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Prognostic Value of Dipyridamole Stress Myocardial Contrast Echocardiography: Comparison with Single Photon Emission Computed Tomography

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Abstract

Aims—Dipyridamole stress myocardial contrast echocardiography (MCE) can be used to detect coronary artery disease (CAD). Because it measures myocardial blood flow velocity in addition to measuring myocardial blood volume, we hypothesized that it should have greater prognostic utility compared to single photon emission computed tomography (SPECT), which only measures myocardial blood volume. Since blood flow mismatch precedes wall thickening (WT) abnormality during demand ischemia, we also postulated that perfusion on MCE will be superior to WT abnormality on echocardiography for this purpose.

Methods and results—The incidence of non-fatal myocardial infarction and cardiac death was determined in 261 patients with known or suspected CAD over a mean follow-up of 14 months who underwent simultaneous dipyridamole stress MCE and ^{99m}Tc-sestamibi SPECT. Comparisons of survival curves were conducted with stratified (and unstratified) log-rank tests. An abnormal MCE was found to be the best predictor of an adverse outcome (OR=23, 95% CI=6–201, p<0.0001) and provided incremental prognostic value over clinical variables (age >60 years, the presence of ≥3 cardiac risk factors, known peripheral vascular disease, prior MI, and left ventricular (LV) systolic function), inducible WT abnormalities, and SPECT. Prognosis was the worst in patients who had both abnormal MCE and inducible WT abnormalities and the best in those who had neither. Patients with abnormal MCE but no inducible WT abnormalities had an intermediate outcome.

Conclusion—In patients with known or suspected CAD undergoing dipyridamole stress, MCE provides powerful prognostic information that is superior to clinical variables, ECG, LV systolic function, WT analysis, and SPECT. MCE may therefore serve as a method of choice for myocardial perfusion assessment in known or suspected CAD. Larger studies are needed to confirm these findings.

Keywords

Dipyridamole; myocardial contrast echocardiography; chronic coronary artery disease; prognosis; outcome

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Introduction

Both echocardiography and single photon emission computed tomography (SPECT) have been used in conjunction with different forms of stress for diagnosis and prognosis in patients with suspected or known coronary artery disease (CAD). The hallmark of echocardiography for this purpose has been an inducible wall thickening (WT) abnormality, while that for SPECT has been a reversible perfusion defect. More recently, the use of microbubbles has allowed the assessment of myocardial perfusion with echocardiography^{1–6}. This approach allows the assessment of both myocardial blood flow (MBF) velocity as well as myocardial blood volume (MBV)^{7–12}. A milder stenosis results in only discernible change in MBF velocity while it takes a more severe stenosis to also cause a measurable change in MBV^{7,13}. Unlike myocardial contrast echocardiography (MCE), SPECT can only measure MBV¹⁴. We, therefore, hypothesized that dipyridamole stress MCE will provide superior prognostic information compared to SPECT in patients with known or suspected CAD. Since blood flow mismatch precedes wall thickening (WT) abnormality during demand ischemia¹⁵, we also postulated that perfusion on MCE will be superior to WT abnormality on echocardiography for this purpose.

Methods

Patient Population and Protocol

The protocol was approved by the Human Investigation Committee. All patients gave written informed consent to participate in the study. Patients with known or suspected CAD scheduled for dipyridamole stress ^{99m}Tc-sestamibi SPECT were enrolled. Exclusion criteria were hepatic failure, hypersensitivity to albumin, blood, or blood products, known intra-cardiac right-to-left shunt, pregnancy and lactation. Patients with inadequate echocardiographic images (defined as an inability to visualize a coronary artery territory in any of the 3 apical windows) were also excluded.

Rest SPECT was performed first, where images were acquired 1 hour after injection of 10 mCi of ^{99m}Tc-sestamibi, after which the rest MCE study was performed. A dose of 0.56 mg·kg⁻¹ of dipyridamole was then administered over 4 min, followed by an intravenous injection of 30–35 mCi of ^{99m}Tc-sestamibi. Two minutes later MCE was repeated followed by SPECT an hour later. Continuous monitoring of the electrocardiogram and vital signs were obtained during stress.

Myocardial Contrast Echocardiography

Imaging was acquired from the apical 2-, 3-, and 4-chamber views using a Sonos 5500 system (Philips Ultrasound). Left ventricular (LV) systolic function and baseline WT were assessed using tissue harmonic imaging with LV contrast opacification. For assessment of MP, ultra-harmonic imaging (transmit/receive frequencies of 1.3/3.6 MHz) was used. Ultrasound transmission was gated to end-systole using the peak of the T-wave on the ECG.

A continuous intravenous infusion of OptisonTM (GE Healthcare) was administered. A total of 9 mL of the agentTM was loaded in plastic tubing and advanced into the patient with a column of normal saline infused using a volumetric pump (Model 7100, IVAC Corporation) at a rate of 15–25 mL·hr⁻¹. The infusion rate was adjusted at the beginning of the study at a pulsing interval (PI) of 5 beats to achieve adequate myocardial opacification with minimal attenuation in the LV cavity at the level of the mitral annulus. The infusion rate was then held constant for the remainder of the study. Gains, compression, depth, post-processing, and transmit focus remained unchanged throughout the study after initial optimization. Once steady-state microbubble concentration was achieved (approximately 2 min after starting the infusion), contrast-enhanced images were obtained at pulsing intervals (PIs) of 1, 2, 3, 5 and 8 cardiac

cycles in each view. To achieve PIs of <1 cardiac cycle, dual triggering was performed. At least 3 to 5 frames were acquired at each PI and stored on magneto-optical disk.

Resting images were compared side-by-side with stress images for both myocardial perfusion (MP) and WT data using a 14-segment model¹⁶. MP and WT were interpreted in separate sessions blinded to all other data. Because WT was assessed using tissue harmonic imaging at a mechanical index (MI) of ~ 0.6, only LV endocardial delineation was present with no tissue contrast enhancement. The MP data were acquired separately using triggered high MI imaging, where only end-systolic frames are available for interpretation and consequently WT cannot be ascertained. Studies were interpreted by 2 independent observers and cases with disagreement were resolved by a third reader.

Digital cine-loops of MCE studies were qualitatively interpreted. Abnormal MBF velocity was defined as incomplete myocardial opacification (reduced or absent) at a pulsing interval >q5 beats at rest, or >q2 beats during stress¹⁷. MP defects that developed during stress but were not present at rest were considered reversible, and if present to the same extent at rest and stress were considered fixed.

Qualitative analyses of WT were performed using the same 14 segment model blinded to MP data. WT was scored in each segment as 1 for normal, 2 for reversible (worse at stress) and 3 for fixed (hypokinetic or akinetic at rest with no change during stress). A study was considered abnormal if >1 segment showed a reversible or fixed WT or MP defect. Global LV systolic function from resting studies were also qualitatively assessed and scored as follows: 1 = normal, 2 = mildly impaired, 3 = moderately impaired, 4 = severely impaired.

Gated Single Photon Emission Computed Tomography Imaging

Imaging was performed with a 3-headed gamma camera, with each head acquiring 20 projections of 40 s each over a 120-degree orbit. After filtered back projection, the reconstructed 3-dimensional data were represented in a 14-segment model¹⁶. Activity in each segment was normalized to that with the highest activity in that view and expressed as % uptake. Normalized counts were assigned colors ranging from red to orange to yellow, where each color represents incremental increases in uptake. WT was measured from gated images as previously described¹⁸.

All SPECT studies were interpreted by a single blinded observer. Quantitative WT and perfusion were evaluated concurrently and used to classify SPECT studies as either normal or abnormal. Abnormal studies were further classified as fixed if abnormal perfusion was noted both at rest and after stress, or reversible if perfusion abnormalities were found either only or mostly after stress. WT was used to differentiate perfusion defects from artifacts such as diaphragmatic and breast attenuation.

Comparison between modalities

For comparisons between modalities, individual segments were collapsed into coronary territories as shown in Figure 1. Agreement was determined on territory-by-territory and a patient-by-patient basis.

Patient Follow-up

All patients (or their family) were sent a questionnaire to determine whether any hospitalizations or events developed during the follow-up period. They were also contacted directly by phone. The primary care provider was contacted for all non-responders to the questionnaire. Events were coded using the discharge diagnosis after a review of the hospital records at the institution where they occurred, or directly through the patient's primary care

provider. Events included in this analysis were non-fatal myocardial infarction (MI) and cardiac death. The minimum follow-up interval for assessment of events was 6 months.

Statistical Methods

Concordance between modalities was determined by kappa (κ) statistics with κ values >0.2 =fair, >0.4 =moderate, >0.6 =substantial, and >0.8 =excellent. To compare events between abnormal and normal groups based on each of the 3 modalities, incidence rate ratios and Kaplan Meier curves were generated. Due to lack of proportionality in hazards, comparisons of survival curves for MCE, SPECT, and WT were conducted with stratified (and unstratified) log-rank tests rather than with Cox regression models. The 3 modalities were examined pair-wise taking one of the imaging tests as a strata variable, and the other as the comparison variable of interest in order to assess the utility of each variable while adjusting for the other. For each pair, two analyses were conducted, reversing the role of the comparison group and strata in the two analyses.

Potential confounders were age (above or below 60 years), sex, LV hypertrophy, number of coronary risk factors (≥ 3 versus < 3), presence of peripheral vascular disease (PVD), known cerebrovascular disease, electrocardiographic abnormalities (Q-waves, ST segment and T-wave abnormalities, bundle branch block, atrial fibrillation or flutter), a history of prior infarction, and LV systolic function. These confounders were selected because they are routinely obtained in a cardiac history and from electrocardiographic interpretation, and have previously been shown to have predictive utility. For each potential confounder, log-rank tests were first conducted to determine if there was evidence of a relationship between the confounder and the time to the primary event. Variables with p-values <0.10 were then used as strata in log-rank tests for comparison of survival curves for each of the modalities.

Results

Patient Demographics

Between October 1998 and April 1999, 285 patients were enrolled in the study. MCE was not interpretable in all 3 territories in 24 patients. The remaining 261 patients are included in this report. Patient demographics and baseline characteristics are shown in Table 1.

Imaging Results

Resting global LV systolic function was considered normal, mildly impaired, moderately impaired, or severely impaired in 200 (77%), 23 (9%), 15 (6%), and 23 (9%) patients respectively.

Table 2 depicts the occurrence of normal and abnormal findings for each of the 3 modalities. Agreement on a territory-by-territory basis is illustrated in Table 3. The overall agreement between the 3 modalities on a patient-by-patient basis was excellent between MCE and WT despite the 2 data sets being blinded to each other ($\kappa = 0.80$). It was only fair between MCE and SPECT and WT and SPECT ($\kappa = 0.40$ and 0.32 , respectively).

Event Predictors

The mean duration of follow-up was 14 ± 5 months. There were a total of 22 events during this period of which 6 were non-fatal MI, and 16 were cardiac deaths.

Of the 6 non-fatal MI patients, 4 each had abnormal MCE and WT, while 2 had an abnormal SPECT. Of the 16 cardiac deaths, all had abnormal MCE, 14 had abnormal WT and 13 had abnormal SPECT. Patients with abnormal results were much more likely ($p < 0.001$) to have events compared to those with normal results: 20/86 (23%) versus 2/175 (1%) for MCE, (18/79

(23%) versus 4/182 (2%) for WT, and 15/89 (17%) versus 7/172 (4%) for SPECT. Results of univariate analysis for event prediction are depicted in Table 4.

Individual event probability estimates (1-survival) curves for the 3 modalities are presented in Figures 2 to 4, respectively. The incidence rate ratio for developing an adverse cardiac event with abnormal MCE was 23 (95% CI: 6–201, $p<0.001$), with abnormal WT was 12 (95% CI: 4–48, $p<0.001$), and with abnormal SPECT study was 5 (95% CI: 2–13, $p=0.007$).

Figure 5 illustrates event probability estimates (1-survival) for the combination of MCE and WT results, since in clinical practice both pieces of information would be available at the same time. Of the 165 patients who had both tests normal only 2 had events (1.2%). There were only 10 patients who had normal MCE but abnormal WT, and none of these had an event. There were 17 patients who had abnormal MCE but normal WT, and 2 of these had an event (11.6%). Eighteen of the 69 patients with both tests abnormal had an event (26%).

Pair-wise testing was performed to determine which of the 3 modalities was the most powerful predictor of an adverse outcome. First, patients were stratified according to whether their SPECT result was normal or abnormal, followed then by a stratified comparison of WT and MCE survival. When outcomes were stratified by SPECT there was a significant divergence in WT (stratified log-rank p -value = 0.002) and MCE survival curves (stratified log-rank p -value <0.001) indicating the ability of both WT and MCE to provide incremental prognostic information even after SPECT results were accounted for. WT was then stratified followed by SPECT and MCE. Whereas MCE provided further prognostic information even after WT results were accounted for ($p=0.01$), SPECT provided no additional information ($p=0.54$). Neither SPECT nor WT data provided any further predictive information after outcomes were stratified based on MCE results.

WT ($p = 0.03$) and MCE ($p=0.001$) were able to provide incremental prognostic utility even after adjusting for all other clinical variables combined (Age > 60 , ≥ 3 risk factors, PVD, Prior MI, and LV systolic function). On the other hand, while SPECT was of incremental utility when each of the clinical variables was considered separately, it no longer remained significant when all five clinical variables were included as strata in the analysis ($p=0.44$).

Discussion

This is the first study that has compared the prognostic value of dipyridamole MCE, WT, and SPECT in ambulatory patients with known or suspected CAD. The main finding is that on an individual basis MCE is superior to both WT and SPECT in predicting cardiac mortality and non-fatal MI. The combination of MCE and WT data also provides useful prognostic information by even better stratifying risk.

Dipyridamole MCE and SPECT have been compared before for CAD detection in ambulatory patients^{2,12,13,19–23}. When patients with prior MI are included, the results of the 2 tests are either comparable or MCE comes ahead slightly^{2,12,13,19,22,23}. However, when patients without a prior MI are examined using quantitative coronary angiography as the gold-standard, MCE is found to have a greater overall sensitivity for CAD detection than SPECT, mostly because it more readily identifies patients with milder disease (40–80% luminal diameter narrowing)^{13,20}. Although we do not have angiographic data from our current study, the same reason may apply for the better prognostic value of MCE compared to SPECT.

The most probable reason for both better detection and prognostication in CAD may be related to the ability of MCE to measure MBF velocity. Because of the good temporal resolution of echocardiography modest abnormalities in MBF velocity can be more readily detected on

visual examination of MCE images than modest changes in MBV. The latter is limited by the ability of the human eye to discern between shades of grey.

We have previously shown that reversible perfusion defects on SPECT are related to reversible changes in MBV and not to alterations in MBF¹⁴. Given the issues with photon attenuation, a significant disparity (>30%) in MBV needs to exist between 2 myocardial regions for a perfusion defect to be seen on SPECT. A 30% reduction in MBV is seen only when coronary stenosis is >70%¹⁴. Since MCE can detect milder forms of CAD, it is possible that it could more readily identify patients with early soft plaques who are more likely to suffer an acute MI or acute coronary syndrome. While MCE predicted twice as many AMI's as SPECT, the numbers are too small to reach a conclusion.

It has been repeatedly shown that inducible WT abnormalities are less frequent than reversible perfusion abnormalities in the setting of coronary stenosis during vasodilator stress^{15,24,25}. This finding has been explained on the basis of the ischemic cascade in demand ischemia¹⁵. However, it has also been shown both in acute as well as chronic experimental models that in moderate to severe forms of disease, particularly multi-vessel disease, dipyridamole can induce reversible WT abnormalities as easily as it can induce reversible perfusion defects because of reduced endocardial MBF reserve^{15,26}. Since advanced disease is more likely to result in adverse outcomes, it should not be surprising that inducible WT abnormality turned out to be an important predictor of events in our study²⁷. It is also important to realize that WT abnormalities are much better assessed on contrast echocardiography²⁸⁻³⁰, which might also explain the results seen in our study.

Our results are in agreement with previous studies on the prognostic value of dobutamine MCE in CAD patients. In a retrospective analysis, 788 patients undergoing dobutamine stress were followed for a median of 20 months. It was shown that myocardial perfusion assessment on MCE had significant incremental value over clinical factors, resting ejection fraction, and wall motion responses in predicting events³¹. The 3-year event free survival was 95% for patients with normal perfusion and WT, 82% for those with normal function but abnormal WT, and 68% for those with both abnormal perfusion and WT. Similar results have been reported in elderly patients³² as well as those with diabetes^{33,34} and advanced liver disease³⁵.

Study limitations

Our results are based on visual analysis. A quantitative approach may provide even better results^{20,36,37}, but is currently not feasible for routine use in all patients presenting to the echocardiography laboratory. We used the 0.56 mg·kg⁻¹ dose of dipyridamole rather than the higher dose used in some studies designed to detect WT abnormalities. We also did not use atropine that can result greater increases in heart rate and consequently greater supply-demand mismatch with more inducible WT abnormalities. This study consequently further reiterates the relatively low sensitivity of low-dose dipyridamole for the detection of CAD using WT alone, although the flow mismatch induced by this dose is adequately evaluated using MCE.

Whereas in our study we separately analyzed WT and MP, in clinical practice these results will likely be available at the same time. The assessment of MP without WT made the separation between a fixed defect and an attenuation artifact more difficult (especially in basal segments), and probably accounted for the relatively lower detection rate of prior infarction by MP alone (as shown in Table 2). Technical limitations (obesity, emphysema, etc) are more likely to preclude the performance of MCE than SPECT studies in clinical practice, so not all patients with suspected or known CAD are currently candidates for MCE.

The study also had a relatively short follow-up (mean of 14 months) and the number of hard events was also relatively small (<10% of all patients). To increase the number of events, we

could have included softer events such as revascularization, unstable angina, or congestive heart failure, but these events are subject to classification and treatment bias. Also events such as revascularization can be influenced by the results of the test themselves.

Conclusions

In patients with known or suspected CAD undergoing dipyridamole stress in whom technically adequate echocardiographic images can be obtained, MCE provides powerful prognostic information that is superior to clinical variables, electrocardiogram, WT analysis, and SPECT. These results are consistent with the reported superiority of MCE compared to SPECT and WT for CAD detection^{2,13,20,31–33,38,39}. MCE may therefore serve as a method of choice for myocardial perfusion assessment in suspected CAD. Larger studies and a greater clinical adaptation of MCE are needed to confirm these findings.

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Figure 1.
14-segment model with coronary territories used for comparison of modalities.

Figure 2. Survival curves for patients stratified according to MCE results. See text for details.

Figure 3. Survival curves for patients stratified according to WT results. See text for results.

Figure 4. Survival curves for patients stratified according to SPECT results. See text for details.

Figure 5.
Survival curves stratified based on combinations of MCE and WT results. See text for details.

Table 1
Patient Characteristics

Variable	N	%
Demographics:		
Median age (range)	64 (28 to 90)	
Male	131	50
Risk Factors:		
Hypertension	198	76
Smoking	159	61
Diabetes mellitus	103	40
Hyperlipidemia	121	47
Family history of early CAD	129	50
Past History:		
CAD history	134	52
Prior MI	99	38
CHF history	52	20
PVD	46	18
Medications:		
Aspirin	135	52
ACE Inhibitors	103	40
Diuretics	90	35
Beta-blockers	88	34
Lipid-lowering agent	77	30
Calcium channel blocker	59	23
Insulin	35	13

Key: CHF = Congestive heart failure, ACE= Angiotensin-converting enzyme

Table 2

Findings on the 3 Modalities

Modality	Normal	Reversible	Fixed	Reversible & Fixed
Wall thickening Perfusion	184	6	61	10
Defects (MCE) Perfusion	175	35	38	13
Defects (SPECT)	172	27	51	11

Table 3Agreement (κ value) Between the 3 Modalities on a Territory-by-territory Basis

	LAD	RCA	LCx
MCE versus WT	0.80	0.75	0.76
MCE versus SPECT	0.40	0.47	0.49
WT versus SPECT	0.32	0.47	0.52

Table 4

Univariate Predictors of Events

Variable	Log-rank p-value
Age > 60 years	0.03
Male sex	0.50
Left ventricular hypertrophy	0.80
≥3 cardiac risk factors	0.02
Peripheral vascular disease	0.01
Q-waves on the Electrocardiogram	0.72
ST-segment abnormalities	0.46
Prior MI	0.001
Cerebrovascular disease	0.36
Electrocardiographic abnormalities	0.01
LV systolic function	<0.001
Abnormal SPECT	<0.001
Abnormal wall motion during stress	<0.001
Abnormal MCE	<0.001