Prognostic Value of Global MR Myocardial Perfusion Imaging in Women With Suspected Myocardial Ischemia and No Obstructive Coronary Disease

Results From the NHLBI–Sponsored WISE (Women's Ischemia Syndrome Evaluation) Study

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OBJECTIVES The purpose of this study was to assess the prognostic value of global magnetic resonance (MR) myocardial perfusion imaging (MPI) in women with suspected myocardial ischemia and no obstructive (stenosis <50%) coronary artery disease (CAD).

BACKGROUND The prognostic value of global MR-MPI in women without obstructive CAD remains unknown.

METHODS Women (n = 100, mean age 57 ± 11 years, age range 31 to 76 years), with symptoms of myocardial ischemia and with no obstructive CAD, as assessed by coronary angiography, underwent MR-MPI and standard functional assessment. During follow-up (34 ± 16 months), time to first adverse event (death, myocardial infarction, or hospitalization for worsening anginal symptoms) was analyzed using global MPI and left ventricular ejection fraction (EF) data.

RESULTS Adverse events occurred in 23 (23%) women. Using univariable Cox proportional hazards regression modeling, variables found to be predictive of adverse events were global MR-MPI average uptake slope (p < 0.05), the ratio of MR-MPI peak signal amplitude to uptake slope (p < 0.05), and EF (p < 0.05). Two multivariable Cox models were formed, 1 using variables that were performance site dependent: ratio of MR-MPI peak amplitude to uptake slope together with EF (chi square: 13, p < 0.005); and a model using variables that were performance site independent: MR-MPI slope and EF (chi square: 12, p < 0.005). Each of the 2 multivariable models remained predictive of adverse events after adjustment for age, disease history, and Framingham risk score. For each of the Cox models, patients were categorized as high risk if they were in the upper quartile of the model and as not high risk otherwise. Kaplan-Meier analysis of time to event was performed for high risk versus not high risk for site-dependent (log rank: 15.2, p < 0.001) and site-independent (log rank: 13.0, p < 001) models.

CONCLUSIONS Among women with suspected myocardial ischemia and no obstructive CAD, MR-MPI–determined global measurements of normalized uptake slope and peak signal uptake, together with global functional assessment of EF, appear to predict prognosis. (J Am Coll Cardiol Img 2010;3: 1030–6) © 2010 by the American College of Cardiology Foundation

In the U.S., cardiovascular disease is the leading cause of mortality in women (1). However, women are less likely than men to have either classic symptoms or obstructive coronary artery disease (CAD), but paradoxically have a worse prognosis (2,3). This may be an expression of the failure to identify factors contributing to a woman's risk (4–6). Conventional noninvasive testing in this population is particularly challenging due to the relatively low prevalence of obstructive CAD, coupled with the observations that first cardiovascular events are often fatal in women (7), and that stenoses <70% are associated with the majority of acute ischemic cardiac events (8). Thus, there is a need to develop risk assessment approaches for women to better assess risk of adverse events as opposed to being at high risk for significant or obstructive CAD (9). The WISE (Women's Ischemia Syndrome Evaluation) study has established that women who are symptomatic of ischemia but without obstructive CAD experience more adverse events than nonsymptomatic controls (10).

Magnetic resonance (MR) myocardial perfusion imaging (MPI) is an evolving high-resolution tomographic modality with no ionizing radiation that allows detection of regional hypoperfusion. We and others have reported that obstructive CAD can be detected with a sensitivity and specificity comparable to conventional radionuclide imaging (11,12). A prior report suggested that MR-MPI can detect nonsegmental, subendocardial abnormalities suggestive of myocardial ischemia in patients without obstructive CAD (13); however, the relationship between this observation and risk has not been evaluated. We hypothesized that in a cohort of women with suspected ischemia but no obstructive epicardial CAD, global MR-MPI measures may predict prognosis.

METHODS

Study population. Symptomatic women with stable angina and suspected myocardial ischemia were prospectively enrolled in the National Institutes of Health–National Heart, Lung, and Blood Institute–sponsored WISE study and underwent quantitative coronary angiography. From this enrolled population, 100 consecutive women with coronary artery stenoses <50% were selected for this substudy and underwent first-pass contrast MR-MPI within 1 week of enrollment. This prospective substudy was performed at a single WISE site, the University of Alabama at Birmingham (UAB), between the dates of November 1993 and October 1998, and included WISE participants with no contraindications for MR examination. All subjects provided informed consent using forms and procedures approved by the Institutional Review Board at UAB.

Baseline evaluation. The WISE methodology for acquisition of MR-MPI and quantitative coronary angiography data has been described previously (14,15). In brief, demographic data, risk factors for ischemic heart disease, medical and reproductive history, functional capacity, and blood samples were acquired and evaluated. Coronary artery status was assessed qualitatively and quantitatively using cine angiographic films evaluated at the WISE angiographic core laboratory (Rhode Island Hospital, Providence, Rhode Island) (15).

MR-MPI acquisition. MR first-pass MPI data were acquired using an optimized Philips ACS 1.5-T scanner (Philips Medical Systems, Best, the Netherlands) using previously described methods (12). In brief, imaging was performed in the short-axis orientation during the passage of a bolus (0.1 mm/kg) of gadolinium contrast agent (ProHance, Berlex, Montville, New Jersey) using a power injector (Spectris MR Injection System, Medrad Inc., Pittsburgh, Pennsylvania). Imaging parameters included a field of view of 250 to 450 mm (depending on patient dimensions) and 2 slices imaged with slice-selective saturation pulse applied 150 ms prior to imaging using a keyhole approach (repetition time/echo time/flip: 7/3.5/20°) to sample 32 lines of k-space inserted into a 128^2 matrix. Data were

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

EF = ejection fraction

LV = left ventricle/ventricular

MI = myocardial infarction

MPI = myocardial perfusion imaging

MR = magnetic resonance

acquired for each heartbeat, and signal reception was accomplished using a body coil. Stress hyperemia was induced by intravenous administration of dipyridamole (0.14 mg/kg/min or 0.56 mg/kg over 4 min). To maximize the hyperemic response, patients were instructed to abstain from foods containing methylxanthine (e.g., caffeine and theobromine), such as coffee, tea, and chocolate, and from use of medications containing nitrates for at least 12 h prior to the study. Myocardial perfusion status was analyzed at rest and under stress hyperemic conditions to extract myocardial perfusion variables.

MR-MPI analysis. Global MPI indices, including average uptake slope and peak signal amplitude, were measured in the time-resolved MR data using custom-designed software developed at UAB (Fig. 1). To compensate for respiratory motion, each image frame was displaced such that the left ventricle (LV)

was registered over the time series. The uptake slopes were low-pass filtered to remove noise (body-coil reception resulted in relatively high noise levels). Perfusion variables were extracted from 6 manually drawn, circumferentially defined regions in each of 2 short-axis slices covering the mid- and apical LV sections. Intensity–time curves for each myocardial region were extracted by semiautomatically identifying the inflection point of signal increase and the peak signal amplitude achieved during the first pass. Using the uptake data between these 2 points, a linear line was curve fitted, and the slope of signal intensity per unit time was extracted. The uptake slope for each myocardial region was normalized by dividing by the slope of the LV blood pool signal (the dominant curve seen in Fig. 1) and the normalized value scaled by multiplication by 1,000 to make the values comparable to average peak signal intensity (arbitrary units). The
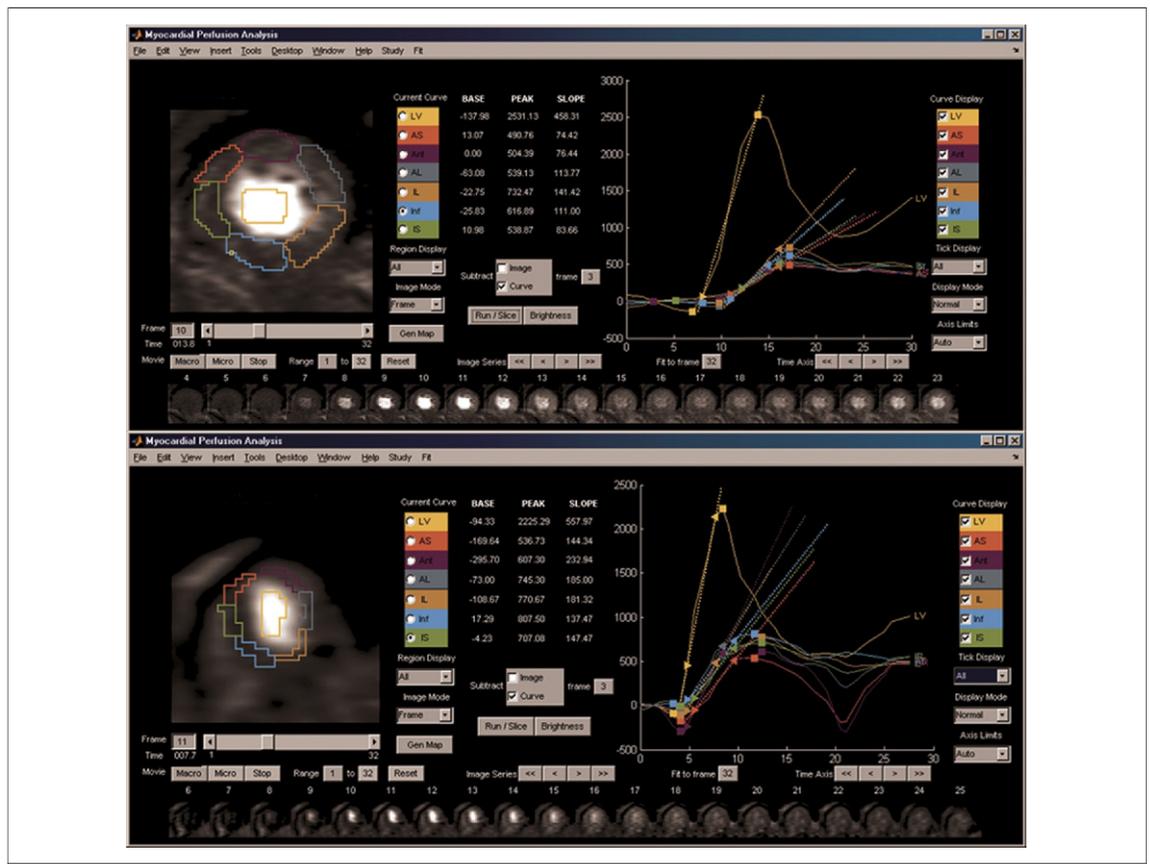
Figure 1. MR-MPI Analysis for Low Average and High Average MPI Levels

The **top panel** shows a patient with a low average myocardial perfusion image (MPI) level and the **lower panel** shows a patient with a high average MPI level. Six myocardial regions and a left ventricular blood pool region are drawn on 1 frame (**lower inset**). Extracted and parameterized intensity–time curves are shown in the **right-hand display section** for the left ventricular blood pool (highest peak) and each of 6 myocardial sections (**closely grouped uptake curves**). In these patients, no perfusion defects or obstructive stenoses were present, whereas the patient with low MPI subsequently died and the patient with high MPI survived event free. MR = magnetic resonance.

peak signal intensity was calculated as the difference between the mean baseline signal prior to contrast arrival and the peak signal intensity. Each parameter was evaluated separately at rest and at stress. All perfusion data were obtained and recorded prior to unmasking clinical and follow-up results.

MR cardiac function acquisition. During the MPI scan, short-axis cine views were acquired using a gradient-recalled echo (repetition time/echo time/ flip: 7/4/30) in multiple contiguous slices covering the base to the apex and oriented parallel to the base. The endocardial boundaries were planimetered using a commercial analysis package (Medis, Leiden, the Netherlands) to extract end-diastolic and -systolic volumes, and the ejection fraction (EF) was calculated.

Follow-up procedures. For follow-up, a scripted telephone interview was performed by experienced research coordinators at 6 weeks after enrollment and yearly thereafter. The events of interest included all-cause mortality, first incidence of myocardial infarction (MI), or hospitalization for worsening anginal symptoms. Median follow-up was 34 ± 16 months. In the event of death, a death certificate and/or hospital record was obtained when available.

Statistical analysis. Continuous values were presented as mean ± SD and categorical variables as percent frequency. Continuous clinical and demographic characteristics were compared between groups using the independent samples t test; the chi-square test was used for categorical comparisons. The predictors of adverse events (death, MI, hospitalization for worsening angina) were identified by univariable Cox regression analyses. Two multivariable Cox proportional hazard regression (Cox) models were formed for variables shown to be predictive in univariable analysis at the level of p < 0.05: 1 model incorporating performance site– dependent variables, and 1 model incorporating performance site–independent variables. Patients in the upper quartile of each of the 2 multivariable Cox models were designated high risk, with not high-risk status assigned to all others. The proportional hazards assumption of invariant hazard ratios was found to be met for the high-risk and not high-risk predictors in the model. Kaplan-Meier analysis was performed to assess the effect of risk stratification on survival and was tested using the log-rank statistic. All p values are 2 tailed. A p value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, Illinois).

Table 1. Population Characteristics of Women

Variable	Total (n = 100)	Event-Free (n = 77)	Adverse Event (n = 23)
Black or Hispanic	30	30	30
Age, yrs	57 ± 11	57 ± 10	58 ± 12
Hypertension	66	63	74
Dyslipidemia	50	49	73
History of smoking	47	43	61
Obesity (body mass index ≥30 kg/m²)	42	39	52
Diabetes mellitus	20	19	22
Typical angina presentation	34	41*	13*
Family history of premature CAD	76	75	78
Coronary artery stenosis, %	19 ± 19	18 ± 19	21 ± 21
Left ventricular ejection fraction, %	62 ± 9	64 ± 7*	59 ± 12*
Left ventricular ejection fraction <55%	15	12	26
Resting heart rate, beats/min	68 ± 13	67 ± 12	71 ± 16
Hyperemic heart rate, beats/min	84 ± 13	83 ± 12	85 ± 14
Systolic blood pressure, mm Hg	137 ± 22	137 ± 22	138 ± 22
Diastolic blood pressure, mm Hg	75 ± 11	75 ± 11	76 ± 10
ATP III 10-year risk of MI	4.5 ± 4.2	4.4 ± 4.4	4.9 ± 3.9

Values are % or mean ± SD. *p < 0.05 between event-free and adverse event groups.
ATP = Adult Treatment Panel; CAD = coronary artery disease; MI = myocardial infarction.

RESULTS

Population characteristics. The mean age was 57 ± 11 years (range 31 to 76 years); 30% were ethnic minorities, primarily African Americans, and the average maximal stenosis level was 19 ± 19% (median 22.0, range 0% to 49%). Demographic data are summarized in Table 1. Adverse events occurred in 23 women (23%), consisting of 19 hospitalizations for worsening anginal symptoms, 2 deaths, and 2 MIs. All deaths were deemed cardiovascular and were confirmed by the National Death Index. Also shown in Table 1 are the demographic values for event and event-free groups.

Site-dependent MR-MPI and cardiac function predictors of adverse events. Imaging variables predictive of events by univariable Cox regression modeling were: the global MR-MPI ratio of average peak signal to normalized uptake slope at stress (p < 0.05) and EF (p < 0.05) (Table 2). Since the peak signal amplitude is measured in arbitrary units, it is

Table 2. Cox Model Parameters

Predictor	Hazard Ratio	95% Lower CI	95% Upper CI
EF	0.949	0.911	0.990
Amp/slope × 1,000	0.516	0.314	0.848
Slope × 1,000	1.005	1.001	1.009

Amp = amplitude; CI = confidence interval; EF = ejection fraction.

Table 3. Population Characteristics of Women in High-Risk Versus Not High-Risk Groups

Variable	Not High-Risk (n = 75)	High-Risk (n = 25)
Black or Hispanic	25	44
Age, yrs	58 ± 11	55 ± 11
Hypertension	67	64
Dyslipidemia	53	60
History of smoking	40*	68*
Obesity (body mass index ≥30 kg/m²)	36*	60*
Diabetes mellitus	17	28
Typical angina presentation	36	28
Family history of premature CAD	75	79
Coronary artery stenosis, %	19 ± 20	20 ± 20
Left ventricular ejection fraction, %	65 ± 7†	57 ± 102†
Left ventricular ejection fraction <55%	9†	32†
Resting heart rate, beats/min	66 ± 12*	72 ± 16*
Hyperemic heart rate, beats/min	82 ± 13*	90 ± 13*
Systolic blood pressure, mm Hg	135 ± 21	144 ± 25
Diastolic blood pressure, mm Hg	73 ± 11*	79 ± 8*
ATP III 10-year risk of MI	4.7 ± 4.5	3.8 ± 3.4

Values are % or mean ± SD. *$p < 0.05$ and †$p < 0.001$ between not high-risk and high-risk groups. Abbreviations as in Table 1.

a performance site–dependent variable. Using the forward selection method, the variables EF and the ratio of average peak signal to normalized uptake slope were entered to form a multivariable Cox model (chi-square: 13.2, $p < 0.001$). The multivariable Cox model was divided into quartiles, and those in the highest-risk quartile were categorized as high risk, with all others categorized as not high

risk. Table 3 compares demographic values between high-risk and not high-risk patients. Kaplan-Meier survival curves indicated that there was a significant difference in time to adverse event between risk groups (log-rank: 15.0, $p < 0.001$) (Fig. 2). Annualized event rates were 12% for those in the high-risk group compared with 4% for patients in the not high-risk group. In the high-risk group, there were 2 deaths and 10 hospitalizations for worsening angina, whereas in the low-risk group, there were 2 MIs and 9 hospitalizations for worsening angina.

Site-independent MR-MPI and cardiac function predictors of adverse events. Since the MR-MPI variable of normalized uptake slope is a ratio, it can be measured in a site-independent manner. The normalized uptake slope at stress was entered into a univariable Cox model and was predictive of events ($p < 0.05$) (Table 2). We formed a multivariable Cox regression model by conditionally entering the normalized uptake slope and EF (chi-square: 12.0, $p < 0.001$). The multivariable Cox model was divided into quartiles, and those in the highest quartile were categorized as high risk, with all others categorized as not high risk. Kaplan-Meier survival analysis showed significant difference in time to adverse event between the high-risk group versus the not high-risk group (log-rank: 13.0, $p < 0.001$). Annualized event rates were 12% for those in the high-risk group compared with 4% for those in the not high-risk group.

DISCUSSION

Ours is the first study, to our knowledge, to show that global MR-MPI variables are predictive of adverse events among women with suspected ischemia but no obstructive CAD. This is an important observation, given the controversy in the current literature concerning the existence of MR-MPI–detected perfusion defects in similar populations of patients. One recent study demonstrated a strong correlation between perfusion defects by MR-MPI and impaired coronary microvascular function (16), whereas another study failed to demonstrate these correlations (17). In a recent editorial, Pennell addressed the divergent opinions by noting the importance of correctly categorizing patient populations (18). The current study represents a well-studied and categorized population of women with symptoms of ischemia and objective evidence of no obstructive CAD, assessed using variables measured
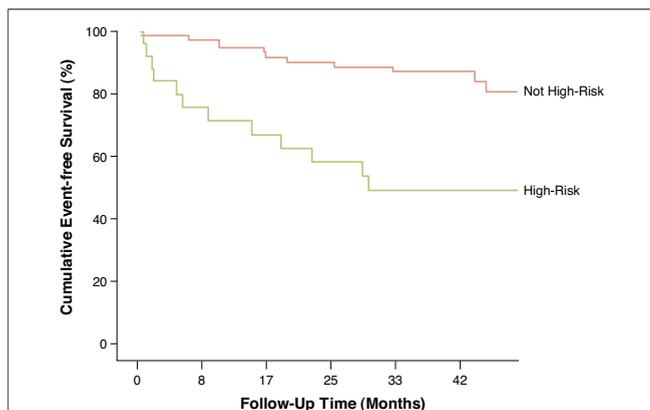

Figure 2. Kaplan-Meier Survival Stratified by MR-MPI and Cardiac Function Risk Measures

Kaplan-Meier cumulative event-free survival curves for adverse events ($p < 0.005$) in high-risk and not high-risk patients stratified by highest quartile of Cox model incorporating the ratio of MR-MPI average amplitude to normalized uptake slope and ejection fraction. Abbreviations as in Figure 1.

in core laboratories and using standardized collection and data analyses methods.

We showed that when considering MPI parameters at stress, averaged over all regions, possessing a low uptake signal with a steep normalized uptake slope was associated with increased events (i.e., a sharp uptake of perfusion, but reaching only a low level). These conditions correspond to low perfusion levels, possibly representative of abnormal subendocardial perfusion secondary to microvascular coronary dysfunction (19). These globally low perfusion conditions would normally not be detected by standard comparative analyses aimed at identifying segmental perfusion abnormalities. Thus, when using the MPI data to evaluate patients with suspected ischemia, 2 separate analyses should be performed, 1 to detect low perfusion regions consistent with obstructive CAD and 1 to detect globally low myocardial perfusion conditions that are independently associated with adverse events.

In addition to globally low perfusion conditions, the highest-risk patients had a low EF value. From Table 3, it is apparent that high-risk patients tended to be obese, with a history of smoking, and had higher resting and stress heart rates. High-risk patients were those with MPI and EF parameters consistent with the presence of microvascular coronary dysfunction. Importantly, a comprehensive evaluation of regional and global perfusion conditions, along with functional status, can be performed noninvasively during a single MPI examination.

Pathophysiologic mechanisms to explain the relatively high prevalence of adverse events associated with abnormal global MR-MPI measures and poor cardiac function include primary myocyte and/or microvascular coronary dysfunction, even in the absence of obstructive CAD. Other WISE data suggest that patients with symptoms of ischemia but no obstructive CAD likely have microvascular coronary dysfunction (20), which is associated with an adverse prognosis (21,22). More work is needed to characterize both the pathophysiology and noninvasive diagnostic tools such as global MR-MPI.

Current diagnostic modalities used to detect myocardial ischemia include radionuclide perfusion and echocardiography imaging. The diagnostic accuracy of these tests in women is limited by the optimization of these techniques for the detection of segmental abnormalities most correlative to obstructive CAD, as well as the confounding effects in radionuclide imaging tissue attenuation (23). Cardiac MR imaging has excellent soft tissue characterization and contrast, 3-dimensionality, and overall good temporal and spatial resolution. Prior studies document its utility for detection of segmental perfusion defects (12), and the current results suggest that cardiac MR may uniquely be positioned to detect global perfusion abnormalities that are of prognostic significance.

Clinical relevance. Women with signs and symptoms suggestive of myocardial ischemia but no obstructive CAD present a major challenge because current management is largely based on the degree of obstructive CAD visualized by traditional coronary angiography. Recent studies demonstrate that there is a sizable subset of patients, often female, with evidence of ischemia but no obstructive CAD who have an adverse prognosis. We showed that global, nontraditional myocardial perfusion variables predicted events. Further validation of these results, with application in patients with suspected ischemia but no obstructive CAD, could enhance diagnosis and prognosis abilities over current modalities.

Study limitations. The sample size and number of events are relatively small, and current results are underpowered to detect the relationship between specific MR-MPI measures and serious adverse events. Due to the small sample size and low number of events, it was not feasible to consider covariates in the Cox models. Improvements in MR-MPI resolution and extent of myocardium covered have occurred since these data were collected that now allow analyses to be performed separately for endocardial, mid-, and epicardial layers, and should provide improved evaluation and understanding of myocardial perfusion. The relatively low resolution of our perfusion images in the current study precluded performing separate analyses for subendocardial versus other myocardial layers. No late gadolinium enhancement was performed to detect nonviable myocardium. Since a body coil was used for acquisition, perfusion uptake signal required filtering to remove excessive noise. Cut points for not high-risk versus high-risk patients for adverse events by global MR-MPI and functional variables were defined using clinical outcomes data for adverse events. This methodology was then used to retrospectively predict outcome and is likely to overestimate the strength of the model. Even lesions <50% could progress during the follow-up time and explain these events.

CONCLUSIONS

Among women with suspected ischemia but no obstructive CAD, global MR-MPI perfusion abnormalities predict adverse events. These data add to the literature and suggest that global MR-MPI abnormalities may be indicative of global myocardial ischemia, possibly secondary to microvascular coronary dysfunction.

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