observations generally apply to an ''average'' member of a similar population and not necessarily to individual patients undergoing clinically indicated MPI.

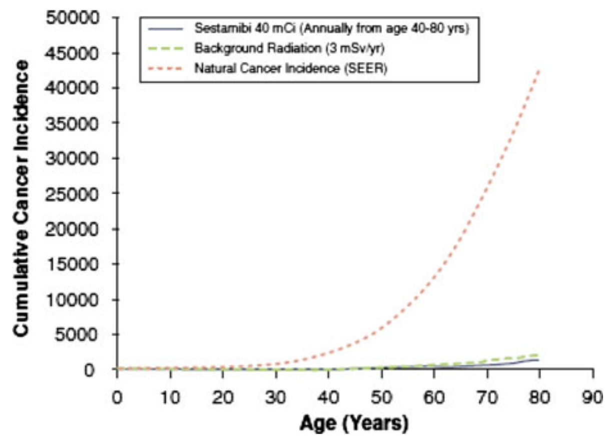

Figure 1. Cumulative cancer incidence (expressed as cases per 100,000 women) attributed to background radiation (3 mSv), an annual dose of 40 mCi of technetium-99m sestamibi from age 40 to 80 years, and naturally occurring cancer. Reproduced with permission from JACC Imaging 2010;3:528–535.

Despite the challenges in methods for risk estimation, it is worth highlighting that the LAR of cancer from a single MPI study is very low (Figure 1). Even when MPI using a higher-dose protocol, such as a dual isotope study, is performed in a younger female patient (thought to be more susceptible to the adverse effects of radiation), the LAR of cancer based on BEIR-VII estimates is very small. The estimated LAR is far less for the typical, 60-year-old patient referred to MPI. From a recent report, it is projected that for a 60-year-old patient undergoing rest-stress Tc-99m SPECT that ~8-9 future cancers per 10,000 scans would result from exposure to ionizing radiation.[21] In a related series for patients ages 50-70 years, the number of future cancers were projected to range from 1-3 per 10,000 scans for coronary artery calcium imaging.[13] By comparison, the lifetime risk of cancer is 1 in 2 for men and 1 in 3 for women.[22] As such, the estimated increase in lifetime cancer risk following exposure to rest-stress Tc-99m SPECT is <1% for both women and men.

EFFECTIVE DOSES FOR NUCLEAR CARDIOLOGY PROCEDURES

There is a substantial body of literature related to the amount of radiation to which patients are exposed from cardiac imaging procedures.[7-9,11,23-27] One metric commonly used to quantify the amount of radiation associated with a procedure is the effective dose, a calculated whole-body value that reflects the concentration of radiation deposited in each organ, the types of radiation, and the relative sensitivity of each organ to the adverse effects from ionizing radiation. Effective dose is commonly reported in units of milliSieverts (mSv). As points of reference, a typical anteroposterior chest x-ray has an effective dose of 0.02 mSv, and a typical mammogram has an effective dose of 0.4 mSv. Average annual background radiation in the US is 3 mSv.

Several studies have now quantified effective doses from nuclear cardiology procedures and effective doses to patients undergoing cardiac imaging.[7,9] Applying the recommended administered activities of the American Society of Nuclear Cardiology (ASNC) (mCi), effective doses of standard nuclear cardiology protocols range from 7 mSv for stress-only imaging using Tc-99m to 24 mSv for dual isotope MPI (rest Tl-201 followed by stress Tc-99m).[7,9] A recent study reported an effective dose of 3.7 mSv for a rest-stress Rb-82 PET protocol with a combined injection of 80 mCi.[23] Additionally, recent results using rapid CZT SPECT MPI stress only imaging was associated with an effective dose of 4.2 mSv.[28]

CLINICAL DECISION-MAKING: ASSESSING THE RISK:BENEFIT RATIO OF MPI

Clinical decision-making regarding the use of imaging should include consideration of radiation-related risks; however, it is important to apply this reasoning in a balanced manner. That is, the long-term latent risks related to radiation exposure should always be considered in the context of the short-term clinical benefit expected from clinical knowledge gained from MPI. As such, for every patient, a clinician needs to consider both the benefit and the risk of testing in terms of added information that may be applied to target clinical decision making based on MPI findings.

APPROPRIATE USE OF MPI

The clinical use of MPI for identifying CAD among patients presenting with suspected myocardial ischemia and cardiac symptoms is widespread, and its accuracy and prognostic value is firmly established in the peer-reviewed literature. An appropriate study, by definition, provides incremental information, combined with clinical judgment, which exceeds the expected negative consequences, such as the risk of ionizing radiation from the procedure.[29] Thus, when appropriately utilized, the clinical benefits of MPI far outweigh the lifetime potential risk of ionizing radiation exposure.[16] Examples of appropriate uses of MPI, where existing evidence highlights its greatest incremental clinical utility, include patients with an intermediate to high likelihood for CAD, cases requiring additional physiologic and prognostic information for patient management, and patients with persistent symptoms that cannot be readily dismissed.[29-31] In patients with established CAD by anatomy (i.e., coronary stenosis or anatomic abnormality of uncertain significance), MPI is commonly applied and considered to be appropriate to ascertain functional ischemia and prognostic information to guide anti-ischemic management strategies.[32] Other examples of appropriate indications for MPI include new or worsening symptoms in patients with abnormal coronary angiography or an abnormal prior stress study, the assessment of myocardial viability in patients with known severe left ventricular dysfunction who are candidates for revascularization, and a risk assessment within 3 months of an acute coronary syndrome in hemodynamically stable patients without recurrent chest pain or heart failure symptoms to evaluate for inducible ischemia in the absence of prior coronary angiography. Published appropriate use criteria are available to guide the identification of patients known to derive the greatest benefit from MPI.[29]

Routine MPI is not indicated in asymptomatic patients for the detection of CAD or for risk assessment without ischemic equivalents.[29] An ASNC statement is available to guide the use of MPI in asymptomatic patients.[33] Other examples of inappropriate indications include patients with a low pretest probability for CAD, preoperative risk assessment for low- and intermediate-risk non-cardiac surgery in patients with moderate-to-good functional capacity and without active cardiac conditions, or risk assessment in asymptomatic patients less than 2 years post-revascularization (including percutaneous coronary intervention or coronary artery bypass surgery). Marked reductions in testing for most of the above inappropriate indications could reduce the projected incident cancer cases following MPI by as much as one-third.[13]

In patients with inappropriate indications for MPI, the estimated LAR of cancer from radiation exposure, although minimal, should still be considered to be unacceptable. Hence, the discussion regarding the use of low-level ionizing radiation for MPI should focus on the appropriate selection of patients and the application of the As Low As Reasonably Achievable (ALARA) principle for the administration of a radiotracer to obtain high-quality, clinically interpretable images.[2,4]

CASE EXAMPLES

When cardiac imaging is limited to appropriate patients and indications, the typical benefit far outweighs the radiation-related risk of the procedure.

Conversely, in cases with inappropriate indications (i.e., where no benefit can be expected) the radiation-related risk provides an added reason not to perform the test. We use two examples below to further highlight this issue. Consider the case of a 60-year-old male smoker with hypertension but no known CAD who presents with several episodes of exertional chest pain. Based on his Framingham risk score, he is at high (>20%) risk of death or myocardial infarction in the next 10 years. Establishing a diagnosis of CAD and initiating secondary prevention with a statin, aspirin, and beta-blocker in such a patient can be expected to yield an absolute risk reduction of 1%-5% for cardiac death and myocardial infarction within the first 5 years. Furthermore, treating his symptoms and allowing him to remain physically active has a significant beneficial impact on his quality of life. On the other hand, the estimated LAR of cancer associated with performing a Tc-99m rest-stress myocardial perfusion SPECT (with an effective dose of approximately 11 mSv) in this setting based on the BEIR-VII model is well below 0.2%.[21] It is clear that the expected benefits of the procedure in this scenario far outweigh its potential latent radiation-related risk.

In contrast, consider a physically active 30-year-old woman with atypical chest pain, a normal electrocardiogram (ECG), and no cardiovascular risk factors. As reflected in the *2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging*,[29] pursuing stress imaging in this patient is inappropriate and cannot be expected to result in any significant benefit. Based on the BEIR-VII model, the LAR for cancer related to a Tc-99m stress-rest myocardial perfusion SPECT study (∼11 mSv) in this patient, while is still less than 0.2%,[21] is higher than in the previous example. In the absence of any expected benefit from the procedure, there is no justification for accepting the radiation-related risk in this patient, however small.

Estimating the risk-benefit ratio of performing stress MPI in most clinical scenarios may not be as simple as was reported in these examples. However, limiting the use of MPI to appropriate indications is an effective strategy for ensuring that the benefit of a study far exceeds any potential risks (Figure 2).

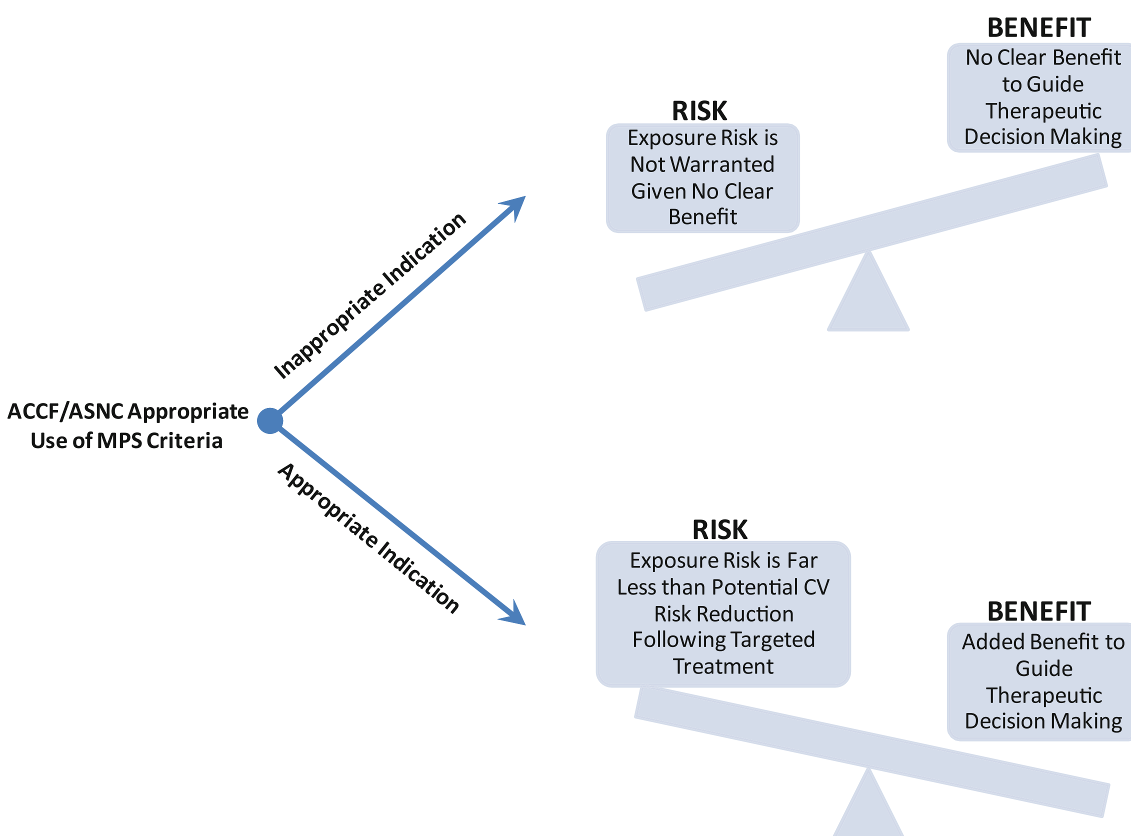

Figure 2. Simplified depiction of the risk-benefit of stress myocardial perfusion SPECT in relation to the ACCF/ASNC appropriate use criteria.

It should be noted that the LAR of cancer from a given radiation exposure is higher for younger and female patients. For example, the LAR of cancer from a coronary CT angiography with tube current modulation in a 20-year-old woman is nearly 5-fold higher than the LAR for a 20-year-old male and almost 3-fold higher than the LAR for a 60-year-old woman.[8] Hence, once the clinical need for imaging has been established, considering alternatives to MPI that have reduced exposure (i.e., PET) or no ionizing radiation is particularly important in younger patients and women. Excluding an appropriate indication, such as known CAD, the application of non-ionizing radiation stress tests including exercise ECGs should be encouraged as a first line diagnostic test for the vast majority of patients <40 years of age. The application of MPI as a secondary test in patients with an abnormal exercise ECG may then be appropriately considered in the younger patient. However, in patients <55 years of age, given an appropriate indication, the use of MPI or lower dose PET should be considered on an individual basis. As noted in Part I of this series, in this patient cohort of <55 years of age with suspected CAD, stress-only imaging should be applied whenever possible.[10]

PATIENT-CENTERED IMAGING AND EMPATHY FOR PATIENT PERCEPTIONS OF RADIATION

Patient concern is understandable with regards to exposure to ionizing radiation. For many clinicians, response to these concerns may be to ''downplay'' the exposure with patients and focus on the benefits of imaging. The following sections are meant to serve as a guide to assist clinicians with effective patient discussions related to the risks and benefits of cardiac imaging.

At the heart of patient-centered imaging is a focus on patient concerns and viewpoints that are addressed with interactive discussions about medically appropriate decisions. This forms the basis for shared clinical decision making. Patients respond more favorably to physicians with more empathetic interactions by engaging in more positive communication behaviors.[34] Thus, much of our discussion will focus on creating an environment where positive interactions will occur between physician and patient.

EXPLAINING RISK

At the core of this discussion lies an understanding of the perception of risk and the societal view of radiation. The explanation of risk to competent adults has been extensively studied and may provide some aid to nuclear cardiologists in improving discussions of risk with patients referred for MPI. For imaging tests using ionizing radiation, the explanation of risk entails some detailing of theoretical risk which is difficult for most patients to assimilate. It is important to note that the concept of risk assessment does not entail the actual measuring of risk but simply providing an estimate. Recall that it is a much easier concept to explain to a patient to lower cholesterol than for a given patient to comprehend the concept of CAD risk reduction. When it comes to medical imaging with ionizing radiation, explaining the risk of exposure is similarly difficult because individuals cling to their perceptions of radiation exposure as dangerous. Some have termed the risk:benefit ratio decision making as akin to the ''safe/dangerous dichotomy,''[35] which purports that people will engage in some degree of risk as long as they understand the amount of substantive diagnostic information that may be ascertained and the degree to which procedural complications are low (i.e., safe). To that extent, it remains vital to simplify the explanation of risk and a means to do this is to think through information goals.[35] For MPI, one should emphasize the appropriateness of the test for that patient and the utility of knowledge gained toward targeted therapeutic decision making. By individualizing the discussion to the patient, one should avoid qualifiers, exceptions, or abstracted concepts that may confuse or mislead an individual. Discussing examples of similar patients and how they approached the medical decision making process can improve patient comprehension and foster trust within the patient-physician interaction.[35]

One helpful suggestion is to provide concrete risk comparisons with every day exposures. Using examples of commonplace nonmedical exposures can help the patient understand that the medical imaging environment is not the sole means of radiation exposure. Naturally occurring background radiation results in an annual exposure of approximately 3 mSv in the United States.[36] Flying coast to coast exposes an individual to about 0.03 mSv. The American College of Radiology (ACR) uses comparisons with these common types of exposure to put imaging procedures in perspective for patients.[37] For example, the radiation exposure from a coronary CT angiogram or a Tc-99m SPECT MPI study is roughly equivalent to 3 to 4 years of background radiation.[37] The next step in this process of educating patients is to provide a hierarchical understanding of doses from dental x-rays to more complex imaging procedures. By providing a range, patients can more accurately understand where MPI fits within the realm of tests with radiation exposure.

Some experts in the field have proposed comparing the relative exposure from MPI to common procedures, such as a mammogram, dental x-ray, or chest radiograph. There are advantages to this, in that most patients would have frequent exposure to this type of imaging. For example, in terms of radiation exposure, a Tc-99m SPECT MPI study is roughly equivalent to ~27 mammograms.[37] Given the extensive public awareness programs to educate patients as to their risk of cancer and the need for early detection, introducing a corollary of the risk of dying from CAD (e.g., 1 in 3 women) and that diagnostic testing for CAD is akin to ~27 mammograms may provide the conceptual framework for enhanced patient comprehension of radiation exposure.

Current estimates are that ~14% of patients may be referred for inappropriate indications.[38] Concurrent to the development of a risk-guided educational program to explain medical imaging radiation risk to patients, physicians should work to focus referring physicians on the appropriate patient. Web-based or other medical education programs may be helpful to inform referring physicians as to appropriate indications.

UNDERSTANDING HEALTH LITERACY

The lack of comprehension of risk and balanced decision making with regards to their risk:benefit of CAD as compared to increased cancer risk is a major hurdle that must be overcome to have more educated healthcare consumers. All ASNC members should approach the subject of informed consent and an explanation of radiation exposure with some knowledge of the patient's health literacy. Health literacy, in the case of medical imaging, requires reasoning of the risk:benefit ratio and incorporation of probabilities and risk that is rarely employed outside of medicine, science, or finance. As such, most patients will have limited experience in this type of reasoning. In some instances, patients with low health literacy overestimate their own risk,[39] leading to increasing levels of distress with regards to the medical decision.[40] This concept of comprehension of health literacy and improved patient understanding serves as a critical foundation for informed decision making on the part of patients. For MPI, aspects of health literacy include information literacy (ability to obtain and apply relevant information), and numerical or computational literacy (ability to calculate or reason numerically).[41]

TARGETING IMPORTANT ELEMENTS OF THE MEDICAL INTERACTION

Critical elements of the patient interaction include the use of simple language that transparently describes the procedure coupled with periodic questions to verify patient comprehension regarding communicated information. There is an abundance of information on effective communication during the medical interview; yet little is known about how we can apply that evidence to the patient discussion on radiation exposure.[42-45] Roter et al[42] identified important components of the patient-physician interaction that might enhance patient understanding including:

1. *Patient data gathering* Key facts should be presented clearly, using simple language detailing the benefit of CAD detection and the importance of prompt therapeutic intervention for improved clinical outcomes.[42]
2. *Partnership building* The patient should have an understanding that you are going to provide advice that is optimal for their health.[42]
3. *Emotionally focused talk* Query the patient with regards to their fear of ionizing radiation and provide a straight-forward discussion of the added risk of exposure relative to their current cancer risk estimate.[42]

Table 1 provides some suggested questions that may help patients make their best health decision regarding the use of MI for detection of CAD.

Table 1. Ten questions I should ask my doctor about a stress nuclear exam

- What is this procedure and how will it tell me whether I have heart disease and define my risk of heart disease?
- How will this test help you with my care and benefit me?
- What is an appropriate indication for stress nuclear exam?
- What is my risk of heart disease and does that make this test right for me?
- Am I exposed to radiation in any other aspects of my life?
- How much radiation is used for the test?
- Is radiation harmful?
- Does radiation from stress nuclear imaging increase my cancer risk?
- Do I have any alternatives?
- If the scan is normal, does that mean that I should not have had the test?

FUTURE DIRECTIONS IN EDUCATION AND RESEARCH ON THE SAFETY AND EFFECTIVENESS OF MPI

In many clinical situations, the comparative effectiveness of imaging procedures is not clearly defined, which highlights the need to support and promote trials and registries to clarify the role of imaging in these scenarios. The Detection of Ischemia in Asymptomatic Diabetics (DIAD) trial is an example of how such studies can guide the effective and efficient use of imaging.[46] The DIAD trial compared screening with MPI as compared to usual care for asymptomatic, type-2 diabetics and found no benefit in terms of cardiovascular disease (CVD) risk reduction with an MPI-guided strategy. A number of trials, such as the *PRO*spective *M*ulticenter *I*maging *S*tudy for *E*valuation of Chest Pain (PROMISE) and *I*nternational *S*tudy of *C*omparative *H*ealth *E*ffectiveness with *M*edical and *I*nvasive *A*pproaches (ISCHEMIA), are currently under way or are being planned and will expand our appropriateness evidence base and further clarify the role of MPI in patients with suspected and known CAD.

MPI protocols should be optimized to achieve the lowest possible radiation exposure while maintaining diagnostic performance. Key aspects of this optimization include the use of radionuclides with shorter half-life (such as Tc-99m and PET tracers), stress-only imaging when feasible, and weight-based dosing. Supporting research and development of camera technology, image reconstruction and acquisition techniques, and approaches to collimation are crucial to continued progress in the field of nuclear cardiology. See Part I of this series for further details.[1]

CONCLUSIONS

Studies consistently show that adequate awareness of radiation doses associated with procedures and the risk attributable to these doses is lacking among physicians.[47-49] ASNC members are encouraged to gain adequate knowledge with regards to radiation exposure. A thorough knowledge of this and prior statements from ASNC should provide a basis for improved understanding of the risks and benefits of imaging with MPI. As understanding these concepts is crucial for informed clinical decision-making regarding the use of imaging procedures, it is necessary to address this knowledge gap among nuclear cardiologists, referring physicians, and trainees.

The current document provides a practical approach to applying the concepts of radiation exposure by targeting MPI utilization to priority populations with appropriate indications. All patients referred to MPI should be informed that MPI requires exposure to ionizing radiation. Additional guidance on methods to improve patient comprehension of the risks and benefits of MPI has also been provided. Our hope is that this series on radiation exposure will serve as core documents to enhance understanding of the risks and benefits of MPI, guide the appropriate use of MPI, and reduce unnecessary radiation exposure for inappropriate test indications.

Conflict of interest

Andrew Einstein, MD, PhD receives research support from Spectrum Dynamics. The authors have no conflicts of interest to disclose except as noted above.

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