Prognosis of Negative Adenosine Stress Magnetic Resonance in Patients Presenting to an Emergency Department With Chest Pain

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OBJECTIVES
This study was designed to determine the diagnostic value of adenosine cardiac magnetic resonance (CMR) in troponin-negative patients with chest pain.

BACKGROUND
We hypothesized that adenosine CMR could determine which troponin-negative patients with chest pain in an emergency department have coronary artery disease (CAD) or future adverse cardiac events.

METHODS
Adenosine stress CMR was performed on 135 patients who presented to the emergency department with chest pain and had acute myocardial infarction (MI) excluded by troponin-I. The main study outcome was detecting any evidence of significant CAD. Patients were contacted at one year to determine the incidence of significant CAD defined as coronary artery stenosis $>50$% on angiography, abnormal correlative stress test, new MI, or death.

RESULTS
Adenosine perfusion abnormalities had 100% sensitivity and 93% specificity as the single most accurate component of the CMR examination. Both cardiac risk factors and CMR were significant in Kaplan–Meier analysis (log-rank test, $p = 0.0006$ and $p < 0.0001$, respectively). However, an abnormal CMR added significant prognostic value in predicting future diagnosis of CAD, MI, or death over clinical risk factors. In receiver operator curve analysis, adenosine CMR was a more accurate predictor than cardiac risk factors ($p < 0.002$).

CONCLUSIONS
In patients with chest pain who had MI excluded by troponin-I and non-diagnostic electrocardiograms, an adenosine CMR examination predicted with high sensitivity and specificity which patients had significant CAD during one-year follow-up. Furthermore, no patients with a normal adenosine CMR study had a subsequent diagnosis of CAD or an adverse outcome. (J Am Coll Cardiol 2006;47:1427–32) © 2006 by the American College of Cardiology Foundation

In the U.S., over eight million patients present to emergency departments annually with chest pain (1). Guidelines by the American College of Cardiology and the American Heart Association provide a systematic approach to the patient with possible acute coronary syndrome (2). The electrocardiogram (ECG) is used to identify ST-segment elevation myocardial infarction (MI) and initiate acute interventions. Biomarkers, particularly serum assays of troponin, identify a group of patients with significantly higher cardiovascular risk. After excluding infarction, there remains the need to detect significant coronary stenoses, because many cases of unstable angina are not identified by the ECG and enzymes. Furthermore, 15% of patients with undiagnosed unstable angina will have an MI in the subsequent two months (3).

This study was designed to determine the diagnostic value of adenosine cardiac magnetic resonance (CMR) in troponin-negative patients with chest pain. The main study outcome attempted to provide clinical reassurance that a diagnosis of important coronary artery disease (CAD) was not missed by adenosine stress CMR. Thus, a normal adenosine CMR would be considered false negative if any clinical evidence of CAD was detected over the year after testing. As will be shown, an abnormal adenosine CMR examination had a high sensitivity and specificity in predicting adverse cardiovascular outcomes, whereas a normal adenosine CMR examination predicted an excellent one-year prognosis.

METHODS
Study group. Patients were prospectively enrolled at a community hospital after giving informed consent ($n = 141$). Inclusion criteria required 30 min of chest discomfort compatible with myocardial ischemia, a negative troponin $>6$ h after the last episode of chest pain, and an ECG not diagnostic of ST-segment elevation MI or ischemia (3-mm T-wave inversion or $>1$-mm ST-segment depression). Patients were imaged within 72 h of presentation. Exclusion criteria were New York Heart Association functional class IV congestive heart failure, second- or third-degree atrioventricular block, hemodynamic instability, history of asthma or bronchospastic disease, and standard CMR contraindications, including cerebral aneurysm clips, metal in the eye, and implanted metallic devices.
Cine CMR. The CMR was performed using a General Electric (Waukesha, Wisconsin) CV/i 1.5-T scanner and a four-element cardiac phased-array coil. Cine CMR was performed in multiple parallel short-axis planes, 8 mm thick, separated by 3-mm gaps and in the two-chamber, three-chamber, and four-chamber long-axis views as previously described (4).

Adenosine perfusion CMR. Adenosine was administered intravenously at 140 μg/kg/min over 6 min. Four minutes into the infusion, the method of Slavin et al. (5) was used to image the first pass of a bolus (0.1 mmol/kg at 5 ml/s) of gadolinium diethylenetriamine pentaacetic acid (Berlex, Wayne, New Jersey). Typically at least nine short-axis slices were acquired gated to every other heartbeat. The patients were monitored by ECG, noninvasive sphygmomanometry, and pulse oximetry.

Delayed enhancement CMR. An inversion recovery fast gradient echo sequence triggered every other heartbeat (6,7) was performed to assess for MI. Images were obtained approximately 20 min after net intravenous injection of 0.2 mmol/kg gadolinium diethylenetriamine pentaacetic acid. The in-plane image resolution was typically 2.5 mm (42 μl/voxel). The infarct imaging planes reproduced the views used on the cine and perfusion images.

Analysis of CMR studies. An abnormal CMR study was defined by the presence of either a regional wall motion abnormality, a perfusion defect during adenosine infusion, or evidence of delayed enhancement. Regional wall motion abnormalities were primarily based upon the short-axis view and if possible, confirmed in an orthogonal long-axis view. Perfusion scans were interpreted qualitatively by consensus of three cardiologists blinded to study end points. A perfusion defect was defined as abnormal if it was definitely darker than surrounding myocardium and if it persisted more than three images beyond initial peak enhancement of the segment which appeared most normal. Delayed enhancement images were displayed with a gray scale to optimally show normal myocardium as dark and the regions of delayed enhancement or fat as bright.

Left ventricular ejection fractions were calculated from end-diastolic and end-systolic endocardial tracings of multiple parallel short-axis images using computer-assisted planimetry. Qualitative assessment of left ventricular wall thickening was summarized using the 16-segment model of the American Society of Echocardiography (8).

Primary outcome. The main study outcome aimed at answering the clinical question in the emergency department of whether important CAD was present in an individual patient with chest pain. This main composite adverse outcome (9) was defined as interval diagnosis of >50% stenosis on X-ray coronary angiography, abnormal correlative stress nuclear imaging with findings consistent with the CMR scan, new MI, or death during one-year follow-up.

Secondary analysis. We also analyzed whether chronic MI could explain apparent false positive perfusion scans based on the presence or absence of delayed enhancement associated with the perfusion defect. Chronic MI was defined as delayed enhancement consistent with MI in this study group where acute MI was excluded on the basis of serial troponin-I, serial ECGs, and clinical evaluation.

Statistical methods. Sensitivity, specificity, positive predictive value, and negative predictive value in predicting an adverse cardiovascular outcome were calculated for each CMR abnormality individually and any CMR abnormality. Survival distributions for the time to event were estimated using the Kaplan–Meier method (10). The differences between survival distributions were assessed using the log-rank test (11).

Cox proportional hazards regression (12) was performed to determine whether a CMR abnormality added significant prognostic value over clinical risk factors in predicting the main study outcome. Because there was significant censoring, Firth’s bias correction procedure (13) was used with the SAS macro developed by Heinze and Schumpe (14).

Because of the number of events, the analysis used the total number of cardiac risk factors at baseline (TLCRF), rather than individual factors. The TLCRF ranged from 0 to 7, and was defined as the number of the following risk factors (15) that were present: hypertension, hyperlipidemia, diabetes mellitus, age >45 years for males or >55 years for females, current tobacco use, history of CAD (as defined by known prior MI or prior angiographically significant coronary disease), and family history of CAD.

Receiver operating characteristic curves were generated for TLCRF and the total number of CMR abnormalities (TLCMR). The TLCMR ranged from 0 to 3 and was defined as the number of the following that were present: regional wall motion abnormality, delayed enhancement, and adenosine perfusion abnormality. The areas under the curves were compared using the method of DeLong et al. (16).

RESULTS

Of the 141 patients enrolled, 139 patients (99%) were followed by telephone contact with the patient or a family member, communication with their primary care physicians, and/or medical record review. Of the two patients lost to follow-up, one was a 31-year-old man and the other was a 36-year-old man. Neither was reported as deceased when cross-referenced against the Social Security Death Index Interactive Search site. Four of the 141 patients had

<table>
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<th>Abbreviations and Acronyms</th>
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<td>CAD = coronary artery disease</td>
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<td>CMR = cardiac magnetic resonance</td>
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<td>ECG = electrocardiogram</td>
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<td>MI = myocardial infarction</td>
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<td>TLCMR = total number of cardiac magnetic resonance abnormalities</td>
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<td>TLCRF = total number of cardiac risk factors</td>
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nondiagnostic perfusion studies and were excluded from analysis but had no adverse events in long-term follow-up. Two of the delayed enhancement studies were considered non-diagnostic but were not considered reason to exclude patients from analysis. Thus, final analysis was performed on 135 patients. The baseline characteristics and cardiac risk factors of the 135 study participants are shown in Table 1 overall and stratified by adverse cardiac outcome.

The median follow-up was 467 days (1.28 years). On follow-up, 20 patients experienced the composite study outcome (14.8%). Fifteen patients had angiographically significant CAD, two patients had an abnormal coregional stress nuclear study, one patient had an MI, and two patients died. Eleven patients underwent coronary revascularization; the remainder were treated with medical therapy based upon their cardiologists' recommendations. As seen in Table 1, hypertension, age as a risk factor, prior coronary revascularization, prior MI, and prior history of CAD were significantly more prevalent in the group with the adverse composite outcome.

CMR results. There were no major complications related to the adenosine stress testing. Adenosine was terminated prematurely in four patients owing to symptoms, but perfusion images were still obtained. One test was terminated because of a panic attack after perfusion imaging, but there were no clinical sequelae.

Figure 1 (top row) demonstrates a perfusion defect in a patient who had no prior CAD. Figure 1 (bottom row) illustrates a case with abnormal resting regional wall motion and delayed enhancement despite no prior clinical history of infarction. However, the adenosine perfusion defect was more extensive than the region of infarction consistent with a stress-induced peri-infarct perfusion defect. Both patients required coronary revascularization.

The mean left ventricular ejection fraction was 65% ± 13.8%, and only five subjects had ejection fractions ≥ 45%.

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\text{Table 1. Baseline Patient Characteristics}\\
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& \text{All Patients} & \text{Adverse Outcome} & \text{No Adverse Outcome} & \text{p Value} \\
& (n = 135) & (n = 20) & (n = 115) & \\
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\text{Males} & 75 (56) & 15 (75) & 60 (52) & 0.0579 \\
\text{Hypertension} & 56 (42) & 14 (70) & 42 (37) & 0.005 \\
\text{Diabetes mellitus} & 14 (10) & 4 (20) & 10 (9) & 0.1259 \\
\text{Hyperlipidemia} & 71 (53) & 14 (70) & 57 (50) & 0.0912 \\
\text{Tobacco use} & 40 (30) & 9 (45) & 31 (27) & 0.1029 \\
\text{Family history of CAD} & 61 (45) & 10 (50) & 51 (44) & 0.6392 \\
\text{Age as risk factor} & 88 (65) & 19 (95) & 69 (60) & 0.0024 \\
\text{History of PCI or CABG} & 16 (12) & 10 (50) & 6 (5) & <0.0001 \\
\text{History of MI} & 9 (7) & 6 (30) & 3 (3) & <0.0001 \\
\text{History of CAD} & 23 (17) & 12 (60) & 11 (10) & <0.0001 \\
\text{Age (yrs)} & 55.7 ± 13.8 & 68.1 ± 10.6 & 53.6 ± 13.2 & <0.0001 \\
\text{Total # of risk factors} & 2.6 ± 1.6 & 4.1 ± 1.9 & 2.4 ± 1.4 & 0.0008 \\
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Data are n (%) or mean ± SD.

CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Figure 1. Examples of abnormal adenosine cardiac magnetic resonance studies demonstrate the ability to detect ischemia in the absence of infarction and peri-infarct ischemia. The top row shows results from a 67-year-old female with no prior coronary artery disease (CAD), no evidence of myocardial infarction (MI), and an inferoseptal to inferolateral perfusion defect (arrows). The bottom row summarizes results from a 56-year-old female with a history of coronary artery bypass graft surgery (h/o CABG), silent micro-inferior myocardial infarction (MI) (black arrow), and a more extensive inferior to inferolateral perfusion defect (white arrows). Both patients had significant coronary stenoses and required revascularization. DE = delayed enhancement; Perf = perfusion.
Fourteen patients had abnormal gadolinium delayed enhancement studies. The mean infarct size was 19 ± 16 g, and 6 of the 14 infarcts were <10 g. Whereas 8 of these 14 patients had a prior clinical history of MI, 6 subjects had clinically unrecognized MI that ranged in size from 2 to 43 g.

The sensitivity, specificity, positive predictive value, and negative predictive value of a regional wall motion abnormality, delayed enhancement, abnormal adenosine perfusion, and any CMR abnormality in predicting an adverse outcome are given in Table 2. Delayed enhancement indicative of MI had a sensitivity of only 55%, and a regional wall motion abnormality had a sensitivity of 70%. However, both techniques had high specificity. Adenosine perfusion abnormalities had 100% sensitivity and 93% specificity as the single most accurate component of the CMR examination. Combining all CMR results to label a CMR study as normal or abnormal only reduced specificity to 91%. In comparison, total cardiac risk factors >3 versus ≤3 as a predictor of adverse outcome had a sensitivity of 65% and a specificity of 76%.

**Prognosis.** Of 135 patients enrolled, 20 experienced adverse outcomes before the end of the study; the remainder were considered censored at the date of last follow-up in the Kaplan-Meier analysis. Figure 2 illustrates the estimated time to event distribution for patients based on any CMR abnormalities. The separation in the survival distributions for those with any CMR abnormality and those without was highly significant (p < 0.0001). The estimated survival distribution for total cardiac risk factors (TLCRF [+] defined as >3 risk factors vs. TLCRF [−] defined as ≤3 risk factors) using the Kaplan-Meier method had less separation but was significant (log-rank test, p = 0.0006).

A Cox proportional hazards regression model on TLCRF showed increasing TLCRF to be a significant negative prognostic factor for future adverse cardiac outcome (likelihood ratio chi-square = 19.22, p < 0.0001) with a hazard ratio of 1.908 (95% confidence interval 1.405 to 2.592), indicating almost a doubling of risk for each additional risk factor. When modeled singly, an abnormal CMR study was a significant negative prognostic factor (likelihood ratio chi-square = 67.47, p < 0.0001) with a hazard ratio of 207.33 (95% confidence interval 28.43 to 26,397). When TLCRF and an abnormal CMR were modeled together, only an abnormal CMR was significant.

The estimated receiver operating characteristic curves for TLCRF and TLMR are given in Figure 3. The estimated area under the curve was 0.758 for TLCRF and 0.973 for TLMR. The observed difference in areas was significant (chi-square 10.14, p < 0.002), demonstrating that the adenosine CMR was a more accurate predictor of adverse outcome than the total number of cardiac risk factors.

**DISCUSSION**

In our study, patients with a normal adenosine stress CMR scan had an excellent prognosis as none of the subjects was diagnosed with an adverse event during one-year follow-up.

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<th>Table 2. Diagnostic Performance of Individual CMR Components in Detecting Future Adverse Cardiac Outcome</th>
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<tr>
<td>Resting RWM (n = 19)</td>
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CMR = cardiac magnetic resonance; NPV = negative predictive value; PPV = positive predictive value; RWM = regional wall motion.
Conversely, the specificity of an abnormal adenosine CMR was high. Furthermore, all but four of the abnormal adenosine perfusion abnormalities without cardiovascular events in follow-up were explainable on the basis of old infarctions, a situation that should not be considered a false positive. Thus, the adenosine stress CMR study not only separates the prognosis of patients as shown in the Kaplan-Meier analysis but also has the sensitivity to reassure the physician that important coronary disease is not missed. These results are striking in that the pretest probability of a patient having important coronary disease or adverse long-term outcomes in those patients with normal troponin levels, normal average ejection fractions, and an ECG not diagnostic of ischemia or infarction (17,18).

Prognosis studies using CMR are still limited in numbers. In a study of 279 patients deemed ineligible for stress echocardiogram because of poor endocardial visualization, Hundley et al. (18) found that dobutamine/atropine CMR had prognostic value. In that study, left ventricular ejection fraction was a powerful prognosticator, but the presence or absence of ischemia modulated these findings significantly.

The current study prognosticates the one-year likelihood of a patient having important coronary disease or adverse cardiac outcomes. Thus, the reference for correct diagnosis is determined by long-term follow-up. It is possible that some patients may have had an intermediate coronary stenosis that was missed. In our study, the absence of adverse long-term outcomes in those patients with normal studies suggests that any missed stenoses were not contributing to the etiology of the chest pain or did not need intervention at the time of the CMR scan. Thus, the CMR scan could fit within current American Heart Association/American College of Cardiology clinical practice guidelines for the management of possible or probable acute coronary syndrome, in which a stress test is recommended in subjects who have MI excluded by serial ECGs and blood tests.

It is not likely that many significant coronary stenoses were missed, because CMR perfusion scans perform as well as or better than current clinical perfusion tests. The sensitivity of subendocardial defects on a CMR study is equivalent to a positron emission tomography scan for detection of coronary stenosis defined by quantitative coronary angiography (19). Using very similar methodologies to those described in the current study, Ishida et al. (20) reported sensitivities of 85%, 96%, and 100% in detecting single-, double-, and triple-vessel disease with a specificity of 85% in 104 patients who underwent coronary angiography. In that same study, stress perfusion single photon emission computed tomography had a sensitivity and specificity of 64% and 79% in depicting stenosis in individual coronary arteries. Al-Saadi et al. (21) have reported sensitivities of 90% in detecting significant coronary stenoses, using semiquantitative analysis of CMR perfusion. Finally, Plein et al. (22) found that adenosine perfusion and coronary angiography are the two most sensitive components of a comprehensive CMR examination performed in patients with acute coronary syndrome undergoing clinically indicated coronary angiography.

The advent of multi-slice detector computed tomography is also promising in the rapid detection of significant anatomic CAD. In 59 patients, Leber et al. (23) demonstrated that 64-slice computed tomography had a sensitivity of 80% in detecting stenoses >75% and a specificity of 97%. Raff et al. reported a sensitivity and specificity of 91% and 92% in the detection of significant disease (>50%) on a per artery basis in 70 patients (24). Mollet et al. (25) reported a sensitivity and specificity of 99% and 95% for detecting significant stenoses (>50%) in 52 patients. Christian recently pointed out that physiological stress testing provides additional prognostic value beyond known coronary anatomy (26). Thus, stress testing and viability assessment may provide more complementary information to the catheterization laboratory where the coronary anatomy ultimately will be definitively defined.

The current study is substantially different from prior work by Kwong et al. (4). In patients very early after presentation to an emergency department, a rest CMR scan had high sensitivity and specificity for acute coronary syndrome. In that study, regional wall motion abnormalities, particularly in the absence of infarction, were strong evidence of recent myocardial ischemia and thus a diagnosis of acute coronary syndrome. In the present study, patients underwent the adenosine CMR scan within 72 h of presentation to the emergency department with chest discomfort. Regional stunning that might have occurred with an ischemic chest discomfort episode could have resolved by the time of our imaging. However, the current approach has the power to detect significant coronary stenoses that might be missed on a rest study.
The relative insensitivity of the delayed enhancement study should not be surprising. By definition, patients in this study had acute MI excluded by serial ECG and troponin assays. However, abnormal delayed enhancement had prognostic significance despite the fact that 43% of infarcts were <10 g. It is also of interest that 6 of the 14 cases of delayed enhancement represented clinically unrecognized MIs.

Concerning the safety of adenosine testing in a CMR scanner, all scanning was performed with a technologist scanning the patient, a nurse administering the adenosine and monitoring vital signs, and a physician interpreting the study, as well as providing additional medical supervision. There were no major adverse sequelae related to administration of adenosine. Overall, vasodilator stress testing is less likely to precipitate serious adverse events than dobutamine stress testing (27).

Conclusions. In patients with chest pain who have had MI excluded by serial cardiac enzymes and at least 6 h of observation, an adenosine CMR examination demonstrated a high sensitivity and specificity in the prediction of a CAD diagnosis and adverse cardiovascular end points at one year. In these low-risk patients, the adenosine perfusion images performed better than rest cine function or delayed enhancement. A normal adenosine CMR examination was associated with no diagnosis of CAD on follow-up and no adverse cardiovascular outcomes.

Acknowledgments

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