

YEAR IN CARDIOLOGY SERIES

The Year in Cardiac Imaging

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This article is the latest in the series of literature reviews that have appeared in the *Journal*. We have attempted to highlight important recent literature and new trends in single-photon emission computerized tomography (SPECT) myocardial perfusion imaging, cardiac positron emission tomography (PET), cardiac computerized tomography (CT), and cardiac magnetic resonance imaging (MRI). With rare exceptions, these articles were published between January 1, 2003, and May 31, 2004, in the English-language literature. Space considerations have forced us to quite arbitrarily include some articles and exclude others. We apologize in advance to those whose work we may have inadvertently overlooked or consciously excluded. Many of the articles that we have not described were very well done and published in prominent journals. In many cases, we felt that they were confirmations of previous literature on the same subject and, therefore, of lesser interest to the readership. Time and the advance of science are likely to prove us wrong in several cases.

We have chosen to organize the literature around topical themes rather than imaging modalities in an attempt to encourage you to think broadly rather than simply within a "silo" of the imaging modality of particular interest to you.

TECHNICAL ADVANCES

SPECT myocardial perfusion imaging. Although SPECT myocardial perfusion imaging is a very mature modality, important reports describing and evaluating technical advances continue to appear. Narayanan et al. reported a very rigorous receiver-operating characteristic analysis of the effects of ordered-subset expectation maximization with attenuation correction (AC), scatter correction (SC), and resolution compensation (RC) on 100 patients using seven different observers (1). The combination of AC + SC + RC provided a greater area under the receiver-operating characteristic curve for the overall detection of coronary artery disease (CAD), as well as for perfusion defects in the left anterior descending and left circumflex territories.

Manrique et al. (2) reported that photon energy recovery

for scatter correction improved the accuracy of left ventricular (LV) volume measurement in phantoms, and increased image contrast and LV volume in patients.

Grossman et al. (3) reported that a gender-independent normal database for attenuation-correction studies significantly improved specificity and normalcy rate without a significant loss of sensitivity.

Svensson et al. (4) reported less positive results from the application of three widely utilized software packages for quantitation to 50 consecutive patients. The summed difference score classification derived from the software packages disagreed in nearly half of the patients and disagreed markedly in 12%.

Cardiac PET. Several studies reported on the use of gated fluorine-18 fluorodeoxyglucose (FDG) cardiac PET imaging. Croteau et al. (5) performed list-mode PET studies and echocardiography in rats. Agreement between PET and echo for volumes ($R^2 = 0.49$ for diseased rats) and for ejection fraction ($R^2 = 0.56$) was only fair. Saab et al. (6) compared gated FDG PET with radionuclide angiography in 48 patients. Global ejection fractions by the two techniques correlated closely ($R = 0.83$). There was moderate agreement in the assessment of regional wall motion score ($\kappa = 0.50$).

Two studies compared gated FDG PET with MRI. Schaefer et al. (7) found that ejection fractions measured by the two techniques were highly correlated ($R = 0.95$), although PET did systematically underestimate ejection fraction by a mean of 2.7 percentage points. Regional wall motion analysis showed good agreement ($\kappa = 0.62$). Freiberg et al. (8) compared gated FDG PET with MRI in a heart phantom and 12 healthy subjects. Left ventricular volume and wall thickness were measured accurately in the phantom. In the healthy subjects, gated PET underestimated regional wall motion and end-diastolic volumes.

CT. Computerized tomography scanners have changed rapidly in the past five years such that the latest generation of scanner, the 16-detector helical scanner, provides robust cardiac imaging. New applications of cardiac CT have become possible, which will be discussed in the various subsections.

MRI. The biggest change in MRI in recent years has been the introduction of clinical scanning at 3-T. In MRI, the signal received is proportional to the strength of the magnet. Until recently, the maximum allowable clinical field strength was 1.5-T. However, in 1998 the Food and Drug Administration increased the allowable field strength from

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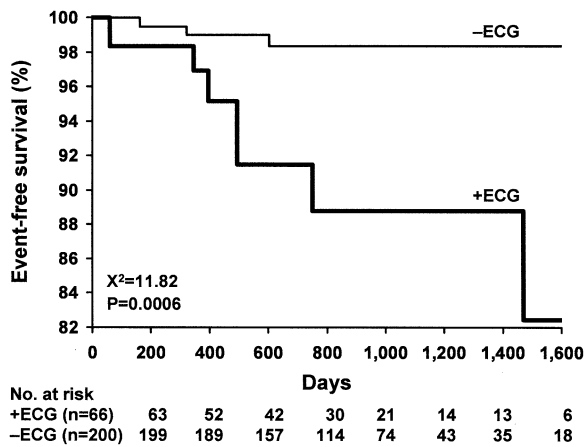


Figure 1. Survival free of myocardial infarction in patients with normal adenosine stress single-photon emission computerized tomography scans and either negative or positive electrocardiographic (ECG) changes (11).

1.5-T to 4-T. By 2002, vendors were producing clinical 3-T scanners designed to image the whole body. In the past year, six initial technical papers using cardiac MRI at 3-T appeared. Most of these papers sought to document that the theoretical advantages from 3-T imaging could be achieved in practice.

McGee et al. (9) showed increasing the field strength from 1.5-T to 3-T resulted in a 1.83 increase in signal-to-noise ratio in five volunteers. They also tested parallel imaging at 3-T. Parallel imaging is a technique that decreases scan time at the expense of signal. Using phantoms, they achieved the expected result: parallel imaging at 3-T cut the scan time in half, but resulted in loss of signal. However, the 3-T parallel images still had more signal than nonparallel acquired images at 1.5-T. Using 3-T may address one of the biggest limitations of MRI-long scan times.

The implications of 3-T scanning are unclear. However, early trends in neurologic and musculoskeletal imaging suggest that once vendors optimize their systems, 3-T may supplant 1.5-T as the standard field strength for MRI.

REFINEMENTS IN TEST INTERPRETATION

SPECT myocardial perfusion imaging. Klodas et al. (10) and Abbott et al. (11) reported on the uncommon finding of patients with ischemic electrocardiogram (ECG) changes but normal myocardial perfusion images after vasodilator stress (Fig. 1). Both studies found that older women comprised more than 82% of this uncommon population. During subsequent follow-up, the rate of cardiac death or nonfatal myocardial infarction (MI) (> 3.5% per year over the next three years in both studies) greatly exceeded that observed for normal images. Dahlberg and Leppo (12) discussed both articles in an accompanying editorial.

Abidov et al. (13) clarified the prognostic value of normal-stress SPECT images in the presence of transient ischemic dilation (TID) of the left ventricle. Patients in the highest TID quartile (>1.21) had a higher rate of cardiac

Table 1. Reproducibility of Gated SPECT Measurements in Patients With Heart Failure (16)

Parameter	Mean Difference	95% Confidence Limits	
		Upper	Lower
LVEF (%)	-0.9	+5.1	-6.9
LVEDV (ml)	3	+23	-17
LVESV (ml)	4	+24	-16

LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; SPECT = single-photon emission computed tomography.

events regardless of stress type. The authors advised caution in the use of prognostic statements implying low-risk when TID is present, especially in patients with typical angina, advanced age, and diabetes.

A second study by Abidov et al. (14) demonstrated the importance of the hemodynamic response to adenosine infusion during stress myocardial perfusion imaging. Patients with a high rest heart rate and low peak-to-rest heart rate ratio had an increased risk of cardiac death, even after adjustment for image findings.

Hayes et al. (15) demonstrated that when prone SPECT imaging was used to clarify the significance of equivocal inferior wall perfusion defects, subsequent hard event rates were similar to those obtained with supine-only imaging.

Finally, De Winter et al. (16) reported on the day-to-day variability in global LV function and perfusion by resting gated SPECT. The 95% limits of agreement (Table 1) provide important guidance for the use of gated SPECT to assess changes in function and perfusion over time in patients with heart failure.

MYOCARDIAL VIABILITY

SPECT myocardial perfusion imaging. Van der Burg et al. (17) reported on 153 survivors of sudden death, most of whom underwent implantation of a defibrillator. Survival free of recurrent ventricular arrhythmias was related to the presence of extensive scar tissue and ejection fraction ≤30%. Thus, although stress-rest SPECT demonstrated jeopardized myocardium and affected subsequent revascularization, neither jeopardized myocardium nor revascularization influenced outcome on multivariate analysis. Dobert et al. (18) reported pilot data on 26 patients who underwent intracoronary infusion of bone marrow-derived cells or circulating blood-derived endothelial progenitor cells after acute MI. Myocardial signal intensity in the infarct zone increased significantly on both SPECT and PET, suggesting that either might prove useful in monitoring therapeutic effect.

The FDG studies often require time-consuming hyperinsulinemic euglycemic clamping. Kam et al. (19) reported the simpler use of the nicotinic acid derivative acipimox in 50 non-diabetic patients for FDG SPECT and simultaneous dual-isotope tetrofosmin perfusion imaging. The FDG image quality was good in 46 patients (92%) and still

interpretable in the other four patients (8%). Tetrofosmin SPECT image quality was maintained.

Cardiac PET. Yang et al. (20) performed rest and stress rubidium perfusion and FDG PET imaging in 64 consecutive patients with non-Q-wave MI and Q-wave MI. Ischemic and viable myocardium was more common in the absence of Q waves.

Beanlands et al. (21) describe the rationale, design, and methods of the PARR-2 study. This important trial in four Canadian centers will evaluate patient outcome and cost-effectiveness using an FDG cardiac PET-guided approach to management of patients with CAD and severe LV dysfunction. It is hoped that this trial will complement the ongoing U.S. (STITCH) and United Kingdom trials exploring this same issue.

CT. As mentioned earlier, there has been recent interest in using CT for functional questions, including viability. In two patient studies, CT scans performed for other indications were retrospectively reviewed for findings of MI. In the larger of the two studies, Nikolaou et al. (22) reviewed CT coronary angiograms in 106 patients. Twenty-seven of these patients were thought to have had previous MI based on coronary angiography and clinical history. Using CT, 23 of the 27 patients were correctly identified as having had previous MI based on perfusion defects and wall motion abnormalities from retrospectively reconstructed gated images.

In the smaller study, Gosalia et al. (23) retrospectively identified 18 patients who had an MI and subsequently underwent a contrast-enhanced CT scan, performed for an unrelated indication, within a month. They then identified 19 control patients who had also had CT scans. Computerized tomography scans were reviewed for areas of decreased enhancement, which was interpreted as a finding of MI. Using these criteria, CT correctly identified 15 of the 18 patients with MI (sensitivity = 83%) and 18 of the 19 patients without MI (specificity = 95%). Positive predictive value was 94% and negative predictive value was 86%. Although very preliminary, these studies suggest a potentially very significant clinical application as CT is already widely used in patients with acute chest pain. Combining this application with direct coronary imaging could be particularly powerful.

MRI. In contrast to CT, there is extensive literature about the use of MRI for detecting myocardial viability. The most commonly used MRI method is delayed contrast enhancement. With this technique, an intravascular contrast agent (gadolinium-DTPA) is injected. The contrast agent rapidly washes in and out of normal myocardium. However, the contrast agent leaks into the interstitium of infarcted tissue and washes out slowly. Images obtained 10 to 15 min after injection show infarcted tissue as enhanced compared to normal myocardium. In prior years, this method was extensively validated in animals and humans. However, in the past year several authors took different approaches to MRI-delayed enhancement for viability.

Nelson et al. (24) compared the ability of dobutamine echo and thallium SPECT to detect scars of different transmural extents, using MRI as the gold standard.

This study is a departure from the recent literature in two important ways. First, the authors use transmural extent of scar as an outcome variable. The ability to detect transmural extent of scar has long been cited as an advantage of MRI. However, to date there have been few research or clinical applications for this information.

Second, the authors use MRI as the gold standard against which they compare the established methods of Thallium SPECT and dobutamine stress echo. This is a fundamental departure. Most recent studies have used established methods as gold standards against which MRI has been measured. The reversal of roles in this study indicates growing acceptance of MRI.

Wellnhofer et al. (25) questioned the superiority of delayed contrast enhancement to wall motion analysis as a means for predicting recovery of function after revascularization. They imaged 29 patients with chronic coronary artery disease. In all patients they obtained rest and low-dose dobutamine stress MRI wall motion images, as well as MRI delayed enhancement. Three months after revascularization they re-imaged the patients and subjectively graded improvement in regional function.

They found that MRI-visualized improvement in wall motion from rest to low-dose dobutamine better predicted recovery of function than did MRI-visualized delayed enhancement. The area under the receiver operator curve for wall motion analysis was 0.838. The area for delayed enhancement was slightly, but significantly less, at 0.728. This raises interesting questions about the optimal physiologic approach for predicting recovery of function, but also points out the ability to image multiple cardiac parameters at one examination.

CARDIAC RESYNCHRONIZATION THERAPY

Multiple studies of cardiac resynchronization therapy (CRT) were published (Table 2) (26-33). These studies generally reported on small numbers of patients with LV dysfunction and increased ECG QRS duration. The studies assessed the impact of CRT at varying intervals after implantation. Control measurements were performed either at baseline before pacemaker implantation or after turning the pacemaker off for a period of hours to days.

SPECT. Using gated SPECT, Sciagra et al. (26) suggested that CRT was not effective in the presence of a severe baseline perfusion defect.

PET. Cardiac resynchronization therapy appears to have modest effects on myocardial perfusion (Table 2), although one study using sestamibi (Nowak et al. [30]) reported an improvement in regional heterogeneity. Regional heterogeneity in FDG uptake resolved with CRT, reflecting an increase in FDG uptake in the septum. Three studies using carbon-11 acetate demonstrated similar results: an increase

Table 2. Studies of CRT

Author (Ref.)	N	Pts	ECG	Nuclear Method	Control	CRT	Major Effect of CRT
Sciagra et al. (26)	10	CHF	LBBB	Gated SPECT	B	3 mo	EF ↑, volumes ↓ if no severe perfusion defect
Sundell et al. (27)	10	IDM	LBBB	C-11 acetate O-15 water	O24h	8 ± 5 mo	SV ↑, K _{mono} /perf. unch, ME ↑; similar with dobutamine
Nowak et al. (28)	14	IDM	LBBB	O-15 water	B	14 days	MBF, corr MBF, resistance unch; little heterogeneity
Braunschweig et al. (29)	6	CHF	QRS >150	C-11 acetate	O2wks	1 yr	Rest: MBF, K _{mono} unch Dobutamine: MBF unch, K _{mono} ↑
Nowak et al. (30)	15	IDM	LBBB	FDG/sestamibi	B	14 days	Regional heterogeneity in FDG resolved
Nielsen et al. (31)	14	CHF	QRS >120	N-13 ammonia	DDD/AAI	≥3 mos	Regional heterogeneity in perfusion improved
Ukkonen et al. (32)	8	CHF	LBBB	C-11 acetate	AAI	1 ± 0.5 yrs	No effect on global/regional perfusion
Neri et al. (33)	8	IDM	LBBB	FDG/N-13	B	21 days	SV ↑, K _{mono} unch, ME ↑ FDG ↑ in septum; MBF ↓ slightly in septum

AAI = pacing mode; B = baseline; CHF = congestive heart failure; corr = corrected; CRT = cardiac resynchronization therapy; DDD = pacing mode; ECG = electrocardiogram; EF = ejection fraction; FDG = fluorodeoxyglucose; IDM = idiopathic dilated cardiomyopathy; K_{mono} = acetate clearance rate; LBBB = left bundle-branch block; MBF = myocardial blood flow; ME = myocardial efficiency; O24h = off for 24 h; O2wks = off for 2 weeks; SV = stroke volume; unch = unchanged.

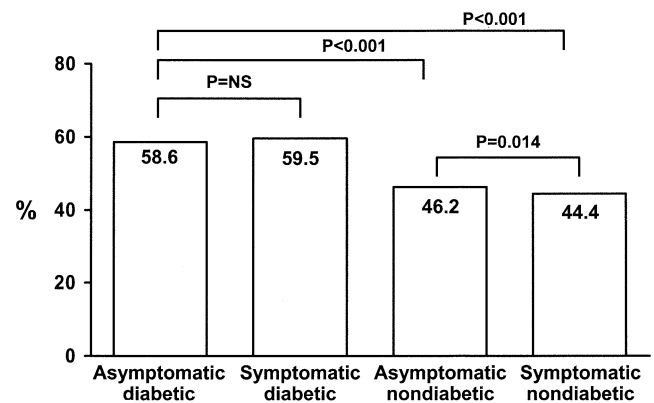


Figure 2. Prevalence of abnormal single-photon emission computerized tomography studies in 1,738 asymptomatic diabetics, 2,998 symptomatic diabetics, 6,215 asymptomatic non-diabetics, and 16,214 symptomatic non-diabetics (36).

in stroke volume, unchanged K_{mono}, and an increase in myocardial efficiency. Braunschweig et al. (29) showed an apparent improvement in myocardial oxygen uptake with CRT during dobutamine infusion without any change in myocardial blood flow, suggesting an improvement in overall oxygen utilization at the mitochondrial level.

MRI. In a dog model, Sorger et al. (34) described the torsion of the left ventricle during cardiac pacing. Employing tagged MRI, a method in which myocardial displacements can be converted into quantitative measures of mechanical motion, they found differences in ventricular torsion among atrial, univentricular, and biventricular pacing.

This group has published extensively on this topic. However, to date there have been no human applications of this method because that would involve performing MRI on patients with pacemakers—not an easy task, as pacemakers have long been an absolute contraindication to MRI scanning. But that may be changing.

Martin et al. (35) performed the first prospective study of the safety of MRI scanning patients with pacemakers. Fifty-four sequential, non-pacemaker-dependent patients underwent 62 clinically indicated MRI scans. No adverse events occurred. Thirty-seven percent of the leads underwent threshold changes, but only 2 of 107 (1.9%) required a change in programmed output. Given the rapid increase in patients undergoing CRT, more studies like this one will be helpful to define when these patients can undergo an MRI.

DIAGNOSIS/PROGNOSIS OF CAD

Diabetes mellitus. Two studies suggested a potential role for stress SPECT imaging in screening asymptomatic diabetics. Miller et al. (36) compared stress SPECT in 1,738 asymptomatic diabetics to both symptomatic diabetics and non-diabetics. Abnormal scans were present in nearly 60% of both asymptomatic and symptomatic diabetics, and significantly more common than in either asymptomatic or symptomatic non-diabetics (Fig. 2). High-risk scans followed a similar pattern (Fig. 3).

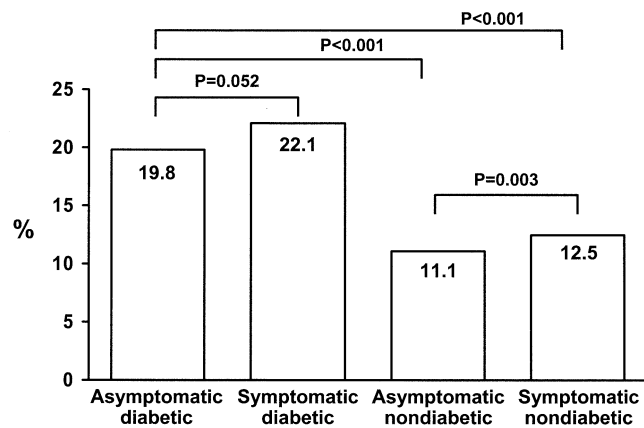


Figure 3. Prevalence of high-risk single-photon emission computerized tomography studies (based on summed stress score) in the same groups shown in Figure 2 (36).

Zellweger et al. (37) examined the prognostic value of dual-isotope SPECT imaging in 1,737 diabetics. The rate of objective evidence of CAD was 39% in 826 diabetic patients without symptoms, who had a subsequent critical event rate of 3.4%. Both of these findings were similar to those found in diabetic patients with angina. Diabetic patients with shortness of breath had a higher rate of objective evidence of CAD and worse subsequent outcomes.

Berman et al. (38) reported the impact of diabetes in 6,173 patients who underwent adenosine sestamibi and rest thallium SPECT. Subsequent cardiac death was more likely in diabetic women compared to other patients, and in patients with insulin-dependent diabetes compared to patients with non-insulin-dependent diabetes.

Peterson et al. (39) employed cardiac PET to explore the impact of obesity alone on myocardial fatty acid metabolism and efficiency. Obesity was a significant predictor of increased myocardial oxygen consumption and decreased myocardial efficiency. Insulin resistance correlated with fatty acid uptake, utilization, and oxidation.

Other patient subgroups. Lima et al. (40) reported stress SPECT results in 328 patients age 74 years or older. Abnormal studies were common, particularly in men, patients with chest pain, and those with resting or exercise ST-T abnormalities. Patients with normal perfusion images had an annual hard event rate of <1.0% per year, and those with abnormal images had an annual hard event rate of 14.3% per year. Studies of SPECT imaging before renal transplantation, before liver transplantation, and in patients with significant aortic stenosis showed potential benefits but also limitations (41-43).

Coronary calcium. Coronary calcium as detected by CT has been a controversial topic. The test has proliferated in the community faster than data to support it. In 2000 the American Heart Association noted the paucity of studies using hard events as end points and showing incremental benefit of coronary calcium over traditional risk factors. In the past year three studies were published that used hard

end points (death or myocardial infarction) and applied multivariate analysis to correct for risk factors.

Kondos et al. (44) identified 8,855 subjects and obtained follow up at a mean of 37 months in 5,635. Their population included 4,151 men and 1,484 women, whom they analyzed separately. Their variables in their multivariate model were age, smoking history, diabetes, hypercholesterolemia, and coronary calcium. In men, after adjusting for other variables, Kondos et al. (44) found that the presence of any coronary calcium conferred a relative risk of 3.86. In women, the multivariate analysis did not show an increase in relative risk with coronary calcium. The authors suggested that this negative result was due to the smaller number of women in their study.

Shaw et al. (45) examined a group of 10,377 individuals for all-cause mortality after a mean of 5.0 years. Their multivariate model included age, gender, diabetes, family history of coronary disease, hyperlipidemia, hypertension, smoking, and coronary calcium scores. They found that even low coronary calcium scores (11 to 100) conferred a statistically significant risk of death (relative risk = 1.64) after adjusting for other risk factors.

Greenland et al. (46) studied 1,312 subjects without diabetes, but with at least one coronary risk factor, who were followed for 8.5 years. Their model had two variables: the Framingham risk score and the coronary calcium score. Increasing coronary calcium predicted adverse outcome even after adjustment for Framingham risk score. Although a smaller study than the ones by Kondos and Shaw, the study by Greenland had the advantages of being prospective and of direct measurement of the risk factors.

Impact of clinical factors. Two studies addressed the issue of pretest likelihood in patient management. Poornima et al. (47) reported that SPECT imaging was of limited prognostic value in patients with low clinical risk and a low-risk Duke treadmill score. In contrast, patients with high-clinical risk and a low-risk Duke treadmill score had an annual cardiac mortality that was not low and were appropriately risk stratified by SPECT imaging. Hachamovitch et al. (48) reported on the value of SPECT imaging in patients with a high pretest likelihood of CAD (>0.85) without previous CAD. Single-photon emission computerized tomography imaging provided important incremental prognostic value and was a more cost-effective initial strategy, compared to initial treadmill testing or direct referral to catheterization. Beller and Watson (49) discussed the implications of both articles in an accompanying editorial.

Direct coronary imaging. It appears that direct coronary imaging with CT is becoming feasible, at least in select patients. Two papers were published on the topic, both from Europe, both using 16-detector CT scanners. These papers suggest that CT coronary angiography can achieve high negative predictive values, even in high-risk populations. However, CT is still limited by the low heart rates required and the limitations on the size of vessels visualized.

Ropers et al. (50) performed CT coronary angiograms on

77 patients scheduled for cardiac catheterization. To decrease motion artifacts, patients received oral beta-blockade before the scan, and the mean heart rate for the group was 69 beats/min. Though the authors limited themselves to vessels with a diameter ≥ 1.5 mm, 12% of the vessels were still uninterpretable. However, accepting these limitations, Ropers et al. (50) showed sensitivity of 92% and specificity of 93% for detecting a $\geq 50\%$ diameter stenosis in the vessels included in the study. The positive predictive value was 79% and their negative predictive value was an impressive 97%.

In a study by Mollet et al. (51), 128 patients scheduled for cardiac catheterization underwent CT coronary angiography. Again, patients received beta-blockers, and the investigators limited themselves to vessels ≥ 2.0 mm in diameter. For detecting a $\geq 50\%$ diameter stenosis the study reported sensitivity of 92%, specificity of 95%, and positive predictive value of 79%. Again, negative predictive value was impressive at 98%.

These results are encouraging but should be interpreted with caution. Early studies with expert readers and cooperative patients typically produce excellent results. However, it is very encouraging that separate groups achieved similar results. The introduction of faster scanners may further improve these results.

Post-test clinical management. Another article by Hachamovitch et al. (52) addressed the important issue of the risk of subsequent hard events after a normal stress SPECT study. Patients without previous CAD had a uniform risk over time, but patients with known CAD had an increasing risk over time. Detailed tables provided guidance regarding the appropriate timing of repeat testing following a normal SPECT study. A third article by Hachamovitch et al. (53) related inducible ischemia on stress SPECT imaging with the survival benefit of early revascularization. Patients with no or mild ischemia appeared to have a survival advantage with medical therapy, where as those with moderate to severe ischemia had a survival benefit with revascularization, which increased in higher risk patients.

Bugiardini et al. (54) reported on women with angina, abnormal stress SPECT studies, normal coronary angiograms, and diffuse vasoconstriction during acetylcholine. Over subsequent follow-up of >10 years, a majority developed angiographic CAD, suggesting that such abnormal SPECT studies may not always be "false positives."

Acute chest pain management. Kontos et al. (55) published a cost study comparing alternative approaches to the management of patients with acute chest pain in the emergency department. Use of acute SPECT imaging in low-risk patients was associated with reduced costs, lower rates of angiography, and shorter lengths of stay.

Molecular imaging. Molecular imaging is the noninvasive imaging of cellular and molecular events. Better understanding of molecular events has led to recent interest in imaging new markers, which is possible with SPECT, PET, and MRI.

The numerous papers in the field cover diverse topics and are well beyond the scope of this article. As examples, we have chosen several papers describing attempts to label the $\alpha v\beta 3$ integrin (a surface receptor involved in angiogenesis), matrix metalloproteinases, and selected individual cells.

SPECT. Meoli et al. (56) imaged the $\alpha v\beta 3$ integrin with an indium-111-labeled. They showed increased activity of their $\alpha v\beta 3$ tracer in the region of an infarct in animal models, suggesting that the $\alpha v\beta 3$ integrin, and therefore angiogenesis, may be imaged. However, they were unable to quantify the absolute amount of tracer.

Aicher et al. (57) labeled circulating human endothelial progenitor cells with indium-111 oxime, the same label used for clinical white blood cell labeling. They intravenously injected the labeled endothelial progenitor cells into eight nude mice with myocardial infarctions. After sacrifice they showed increased radioactivity in the area of infarction. The inability to absolutely quantitate cells in the area of infarction is again a limitation of this promising approach.

Schefers et al. (58) modified the broad-spectrum matrix metalloproteinase inhibitor CGS 27023A for labeling with iodine-123. They demonstrated the feasibility of in-vivo imaging in a mouse model of carotid artery ligation.

MRI. Winter et al. imaged the $\alpha v\beta 3$ receptor using MRI (59). They developed a novel nanoparticle, a lipid-encapsulated perfluorocarbon with 90,000 particles of MRI contrast agent attached to its surface. They targeted this nanoparticle to the $\alpha v\beta 3$ receptor in cholesterol-fed rabbits and found increased signal in the aortic walls of rabbits that were injected with the targeted particles. They achieved a degree of histologic confirmation by showing neovascularity in the aortas including colonization of vessels by $\alpha v\beta 3$.

There has been extensive interest in labeling cells with iron particles for imaging with MRI. For technical reasons a gadolinium-based label, like the one used by Winter et al. (59) would be preferable. However, as iron is nontoxic and taken up by a variety of cells, most of the papers on this topic have used various forms of iron labeling.

Hill et al. (60) created an iron-labeled fluorescent particle. The iron part of the particle allowed for noninvasive imaging with MRI. The fluorescent part of the particle allowed for confirmation at histology. They incubated the mesenchymal stem cells (MSCs) with the particle and through a catheter injected them directly into infarcted tissue in swine. Serial MRIs performed at 4, 8, and 21 days showed the expected signal changes in the myocardial tissue and histology confirmed the presence of intact MSCs.

At a more basic level, Frank et al. (61) showed that one does not need to have novel or unique particles to perform cell labeling. They incubated several commercially available transfection agents with commercially available iron particles. They then took their transfection agent/iron particle combination and incubated them with different cell lines. They showed that their cells took up the transfection agent/iron particle combination better than incubation with iron particles alone, and that cell viability and proliferation

were not affected by the presence of the label. They also quantified the MRI signal produced by their labeled cells.

CONCLUSIONS

We hope that this review has highlighted some of the important emerging literature in cardiac imaging. It has been an educational experience for us. If we have stimulated you to read at least a few of the original articles, we hope that it will have also been an educational experience for you.

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