This review is a sequel to our previous reports highlighting the most important recent literature in single-photon emission computed tomography (SPECT) myocardial perfusion imaging, cardiac positron emission tomography (PET), cardiac computed tomography (CT), and cardiac magnetic resonance imaging (MRI). In almost all cases, these studies were published in the English-language literature between April 1, 2005, and March 31, 2006. The explosion of literature on cardiac CT has led us to add another author, Eric E. Williamson, who has particular expertise in that area. The decision to arbitrarily include some articles and exclude others has become even more difficult. We once again apologize to those whose work we have excluded or inadvertently overlooked. We can assure both authors and readers that we have done our best to ignore any personal biases in reaching these decisions. We continue to believe that the optimal application of imaging to clinical problems requires careful assessment across imaging modalities (i.e., thinking outside the “silos” in which most imagers work). We have therefore again organized this summary around topical themes in an effort to encourage a broad approach.

TECHNICAL ADVANCES

SPECT. Although SPECT myocardial perfusion imaging is a relatively mature technique, there continue to be important technical advances. Leslie et al. examined the potential value of stress lung-to-heart ratio in 718 patients undergoing sestamibi SPECT imaging (1). Similar to previous studies evaluating this ratio using thallium imaging, this ratio provided important prognostic information independent of other clinical, stress, and perfusion variables. Somewhat surprisingly, in this series it appeared more important than the summed stress score.

Several studies added to our understanding of attenuation correction. Masood et al. (2) published multi-center results using CT-based attenuation correction of SPECT imaging from a multi-center study. The major benefit of attenuation correction was an improved normalcy rate. The degree of benefit in sensitivity, specificity, and accuracy varied among readers. Fricke et al. (3) compared CT-based attenuation correction of SPECT with nitrogen-13 ammonia in 23 patients. Attenuation correction improved the concordance between SPECT and PET studies in the inferior wall, but differences between SPECT and PET persisted in the apex and anterolateral wall.

Hesse et al. (4) published procedural guidelines for myocardial perfusion imaging on behalf of the European Association of Nuclear Medicine and the European Society of Cardiology. The sections of that document describing quality control and reconstruction methods, as well as attenuation and scatter compensation, are of particular value to the practicing clinician.

PET. Johnson et al. (5) quantified the heterogeneity of rubidium PET perfusion using a detailed Markovian homogeneity analysis. Patchy resting perfusion predicted mild stress-induced defects; the authors suggested that these findings may reflect coronary microvascular dysfunction.

CT. Technical advances in CT continue to be very rapid, with development of a new generation of multi-detector-row CT scanners approximately every 2 years. In 2005, the first publications regarding the capabilities of the 64-detector-row CT systems appeared. Interestingly, the different CT vendors branched out into different directions. Increasing the number of detector rows remains a priority in development, but how this increase is applied differs considerably among the new systems. Kondo et al. (6) reported their initial experience performing non-electrocardiogram (ECG)-gated volumetric cardiac imaging using a 256-detector-row CT. Although temporal resolution of this system is limited, the greatly increased coverage region, improved spatial resolution, and elimination of ECG-gating artifacts show promise for future cardiac applications. Flohr et al. (7) published the first evaluation of a dual-source CT system using 2 X-ray tubes and corresponding detector arrays mounted on a single gantry offset from each other by 90°. This system offers superior temporal resolution (83 ms) compared with current 64-row systems, with obvious benefits of improved functional assessment and decreased motion-related artifacts.

MRI. Several recent advances in MRI have involved tissue properties. Wen et al. (8) applied a combination of in vivo MRI displacement and velocity measurements to calculate regional myocardial stiffness and compared their results to ex vivo strain gauge measurements in dogs. Magnetic resonance imaging–based temperature mapping has been possible since the early 1990s, but improved scanner performance has increased interest in using this technique. Several investigators used MRI temperature mapping in
organs such as the liver (9), esophagus (10), and prostate (11). It remains to be seen whether similar techniques could be applied to the heart.

Although MRI has not witnessed the complete redevelopment of scanner hardware that is occurring with CT, one area of potential revolutionary advancement is interventional MRI. The interventional MRI literature remains very preliminary although promising. Under MRI guidance, Arepally et al. (12) guided catheters across the interatrial septum in 5 pigs (Fig. 1). Krombach et al. (13) performed intramyocardial injection of contrast into 7 pigs. Raval et al. (14) performed coarctation stenting in 13 pigs. Wider application of this technology will require MRI-compatible catheters and better tracking systems.

### VIABILITY

Chareonthaitawee et al. (15) published a comprehensive review of the available evidence regarding revascularization in patients with left ventricular (LV) systolic dysfunction, which highlighted the deficiencies of the existing literature and placed viability studies in an appropriate clinical context.

**PET.** Several studies attempted to define the role of PET viability studies in revascularization decisions. Stankewitz et al. (16) compared rubidium perfusion defect severity and washout with fluorodeoxyglucose (FDG)-perfusion mismatch in 194 patients and found that perfusion imaging alone could not identify viability defined by FDG-perfusion mismatch. Desideri et al. (17) performed PET viability assessment with ammonia and FDG in 261 patients with ischemic cardiomyopathy. Patients who were revascularized had better outcomes than those patients who were treated medically. In the medically treated patients, the extent of mismatch was a predictor of adverse outcomes, but only if it exceeded 20% of the left ventricle. In contrast, Sawada et al. (18) performed PET viability assessment in 61 patients with diabetes and ischemic LV dysfunction and reported that mismatch of a much smaller 3% of the left ventricle identified patients whose survival was poorer with medical therapy.

Slart et al. (19) reported that a threshold of 50% or greater for FDG uptake predicted improvement in segmental function after revascularization in 38 patients. In a second paper, Slart et al. (20) reported in 47 patients that dual-isotope simultaneous SPECT acquisition with sestamibi and FDG predicted post-revascularization improvement just as well as ammonia-FDG PET.

Tarakji et al. (21) described a large series of 765 patients who underwent comprehensive PET imaging assessment of both viability and stress-induced ischemia (Fig. 2). In a carefully performed propensity analysis, early revascularization was associated with a significantly better survival. In an accompanying editorial, Gibbons et al. (22) highlighted the strengths and weaknesses of this very large study.

**CT.** Two CT methods have been used to detect infarcted myocardium. The first is decreased myocardial perfusion during the first pass of contrast material. The second is decreased washout of contrast material on delayed images, called “delayed enhancement” or “delayed hyperenhancement,” similar to the technique used with MRI.

Although both methods were first reported over 20 years ago, CT is still at an early stage in its assessment of viability; the literature to date consists of animal studies or very small human trials (23) (Fig. 3). Last year, 4 small studies investigated the potential of myocardial viability assessment using contrast-enhanced CT (23–26) (Table 1). Although MRI can provide the same information without radiation, important viability information is potentially available from cardiac CT for patients undergoing CT for other reasons.

![Figure 1. Intervventional magnetic resonance imaging (MRI). (A) MRI 4-chamber view shows a wire (arrowhead) that has been passed into the left atrium (LA) through the fossa ovalis. RA = right atrium. (B) MRI short-axis view better shows the catheter (black arrowheads) passing through the fossa ovalis (white arrow). (C) Injection of contrast material through the catheter produces an MR angiogram in which the left-side chambers and aorta but not the right-side chambers are visualized. (D) Gross pathologic photograph of the fossa ovalis viewed from the left atrial side shows the site of septal puncture (black arrow). Modified from Arepally et al. (12).](image)

![Figure 2. Mortality for patients treated medically (no intervention) and patients undergoing early intervention, using propensity-matched groups. From Tarakji et al. (21). FDG = fluorodeoxyglucose; PET = positron emission tomography.](image)
MRI. Delayed enhancement by MRI has been extensively validated and is frequently used as a reference standard for myocardial infarction (MI). Slomka et al. (27) used MRI delayed enhancement to validate a SPECT myocardial infarct quantification tool, a reversal from previous years when nuclear methods were used to validate MRI. In 29 patients with chronic ischemic cardiomyopathy, Kuhl et al. (28) showed that MRI delayed enhancement predicted recovery of function as well as 18F-FDG PET.

Several other studies attempted to combine delayed enhancement with other MRI parameters to make a comprehensive evaluation of viability. Bodi et al. (29) examined 40 patients with ST-segment elevation myocardial infarction (STEMI). Using a combination of 4 MRI-measured indexes, including delayed enhancement, they developed a scoring system that predicted recovery of function as well as 18F-FDG PET.

Although delayed enhancement indicates tissue damage, it is not specific for infarction. Knappen et al. (30) measured delayed enhancement with MRI and blood flow with PET. In 12 patients with chronic MI, blood flow was decreased in areas of delayed enhancement, but in 21 patients with hypertrophic cardiomyopathy, blood flow was slightly increased in areas of delayed enhancement. Thus, delayed enhancement due to MI seems to represent a different form of tissue damage than delayed enhancement due to hypertrophic cardiomyopathy.

Hunold et al. (31) showed that other disease states causing delayed enhancement can be distinguished from infarction by the distribution of the enhancement (Fig. 5). All 391 patients with known infarction had delayed enhancement in a vascular distribution (i.e., it proceeded from the endocardial to epicardial border and was confined to vascular territories). Nineteen patients had other myocardial diseases (including myocarditis and sarcoidosis), no history of MI, and normal coronary arteries at cardiac catheterization. Although these patients also showed delayed enhancement, it was in a nonvascular distribution.
CORONARY ARTERY DISEASE

Diagnosis. SPECT. Patients with previous radiation therapy for breast and chest cancer are increasingly studied by SPECT. In the oncology literature, Marks et al. (32) prospectively studied 114 patients after radiation therapy for left-side breast cancer by SPECT. New perfusion defects appeared in 42% of the patients within 2 years and were more common in patients with more than 5% of their left ventricle included within the radiation therapy field.

The relationship between perfusion defects and ECG evidence of ischemia is not fully defined. Weinstaft et al. (33) carefully compared inducible ST-segment depression and reversible perfusion defects in 129 patients undergoing SPECT. The ST-segment depression correlated with defect size and severity in those patients with contiguous ischemia but not in those patients with anatomically opposed ischemia.

PET. The diagnostic use of PET imaging is increasing. Bateman et al. (34) compared PET rubidium-82 imaging in...
112 patients with 112 SPECT controls. In those matched pharmacologic stress patients with a mean body mass index of >32, PET had superior diagnostic accuracy. In a comprehensive editorial, Di Carli et al. (35) outlined the need for clinical outcomes data to better establish the correct role of PET. Chow et al. (36) compared exercise and dipyridamole stress in patients studied with ammonia-13. Perfusion defects were larger with exercise, suggesting that it is the preferred stress technique.

In a mechanistic study, Brunken et al. (37) assessed myocardial perfusion reserve using nitrogen-13 ammonia PET imaging in 14 patients with cyanotic congenital heart disease and carefully compared them to 10 healthy controls. Although myocardial perfusion reserve was diminished in the patients with congenital heart disease, this primarily reflected higher perfusion in the basal state which preserved oxygen delivery to the myocardium. At hyperemic stress, perfusion measurements and coronary vascular resistances were similar to those of normal subjects.

**CT CORONARY ANGIOGRAPHY.** The most recent generation of scanner, the 64-detector-row CT, represents an improvement over the 16-detector-row systems evaluated previously (Fig. 6). Table 2 lists the prospective 64-detector studies that compare coronary CT angiography (CTA) to cardiac catheterization for the detection of coronary stenosis (38–44). The main benefits realized by the 64-detector systems are in the number and size of coronary segments that are considered analyzable. Of the 64-detector studies listed this year, nearly one-half (3 of 7) analyzed all segments compared with less than one-third (3 of 10) of the 16-detector studies reviewed last year. Four of the seven 64-detector studies evaluated this year did not exclude any vessels on the basis of size. In spite of these improvements, low heart rates are required to limit motion artifacts. Therefore, patients still receive beta-blockers before imaging and heart rates in the studies remain in the 50s and low 60s (beats/min). Calcium remains a source of false positive results; Mollet et al. (38) and Raff et al. (43) published separate studies showing that specificity decreases with increasing calcium.

**MRI.** Myocardial perfusion is the most extensively validated method of detecting CAD with MRI. Although these studies date back to the early 1990s, there are numerous ways to analyze the images, with little standardization between studies. Redrigues de Avila et al. (45) compared different semiquantitative measures of perfusion reserve in 37 patients with known CAD. Using cardiac catheterization...
as the reference standard, they found that signal intensity upslope was the best parameter for distinguishing different degrees of stenosis. Using deconvolution of signal intensity curves, Selvanayagam et al. (46) provided evidence that resting myocardial blood flow is decreased in hibernating segments.

One limitation of MRI perfusion is the frequent presence of a dark rim-like artifact that can be mistaken for a perfusion defect. Some have suggested that the rim is caused by high local concentrations of contrast material (a well known phenomenon in MRI). Others have suggested that the rim is caused by motion or by limits in spatial resolution. Di Bella et al. (47) studied explanted canine hearts and concluded that the main cause of the artifact was limited spatial resolution.

Several centers have attempted to use MRI for direct coronary visualization. Sakuma et al. (48) studied 39 patients with a coronary MRI sequence that corrected for patient respiration. In the subset of 20 patients who underwent cardiac catheterization they reported a (per patient) sensitivity and specificity of 83% and 75%, respectively.

**Plaque characterization. CT.** Computed tomography has the potential to provide a noninvasive means of characterizing coronary plaque. Evaluation of the vessel wall using the cross-sectional capability of CT could theoretically distinguish “vulnerable plaques” from those that are less so. Until recently, few data were available; however, 3 studies were published in the past year evaluating the ability of CT to characterize noncalcified atherosclerotic plaques.

Carrascosa et al. (49) compared coronary CTA to intravascular ultrasound (IVUS) for the characterization of calcified and noncalcified coronary plaque in 40 patients with known CAD. They studied 276 coronary plaques using a 4-detector row system and found perfect discrimination between calcified and noncalcified plaques (receiver operating characteristic [ROC] area = 1.00) and good discrimination between fibrous and soft plaques (ROC area = 0.82), using 185 Hounsfield units (HU) and 88 HU as the respective cutoff values. Interobserver variability was not studied.

Ferencik et al. (50) evaluated the interobserver reproducibility of coronary plaque detection in 45 patients using 16-detector coronary CTA. They evaluated 735 coronary segments, excluding 50 for motion artifact or insufficient caliber (patients with a heart rate of >65 beats/min were excluded). High interobserver agreement was reported for both calcified (97.7% agreement; kappa = 0.93) and noncalcified plaque (92.4%; kappa = 0.82). Plaque volume was not quantified.

Leber et al. (51) compared 64-detector-row CTA to IVUS for the detection and characterization of noncalcified atherosclerotic plaque in 38 nonstenosed coronary arteries from 20 patients. Although CT systematically overestimated volumes of calcified plaque and underestimated noncalcified and mixed plaque volumes, there was a good

<table>
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<tr>
<th>Table 2. Studies of 64-Detector Computed Tomography Angiography Using Invasive Coronary Angiography as a Reference Standard</th>
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<tbody>
<tr>
<td>Author (Ref.)</td>
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<tr>
<td>Pugliese et al. (39)</td>
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<td>Fine et al. (40)</td>
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<td>Ropers et al. (41)</td>
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<td>Leber et al. (42)</td>
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<td>Raff et al. (43)</td>
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<td>Mollet et al. (38)</td>
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<td>Leschka et al. (44)</td>
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Table 2. Studies of 64-Detector Computed Tomography Angiography Using Invasive Coronary Angiography as a Reference Standard
overall correlation of plaque volumes between CTA and IVUS ($r^2 = 0.69$). Unfortunately, interobserver variability for CT plaque volume measurements was high (37%).

MRI. Because the coronary arteries are too small and fast-moving to be reliably imaged with MRI, plaque characterization studies have focused on larger, more stationary vessels such as the carotid arteries. In 21 patients scheduled for carotid endarterectomy, Cai et al. (52) performed pre-endarterectomy in vivo MRI for carotid plaque characterization and compared it with postoperative histology. They found good correlation of measurements of the length ($r = 0.73; p < 0.001$) and area ($r = 0.80; p < 0.001$) of the plaques’ fibrous caps and of the area of the necrotic core ($r = 0.87; p < 0.001$).

Saam et al. (53) reported good interobserver variability of carotid plaque measurements. They measured 16 different variables, including wall and lumen volume. Their intraclass correlation coefficient was $>0.90$ for all their measurements. From their data, they calculated that a study of 43 patients would have adequate (80%) power to show a 5% change in 2 of their measurements (wall/outer wall ratio and wall volume) and a 10% change in a third measurement (percentage of lipid-rich necrotic core of the plaque).

Prognosis. SPECT. The potential prognostic value of the symptom of dyspnea has not been well defined. Abidov et al. (54) reported on 17,991 patients undergoing stress SPECT imaging. Dyspnea was associated with an increased risk of death in patients with and without a known history of CAD, after adjustment for all other significant factors (Fig. 7). In an accompanying editorial, Marwick (55) outlined the uncertainty regarding the pathophysiologic mechanism responsible for this finding but suggested ischemia, LV dysfunction, and obesity as possibilities.

Shaw et al. (56) compared the prognostic value of stress SPECT imaging in 1,993 African Americans, 464 Hispanics, and 5,258 Caucasian non–Hispanic patients (Fig. 8). African American and Hispanic patients had worse baseline clinical parameters, more abnormal SPECT scans, and worse outcomes, even after adjustment for baseline inequalities.

In 1,367 selected patients, Navare et al. (57) showed the prognostic value of dobutamine stress SPECT, as well as the importance of the stress ECG and heart rate response in image interpretation.

Dakik et al. (58) demonstrated the prognostic value of adenosine SPECT imaging in 126 stable patients early after acute myocardial infarction. Acampa et al. (59) reported that event-free survival was better in 196 patients with negative SPECT studies after a myocardial infarction compared with those with negative dobutamine echocardiograms.

Three studies reported on the prognostic value of stress SPECT imaging in the elderly. Valeti et al. (60) examined 247 patients aged ≥75 years; SPECT classified most patients as low risk or high risk and performed considerably better than the Duke treadmill score. De Winter et al. (61) demonstrated the incremental prognostic value of gated SPECT LV functional data in 294 patients aged ≥75 years. Zafiri et al. (62) demonstrated the prognostic value of LV dilatation and myocardial ischemia assessed by SPECT in 162 patients aged ≥80 years.

Additional studies of diabetic patients continue to emerge. Elhendy et al. (63) reported that reversible perfu-
tion defects and summed stress score were independently predictive of all-cause mortality and hard cardiac events in 297 diabetic patients. Valensi et al. (64) recruited 370 asymptomatic diabetic patients with at least 2 additional risk factors for SPECT imaging. Silent myocardial ischemia detected by SPECT predicted major cardiac events for the patients >60 years of age but not for those <60 years of age. Le Feuvre et al. (65) performed stress SPECT in 100 high-risk diabetic patients and dobutamine echocardiography in 75 of these patients. Silent myocardial ischemia was more frequently detected by SPECT and led to coronary revascularization in 15 patients (65).

PET. Previous studies have reported a considerable cardiac event rate in patients with vasodilator-induced ST-segment depression despite normal SPECT images. Chow et al. (66) followed 72 patients with dipyridamole-induced ischemic ECG changes but normal perfusion by rubidium PET for more than 2 years. There were no cardiac deaths and only 1 nonfatal MI, suggesting that those patients had an excellent prognosis, in contrast to the previous reports using SPECT.

Schindler et al. (67) employed nitrogen-13 ammonia PET imaging to detect perfusion abnormalities in response to sympathetic stimulation with cold pressor testing. Impaired blood flow increases were associated with a higher incidence of subsequent cardiovascular events.

CT: CORONARY CALCIUM SCANNING. Four prospective studies correlating the presence and/or quantity of coronary calcium with outcomes in asymptomatic patients were published in the past year (68–71) (Fig. 9, Table 3). Despite a modest number of total cardiovascular events and incomplete measurement of risk factors, these studies confirm the incremental prognostic value of coronary calcium quantification compared with conventional risk factor assessment.

Figure 8. Estimated annual death rates for different patient groups according to the summed stress score risk group on perfusion imaging. The differences between African American, Hispanic, and Caucasian non-Hispanic patients were highly significant (p < 0.0001). CV = cardiovascular; IHD = ischemic heart disease. *Not reported. From Shaw et al. (56).

Figure 9. Survival curves demonstrating the association between initial calcium score categories and survival free from new coronary heart disease events (A) and total new cardiovascular disease events (B), adjusted for age and gender differences. From Vliegenthart et al. (69).
MRI. Previous animal studies have shown that with severe ischemia myocytes and capillaries may be damaged to a degree that contrast cannot enter the infarct (72) to cause delayed enhancement by MRI. In these cases the infarct may have an enhancing rim of tissue surrounding a nonenhancing core. The presence of a central nonenhancing core has been attributed to “microvascular obstruction” and also linked with prognosis in a previous small study (73).

Hombach et al. (74) examined 110 patients within a week of an acute MI. All patients were classified as having infarcts with or without a nonenhancing core (called “persistent microvascular obstruction”). During follow up of 225 ± 92 days, 16 of the patients had a “major cardiac event,” which was defined as death, MI, or a variety of soft events, including revascularization. The presence of microvascular obstruction at baseline MRI was associated with cardiac events (p = 0.04) and decreased “event-free survival” (p = 0.04). However, microvascular obstruction was also associated with larger infarcts; with only 16 events, most of which were soft, the authors were unable to control for infarct size and other confounding variables.

The presence of delayed enhancement itself is clinically important. Nazarian et al. (75) performed MRI on 26 patients referred for electrophysiologic (EP) study. Although only 5 of their 26 patients had inducible tachycardia, the presence of delayed enhancement involving 26% to 50% or 51% to 75% wall thickness was predictive of inducible ventricular tachycardia at EP study (p < 0.001).

VENTRICULAR FUNCTION

CT. As we described last year, previous studies have demonstrated the ability of 16-detector-row systems to accurately calculate LV ejection fraction (LVEF). There were 2 notable additions this year. Salm et al. (76) showed good correlation between 16-detector-row coronary CTA and both echocardiography (kappa = 0.78) and MRI (kappa = 0.86) for the assessment of LV regional wall motion in 25 patients. Coche et al. (77) demonstrated similar correlation between ECG-gated pulmonary arterial CTA and radionuclide ventriculography for both LVEF (r = 0.91) and right ventricular ejection fraction (RVEF) (r = 0.89).

MRI. Magnetic resonance imaging volume measurements are highly reproducible and are becoming a reference standard. Recent studies focusing on normal values or refinements of the measurements reflect the maturity of this literature. Hudsmith et al. (78) published normal values for LV, RV, and atrial measurements based on 108 subjects (Table 4). This study also demonstrated the reproducibility of MRI volume measurements with excellent intraobserver and interobserver variability of LV measurements. In 111 normal subjects, Sievers et al. (79) determined normal values of left atrial measurements.

Currently, the acquisition of functional images requires multiple breath holds, typically 9 to 12, to cover the whole
heart. Several investigators studied a faster process. Narayan et al. (80) developed a rapid ungated imaging sequence which allowed for coverage of the heart in a single breath hold. They tested it on 20 patients and compared it with the traditional gated cardiac sequence. They found the 2 methods to be very comparable, as shown by the narrow 95% confidence intervals for the mean difference between the rapid and conventional measurements of LVEF (−1.1% to 5%) and RVEF (−7.2% to 1.3%). Taylor et al. (81) developed a similar non-breath hold method, which they tested in 28 patients with congenital heart disease. The 95% confidence intervals as calculated from their data were also tested in 28 patients with congenital heart disease. The 95% confidence intervals for the mean difference between the rapid and conventional measurements of LVEF (−1.1% to 5%) and RVEF (−7.2% to 1.3%). Taylor et al. (81) developed a similar non-breath hold method, which they tested in 28 patients with congenital heart disease. The 95% confidence intervals as calculated from their data were also very small (LVEF: −4.4% to 0.4%; RVEF: −3.9% to 0.5%).

**STEM CELL THERAPY**

**Trials.** There is great interest in using stem cells for treating damaged myocardium. Most trials of this therapy have used imaging end points, especially MRI volume measurements and infarct sizes. Two main types of treatment have been studied in patients with acute STEMI. In one line of study, granulocyte colony-stimulating factor, a cytokine that stimulates the bone marrow to produce neutrophil precursor cells, was injected subcutaneously. In the other line of study, stem cells were harvested from a patient and then reinjected, typically directly into the coronary arteries. The results of the studies (82–93) are tabulated in Tables 5 and 6. A similar smaller literature exists for stem cell therapy of chronic infarction (94).

The results of these small studies are generally mixed. The imaging end points used in these studies measure effects on ventricular function, apparent infarct size, and restenosis. Although these end points are clinically meaningful, they do not offer any insight into the fate of the injected or mobilized cells, which has stimulated interest in the direct imaging of stem cells.

**Direct imaging. MRI.** Studies in which stem cells have been tracked to the myocardium (95–99) are summarized in Table 7. The discovery that stem cells can phagocyte commercially available iron particles, which are detectable by MRI, has led to recent heightened interest in MRI for directly imaging stem cells. Although MRI has better spatial resolution than SPECT or PET, MRI imaging of stem cells has 2 major limitations compared with nuclear methods. First, the signal detected by MRI is not proportional to the iron load, so that it is very difficult to use MRI

<table>
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<tr>
<th>Table 4. MRI Volume Measurements in 108 Normal Volunteers</th>
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<td><strong>Intraobserver</strong></td>
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<td><strong>Mean Difference</strong></td>
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<td><em>(95% Limits of Agreement)</em></td>
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<td>LV ejection fraction</td>
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<td>LV end-diastolic volume index</td>
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<td>LV mass</td>
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<td>RV ejection fraction</td>
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<tr>
<td>RV end-diastolic volume index</td>
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<td>LA ejection fraction</td>
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Interstudy reproducibility was measured in only 12 of the 108 volunteers. Data from Hudsmith et al. (78).

LA = left atrium; LV = left ventricular; RV = right ventricular.

<table>
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<tr>
<th>Table 5. Human Granulocyte Colony-Stimulating Factor (G-CSF) Trials in Acute ST-Segment Elevation Myocardial Infarction</th>
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<tr>
<td><strong>Author</strong></td>
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<tr>
<td>Rips et al. (82)</td>
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Cath = cardiac catheterization; Co = control; Echo = echocardiography; LV EF = left ventricular ejection fraction; MC = matched controls; MIBI = technetium 99m sestamibi myocardial scintigraphy; MUGA = technetium 99m-labeled red blood cell multi-gated acquisition; PI = placebo; RT = randomized trials; Rx = treated; other abbreviations as in Tables 1 and 4.
### Table 6. Human Stem Cell Trials in Acute ST-Segment Elevation Myocardial Infarction

<table>
<thead>
<tr>
<th>Author (Ref.)</th>
<th>Design</th>
<th>n</th>
<th>Rx</th>
<th>Pl</th>
<th>Co</th>
<th>Treatment</th>
<th>Delivery</th>
<th>Primary End Point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssens et al. (87)</td>
<td>RT</td>
<td>33</td>
<td>34</td>
<td>—</td>
<td></td>
<td>BMSC</td>
<td>Intracoronal injection</td>
<td>LVEF (MRI) Wall thickening (MRI) Infarct size (MRI) Metabolism (PET) Perfusion (PET)</td>
<td>Greater decrease in infarct size (p = 0.036) in treated group. No other difference between groups.</td>
</tr>
<tr>
<td>Ruan et al. (88)</td>
<td>RT</td>
<td>9</td>
<td>11</td>
<td>—</td>
<td></td>
<td>BMSC</td>
<td>Intracoronal</td>
<td>LVF (echo) Wall thickening (MRI) Infarct size (MRI) Metabolism (PET) Perfusion (PET)</td>
<td>Improvement in strain parameters in treatment group (p &lt; 0.001), but not control, LVEF higher in treated than control group after 6 months (p &lt; 0.05).</td>
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<tr>
<td>Bartunek et al. (89)</td>
<td>MC</td>
<td>19</td>
<td>—</td>
<td>16</td>
<td></td>
<td>BMSC</td>
<td>Intracoronal</td>
<td>LVEF (MRI) Infarct size (MRI) Metabolism (PET) Perfusion (PET)</td>
<td>LVEF, infarct size, metabolism in infarct improved in treated group (p &lt; 0.05), not control. Higher incidence in coronary events at 4 months in treated group.</td>
</tr>
<tr>
<td>Wollert/Meyer et al. (90,91)</td>
<td>RT</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td></td>
<td>BMSC</td>
<td>Intracoronal</td>
<td>LVEF (MRI) Wall thickening (MRI) Infarct size (MRI) Metabolism (PET) Perfusion (PET)</td>
<td>LVEF significantly increased at 6 months in treated group compared to controls (p = 0.0026). No difference in infarct size. After 18 months difference in LVEF improvement less pronounced and no longer significant (p = 0.27).</td>
</tr>
<tr>
<td>Chen et al. (92)</td>
<td>RT</td>
<td>34</td>
<td>35</td>
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<td></td>
<td>BMSC</td>
<td>Intracoronal</td>
<td>LVEF (MRI) Wall thickening (MRI) Infarct size (MRI) Metabolism (PET) Perfusion (PET)</td>
<td>Smaller infarct size and higher LVEF in treatment group than control at 3 months (p &lt; 0.05).</td>
</tr>
<tr>
<td>Schachinger et al. (93)</td>
<td>RT</td>
<td>30 CPC</td>
<td>29</td>
<td>BMC</td>
<td>—</td>
<td>CPC, BMC</td>
<td>Intracoronal</td>
<td>LVEF (MRI) Wall thickening (MRI) Infarct size (MRI) Metabolism (PET) Perfusion (PET)</td>
<td>Increase in LVEF and decrease in infarct size, but no difference between cell groups.</td>
</tr>
</tbody>
</table>

Several of these studies were published in 2004.

BMSC = bone marrow derived stem cell; CPC = circulating progenitor cells; G-CSF = granulocyte colony-stimulating factor; other abbreviations as in Table 5.
<table>
<thead>
<tr>
<th>Author/Ref.</th>
<th>Model</th>
<th>n</th>
<th>Disease Model</th>
<th>Cell</th>
<th>Delivery</th>
<th>Dose</th>
<th>Label</th>
<th>Imaging Method</th>
<th>Results</th>
<th>Histologic Confirmation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arai et al. (95)</td>
<td>Mouse</td>
<td>21 total (4 with non-labeled cells, 3 with labeled cells)</td>
<td>Acute MI</td>
<td>ES</td>
<td>DM</td>
<td>$2.5 \times 10^5$</td>
<td>Iron (Feridex-PLL)</td>
<td>MRI 1.5 T</td>
<td>Focal area of signal loss at site of labeled cell injection.</td>
<td>Yes</td>
</tr>
<tr>
<td>Kraitchman et al. (96)</td>
<td>Canine</td>
<td>6</td>
<td>Acute MI</td>
<td>MSC</td>
<td>IV</td>
<td>$1.6 \times 10^8$</td>
<td>Iron (Feridex-PLL) In111Oxime</td>
<td>MRI 1.5 T SPECT/CT</td>
<td>SPECT/CT uptake in infarcted myocardium, liver, kidney, spleen by 24-48 h, no MRI detectable uptake.</td>
<td>Yes</td>
</tr>
<tr>
<td>Kustermann et al. (97)</td>
<td>Mouse</td>
<td>21 (8 with infarct and no cells, 5 normal animals with cells, 8 infarct animals with cells)</td>
<td>Acute MI</td>
<td>Embryonic ventricular cardiomyocytes</td>
<td>DM</td>
<td>$10 \times 10^4$</td>
<td>Iron (USPIO)</td>
<td>MRI 7 T</td>
<td>Focal area of signal loss at site of labeled cell injection.</td>
<td>Yes</td>
</tr>
<tr>
<td>Hofmann et al. (98)</td>
<td>Human</td>
<td>9 patients (3 with unselected BMCs injected intracoronary, 3 with unselected BMCs injected IV and then intracoronary, 3 with CD34+ enriched BMCs injected intracoronary)</td>
<td>Acute MI</td>
<td>BMC, CD34+ enriched BMC</td>
<td>IC and/or IV</td>
<td>Unclear 1.3 $\times 10^6$ to 45.5 $\times 10^8$</td>
<td>F18-FDG</td>
<td>PET</td>
<td>After intracoronary injection of unselected BMCs less than 3% was in the myocardium, the remainder was in the liver and spleen. IV infusion produced no significant myocardial activity. Intracoronary injection of CD34+ enriched cells showed 14-39% of total activity in the myocardium.</td>
<td>No</td>
</tr>
<tr>
<td>Cao et al. (99)</td>
<td>Rat</td>
<td>26 total (20 with labeled cells, 6 with unlabeled cells)</td>
<td>None</td>
<td>ES</td>
<td>DM</td>
<td>$1 \times 10^7$</td>
<td>F18-FHBG</td>
<td>MicroPET Bioluminescence</td>
<td>Repeated imaging over 4 weeks showed good correlation between MicroPET, bioluminescence, and ex-vivo assays for detection of ES cells.</td>
<td>Yes</td>
</tr>
</tbody>
</table>

BMC = bone marrow cells; DM = direct myocardial; ES = embryonic stem cells; F18-FDG = F18 fluorodeoxyglucose; F18-FHBG = 9-(4-F18-fluoro-3-hydroxymethylbutyl)guanine; IC = intracoronary; IV = intravenous; MSC = mesenchymal stem cells; PET = positron emission tomography; PLL = poly L lysine; SPECT = single-photon emission computerized tomography; USPIO = ultrasmall superparamagnetic iron oxide; other abbreviations as in Tables 1 and 3.
to quantitate cell concentration. Second, MRI requires much higher concentrations of cells to generate any measurable signal, so that direct percutaneous injection of the cells into the site of interest is usually required. This is well demonstrated in the study by Kraitchman et al. (96), in which intravenously injected cells were detectable by SPECT and not by MRI.

**MOLECULAR IMAGING**

The enormous emerging literature in this field is beyond the scope of this article. In addition to the studies listed in Table 7 for stem cells, 2 other SPECT studies were noteworthy. Su et al. (108) reported on the use of an indium-111-labeled matrix metalloproteinase–targeted radiotracer in a mouse model of acute MI. They demonstrated a 5-fold increase in myocardial uptake in the infarct region and a lesser increase in remote regions. This novel radiotracer has potential for in vivo localization and tracking of matrix metalloproteinase activity.

Hua et al. (109) demonstrated the potential value of a technetium-99m-labeled peptide targeted at alpha<sub>4</sub> beta<sub>3</sub> integrin in the identification of angiogenesis distal to femoral occlusion in a mouse model. This radiotracer has potential value in tracking therapeutic myocardial angiogenesis.

**CONCLUSIONS**

The authors hope that this review will stimulate the reader to examine at least a few of these current original articles on cardiac imaging in detail. If so, we will have achieved our goal.

**Acknowledgments**

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**REFERENCES**

8. Wen H, Bennett E, Epstein N, Plehn J. Magnetic resonance imaging assessment of myocardial elastic modulus and viscosity using dis-


91. Meyer GP, Wollert KC, Lotz J. Intracoronary bone marrow cell transfer after myocardial infarction: eighteen months follow-up data from the randomized, controlled BOOST (Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration) trial. Circulation 2006;113:1287–94.


