Imaging in the Evaluation of the Patient with Suspected Acute Coronary Syndrome

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Patients presenting to the emergency department with chest pain have a common problem. Definitive diagnosis at presentation is difficult due to limitations of the initial evaluation, and, thus, the majority of patients are admitted. Recognition of these limitations has driven the investigation of alternative evaluation techniques and protocols to attempt to improve diagnostic sensitivity without increasing overall costs. Acute myocardial perfusion imaging has been a highly valuable technique for risk stratification of intermediate to low-risk patients with chest pain. However, for a variety of reasons, it has not been widely embraced. In the past few years, alternative techniques have been investigated for use in the diagnosis of acute coronary syndromes in the acute setting. Coronary calcium scoring and cardiac magnetic resonance imaging show promise as new tools in the armamentarium for acute coronary syndromes. The challenge now lays in developing a strategy that uses these and future techniques most appropriately to support optimal medical decision making.

OVER THE LAST decade, major advances have been made in the treatment of acute coronary syndromes (ACS), both in acute intervention and in risk reduction through behavior modification and important pharmaceutical interventions. However, these advances have not diminished the challenge of correctly identifying patients with ACS among those presenting to the emergency department (ED) with symptoms suggestive of ACS. In fact, the triage challenge has become more difficult as the ED increasingly assumes the role of a last safety net and becomes more and more crowded, especially in large urban areas. Adding to the complexity of the problem is that the opportunity for marked outcome improvement through acute intervention is time-dependent, thereby raising the bar for early and accurate identification of the patient with true ACS.

ACUTE MYOCARDIAL PERFUSION IMAGING (MPI)

Over the years, ED physicians have increasingly relied on technology, including imaging, for diagnosis. Now, with new bedside biomarkers and advanced imaging techniques available in the ED, triage decisions are being made with more comprehensive yet rapid information. For patients with chest pain, who account for more than 6 million ED visits per year in the United States alone,[1] the electrocardiogram remains the most important initial risk assessment tool. In patients with significant ST segment changes on the electrocardiogram or increases in myocardial markers of necrosis, myocardial ischemia or infarction is highly likely. In those with nonischemic electrocardiogram and negative markers, identification of high-risk patients is more difficult. Because of the limitations of the initial risk stratification tools, many patients who do not actually have myocardial ischemia are admitted. Despite this low threshold for admission, a significant minority of patients are inadvertently discharged with myocardial infarction, often with adverse outcomes.[2,3]

Because the initial evaluation does not often yield a definitive diagnosis, one important aspect of the ED evaluation of the patient with chest pain is risk stratification. Numerous alternative approaches to identify high-risk patients quickly as well as to increase cost effectiveness have been explored. The area of highest focus has been the identification of patients with true ACS among those who are initially considered low risk based on the absence of diagnostic electrocardiogram changes and a history of coronary artery disease (CAD). Importantly, these low-risk patients account for nearly 2/3 of those presenting to the ED with chest pain, representing as many as 4 million patients per year in the United States.[4,5] The advantages of rapid, accurate diagnosis are obvious and include early initiation of appropriate therapy in those patients with myocardial infarction or unstable angina, reduction in the inadvertent discharge of those with ongoing ischemia, and shortened length of stay and reduced unnecessary admissions for those with noncardiac chest pain. In this context, acute MPI has been a valuable technique.

Thallium Studies

Using MPI to identify patients with ACS is not a new concept. In one of the first studies, Wackers and coworkers performed planar thallium-201 imaging in 203 patients admitted for possible myocardial infarction.[6] Images were abnormal in all 34 patients who had myocardial infarction, as well as in 27 (58%) of the 47 who had unstable angina. In contrast, none of the 98 patients diagnosed with stable angina or atypical chest pain had abnormal studies. Other investigators using similar techniques reported similar results, with a high

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Table 1. A Summary of Reported Studies Showing the Sensitivity and NPV of MPI in the Acute Setting

Investigator (year)	Total No. Pts.	No. Myocardial Infarctions	No. Normal MPI	% Sensitivity	% NPV
Varetto et al[18] (1993)	64	13	34	100	100
Hilton et al[15] (1994)	102	12	70	100	99
Kontos et al[16](1997)	532	28	361	93	99
Tatum et al[19] (1997)	438	7	338	100	100
Heller et al[17] (1998)	357	20	204	90	99
Kontos et al[20] (1999)	620	6	379	100	99

sensitivity for identifying patients with myocardial infarction or other cardiac events.[7]

Despite these promising studies, thallium planar imaging has important limitations that have prevented the widespread use of this approach. Planar imaging has a lower sensitivity for detecting small areas of ischemia and for detecting ischemia in the posterior distribution, an area that often is not associated with diagnostic electrocardiogram changes. Because of dose limitations, energy characteristics, and relatively rapid redistribution, thallium-201 is not an optimal agent for acute imaging. Although some logistical problems could be overcome by using portable gamma cameras placed in the ED, single photon emission computerized tomography (SPECT) is the preferred technique for cardiac imaging, especially when coupled with the superior image quality with technetium-based myocardial perfusion agents.[8,9]

SPECT Imaging with ^{99m}Technetium Agents

^{99m}Technetium sestamibi and tetrofosmin are taken up by the myocardium in proportion to blood flow, with no significant redistribution.[10] Therefore, patients can be injected while having symptoms and imaged up to several hours later, enabling most logistical barriers to be overcome. These agents have been referred to as "chemical microspheres," a term that, although a misnomer, conveys a characteristic that is important for acute applications: the image, even if acquired hours later, defines the risk zone present at the time of injection.

In addition, the favorable energy and dosimetry of ^{99m}technetium allow the acquisition of not only high-resolution tomographic images but gated reconstructions as well, thereby providing the simultaneous assessment of regional and global ventricular function. Ejection fraction can be quantitated using computer algorithms. The qualitative assessment of regional wall motion by gating can be correlated with perfusion defects, assisting in the determination of whether a perfusion defect reflects true ischemia or infarction, or is the result of artifact or tissue attenuation.[11] This ability to correlate wall motion and perfusion significantly improves specificity and is particularly valuable in acute MPI, in which important determinations must be made from a single image set.[12,13]

Numerous studies have shown that acute MPI with these ^{99m}Tc myocardial perfusion agents can accurately identify patients with myocardial infarction and/or unstable angina. In one of the first studies, Bilodeau and coworkers imaged 45 patients without a previous history of myocardial infarction who had been admitted for unstable angina.[14] The presence of a perfusion defect had a sensitivity of 96% and specificity of 79% for predicting angiographic coronary disease in patients injected during an episode of pain, compared with a sensitivity of only 65% for the electrocardiogram.

A similar high diagnostic accuracy was seen when acute MPI was used in patients presenting to the ED who were initially considered low risk based on the absence of ischemic electrocardiogram changes. Hilton and coworkers used ^{99m}Tc sestamibi SPECT to study 102 patients presenting to the ED with typical angina and either a normal or nondiagnostic electrocardiogram.[15] Seventy patients had a normal perfusion scan, only one of whom had a cardiac event. In comparison, 2 (13%) of the 15 patients with equivocal scans and 12 (71%) of the 17 with perfusion defects had cardiac events. When equivocal scans were classified as abnormal, the sensitivity and specificity of an abnormal study for predicting adverse cardiac events were 94% and 83%, respectively. In a study of 532 patients who were admitted for possible myocardial infarction, we found that sensitivity (93%) was similarly high.[16]

Although most studies were performed with sestamibi, comparable results have been obtained with tetrofosmin. In a multicenter study, Heller and coworkers found a sensitivity of 90% in 357 patients who underwent acute MPI.[17] Negative predictive value (NPV) was equally high, at 99%, with only 2 patients who had small non-Q wave myocardial infarctions having negative acute MPI.

These studies showed that acute MPI is predictive of cardiac events, with reported sensitivities of 90% to 100%, and NPVs greater than 99% for identifying and excluding patients who had cardiac events (Table 1).[15-20] The high NPV allows safe selection of patients who can be placed in lower intensity settings or discharged home, while the high sensitivity enables identification of those who require further evaluation in an inpatient setting. Because most studies used acute MPI only in low-risk patients, the absolute numbers of patients with myocar-

dial infarction in any one study was relatively small, resulting in relatively wide confidence intervals. In a study that included 141 patients with myocardial infarction, sensitivity was 89% (95% CI 83% to 94%), similar to prior reported studies. Patients with negative MPI had small myocardial infarctions, as estimated by peak creatine kinase (CK) values, with an average CK of 313 ± 227 U/L, compared with 590 ± 620 U/L ($P < 0.001$) in those with positive MPI.[21]

Prognosis

One of the most important outcome determinants in patients with myocardial infarction is infarct size.[22-25] The most important determinant of infarct size is the ischemic risk zone or the amount of myocardium at risk.[26] MPI is the only technique among those commonly available that provides a direct measurement of myocardium at risk, as compared with the gold standard, radiolabeled microspheres.[27-29] In studies in which defect size at patient discharge was measured with MPI, defect size correlated well with other outcome predictors in patients with myocardial infarction, including left ventricular ejection fraction, regional wall motion index, end-systolic volume, and peak CK levels.[30-32]

It has also been shown that, despite the absence of ischemic electrocardiogram changes, the ischemic risk area can be large. We found that the ischemic risk area ranged from 0% to 62% of the left ventricle, with a mean risk area of 18% ± 11%, and that the risk area in patients with normal electrocardiogram was similar to the risk area in those with abnormal electrocardiogram (16% ± 12% versus 19% ± 12%, $P = 0.25$, respectively).[33] An important observation is that normal acute MPI can identify patients who are at low risk for short and long-term cardiac complications. Hilton and coworkers found that patients with normal perfusion imaging had an excellent prognosis, with no late events at 90-day follow-up.[34] Similarly, we reported that patients with negative acute MPI had an event rate of only 3% during the subsequent year.[19]

Comparison With Troponin

Troponin has a higher sensitivity and specificity than other cardiac markers and, therefore, has become the preferred marker for diagnosing myocardial necrosis. Because there is a threshold for ischemia that can be detected by MPI, which is approximately 3% to 4% of the left ventricle, one would expect that some patients with troponin increase would have negative MPI.[35] This result has been supported by a number of small studies, which reported that, although the sensitivity of MPI was high, it was lower than that of troponin-I and troponin-T.[20,36] In a larger study, we analyzed outcomes in 266 patients with increased troponin-I values who were initially considered low risk for myocardial infarction and underwent acute rest MPI as part of standard chest pain evaluation protocol.[37] Myocardial perfusion abnormality was graded using a summed defect score derived from a 17-segment model. A total of 66 patients had negative MPI, giving a sensitivity of only 75%, much lower than the prior studies. Patients with positive MPI had a mean total of 2.7 ± 1.3 abnormal segments and a mean summed defect score of 6.4 ± 3.8. Patients with negative MPI had lower peak CK-MB (18 ± 23 versus 42 ± 66 ng/mL, $P < 0.001$) and higher ejection fractions (55% ± 15% versus 47% ± 12%, $P < 0.01$), and were more likely to have nonsignificant disease (62% versus 83%, respectively, $P < 0.01$) than those with positive MPI. Of the 66 patients with negative MPI, 37 (56%) had a peak CK-MB less than 8 ng/mL, which was the former institutional threshold value for myocardial infarction and, therefore, would not previously have been diagnosed with myocardial infarction. Similarly, almost 3/4 of patients with negative MPI had peak CK values less than 300 U/L, and only 17% had a peak CK more than 500 U/L.

The use of markers and MPI should be considered complementary rather than competitive for evaluating patients presenting at the ED with chest pain. Acute MPI has a number of advantages. First, myocardial markers can diagnose only infarction and cannot identify ischemia in the absence of necrosis. Therefore, the sensitivity for identifying non-necrosis events, such as revascularization or significant coronary disease, is higher with MPI than with troponin.[20,36] Also, because of the time required for imaging and processing, acute MPI results can be available within 1 to 2 hours after injection. In contrast, markers of necrosis are not detectable in the blood until several hours after the damage has occurred. To achieve a high sensitivity, sampling must be performed over an 8 to 9-hour period.[38] Further delays in diagnosis may result because of the time required for blood draws, as well as laboratory delivery and analysis. A third advantage of acute MPI is that it can identify risk area, as discussed previously.

Acute MPI has some limitations when used to assess patients with chest pain. Acute infarction, acute ischemia, and prior infarction all cause perfusion defects, and differentiation is not possible based on the images alone. However, patients with prior infarction are at higher risk for acute events and are usually not candidates for primary triage to a subsequent outpatient evaluation. Biomarkers may play a key role in this population, but MPI still adds important information for the purposes of risk assessment.

Timing of Tracer Injection

Despite injection during the absence of symptoms, studies using either thallium or technetium agents have found a high sensitivity for identifying patients with infarction or ischemia, even when the pain-free period

was prolonged. However, there is clear evidence that sensitivity decreases as the pain-free interval increases. Wackers and coworkers performed thallium-201 scintigraphy in 98 patients admitted with chest pain in whom myocardial infarction was excluded.[6] When imaged within 6 hours of the last anginal symptoms, 57% of the patients had abnormal studies. When imaged after 12 hours, only 8% had abnormal studies. Similar results were reported by van der Wieken and colleagues.[7]

Studies using technetium agents also show higher sensitivity when injection is performed during or soon after pain. Bilodeau and coworkers found that the sensitivity of MPI for detection of CAD was 96% in 45 patients imaged during chest pain.[14] When the same patients were reinjected later, while pain-free, the sensitivity was 65%. In both instances, the sensitivity was significantly higher than that of the initial electrocardiogram (ie, 35%). We found that when patients were injected within 6 hours of symptoms, there was no difference in sensitivity for identifying those who had myocardial infarction, revascularization, or significant coronary disease among those who were injected with and without symptoms.[16] Other investigators have also reported high sensitivity despite the absence of symptoms during injection.[14,16,18]

It is important to remember that, although defects on MPI are the result of flow abnormalities, the underlying mechanism and resulting physiology are distinctly different in patients undergoing stress testing and those with ACS. Stress testing causes flow imbalances and possibly ischemia by increasing myocardial demand in the setting of fixed supply or by inducing flow heterogeneity by vasodilation. Stress protocols are designed to ensure that the perfusion tracer is injected at the time of maximal flow imbalance, but when the patient stops exercising, flow quickly returns to normal. In contrast, ischemia in patients with ACS is caused by thrombotic occlusion, with intermittent vasoconstriction and complex coronary morphology, resulting in further decreased coronary blood flow.[39,40] These flow abnormalities can persist despite prolonged antithrombotic and antiplatelet treatment with heparin or glycoprotein IIb/IIIa inhibitors.[41-43]

In addition, it is known that a proximal thrombus may lead to distal microvascular obstruction.[44] In a study of 75 patients who underwent sestamibi injection during rotational atherectomy, a procedure in which distal embolization of microparticles is frequent, perfusion defects were present in 65%.[44] In an interesting study of 40 patients who underwent percutaneous transluminal coronary angioplasty (PTCA), Fram and coworkers found that perfusion abnormalities persisted in patients injected with ^{99m}Tc sestamibi at varying times after PTCA, although the size of the perfusion defect decreased as the interval after PTCA increased.[45] This finding suggests that transient ischemia induces alterations in myocyte membrane function that persists after flow is returned to normal. This result may explain the frequent occurrence of perfusion defects in patients injected while symptom free.

All these findings strongly support the conclusion that the sensitivity of acute MPI will depend on the extent, duration, severity, and reperfusion status of the ischemic insult. It must be kept in mind that "chest pain" is not the gold standard for myocardial ischemia and that silent ischemia is common. In patients who have been pain-free for prolonged periods, acute MPI will have a lower sensitivity for detection of the presence of CAD, but persistent abnormality may suggest a more complex and possibly unstable condition with risk implications.

Cost-Effectiveness

The ability to discharge patients directly from the ED has obvious cost implications. Despite the application of relatively complex and expensive technology, ED MPI can be cost-effective. A number of observational studies estimated that significant cost savings would occur due to changes in disposition made based on the results from acute MPI.[17,46-48] Preliminary data from a large prospective study confirm these findings. The Emergency Room Assessment of Sestamibi for Evaluating Chest Pain study randomized 2,475 patients to routine care or ED MPI, in which patients were injected with sestamibi in the ED and then underwent acute imaging, with the results called back to the ED physician.[49] All patients, whether admitted or discharged, underwent subsequent marker analysis and stress testing. There was no difference between the 2 groups in the percentage of patients with myocardial infarction (97% versus 96%) or unstable angina (83% versus 81%, respectively) who were admitted with one patient with myocardial infarction from each group discharged from the ED. However, the use of acute MPI resulted in a significantly lower admission rate and a higher rate of direct discharge from the ED. Preliminary results indicate that, despite the addition of high cost technology, this strategy was cost-effective, with a reduction in costs of $70 per patient.[50]

Incorporation into Chest Pain Evaluation

A set of recommendations for using MPI in the ED has recently been published.[51] The recommended patient selection criteria are similar to those used for admission to a chest pain evaluation unit. Patients should be low risk (ie, no ischemic electrocardiogram changes or history of coronary disease) and hemodynamically stable. The optimal use of MPI as a triage tool is in patients who will be discharged home and have stress testing as an outpatient if imaging is negative.

Although a number of centers have used acute MPI on a patient-by-patient basis, the optimal use is to incorpo-

Table 2. A Summary of the Strategy Used at Our Institution for the Evaluation of Patients Presenting to the ED with Chest Pain or Other Symptoms Suggestive of ACS

Level: Category	Probability of AMI	Probability of UA	Diagnostic Criteria	Disposition	Diagnostic Strategy	Treatment Strategy
1: Definite or highly probable AMI	Very high	Very high	Ischemic ST elevation, acute posterior MI	Admit CCU	Serial ECG, markers at 0, 6, 12, 18, and 24 hrs; continue q 6 hrs until peak reached	Lytics within 30 min or primary PTCA within 90 min
2: Definite or highly probable AMI or UA	Moderate	High	Typical symptoms and/or ischemic ECG, known CAD, acute CHF	Admit CCU	Serial ECG, markers at 0, 3, 6, and 8 hours; if (+), continue every 6 hrs until peak reached	Aspirin, enoxaparin, IV NTG, IV beta blocker, consider GP IIb/IIIa inhibitor and clopidogrel
3: Possible AMI or UA	Low	Moderate	Typical, prolonged (>30 minutes) symptoms and nonischemic ECG, or prolonged atypical symptoms, known CAD and nonischemic ECG	Admit to CCU for observation, fast track rule-in protocol	Serial ECG, markers at 0, 3, 6, and 8 hrs. Rest MPI imaging	ASA. If rest MPI (+), advance to level 2 treatment protocol
4: Possible UA	Low	Low	Typical but not prolonged symptoms and a nonischemic EGG, or prolonged, atypical symptoms and a nonischemic ECG	Evaluation in ED; admission depending on rest MPI	If rest MPI (+), admit CCU If rest MPI (−), discharge and stress within 24-72 hrs	Discretionary
5: Very low suspicion of AMI or UA	Very low	Very low	Symptoms and evaluation clearly document noncardiac cause of symptoms	Evaluation in ED as deemed necessary	Discretionary	Discretionary

Abbreviations: AMI, acute myocardial infarction; ASA, aspirin; CAD, coronary artery disease; CCU, coronary care unit; CHF, congestive heart failure; ECG, electrocardiogram; ED, emergency department; GP, glycoprotein; IV, intravenous; MPI, myocardial infarction; MPI, myocardial perfusion imaging; NTG, nitroglycerin; PTCA, percutaneous transluminal coronary angioplasty; UA, unstable angina; (+), positive; (−), negative. Serial markers includes CK and CK-MB at 0, 3, 6, and 8, troponin 1 at 0 and 8, and myoglobin at 0 hrs.

rate acute MPI as part of a chest pain evaluation strategy. In one model, patients who are actively having chest pain undergo both acute ^{99m}technetium MPI and serial marker analysis. Patients who are evaluated while pain-free are injected with thallium and imaged immediately. In those patients with normal images, immediate stress MPI with ^{99m}technetium can be performed. A modification of this protocol, in which patients undergo a 2-hour initial assessment with serial markers and ST segment trend monitoring followed by dual isotope stress testing, has also been successful.[52]

In contrast to most chest pain programs, the systematic chest pain protocol developed and implemented at the Medical College of Virginia Hospitals is designed for all patients with chest pain, with MPI used for evaluation of lower risk patients (Table 2).[19] All patients presenting to the ED with chest pain or other symptoms consistent with myocardial ischemia undergo rapid evaluation, with assignment to a triage level based on the probability of having myocardial infarction or myocardial ischemia as derived from clinical and electrocardiogram variables. After the initial evaluation, patients thought to be at high risk (ie, those with ischemic electrocardiogram changes and those with known coronary disease having typical symptoms; levels 1 and 2) are admitted directly to the critical care unit. Patients considered at low to moderate risk for ACS (eg, absence of ischemic electrocardiogram changes) undergo further risk stratification using acute rest MPI.[19] Level 3 patients are admitted as observation patients and undergo a rapid rule-in protocol. Level 4 patients are evaluated in the ED. If images are either negative or unchanged from previous studies, patients are discharged home and scheduled for outpatient stress testing. If MPI is positive, they are admitted and advanced to the level 2 treatment protocol.

It is important to appreciate the difference in the role of acute rest MPI between levels 3 and 4 patients. In level 3 patients, the presence of a significant perfusion defect identifies a high-risk patient in whom early initiation of aggressive treatment is indicated, with the potential for early intervention. On the other hand, negative MPI and negative markers identify patients who can safely undergo early stress testing and discharge. Although the identification of higher risk patients is the focus of much interest, the improved ability to risk stratify intermediate risk patients into low risk who can be stressed safely is an important advantage. In contrast, the role of MPI in the level 4 patients is to diagnose unsuspected ACS and prevent the inadvertent discharge of these patients from the ED (see Case Report). Follow-up stress testing is used to exclude significant coronary disease.

This simple risk stratification scheme accurately separates patients into high, intermediate, and low risk groups. The ability of MPI to risk stratify lower risk

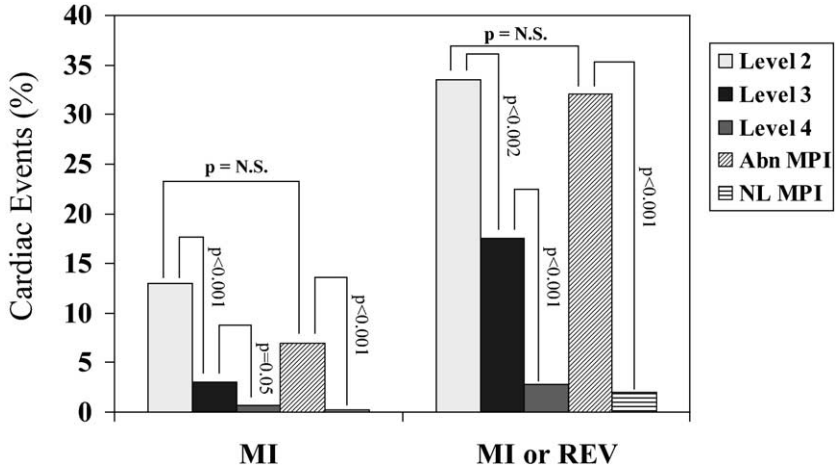

Fig 1. An outcomes comparison. Notably, there was no significant (NS) difference in the incidence of myocardial infarction (MI) or MI and revascularization (REV) among patients triaged to the high-risk level 2 and those initially triaged as lower risk who had abnormal (Abn) myocardial perfusion imaging (MPI). NL, normal.

patients further is also seen, as outcomes in those with positive MPI were similar to those in the high risk level 2 patients (Fig 1).[19]

CORONARY CALCIUM SCORING (CCS)

CCS is a technique that has potential applications for evaluating low-risk patients with suspected acute coronary syndromes (ACS). Multiple studies have shown that coronary calcium detected by electron-beam computerized tomography (EBCT) is associated with coronary artery disease (CAD). In conjunction with a clinical risk profile, calcium score noninvasively identifies patients with a high likelihood of having 3 vessel or left main CAD.[53] It provides incremental and independent power in predicting the severity and extent of obstructive CAD.[54] Additionally, a high calcium score identifies patients having a moderate to high risk of a cardiovascular event in the next 2 to 5 years.[55] A recent meta analysis found that EBCT had a sensitivity of 92% and a specificity of 51% for diagnosing coronary disease.[56]

EBCT has a diagnostic accuracy similar or superior to exercise treadmill testing for identifying angiographically significant CAD.[57,58] Schmermund and coworkers examined 323 patients with a normal rest electrocardiogram and no history of CAD who were referred for coronary angiography. Sensitivity of exercise treadmill testing was 50%, with a specificity of 84%, compared with EBCT sensitivities ranging from 78% to 90% and specificities 69% to 82%, depending on the calcium score cut point chosen.[57]

Data have also been reported in patients having calcium scoring and stress SPECT. He and colleagues found that the calcium score correlated with the degree of ischemia shown on stress SPECT, regardless of age or sex.[59] Only 1.4% of patients with scores less than 100 had an abnormal SPECT, compared with 46% of those with higher calcium scores. Importantly, 99% of the perfusion defects in patients with scores less than 400 were small. In a study of symptomatic patients, Shavelle and coworkers found that the positive predictive value of EBCT was similar to that of SPECT myocardial perfusion imaging (MPI) (80% versus 83%), but EBCT had a higher negative predictive value (NPV) (82% versus 57%, respectively), although the difference was not statistically significant.[58]

Most studies using EBCT have been applied to the imaging of asymptomatic patients as a way to identify angiographic coronary disease or as a screening test to identify those who are at risk for coronary events. It should be noted, though, that the absence of coronary calcium by EBCT also provides important information. A negative EBCT is unlikely in the presence of significant obstructive CAD and makes the presence of atherosclerotic plaque less likely. The lack of coronary calcium has been associated with a less than 1% prevalence of angiographic disease, regardless of age or sex, as well as a low risk of cardiovascular events.[60-62] This finding has applications for the evaluation of the low-risk patient with chest pain. Because significant coronary disease is unlikely when coronary calcium is not detected, follow-up stress testing may not be necessary in these patients.

Two types of scanners are capable of rapidly quantifying coronary calcium. EBCT is performed when a tungsten arc is activated by a beam from an electron gun. Multidetector computerized tomography (MDCT) overcomes the limitation of imaging heart motion by rapidly rotating an x-ray tube along with several rows of detectors. Importantly, a significant number of hospitals already have MDCT capability, and the only required

addition would be the software for coronary calcium quantification. MDCT has a high diagnostic accuracy for detecting coronary calcium and is similar to EBCT in comparative studies.[63-67] In a large ongoing study of 2,200 patients, there was no difference in reproducibility between MDCT and EBCT.[68]

Data examining the use of EBCT for risk stratification of patients with chest pain is limited. Laudon and coworkers studied 105 low-risk patients (ie, no history of CAD, nonischemic electrocardiogram) evaluated for chest pain.[69] Coronary calcium was present in 47 (45%), 14 of whom had positive cardiac evaluations. Considering the presence of any coronary calcium as a positive resulted in a sensitivity of 100% with a specificity of 53% for identifying patients who had a subsequent positive cardiac evaluation. McLaughlin and colleagues studied 137 patients without a history of coronary disease.[70] EBCT was negative in 36% of patients, one of whom had acute myocardial infarction. These 2 small studies in the emergency department (ED) indicate that coronary calcium scoring (CCS) in these patients is logistically possible and that sensitivity is high for the detection of CAD. However, with moderate specificity, CCS may best be used to identify patients who do not have obstructive CAD and may not be appropriate for initial risk assessment in the acute setting.

Limitations of EBCT for Chest Pain Imaging

One potential limitation of CCS is that it may not detect fissure or erosion of noncalcified plaque.[55] The use of rest MPI in conjunction with electrocardiogram overcomes this limitation. The use of MDCT at the initial ED visit will improve risk stratification, thereby decreasing the number of patients who need further evaluation by stress testing. Another limitation to using EBCT to assess ACS in ED patients is the increase in calcium with increase in age. In males younger than 44 years and females younger than 59 years, fewer than 25% of patients have detectable calcium.[71] In contrast, even in an asymptomatic population, the majority of men older than 50 years and women older than 65 years have coronary calcium.[71] Therefore, the best use of this imaging technique would be limited to the younger patient.

CARDIAC MAGNETIC RESONANCE (CMR) IMAGING

Despite successes thus far, there is room for improvement in current techniques (ie, MPI and CCS) for the detection of the early stages of ACS. CMR imaging is a technique that is increasingly being used clinically in multiple cardiac applications, including atherosclerotic disease. Studies using dobutamine stress CMR imaging have shown accuracy in the identification of CAD that is comparable with stress echo.[72] Other studies have shown that CMR imaging provides risk assessment information equivalent to that of stress perfusion imaging and stress echo.[73]

Kwong and coworkers recently published results using CMR imaging for evaluation of ACS in the acute setting.[74] They reported good accuracy in a small selected population by detection of alterations in wall thickening. Remarkably, wall-thickening abnormalities were observed as late as 12 hours after the presentation of the patient, even without evidence of acute myocardial infarction. One proposed explanation is that the superior resolution of CMR imaging allows identification of residual stunning that would not be possible with lower resolution techniques, such as echocardiography or nuclear imaging. However, it should be noted that direct comparison with these modalities was not performed. The limited body of data available is not convincing that current CMR techniques would provide a superior tool for risk assessment in the acute setting. Several significant limitations, including limited availability, and higher cost than echocardiography and acute MPI, hamper its usefulness in acute applications. Only if CMR imaging can provide new and unique information that significantly impacts patient outcomes will it displace the current limited use of acute MPI.

In fact, it appears that CMR imaging may have this ability, one for which there is currently no nuclear imaging equivalent. The ability to identify patients at high risk for ACS but without clinical evidence of plaque disruption would be a fundamental shift with significant impact. The 3 characteristics that define plaque vulnerability are the composition and thickness of the fibrous cap, the presence of a lipid core, and the inflammatory status, including macrophage density and activity.[75,76] Although other metabolic processes, such as apoptosis, angiogenesis, and activation of metalloproteases, play a significant role, the presence of activated macrophages may be the most significant molecular process amenable to in vivo imaging.

The feasibility of plaque characterization by multicontrast MRI has been described for imaging in the aorta, carotid, and, most recently, the right coronary artery.[77,78] However, high-resolution imaging of the entire coronary tree is a significant technical challenge that has not yet been realized. Although it may require several years of technical development for high-resolution, noninvasive clinical CMR imaging of the entire coronary tree, the useful application of CMR imaging in ACS may be possible in the near future because it is now accepted that atherosclerosis and plaque vulnerability are systemic processes with pan-vascular manifestations.[79] In an intravascular ultrasound study in patients with ACS, Rioufol and coworkers showed that, although one plaque might be responsible for the culprit lesion, there was evidence of pan coronary plaque instability.[80] This observation may prove crucial in allowing determination of plaque status in patients with suspected ACS.

The role of inflammation in ACS is becoming increasingly apparent, as evidenced by the greater risk associated with increased inflammatory markers, and the association of activated macrophage accumulation with plaque vulnerability and instability. There appears to be a sound basis for the use of CMR imaging with molecular probes that interrogate this inflammatory process.

A significant body of preclinical work has been performed with a family of promising magnetic resonance (MR) contrast agents known as the ultra small particles of iron oxide (USPIO). Recent work has shown that these carboxydextran-coated iron oxide particles accumulate in activated macrophages within atherosclerotic plaques.[81] Iron oxide produces a strong susceptibility effect with significant shortening of T-2 and T-2* on MR imaging. Therefore, the accumulation of these particles in the inflammatory reaction allows imaging of the vulnerable plaque. Schmitz and coworkers showed accumulation of USPIO in atherosclerotic plaques with high macrophage content in a rabbit model of atherosclerosis.[82] They further showed good correlation of focal signal loss on MR imaging to iron content and macrophage accumulation within the aortic wall. In a subsequent study by the same group, they showed high accuracy and good interobserver agreement in a receiver operating characteristics analysis.[83] Ruehm and colleagues reported similar imaging characteristics with Sinerem (Guerbet Laboratories, France), which is a USPIO derivative product that is being used in clinical trials as a contrast agent for MR lymph node imaging.[84]

Schmitz and coworkers have also reported incidental findings in the vessel walls of patients undergoing nodal imaging with this compound.[85] The findings consisted of focal signal loss in the images of the vessel walls of the aorta, iliac, and superficial femoral arteries on postcontrast images that were not present on the precontrast images. Considering the patient population, this result appears to be consistent with the accumulation of the USPIO in macrophage-rich plaques. Very recent work by Kooi and colleagues has shown similar MR imaging with this agent in patients undergoing endarterectomy.[86] Particularly noteworthy in this study is that uptake of the USPIO was correlated with histologic data, showing accumulation in the macrophages and distinguishing vulnerable (including ruptured) plaques from stable ones. Preliminary work with a newer USPIO agent that is in clinical trials for MR angiography appears to be providing similar results regarding plaque imaging.[87] If the potential for plaque imaging with an agent that can also be used for MR angiography is realized, the role of CMR imaging in the evaluation of ACS will change dramatically. There are a number of other contrast agents and molecular probes at various stages of development,[77] but, considering the timeline of the development and approval process, it is unlikely that they will enter routine clinical use for several years.

CASE REPORT

A 40-year-old male presented to the Medical College of Virginia Hospitals ED with a 3-day history of intermittent, indigestion-like chest discomfort. He had no history of coronary disease and a nonischemic electrocardiogram, and was, therefore, classified as level 4 (ie, low risk). He was injected while having chest pain, and the acute MPI study revealed a large, anterior defect (Fig 2A), which quantitated to 30% of the left ventricle, despite the absence of electrocardiogram changes. Upon admission, myocardial markers showed small increases in troponin. Cardiac catheterization the next day (Fig 2B) revealed a 95% proximal left anterior descending (coronary artery) lesion, and percutaneous transluminal coronary angioplasty (PTCA) was performed. A follow-up study 2 days later was nearly normal, showing almost complete reperfusion of the risk zone (Fig 2C).

SUMMARY

The rapid triage of the patient with suspected acute coronary syndromes (ACS) continues to be a challenge. “Chest pain” and other symptoms suggestive of ischemia remain a nonspecific and frequent presentation to the emergency department (ED). The vast majority of these patients will not require admission, but identification of the patient with ACS among this population is risky business. The electrocardiogram appropriately remains the first triage tool and is essential for identifying the patient who requires immediate revascularization. However, numerous studies have shown that it is inadequate for triaging the vast majority of remaining patients. Acute myocardial perfusion imaging (MPI) has a high negative predictive value (NPV) and is a powerful risk stratification tool. When MPI is used in conjunction with the newer biomarkers, such as troponin, the combination provides an impressive risk profile.

Despite evidence that the technique can be cost-effective when used appropriately and systematically, acute MPI has not become widely available for various reasons, mainly political and logistical. One serious barrier to the implementation of this and other strategies for triage of the patient with chest pain has been the subtle difference between cost-effectiveness and profitability. Cost-effectiveness is a term that is applicable to a population or a health network that bears the economic risk across a population, but the term is not necessarily applicable to or in the best interest of the single hospital whose profitability is based on occupied beds, especially with low intensity patients. The institutions that have used these techniques most successfully are generally larger urban centers whose ED are frequently on diversion due to saturation of intensive care units and step-down beds.

This economic paradigm is important to recognize as we see the emergence of new technology that further advances the evaluation of ACS in the acute

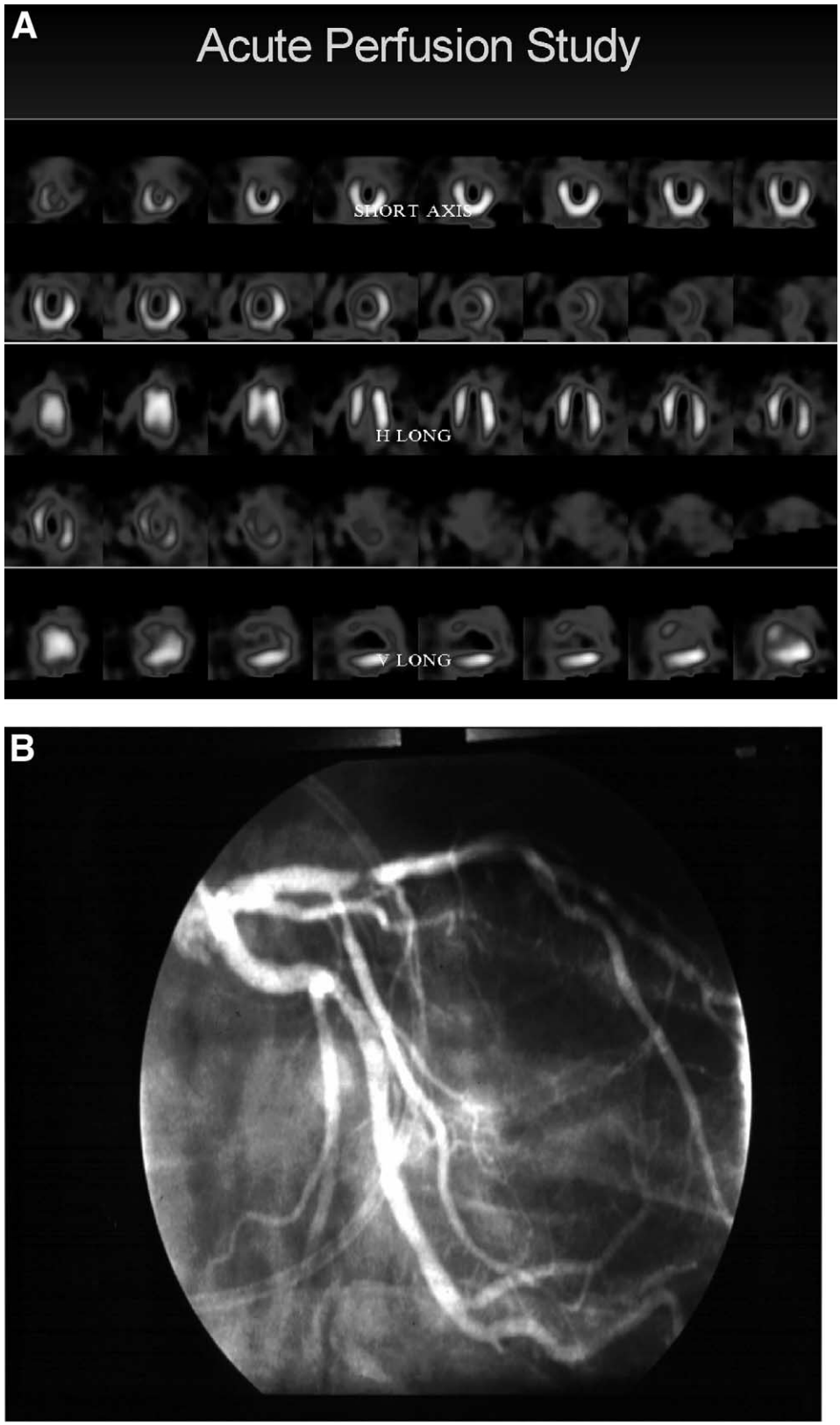

Fig 2. Case report. (A) Acute resting myocardial perfusion study showing large anterior perfusion defect equal to 30% of left ventricular myocardium. (B) Cardiac catheterization the next day showing 95% proximal left anterior descending artery lesion. (C) Comparison between acute study (top) and follow-up study done 2 days after angioplasty (bottom) showed almost complete reperfusion of the risk zone.

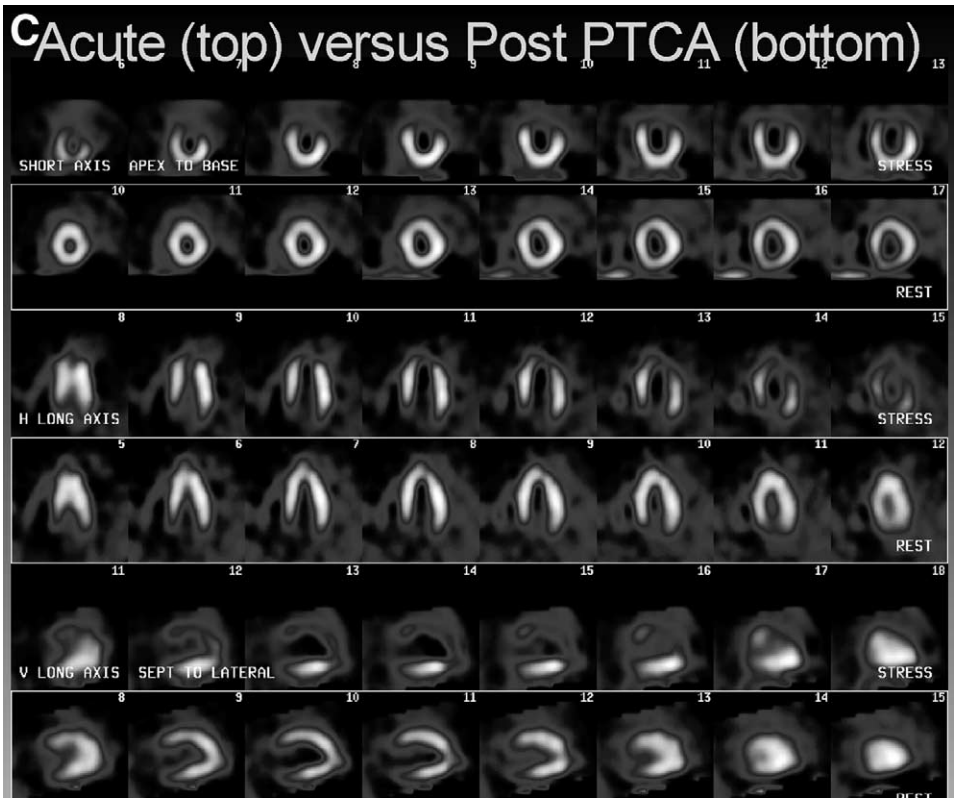

Fig 2 (cont'd)

and treatment settings. The role of coronary calcium scoring (CCS) needs to be better defined but shows promise as a part of a comprehensive strategy. Cardiac magnetic resonance (CMR) imaging offers potential, but, due to its high cost and limited availability, it must significantly exceed the abilities of MPI to gain clinical acceptance. However, as we shift our focus from "ischemic" insult to vulnerable plaque, CMR imaging will likely become an important part of the technology family used to evaluate the patient with possible ACS. The challenge will be to intelligently develop a clinical strategy and associated clinical pathways that use each of these tools most appropriately for optimal medical decision making.

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