Review of cardiovascular imaging in the Journal of Nuclear Cardiology in 2017. Part 2 of 2: Myocardial perfusion imaging

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In 2017, the *Journal of Nuclear Cardiology* published many high-quality articles. In this review, we will summarize a selection of these articles to provide a concise review of the main advancements that have recently occurred in the field. In the first article of this 2-part series, we focused on publications dealing with positron emission tomography, computed tomography, and magnetic resonance. This review will place emphasis on myocardial perfusion imaging using single-photon emission computed tomography summarizing advances in the field including prognosis, safety and tolerability, the impact of imaging on management, and the use of novel imaging protocols. (J Nucl Cardiol 2018;25:1390–9.)

Key Words: Myocardial perfusion imaging • SPECT • Prognosis • Exercise • Phase analysis • Regadenoson

Abbreviations			
AV	Atrioventricular	ESRD	End-stage renal disease
CAD	Coronary artery disease	LVEF	Left ventricular ejection fraction
CTCA	Computed tomography coronary angiography	MI	Myocardial infarction
CZT	Cadmium-zinc-telluride	MPI	Myocardial perfusion imaging

Each year, we summarize a selection of articles that appeared in the prior year in the *Journal* to provide the reader with a concise review of the main advancement in the field.[1–6] In the first part of this 2-part series, we addressed advancements in positron emission tomography, computed tomography, and magnetic resonance.[7] Since SPECT is of major interest to our readers, we have dedicated this review entirely to the advancements in SPECT that were published in the *Journal of Nuclear Cardiology* in 2017.

PROGNOSTIC VALUE OF MPI

A large body of literature has established the prognostic value of myocardial perfusion imaging (MPI),[8,9] Recent advances in imaging have allowed for faster imaging with lower radiation exposure using cadmium-zinc-telluride (CZT) camera technology. Lima et al from Rio de Janeiro, Brazil[10] reported on the prognostic data of 3,554 patients (selected from a total of 6128 patients based on propensity matching) who

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underwent either a 2-day MPI using traditional Anger camera or a 1-day MPI using a CZT camera. Abnormal perfusion was more prevalent in patients who underwent traditional MPI (27.4% vs. 21.6%, $P < 0.001$). While the rate of annualized hard events was the same between the two groups in patients with abnormal perfusion (3.3% vs. 3.2%, P = NS), it was lower in those with normal perfusion with CZT vs. Anger camera (0.5% vs. 1.0%, $P < 0.0$). These data are reassuring regarding the prognostic value obtained using lower radiation exposure and shorter protocols with CZT cameras.[11]

Yao et al reported on the outcomes of older patients ($\geq$ 70 years) undergoing adenosine triphosphate MPI confirming the prognostic value of vasodilator MPI in an elderly population with suspected coronary artery disease (CAD).[12] Saab and Hage reviewed the different vasodilators used as stress agents in MPI.[13] Other studies evaluated the accuracy of MPI for the detection of multi-vessel CAD,[14,15] the prevalence of myocardial ischemia in patients with nonobstructive CAD,[16–18] and the ability of conventional SPECT to measure myocardial blood flow,[19,20] which have implications for prognosis and risk stratification.

Patients with end-stage renal disease (ESRD) are at increased risk of cardiovascular events.[21] Doukky et al reported on the prognostic data provided by regadenoson MPI in patients with ESRD followed prospectively in the ASSAUGE and ASSUAGE-CKD trials.[22] Abnormal myocardial perfusion (summed stress score $\geq$ 4) was associated with increased risk of cardiac death, myocardial infarction (MI), or late coronary revascularization (> 90 days post MPI) with an adjusted hazard ratio of 1.80 (95% CI 1.03-3.14, P = 0.039) (Figure 1). Further, a stepwise increase in the severity of perfusion abnormality was associated with a stepwise increase in cardiac events during follow-up. In an accompanying editorial, Miller and Schwartz elaborate on the implications of these findings on the evaluation of ESRD patients prior to renal transplantation [23]. In a separate study, Abuzeid et al reported on the outcome of ESRD after renal transplantation in relation to MPI findings.[24] Abnormal myocardial perfusion was associated with increased risk of cardiovascular events after adjustment for relevant covariates. These data are useful to extend the value of MPI in risk stratification to the postrenal transplant population, but questions remain regarding the best treatment strategy in this patient population.[25]

While the prognostic value of myocardial perfusion abnormalities with MPI has been extensively studied (see the following articles regarding the variability of different software programs used for quantitative assessment of perfusion abnormalities),[26,27] nonperfusion abnormalities on MPI also provide useful prognostic data.[28] Multiple studies have demonstrated the robust association of a blunted heart-rate response to vasodilator stress and subsequent outcomes.[29–34] Gomez et al demonstrated that integrating the heart-rate response to vasodilator stress with MPI interpretation improves risk stratification in ESRD patients.[35] In particular, patients with normal perfusion, left ventricular ejection fraction (LVEF), and heart-rate response had the best outcomes, while those with abnormal traditional MPI findings and a blunted heart-rate response had the worse outcomes [36]. In contrast, and while a drop in blood pressure during

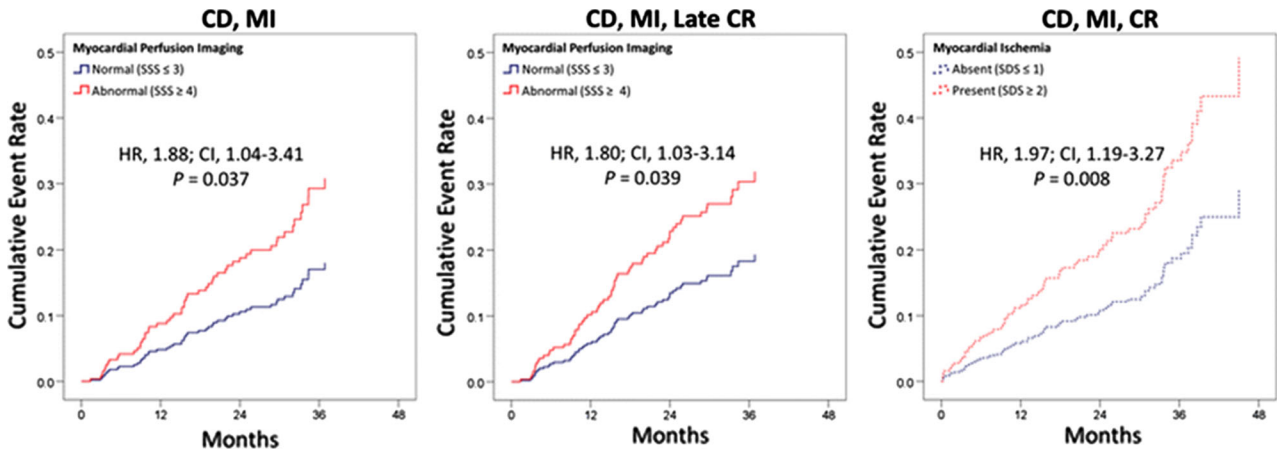

Figure 1. Impact of regadenoson-induced perfusion abnormalities on cardiac outcomes adjusted for clinical covariates, depicting Cox proportional hazards survival plots adjusted for age, gender, diabetes, dyslipidemia, smoking, and history of coronary artery disease. *SPECT* single-photon emission computed tomography, *MPI* myocardial perfusion imaging, *ESRD* end-stage renal disease, *CD* cardiac death, *MI* myocardial infarction, *CR* coronary revascularization, Late CR coronary revascularization occurring > 90 days post-MPI, HR hazard ratio, and CI 95% confidence interval. Reproduced with permission from[22].

exercise stress is associated with worse outcomes, Witbrodt et al demonstrated that the blood pressure response to vasodilator stress does not provide useful prognostic data.[37,38] Another MPI variable that has been used in conjunction with perfusion for risk stratification is transient ischemic dilation.[39,40] Jameria et al validated cutoffs for transient ischemic dilation using upright imaging on a CZT camera.[41,42]

SAFETY AND TOLERABILITY

The safety and tolerability of regadenoson and other stress agents have received increased scrutiny over the last few years.[43,44] The safety of regadenoson in patients with elevated cardiac markers have not been demonstrated. Rai et al evaluated the safety of different stress agents in 703 (51% with regadenoson) patients who had elevated troponin levels $\leq$ 7 days prior to testing .[45] The composite outcome of death, nonfatal MI, heart failure, stroke, ventricular arrhythmias, atrial fibrillation/flutter, or atrioventricular block requiring intervention within 24 h of testing occurred in 1.6% of patients undergoing regadenoson stress compared to 1.0% with dipyridamole, 1.4% with adenosine, 11.1% with dobutamine, and 3.3% with exercise. The high event rates in patients receiving dobutamine or undergoing exercise should be interpreted with caution given the small sample size of these subsets.[46] However, the risk appears to be low in patients undergoing vasodilator stress with no signal of increased risk with any particular vasodilator agent. Another patient population that lacked data on safety of vasodilator stress is the one of severe aortic stenosis. This is of particular interest in the current era with the increasing use of percutaneous aortic valve replacement as a treatment strategy for severe aortic stenosis with percutaneous coronary intervention in those with coexisting CAD. Hussain et al reported on the safety of vasodilator stress (45% regadenoson, 31% dipyridamole, and 24% adenosine) in 95 cases with severe aortic stenosis.[47] Common symptoms accompanying vasodilator stress included dyspnea (17%), headache (7%), flushing (6%), and nausea (4%). None of the cases experienced advanced heart block, sustained atrial flutter/fibrillation, ventricular tachycardia or ventricular fibrillation, unstable angina, peri-procedure MI, or death. A significant drop in blood pressure ($>$ 20 mm Hg) occurred in 45% of patients with no significant difference between the stress agents, and this was not accompanied by symptoms of hypotension. In the subset of patients who underwent angiography, the diagnostic performance of MPI was acceptable. These findings suggest that vasodilator stress is well tolerated in patients with severe aortic stenosis although significant drop in blood pressure is common and should be anticipated.[48]

A known complication associated with the use of adenosine, dipyridamole, and regadenoson for MPI is atrioventricular (AV) block.[49] Massalha et al reported on the incidence of conduction abnormalities among 2010 patients who underwent dipyridamole stress testing.[50] At baseline, 17% of patients had conduction abnormalities although patients with second or third degree AV block were excluded. After dipyridamole infusion, 0.8% of patients developed a transient change in AV conduction and/or severe sinus bradycardia. A single patient developed sinus arrest that lasted several seconds causing syncope which was treated with aminophylline and atropine. Another patient with atrial fibrillation at baseline developed asystole that lasted for 10 seconds and was treated with aminophylline. Second or third degree AV block occurred in 8 (0.4%) patients. The rate of AV block was higher in patients with baseline conduction abnormalities than in those without (3.1% vs. 0.3%). Subbiah and Patil summarized the rate of clinically significant arrhythmias seen with the different vasodilator stress agents.[51] Also, a recent meta-analysis of 34 studies that included data on 22,957 patients who underwent adenosine or regadenoson MPI reported an estimated incidence of AVB of 8.58% (95% CI 5.55-12.21%) with adenosine vs. 0.30% (0.04-0.82%, $P < 0.001$) with regadenoson.[52] In this meta-analysis, the estimated incidence of high-grade AV block (second or third degree) was 5.21% (2.81-8.30%) with adenosine vs. 0.05% ($<$ .001-0.19%, $P < 0.001$) with regadenoson. These data demonstrate that AV block is infrequent but occurs at a higher frequency with nonselective adenosine agonist, such as adenosine, as compared with selective A2A agonists, such as regadenoson.

The safety and tolerability of repeat consecutive doses (100, 200, or 400 μg or placebo, 10 minutes apart) of regadenoson was assessed in a randomized, repeat-dose, placebo controlled study in 36 healthy subjects.[53] There was no consistent pattern of effects on systolic blood pressure associated with repeat-dose administration of regadenoson. Repeat dosing was associated with small reductions in diastolic blood pressure and transient increases in heart rate. There were a total of 27 adverse effects and no serious adverse effects. There was no obvious pattern in the incidence of adverse effects with respect to sequential doses. This study demonstrates that repeat dosing of regadenoson is well tolerated and provides reassurance for repeat dosing in case of intravenous infiltration of the drug or if the radiotracer was unavailable.[54] Based on the pharmacodynamics effects of regadenoson, Thomas et al suggest a reasonable re-dosing interval of 2.5 hours.[54]

Aminophylline, a nonselective adenosine receptor antagonist, is often used to counter the adverse effects of regadenoson, adenosin, resp dipyridamole. However, in case of shortage of aminophylline, an alternative reversal agent is needed. Doran et al compared the use of IV aminophylline (100 mg) with IV (60 mg) and oral caffeine (coffee or diet cola) in patients undergoing regadenoson MPI.[55] While IV caffeine provided rapid reversal of regadenoson-induced adverse events, PO caffeine was inferior with respect to complete or predominant reversal. In order to allow for almost complete extraction of the radiotracer, the reversal agent should not be administered at less than 2 minutes from regadenoson administration and preferably after 3 minutes.[56] In a separate study, Fughhi et al demonstrated that 75 mg IV aminophylline at 2 minutes following regadenoson does not seem to substantially interfere with the effects of regadenoson on myocardial perfusion by MPI.[57,58]

REGADENOSON AND EXERCISE

Regadenoson, or other pharmacologic agents, is used in lieu of exercise in patients who are unable to exercise to an adequate level. Exercise stress is the preferred modality since it provides prognostic data related to exercise tolerance and hemodynamic changes accompanying activity. It may be difficult to predict whether some patients can achieve adequate exercise making it necessary to switch from exercise to pharmacologic stress. The EXERRT trial assessed the noninferiority and safety of regadenoson administration during recovery from inadequate exercise compared with administration without exercise.[59] The study randomized 1,147 patients who were unable to achieve adequate exercise stress to regadenoson at 3 minutes during recovery (Reg-recov) vs. 1 hour after exercise (Reg-rest). All patients underwent a regadenoson-only MPI at least 1 day later (MPI 2). The agreement rate between MPI 1 and MPI 2 was not different between the two groups implying that administering regadenoson during recovery does not alter the interpretation of the images compared to administering it at rest (Figure 2).[60] An important limitation of this study is high prevalence of no or minimal ischemia on imaging confounding the results. The study also showed that administration of regadenoson during recovery results in a higher target-to-background ratio. This did not result in improved image quality, since image quality was deemed good/excellent in the majority of patients in both groups. Nevertheless, subdiaphragmatic activity was significant lower for Reg-recov. The study also suggested the safety of this approach when careful monitoring is applied. Overall, adverse events were not different between the two groups although flushing and headaches were numerically less for Reg-recov. As expected, systolic blood pressure decreased with regadenoson administration and was more pronounced in the Reg-recov group, but severe hypotension (systolic blood pressure < 90 mm Hg) was uncommon ($< 4\%$) and not different between groups. Serious adverse events occurred more frequently in Reg-recov (0.9%) than for MPI 2 (0.4%) and for the Reg-rest (0.2%). Importantly, two patients in the Reg-recov group experienced acute coronary syndrome (one with myocardial infarction) although both patients exhibited ischemic ST changes and symptoms prior to regadenoson administration. The authors recommend 'careful monitoring for symptoms and ECG changes' during recovery and, if these are present, administration of the tracer and proceeding with MPI without regadenoson.

Janvier et al investigated whether addition of isometric exercise (handgrip started 2 minutes before regadenoson injection and continued to 5-7 minutes after injection) improves the side-effect profile of regadenoson while providing better image quality in a small proof-of-concept study.[61] Patients who performed handgrip exercise reported fewer side-effects and experienced a drop in blood pressure less frequently (drop in blood pressure by > 10 mm Hg of 45% vs. 77.5%, $P = 0.12$). Further, this was associated with improved image quality.[62] These results, although preliminary, indicate the feasibility of low-level exercise for patients undergoing regadenoson MPI and the potential of such an approach to minimize side-effects and improve image quality using a simple approach.[63]

IMPACT OF IMAGING ON MANAGEMENT

The benefit of coronary revascularization in patients with stable CAD on hard cardiovascular outcomes is not well established.[64] Serial MPI imaging can be used to assess changes in myocardial perfusion over time and in response to interventions such as coronary revascularization.[65–67] Nudi et al evaluated the impact of revascularization on myocardial ischemia in 3631 patients undergoing serial MPI of whom 27% underwent revascularization (Figure 3).[68] In patients with moderate or severe ischemia at baseline, coronary revascularization was associated with a higher prevalence of no, minimal, or mild ischemia on follow-up imaging compared with medical therapy alone (80% vs. 43%, $P < 0.001$). These results were supported by multivariable-adjusted, propensity score-adjusted, and propensity score-matched analyses.

Several studies have compared an anatomic approach towards chest pain with computed tomography coronary angiography (CTCA) with a functional

Agreement for 3 Categories by Number of Reversible Defects

MPI1 Median No. of Reversible Defects	MPI2 Median No. of Reversible Defects 0–1	2–4	≥5	All	Agreement Rate % (95% CI)	Agreement Rate Difference* for All† % (95% CI)
Ex-Reg						
0–1	471	27	1	499	94 (92 to 96)	
2–4	17	19	1	37	51 (34 to 68)	
≥5	0	1	1	2	50 (1 to 99)	
All	488	47	3	538	73 (69 to 77)	–2 (–7 to 4)
Regadenoson						
0–1	486	23	0	509	95 (93 to 97)	
2–4	11	14	1	26	54 (33 to 73)	
≥5	0	0	0	0	NC	
All	497	37	1	535	75 (71 to 78)	

Agreement for 2 Categories by Number of Reversible Defects

MPI1 Median No. of Reversible Defects	MPI2 Median No. of Reversible Defects 0–1	≥2	All	Agreement Rate % (95% CI)	Agreement Rate Difference* for All % (95% CI)
Ex-Reg					
0–1	471	28	499	94 (92 to 96)	
≥2	17	22	39	56 (41 to 72)	
All	488	50	538	75 (68 to 83)	–1 (–14 to 11)
Regadenoson					
0–1	486	23	509	95 (94 to 97)	
≥2	11	15	26	58 (39 to 77)	
All	497	38	535	77 (67 to 86)	

Figure 2. Summed stress scores and summed difference scores agreement rates. Reproduced with permission from[59].

approach using imaging stress test.[69,70] The PERFECT trial randomized 411 patients who were admitted form the emergency room with chest pain with negative initial cardiac marker and ECG to CCTA vs. imaging stress test (MPI or stress echocardiography). The two approaches were comparable with respect to time-to-discharge, initiation of cardiac medications, downstream noninvasive cardiac testing, and subsequent hospitalizations.[71]

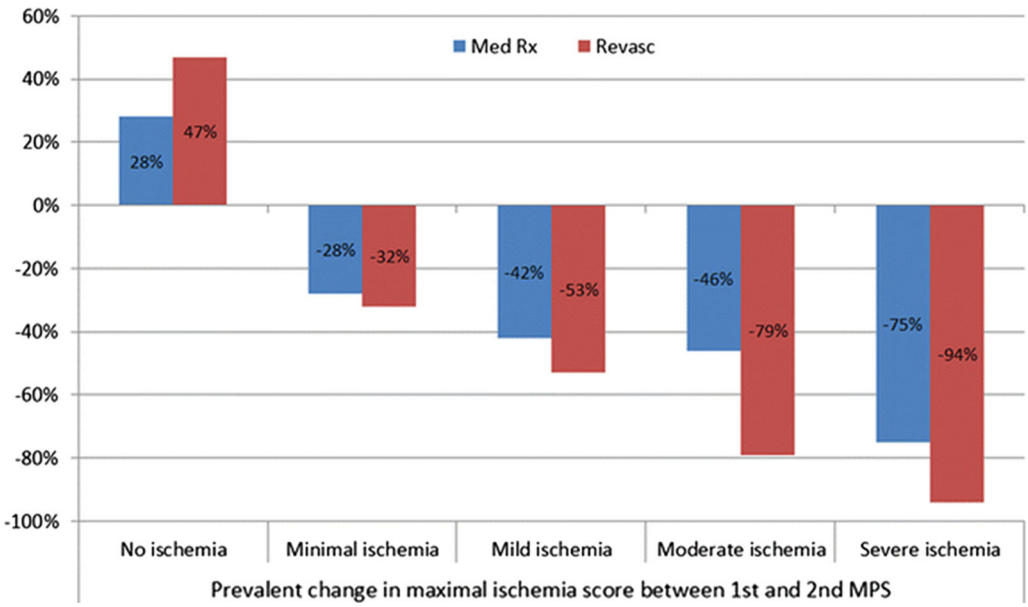

Figure 3. Prevalent changes in maximal ischemia scores (MISs) between baseline and repeat myocardial perfusion scintigraphy (MPS) comparing medical therapy (Med Rx) vs. coronary revascularization (Revasc). Negative values indicate an overall decrease (i.e., improvement) in MIS, and positive values an overall increase (i.e., worsening) in MIS. Reproduced with permission from [68].

However, the CTCA arm was associated with significantly higher rates of invasive angiography (11% vs. 2%, $P = 0.001$) and PCI (6% vs. 0%). Karthikeyan et al reported on an international, multicenter, randomized controlled trial (IAEASPECT/CTA study) which randomized 303 patients with suspected CAD to an initial strategy of CTCA vs. MPI.[72,73] Patients undergoing stress MPI as the initial test were half as likely (adjusted OR 0.51, 95% CI 0.28-0.91, $P = 0.023$) as those undergoing CTCA to have further downstream noninvasive or invasive cardia testing within 6 months. Both studies, while performed in diverse populations, point to the lower utilization of downstream testing when a functional approach is used.

An ASNC Consensus Statement summarized the evidence base supporting the use of MPI in the clinical evaluation of women presenting with symptoms of stable ischemic heart disease.[74] The *Journal* also published the ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease[75] which was accompanied by a Guidelines in Review concise summary.[76]

STRESS-ONLY, EARLY IMAGING, AND REDUCTION IN RADIATION EXPOSURE

Stress-only imaging is increasingly being used to decrease radiation exposure, shorten MPI time, reduce cost, and streamline patient evaluations.[77] Chaudhry et al compared the accuracy of technologist determination of the need of rest imaging to the reference gold standard of nuclear cardiologist determination.[78] Based on the reference gold standard nuclear cardiologist assessment, 83% of patients did not require rest imaging. Technologists correctly classified 92% of patients as either needing or not needing rest imaging, while quantitative automated software correctly classified only 72% studies primarily due to incorrectly requesting rest images in 24% of patients. In a simulated model whereby the computer or technologist could correct for the other's incorrect classification, 97% stress-first images were correctly classified. Using such an approach would greatly facilitate the use of stress-only imaging at sites where nuclear cardiologists are not available to review the images in real time and make a determination for the need of rest images. A separate study demonstrated the value of attenuation correction in decreasing the need for rest imaging in stress-first MPI using CZT cameras with no effect on long-term outcomes.[79,80]

Typically, imaging is delayed for 30-45 minutes after tracer injection. Earlier imaging would shorten the time required for completing the MPI protocol providing convenience to the patient and improved throughput to the stress laboratory.[81] Early imaging may also allow for assessment of LVEF reserve providing additional prognostic data.[82] In two separate studies, Katsikis et al and Meyer et al demonstrate the feasibility of early imaging using traditional Anger cameras and CZT cameras.[83,84]

The use of CZT cameras can result in significant reduction in radiation exposure. Nevertheless, since traditional Anger cameras are widely used, there is significant interest in advancements in imaging that can lead to reduction in radiation using software upgrades such as resolution recovery.[85] Lecchi et al investigated how a reduction in counts impacts imaging in normal weight and obese individuals using Bright View gamma camera and Astonish algorithm.[86] The investigators altered acquisition time to decrease count statistics simulating a lower dose. They reported that this software allowed for a reduction in acquisition time up to 25% in normal weight subjects and up to 50% in obsess subjects using objective quantitative analysis of perfusion and function.

PHASE ANALYSIS

Phase analysis of MPI can provide an assessment of mechanical dyssynchrony.[87,88] Zafrir et al evaluated the relationship between mechanical dyssynchrony by phase analysis and cardiac outcomes in patients scheduled to undergo either ICD or CRT-D.[89] In multivariate analysis, phase standard deviation was an independent predictor for cardiac death. Their data suggest that phase analysis may be used as an alternative indication for ICD implantation in the future.[90] Chiang et al demonstrated that cardiac reverse remodeling after CRT is associated with the prevalence of ventricular arrhythmias.[91,92] In a separate study of 1244 patients with CAD undergoing MPI, Hess et al showed that mechanical dyssynchrony by phase analysis was independently associated with mortality and was a stronger predictor of death than electrical dyssynchrony as assessed by QRS duration.[93] Thus, assessment of mechanical dyssynchrony may be of benefit in patients undergoing MPI in addition to perfusion and LV function.[94]

Disclosure

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