REVIEW ARTICLE

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Review of Cardiovascular Imaging in the Journal of Nuclear Cardiology in 2015—Part 2 of 2: Myocardial perfusion imaging

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In 2015, the *Journal of Nuclear Cardiology*® published many high-quality articles. In this series, we will summarize key articles that have appeared in the Journal last year to provide for the interested reader a quick review of the advancements that have recently occurred in the field. In the first article of this 2-part series, we concentrated on publications dealing with plaque imaging, cardiac positron emission tomography, computed tomography, and magnetic resonance. This review will focus on myocardial perfusion imaging summarizing advances in the field including in diagnosis, prognosis, and appropriate use. (J Nucl Cardiol 2016;23:493–8.)

Key Words: Myocardial perfusion imaging · SPECT · phase analysis · dyssynchrony · appropriateness · safety · regadenoson

Abbreviations			
AUC	Appropriate Use Criteria	MACE	Major adverse cardiac events
CAD	Coronary artery disease	MI	Myocardial infarction
CR	Coronary revascularization	MPI	Myocardial perfusion imaging
HRR	Heart rate response	SSS	Summed stress score
LAD	Left anterior descending		
LVEF	Left ventricular ejection fraction		

INTRODUCTION

This review is the second part of a 2-part series that reviews key articles that were published in the *Journal of Nuclear Cardiology*® in 2015.[1] Similar to last year's reviews[2,3], we have dedicated a separate article for the field of myocardial perfusion imaging (MPI) using SPECT since this is of particular interest to our readers.

APPROPRIATE USE

Appropriate use criteria (AUC) were developed to curb the growth in imaging by allowing for its use in clinical scenarios where it may guide therapy, while avoiding it in scenarios where there is a consensus that imaging is of low clinical value. Many studies have reported on the rate of inappropriate use of MPI according to the AUC. Elgendy et al[4] conducted a meta-analysis of 22 studies, encompassing more than

23,000 patients, that reported the prevalence of appropriate and inappropriate MPI testing and had data on clinical outcomes or on the variation among clinicians in ordering MPIs. Overall, inappropriate testing was done in 15% of patients (95%CI 12-19%) with a wide variability among included studies that ranged from 5% to 46%. When compared to appropriate MPIs, inappropriate ones were less likely to be abnormal (16% vs 42%, odds ratio 0.41, $P < .0001$) or to show myocardial ischemia (6% vs 19%, 0.40, $P < .0001$). There was no difference in the rate of inappropriate testing based on the provider (cardiology vs non-cardiology). This meta-analysis suggests low utility of MPI when performed in scenarios that are considered inappropriate (labeled rarely appropriate in more recent AUCs) since these studies are much less likely to be abnormal or to show myocardial ischemia. Importantly, the rate of inappropriate studies was stable over time but showed wide variability among studies which suggests the need for targeted interventions to decrease this rate.[5]

Mahajan et al[6] assessed the feasibility of using a smartphone app based on the 2009 AUC at the point of care for inpatients in a teaching community hospital. Of 403 MPIs ordered (52% female, 31% diabetes, 18% prior coronary revascularization, 27% current smokers), 29% were inappropriate. The majority of the inappropriate studies were for evaluation of non-acute chest pain with low pretest probability in patients who can exercise and have interpretable ECGs (52%), for risk assessment in patients undergoing non-cardiac surgery (20%), or for risk assessment in patients known to have coronary artery disease (CAD) who have stable symptoms (12%). MPIs labeled as inappropriate were more common in female vs male patients (43% vs 17%, $P < .0001$). Similar to the findings in the meta-analysis by Elgendy et al,[4] inappropriate MPIs were less likely to be abnormal than appropriate ones (13% vs 26%, $P = .003$). The smartphone app was able to assess appropriateness in 44 ± 9 seconds. While this freely available app may be feasible to use at the point of care, it is not clear whether its use will decrease the proportion of inappropriate studies ordered.

As seen in the study by Mahajan et al,[6] women are more likely to undergo MPI for inappropriate indications compared to men. This is thought to be related to the lower pretest risk of women compared to men. Doukky et al[7] analyzed a multi-site prospective cohort of 1511 patients (43% women) referred for outpatient MPI to determine whether outcomes are different between men and women when classified according to AUC. As expected, women were more likely to undergo an inappropriate MPI compared to men (61% vs 34%, hazard ratio 3.0, $P < .001$), an association that was even more pronounced after adjustment for clinical covariates (adjusted odds ratio 27.9, $P < .001$). Female gender was associated with a lower risk of having abnormal MPI as well as major adverse cardiac events (MACE) irrespective of appropriateness and there was no interaction between gender and appropriateness as a determinant of abnormal MPI or MACE. However, an abnormal MPI was associated with greater risk of MACE in both men and women irrespective of appropriateness. Thus, this study found no difference between genders on the impact of AUC on the diagnostic and prognostic utility of MPIs. Finally, it demonstrated the prognostic value of MPI in both genders irrespective of appropriateness according to the AUC (Figure 1).

PROGNOSTIC VALUE OF REGADENOSON MPI

Regadenoson is the most widely used pharmacologic stress agent in the United States.[8] The diagnostic value of regadenoson MPI has been well established but there was a paucity of prognostic data supporting the use of regadenoson MPI. A previous study had established the low incidence of MACE in patients with normal regadenoson MPI.[9] Hage et al[10] studied 1400 patients (700 with normal and 700 with abnormal MPI) who underwent regadenoson MPI for clinical indications. There was a stepwise increase in the incidence of the composite outcome of cardiac death, myocardial infarction (MI), and late coronary revascularization (CR) with increasing perfusion defect size (Figure 2A). Importantly, this association persisted even after adjustment for multiple covariates. With normal MPI as the reference group, the hazard ratio for the composite outcome was 2.7 (95% CI 1.8-4.1) for a perfusion defect <10% of left ventricle, 3.3 (2.3-4.8) for 10-20% defect, and 4.1 (2.8-5.9) for >20% defect. A similar association was seen for the components of the composite outcome and for early CR, demonstrating the powerful prognostic data derived from regadenoson MPI. Farzaneh-Far et al[11] compared the prognostic value of regadenoson MPI to adenosine MPI in 3698 consecutive patients. After 12 months of follow-up from index MPI, the primary endpoint of cardiovascular death or MI occurred in 4.9% of patients undergoing regadenoson MPI vs 6.2% of patients undergoing adenosine MPI. Using inverse probability weighing adjusted to clinical variables, there was no difference in outcomes between the 2 stress agents (Figure 2B). The summed stress score (SSS) was a significant predictor of outcomes even after inverse probability weighing adjustment to propensity for stress agent and there was no interaction of SSS with agent ($P = .35$). Together, these 2 studies[10,11] establish the prognostic value of regadenoson MPI and add to the large literature on the prognostic value of MPI.[12-14]
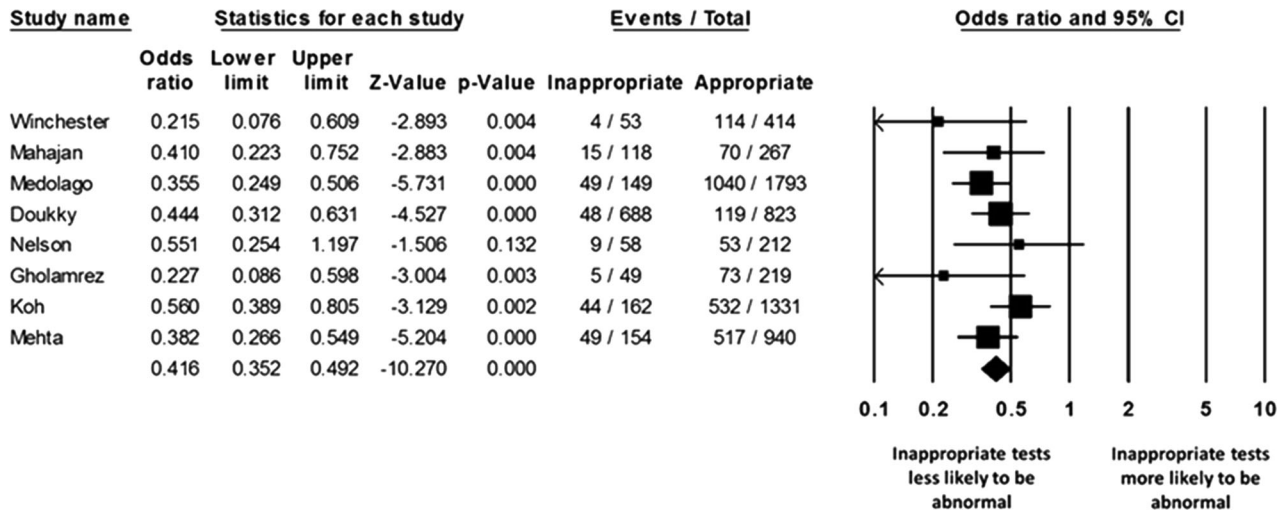
Figure 1. Inappropriate MPI studies are less likely to be abnormal compared to appropriate studies. Summary plot for abnormal test results. The relative size of the data markers indicates the weight of the sample size from each study. *CI* confidence interval. Reproduced with permission from[4].
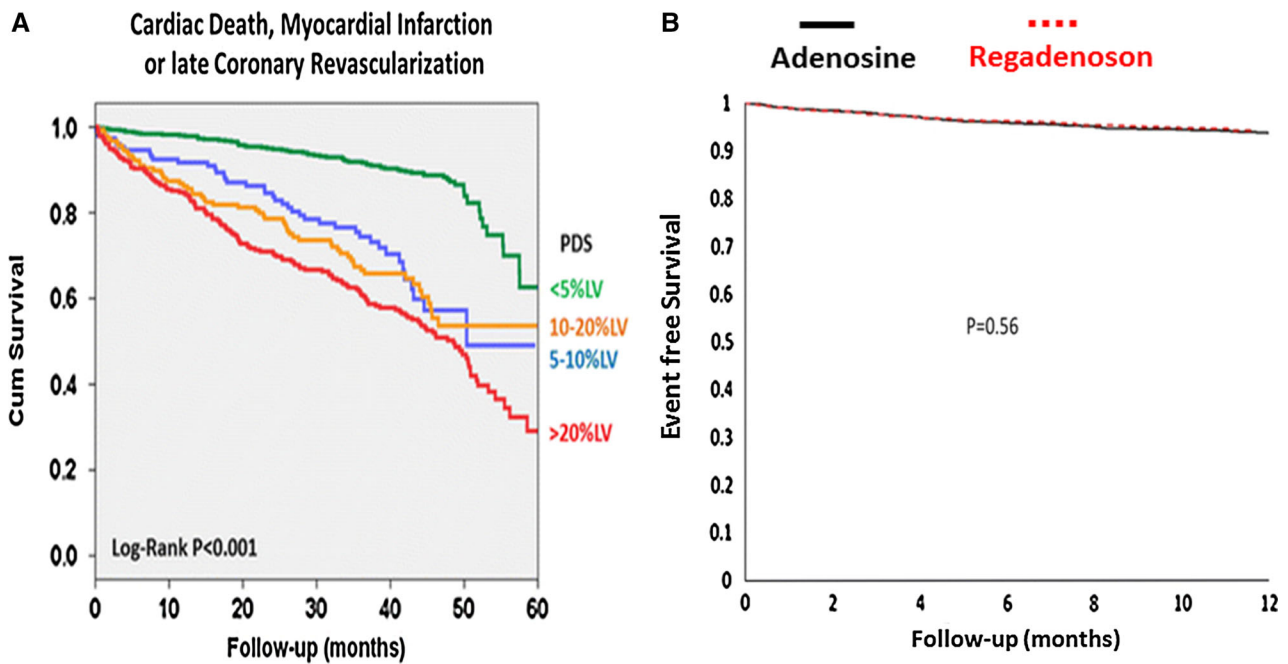
Figure 2. Prognostic value of regadenoson MPI. **A** Kaplan-Meier survival curve for the composite outcome of cardiac death, myocardial infarction, and late CR stratified by perfusion defect size. **B** Kaplan-Meier curves, inverse probability weighing adjusted to clinical variables for the composite endpoint of cardiovascular death or MI (*P* = .56) for adenosine vs regadenoson MPI. Interaction of SSS with agent was not significant (*P* = .35). **A** reproduced with permission from[10] and **B** from[11].

The heart rate response (HRR) to regadenoson during MPI has been shown to carry important prognostic information.[15,16] Aljaroudi et al[17] used the ASSAUGE and ASSAUGE-CKD trials to determine the prognostic value of HRR to regadenoson in patients with end-stage renal disease followed for 35±10 months. A blunted HRR (<28%) was associated with increased risk of death (24% vs 7%, adjusted hazard ratio 2.75, *P* = .003). Importantly, this relationship was maintained after the cohort was stratified into normal vs abnormal
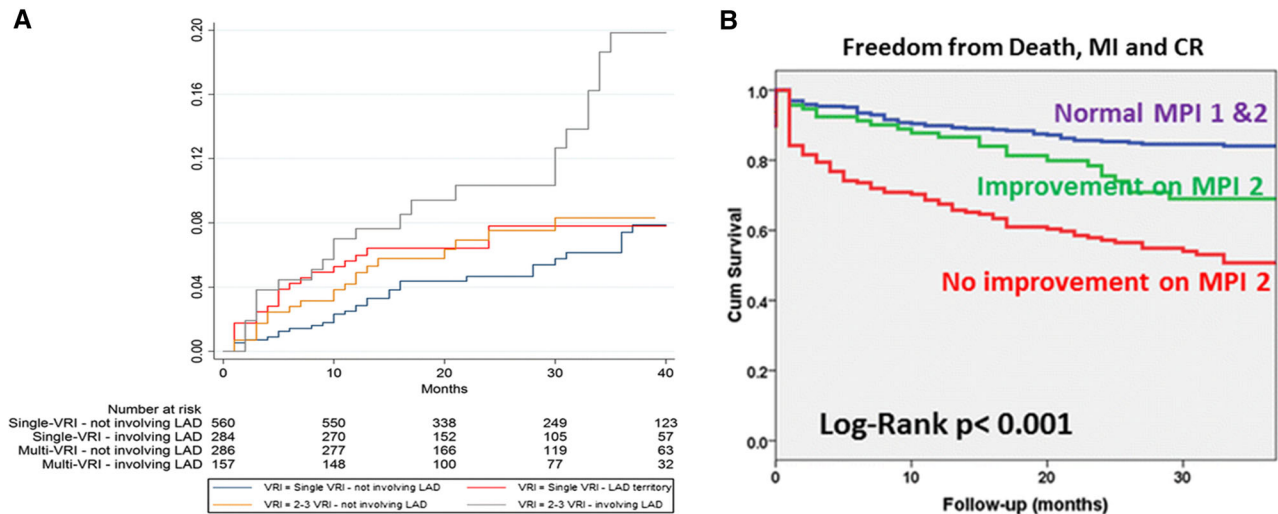
Figure 3. Location of perfusion defect and change in defect size over time. **A** Kaplan-Meier failure curve for the occurrence of death or myocardial infarction, distinguishing patients according to vessel-related ischemia (VRI), and excluding patients undergoing revascularization as first follow-up event [overall log-rank $P < .001$]. Color codes: *green*, single-VRI involving LAD; *dark orange*, single-VRI not involving LAD; *gray*, multi-VRI involving LAD; *red*, multi-VRI not involving LAD. **B** Kaplan-Meier curve illustrating freedom from the composite endpoint of death, MI or CR of three groups of patients: group 1 (normal MPI-1 and MPI-2); group 2 (improvement on MPI-2); group 3 (no change or worsening on MPI-2). **A** reproduced with permission from[29] and **B** from[31].

MPI and in a propensity-matched cohort. Similar associations were seen for cardiac death or MI, and for cardiac death or MI or late CR. This study adds to the rapidly growing literature supporting the use of HRR to regadenoson for prognostication in daily clinical practice.[16]

NORMAL MPI

A normal MPI confers a good overall prognosis.[12] A small subset of patients with normal perfusion on MPI has evidence of ischemia on the stress test (ST depression and/or angina). Romero-Farina et al[18] reported data on 2414 consecutive patients (mean age 62.8 ± 13.5 years, 1,438 women) with normal perfusion on MPI (69% exercise, 15% dipyridamole, 16% submaximal exercise + dipyridamole). Of these patients, 407 (17%) had a positive stress test with no difference according to gender. During a follow-up of 5.1 ± 3.4 years, cardiac death or non-fatal MI occurred in 2.7% of patients. No difference was seen in event rates in women with and without a positive stress test, while men with a positive stress tests had more events with a negative stress test (6.5% vs 2.3%, $P = .005$). Similar results were seen for cardiac death, MI or CR. These studies are consistent with previous studies that have demonstrated good overall prognosis in patients with normal perfusion on vasodilator MPI with ST depression on the ECG, the vast majority of whom were women.[19]

Nakanishi et al[20] studied 580 patients with normal MPI (59% with vasodilator stress) who were found to have CAD by invasive coronary angiography within 60 days. Of these patients, 42 (7%) had high-risk CAD defined as left main disease $\geq 50\%$, 3 vessel disease $\geq 70\%$, or 2 vessel disease including proximal left anterior descending (LAD) artery. Important predictors of high-risk CAD in this cohort of patients with normal perfusion (SSS < 4) included a SSS 1-3, transient ischemic dilation and/or abnormal LVEF response ($\geq 5\%$ decrease from rest to stress), and a high-pretest likelihood of CAD. Yokota et al[21] pointed out in an accompanying editorial that these 580 patients who underwent coronary angiography were a small fraction of the 25, 698 patients with normal MPI. As such, the proportion of patients with high-risk CAD is quite small (0.16%). Further, some of the patients with high-risk angiographic disease may not have significant disease by fractional flow reserve assessment which was not used in this study. Finally, recent work has questioned the predictive value of transient ischemic dilation in the presence of normal perfusion for hard cardiovascular events.[22-25]

The Duke treadmill score is a well-validated prognostic tool. Vitola et al[26] studied 310 patients with high Duke treadmill score (≤ -11) from a large registry of 17,972 patients who were followed for a mean of 4 years. Of these patients, 90 (29%) had normal perfusion on MPI. Cardiovascular mortality (0% vs 5%, $P = .02$)

and cardiovascular mortality or MI (4% vs 15%, $P = .009$) were lower in patients with normal vs abnormal perfusion. These data suggest that patients with high Duke treadmill score who have normal perfusion on imaging could be managed conservatively without referral for coronary angiography and questions the practice of referring patients with high Duke treadmill score directly to angiography without undergoing MPI.[27] In a different report, Koh et al[28] showed that risk reclassification is predominantly influenced by the Duke treadmill score in patients with suspected CAD, while MPI variables become more important in patients with known CAD.

LOCATION OF PERFUSION DEFECT AND CHANGE IN DEFECT SIZE OVER TIME

MPI is well adept at localizing the area of ischemia in addition to determining its presence, severity, and extent. Nudi et al[29] conducted a retrospective study of 13,254 patients (20% of whom had moderate or severe ischemia) who underwent MPI to determine the prognostic impact of the location of ischemia. After 32±21 months, death or MI occurred in 5.5% of patients with single vessel-related ischemia not involving LAD, 8.4% in patients with single vessel-related ischemia involving LAD, 7.3% of patients with multivessel-related ischemia not involving LAD, and 16.5% of patients with multivessel-related ischemia involving LAD (Figure 3A, $P < .001$). These data demonstrate that the location of ischemia carries important prognostic information. Specifically, patients with multivessel ischemia involving the LAD have a particularly unfavorable prognosis. In an insightful editorial, Elhendy[30] proposes several hypotheses to explain this association.

In clinical practice, performing serial MPI is very common. Nevertheless, there are limited data on the prognostic significance of changes in perfusion pattern on serial MPI. EL-Hajj et al[31] study 698 patients who underwent 2 regadenoson MPIs at a single institution within 16 ± 9 months. During 24 ± 16 months of follow-up after the second scan, 167 (24%) patients experienced death, MI or CR (8% death, 9% MI, 15% CR). The best outcomes were seen in patients with normal perfusion on both scans and the worst outcomes in patients with persistent or worsening perfusion defect on the follow-up MPI (Figure 3B). In a Cox model that adjusted for baseline factors including perfusion defect size and LVEF on the first MPI, patients with persistent or worsening perfusion defect on the follow-up MPI had a 4-fold increased risk compared to those with normal perfusion on both scans ($P < .001$). Further, an LVEF drop on the subsequent scan was associated with an independent risk. These data establish the prognostic value of serial MPI.[32-34]

CZT CAMERA: DIAGNOSTIC AND PROGNOSTIC DATA

MPI using cadmium zinc telluride (CZT) camera systems have been shown to shorten imaging time and decrease radiation exposure when compared to traditional MPI using sodium iodide Anger cameras. Olden et al[35] analyzed data on 1993 patients (57%CZT, 43% Anger) who underwent MPI at a single institution for clinical purposes. Perfusion defect size and extent of ischemia were associated with outcomes (death or MI) with no difference between the 2 camera systems and no interaction between camera type, imaging variables, and outcomes. These data confirms the prognostic value of the imaging data obtained using CZT cameras and place them on the same prognostic level as those obtained using the traditional Anger cameras which are supported by a large prognostic literature.[36] Sharir et al[37] found similar diagnostic accuracy of very low stress dose (stress-only 1.7 ± 0.3 mSv, stress-rest 6.9 ± 1.1 mSv) compared to standard dose (2.9 ± 0.1 mSv and 11.7 ± 0.4 mSv) MPI using a CZT camera with invasive coronary angiography as a gold standard. Thus, using a stress-first (or stress-only) protocol with low tracer dose and a CZT camera, substantial reductions in radiation dose can be achieved while maintaining diagnostic accuracy.[38] A separate study demonstrated the high image quality and diagnostic accuracy of CZT MPI for detection of CAD in obese patients (body mass index 44 ± 9 kg/m^2), a particularly challenging population for MPI.[39,40]

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