Identification of Hibernating Myocardium: Comparative Accuracy of Myocardial Contrast Echocardiography, Rest-Redistribution Thallium-201 Tomography and Dobutamine Echocardiography

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Objectives. **We sought to evaluate the comparative accuracy of myocardial contrast echocardiography (MCE), quantitative rest-redistribution thallium-201 (Tl-201) tomography and low and high dose (up to 40 μg/kg body weight per min) dobutamine echocardiography (DE) in identifying myocardial hibernation.**

Background. **Myocardial contrast echocardiography can assess myocardial perfusion and may therefore be useful in predicting myocardial hibernation. However, its accuracy in comparison to myocardial perfusion scintigraphy and to that of high dose DE remains to be investigated.**

Methods. **Eighteen patients (aged [±SD] 57 ± 10 years) with stable coronary artery disease and ventricular dysfunction underwent the above three modalities before coronary revascularization. Myocardial contrast echocardiography was achieved with intracoronary Albunex. Rest echocardiographic and Tl-201 studies were repeated ≥6 weeks after revascularization.**

Results. **Of 109 revascularized segments with severe dysfunction, 46 (42%) improved. Left ventricular ejection fraction increased from 38 ± 14% to 45 ± 13% at follow-up ($p = 0.003$). Rest Tl-201 uptake and the ratio of peak contrast intensity of dysfunctional to normal segments with MCE were higher ($p < 0.01$) in segments that recovered function compared with those that did not. Myocardial contrast echocardiography, thallium scintigraphy and any contractile reserve during DE had a similar sensitivity (89% to 91%) with a lower specificity (43% to 66%) for recovery of function. A biphasic response during DE was the most specific (83%) and the least sensitive (68%) ($p < 0.01$). The best concordance with MCE was Tl-201 (80%, kappa 0.57). Changes in ejection fraction after revascularization related significantly to the number of viable dysfunctional segments by all modalities ($r = 0.54$ to 0.65).**

Conclusions. **In myocardial hibernation, methods evaluating rest perfusion (MCE, Tl-201) or any contractile reserve have a similar high sensitivity but a low specificity for predicting recovery of function. A limited contractile reserve (biphasic response) increases the specificity of DE. Importantly, the three techniques identified all patients who had significant improvement in global ventricular function.**

(J Am Coll Cardiol 1997;29:985–93)

In patients with severe coronary artery disease, chronic rest ventricular dysfunction may represent necrotic or viable myocardium, or a combination of both (1,2). Identification of viable myocardium may allow better selection of patients in whom ventricular function may improve after revascularization (hibernating myocardium), and prognosis may be ameliorated (1,2). Techniques evaluating hibernating myocardium have included metabolic and perfusion imaging (3–5), as well as assessment of contractile reserve in response to graded dobutamine administration (6–8). Recently, myocardial contrast echocardiography (MCE) has emerged as a modality that allows the assessment of myocardial perfusion and may have the potential for prediction of myocardial viability in the acute and subacute phases of myocardial infarction (9,10). The underlying basis for the assessment of myocardial viability with MCE is that myocardial contrast enhancement depends on an intact microcirculation, among other factors. Kloner et al. (11) noted that with myocardial infarction, myocyte loss is accompanied by a loss of microvasculature. Accordingly, the absence of myocardial opacification with MCE may be evidence of a lack of myocardial viability. There is a paucity of data evaluating MCE in myocardial hibernation (12). Furthermore, its accuracy in predicting recovery of ventricular function after revascularization compared with modalities that assess myocardial perfusion and cellular integrity (thallium-201 [Tl-201] scintigraphy) or contractile reserve (high dose dobutamine echocardiography [DE]) has not been previously investigated.

From the Section of Cardiology, Department of Medicine, Baylor College of Medicine, and the Echocardiography and Nuclear Cardiology Laboratories of The Methodist Hospital and the Veterans Affairs Medical Center, Houston, Texas. This study was supported by an investigator-initiated grant from the John S. Dunn, Sr. Trust Fund and was presented in part at the 69th Annual Scientific Sessions of the American Heart Association, New Orleans, Louisiana, November 1996.

Manuscript received August 9, 1996; revised manuscript received November 14, 1996, accepted December 19, 1996.

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Published by Elsevier Science Inc.
0735-1097/97/$17.00
PII S0735-1097(97)00001-6

JACC Vol. 29, No. 5
April 1997:985–93

Abbreviations and Acronyms

ANOVA	=	analysis of variance
DE	=	dobutamine echocardiography
MCE	=	myocardial contrast echocardiography
PI	=	peak intensity
SPECT	=	single-photon emission computed tomography
Tl-201	=	thallium-201

The aims of this study was therefore to evaluate the accuracy of quantitative MCE in the prediction of recovery of function after revascularization and to compare its accuracy to that of quantitative rest-redistribution Tl-201 tomography and high dose DE in the same patient group.

Methods

Patients were enrolled between January and December 1995 if they had left ventricular dysfunction on echocardiography or contrast ventriculography in the distribution of a stenosed coronary artery (≥70% lumen diameter stenosis) and were scheduled to undergo cardiac catheterization and revascularization. Patients were recruited consecutively, and the studies performed did not influence the decision to proceed with revascularization. These patients represent a separate group from those reported previously from our laboratory (8). The protocol was approved by the Institutional Review Board of Baylor College of Medicine, and all patients gave written informed consent.

Exclusion criteria included the presence of unstable angina, acute myocardial infarction in the preceding 6 weeks, valvular heart disease, sustained ventricular tachycardia or a history of allergy to blood or blood products. Subjects underwent low and high dose DE, rest-redistribution Tl-201 tomography and MCE with intracoronary sonicated albumin (Albunex) within 1 to 7 days (mean 2) before revascularization (Fig. 1). All patients underwent follow-up studies ≥6 weeks after revascularization, which included rest-redistribution Tl-201 scintigraphy and rest two-dimensional echocardiography.

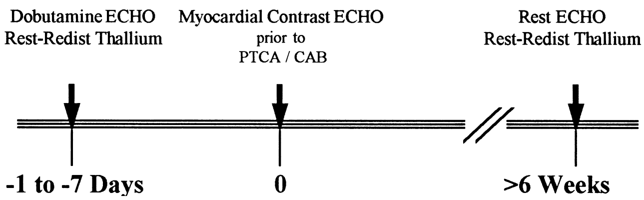
Echocardiographic studies. Echocardiographic imaging was performed in the left lateral decubitus position using standard parasternal and apical views (Hewlett Packard Sonos 1000, 2.5- or 3.5-MHz transducer). For analysis of regional wall motion, MCE and scintigraphic studies, the 16-segment model recommended by the American Society of Echocardiography was used (13). Regional function was graded from 0 to 5: 0 = hyperkinesia; 1 = normal; 2 = mild hypokinesia; 3 = severe hypokinesia; 4 = akinesis; and 5 = dyskinesia. A wall motion score index was derived as the sum of individual scores divided by the number of segments visualized. Ejection fraction was quantitated by the multiple diameter method (14). The initial and follow-up rest studies were displayed side by side in a quad-screen digital format, randomized in sequence and interpreted by a single investigator who had no knowledge of the sequence of the studies and all other data. Recovery of regional function was defined as improvement of 2 or more grades, based on a previous study of variability in our laboratory (8).

For the purpose of matching myocardial segments with coronary distribution on angiography, the anterior wall, septum and apex were assigned to the left anterior descending coronary artery, the lateral wall to the left circumflex coronary artery and the inferoposterior wall to the right coronary artery. For vascular territory and patient analysis, improvement in function by 2 or more grades in ≥2 contiguous segments was required (8).

Dobutamine echocardiography. This modality was performed as previously described (8). In brief, the infusion was started at a dose of 2.5 μg/kg body weight per min and increased at 3-min intervals to 5, 7.5, 10, 20, 30 and 40 μg/kg per min. Images at baseline, 5 μg/kg per min, 7.5 μg/kg per min and peak dobutamine doses were digitized on-line in a quad-screen format. This display has been shown previously to be the most optimal for the assessment of viability (8). The response of the dysfunctional segments to dobutamine was classified as previously described (8) as biphasic (improvement at low dose and worsening at high dose), worsening, no change and sustained improvement (with improvement in function at high dose). A biphasic response and any improvement in function with dobutamine (biphasic or sustained improvement) were both analyzed for the prediction of recovery of function. All studies were interpreted by one investigator who had no knowledge of all the other data.

Myocardial contrast echocardiographic studies. At catheterization and before revascularization, MCE was achieved with intracoronary injections of sonicated albumin (Albunex), performed separately into the left and right coronary arteries. Simultaneous transthoracic imaging (Hewlett-Packard Sonos 1000, 2.5-MHz transducer) was performed using standard views which best showed the dysfunctional segments. Separate injections were made with each view. One to 1.5 ml of Albunex diluted with normal saline (range of dilution 1:3 to 1:1) to optimize myocardial enhancement and decrease intense attenuation was administered per injection. The catheter was flushed with 3 ml of saline immediately after injection. Once optimized, the gain settings were unchanged. Images were recorded on videotape for later interpretation and quantitation.

Figure 1. Study protocol with the sequence of investigations before revascularization and at follow-up. CAB = coronary artery bypass; ECHO = echocardiography; PTCA = percutaneous transluminal coronary angioplasty; Redist = redistribution.



Semiquantitative analysis. Videotapes of MCE studies were reviewed on an off-line station. Segments were scored according to the intensity and distribution of MCE enhancement: 0 = no opacification; 1 = patchy or epicardial opacification only; and 2 = maximal uniform contrast effect. A perfusion score for the whole heart was derived as the sum of individual scores divided by the number of visualized segments.

Quantitative analysis. Images were digitized and MCE quantitated off-line (TomTec Imaging Systems Inc.). End-diastolic frames gated to the R wave were digitized starting at 2 cycles before contrast appearance and for 20 to 30 cycles afterward. A region of interest comprising each visualized segment, excluding the bright epicardial border, was traced. Peak contrast intensity in each segment was determined and corrected for background myocardial intensity. Mean percent error of this measurement was 12 ± 8%, which is similar to that previously reported (15). A peak intensity (PI) ratio was derived for each segment as the ratio of PI in that segment to that of the normal control, defined as the segment with highest contrast intensity and normal wall motion. The overall extent of opacification was derived as the sum of PI ratios of individual segments divided by the number of segments visualized.

Rest-redistribution Tl-201 tomography. Rest and then 4-h redistribution Tl-201 single-photon emission tomographic (SPECT) scans were acquired after the intravenous administration of 3 mCi of Tl-201, on the same day as DE, before revascularization and repeated at late follow-up (Fig. 1). Thallium-201 SPECT was performed using methods previously reported from our laboratory (16,17). A large field-of-view rotating gamma camera with a high resolution, parallel-hole collimator was used. Thirty-two frames were acquired over a 180° arc (45° left posterior oblique to 45° right anterior oblique view). The images were reconstructed using a filtered back-projection algorithm using a Butterworth filter with a cutoff frequency of 0.50 Nyquist and an order of 5. Reconstructed tomograms were then reoriented in the standard short, horizontal long and vertical long axes for interpretation and quantitation of Tl-201 uptake.

Thallium-201 images were analyzed quantitatively by experienced nuclear cardiologists who had no knowledge of all the other data. Computerized two-dimensional polar maps of the three-dimensional myocardial radioactivity were generated (16,17). A 16-segment model comparable to that of echocardiography was used. The myocardial Tl-201 activity in each segment was determined using a region of interest of 40 × 40 pixels in size. Thallium-201 uptake in each segment was normalized to the segment with the highest uptake. A maximal Tl-201 uptake ≥60% at rest or redistribution was considered indicative of myocardial viability, as previously shown by our group (16).

Coronary angiography. Selective coronary angiography was performed in multiple views using standard techniques. All angiograms were analyzed by an investigator who had no knowledge of all the other data. The severity of coronary stenosis was determined by calipers and expressed as percent lumen diameter reduction. Significant coronary artery disease was defined as ≥70% diameter stenosis of at least one major epicardial artery.

Statistical analysis. Categorical data are presented as percentages and continuous data as mean value ± SD. Prerevascularization and postrevascularization changes in Tl-201 uptake, wall motion score index and ejection fraction were compared using the paired Student *t* test. To evaluate whether a myocardial region subtended by the revascularized artery responded in a statistically independent manner compared with adjacent regions, baseline and changes in wall motion score index after revascularization in the revascularized and nonrevascularized regions were compared in the same patients using linear regression analysis and the paired *t* test. Linear regression analysis was also used to correlate contrast scores, ejection fraction and wall motion score index. The Spearman rank correlation was used to relate changes in ejection fraction to the number of viable segments. Differences in frequency of recovery between revascularized and nonrevascularized segments were analyzed using the chi-square test. Differences in wall motion score index and contrast score among groups are compared using analysis of variance (ANOVA) and the Bonferroni *t* test. To assess agreement between modalities, kappa statistics were used. Statistical significance was set at $p \le 0.05$.

Results

Patient group. Twenty-two patients were enrolled in the study. Two patients did not undergo cardiac catheterization after having had DE and Tl-201 scintigraphy. Another patient had normal ventricular function, although apical hypokinesia was present on the initial contrast ventriculogram. Data on the remaining 19 patients are presented. Eighteen patients had revascularization (coronary angioplasty in 16, coronary artery bypass surgery in 2). In one patient, the vessels were considered unsuitable for revascularization. Table 1 summarizes the clinical data. Mean percent coronary stenosis decreased from 92 ± 10% before angioplasty to 28 ± 20% after the procedure ($p < 0.0001$). There were no clinical events noted after revascularization, and all patients were asymptomatic at late follow-up.

Changes in rest left ventricular function. Of 304 myocardial segments, 296 were adequately visualized. All eight nonvisualized segments were in the nonrevascularized group. There were 143 segments in the revascularized territory, 29 of which had normal wall motion at baseline, 5 mild hypokinesia, 59 severe hypokinesia, 40 akinesia and 10 dyskinesia. In the revascularized segments, 17 improved by one grade, 46 by two grades and 3 showed worsening by one grade. Of the nonrevascularized segments, 11 improved by one grade, 2 by two grades and 4 worsened by one grade. No segment had worsening of two or more grades in either group.

Figure 2 shows the recovery rate of the 155 abnormal segments with severe dysfunction (severe hypokinesia, akinesia and dyskinesia). Of the 109 segments revascularized, 46 (42%) had functional recovery of two or more grades compared with

Table 1. Baseline Characteristics of 19 Study Patients

Age (yr)	57 ± 10
History of previous infarction	11 (58%)
Angina	13 (68%)
Congestive heart failure	10 (52%)
Q waves in revascularized segments	7 (37%)
Left ventricular ejection fraction (%)	38 ± 13
Risk factors	
Diabetes	8 (42%)
Hypertension	12 (63%)
Hyperlipidemia	9 (47%)
Smoking	10 (52%)
Cardiac medications	
Beta-blockers	9 (47%)
Calcium channel blockers	3 (16%)
ACE inhibitors	6 (32%)
Coronary angiography	
Single-vessel disease	11 (58%)
Multivessel disease	8 (42%)
Angiographic collateral channels	5 (26%)
Mean % diameter stenosis	92 ± 10

Data are presented as mean value ± SD or number (%) of patients. ACE = angiotensin-converting enzyme.

only 2 (4%) of 46 nonrevascularized segments ($p < 0.0001$). Segments with severe dysfunction at baseline were analyzed for prediction of recovery of function with MCE, DE and Tl-201 scintigraphy.

Relation of MCE to baseline left ventricular function. No patient developed an allergic reaction or significant hemodynamic changes during the administration of Albunex. Myocardial enhancement was best achieved with a 1:1 dilution in 13 of 18 patients. Normal myocardial function was associated with the highest contrast opacification. Overall, the degree of opacification decreased as myocardial function worsened (Fig. 3). The PI ratio decreased from 0.94 ± 0.2 for normal segments to 0.46 ± 0.47 for dyskinetic segments ($p < 0.0001$ by ANOVA). Findings were similar for semiquantitative MCE analysis (contrast score ranged from 1.91 ± 0.31 for normal segments to 0.87 ± 1 for dyskinetic segments).

Myocardial contrast echocardiography and recovery of ventricular function. Compared with segments that did not recover function, those that ultimately improved had a higher baseline visual score (1.6 ± 0.69 vs. 1 ± 0.9; $p = 0.001$) and PI ratio (0.79 ± 0.33 vs. 0.5 ± 0.46; $p = 0.008$). Significant correlations were observed between follow-up wall motion score index and contrast score ($r = -0.63$) as well as PI ratio ($r = -0.75$). Significant correlations were also present between follow-up ejection fraction and contrast score ($r = 0.65$) and PI ratio ($r = 0.52$).

The prediction of recovery of function with MCE is shown in Tables 2 and 3. For the semiquantitative analysis, contrast scores ≥1 provided the best prediction, with a sensitivity of 89% and a specificity of 51% (Table 2). The prediction of recovery of severely hypokinetic versus akinetic segments is shown in Table 3. Overall specificity was slightly higher in akinetic segments.

With a PI ratio of 0.15, sensitivity was 98% and specificity was 30%. As the cutoff value increased, the specificity increased, but with a decline in sensitivity (sensitivity of 45% and specificity of 80% for PI ratio of 0.85). Using a receiver operating characteristic curve, a PI ratio >0.25 provided the best combination of sensitivity and specificity. For all 109 segments, the sensitivity was 89% with a specificity of 57% (Table 2). Findings in hypokinetic versus akinetic segments are shown in Table 3. Overall higher sensitivity and lower specificity were observed in hypokinetic segments.

Rest-redistribution Tl-201 scintigraphy and recovery of function. Rest Tl-201 uptake was higher in revascularized segments that recovered function compared with those that did not (76 ± 12.5% vs. 62 ± 14.7%; $p < 0.0001$). After revascularization, rest Tl-201 uptake increased in segments with recovery of function (76 ± 12.5% to 85 ± 10%; $p = 0.0003$) and in those without (62 ± 15% to 71 ± 11%; $p = 0.0003$). However, rest Tl-201 uptake after revascularization remained higher in those that recovered function ($p < 0.0001$). Neither group of segments (recovery and no recovery) showed significant redistribution before or after revascularization. In contrast, in the nonrevascularized segments, Tl-201 uptake was

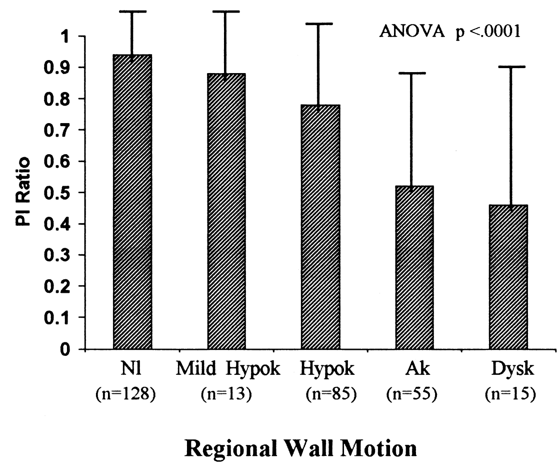


Figure 3. Relation of contrast PI ratio to baseline regional left ventricular function. Ak = akinesia; Dysk = dyskinesia; Hypok = hypokinesia; Nl = normal.

Figure 2. Fate of abnormal segments with severe dysfunction in the study and the recovery rate in the revascularized and nonrevascularized segments.

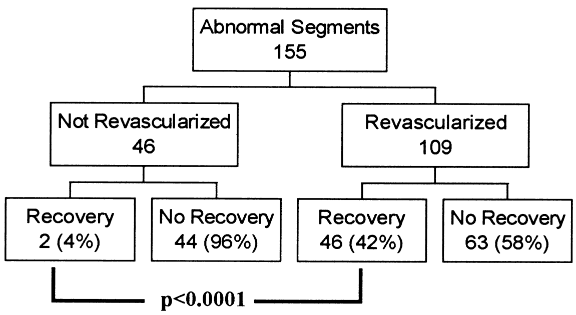


Table 2. Accuracy of Various Modalities in Prediction of Recovery of Function After Revascularization in Severely Dysfunctional Segments

Imaging Modality	Sensitivity	Specificity	PPV	NPV	Accuracy
DE (biphasic)	23/34 (68%)*	49/59 (83%)*	23/33 (70%)	49/60 (82%)	72/93 (77%)
DE (any improvement)	31/34 (91%)	39/59 (66%)	31/51 (61%)	39/42 (93%)	70/93 (75%)
MCE (visual score)	41/46 (89%)	32/63 (51%)	41/72 (57%)	32/37 (86%)	73/109 (67%)
MCE (PI ratio >0.25)	41/46 (89%)	36/63 (57%)	41/68 (60%)	36/41 (88%)	77/109 (71%)
Tl-201 (R-R ≥60%)	42/46 (91%)	27/63 (43%)	42/78 (54%)	27/31 (87%)	69/109 (63%)

*p < 0.01 versus dobutamine echocardiography, any improvement, thallium-201 and myocardial contrast echocardiography. Data are presented as number (%) of patients. DE = dobutamine echocardiography; MCE = myocardial contrast echocardiography; NPV = negative predictive value; PI = peak intensity; PPV = positive predictive value; R-R = rest-redistribution; Tl-201 = thallium-201.

unchanged from baseline to late follow-up (68 ± 16% vs. 71 ± 13%, respectively, $p = 0.39$).

Prediction of recovery of function using a maximal Tl-201 uptake of ≥60% is shown in Table 2. In the 109 revascularized segments, sensitivity was 91% with a specificity of 43%. Similar to MCE, sensitivity was higher and specificity was lower in hypokinetic compared with akinetic segments (Table 3).

Dobutamine echocardiography and recovery of function. Of the 18 patients who underwent revascularization, 17 had DE before the procedure. All patients finished the infusion protocol or reached ≥85% of their target heart rate, or both. The frequency of the different responses of the dysfunctional myocardium to DE was as follows: biphasic response in 35.5%, sustained improvement in 19.3%, progressive worsening in 3.2% and no change in wall motion in 42%. The prediction of recovery of function using biphasic response and any improvement are shown in Table 2. Biphasic response alone had a sensitivity of 68% and a specificity of 83%. Any improvement in wall motion to DE increased the sensitivity to 91% with a decrease in specificity to 66%. Compared with akinetic segments, higher sensitivity and lower specificity were observed in hypokinetic segments (Table 3). The PI ratio was higher in segments with contractile reserve. The PI ratio was 0.78 ± 0.35 in segments with a biphasic response and 0.72 ± 0.35 in those with sustained improvement. In contrast, the PI ratio was 0.36 ± 0.42 in the absence of any change in function during DE ($p < 0.001$ by ANOVA).

Comparison of the three modalities. The percentage of severely dysfunctional segments judged to be viable at baseline by the three modalities was as follows: 62% by MCE, 72% by Tl-201, 55% by DE using any improvement in function and 35% with a biphasic response. Concordance among the modalities tested in assessment of viability is shown in Figure 4. As expected from these findings, a high concordance was observed between MCE and Tl-201 scintigraphy (80%; kappa = 0.57). Using a biphasic response during DE, concordance between Tl-201 scintigraphy and DE was 56%, and between MCE and DE 67%. When any improvement during dobutamine was considered an indicator of viability, concordance increased between DE and both Tl-201 scintigraphy and MCE (66% and 72%, respectively).

Comparison of sensitivity and specificity for recovery of function among the various modalities revealed that biphasic response was less sensitive but more specific for recovery of function compared with MCE or rest-redistribution Tl-201 scintigraphy ($p < 0.01$; Table 2). The use of any improvement of function during DE increased its sensitivity with a significant decrease in specificity, which was comparable to MCE and Tl-201 tomography. A combination of imaging modalities overall resulted in an increased sensitivity with a further decrease in specificity. A combination of DE (biphasic response) and rest-redistribution Tl-201 scintigraphy resulted in a sensitivity of 100% and a specificity of 46%. Similarly, combining DE and MCE allowed for a higher sensitivity of 97% with a specificity of 64%.

Analysis by vascular territories. The study group had 37 vascular territories with abnormal baseline function (≥2 segments with severe hypokinesia, akinesia or dyskinesia). Twenty-five vascular territories were revascularized. At baseline, there was no relation between the wall motion score index of the revascularized region and that of the nonrevascularized region in the same patients ($r = 0.03$, $p = 0.89$). After

Table 3. Sensitivity and Specificity of Different Techniques in Hypokinetic and Akinetic Segments

	Hypokinetic		Akinetic	
Imaging Modality	Sensitivity	Specificity	Sensitivity	Specificity
DE (biphasic)	17/24 (71%)	18/26 (69%)	6/10 (60%)	31/33 (94%)
DE (any improvement)	24/24 (100%)	12/26 (46%)	7/10 (70%)	27/33 (82%)
MCE (visual score)	28/29 (97%)	13/30 (43%)	13/17 (76%)	19/33 (58%)
MCE (PI ratio >0.25)	28/29 (97%)	13/30 (43%)	13/17 (76%)	23/33 (70%)
Tl-201 (R-R ≥60%)	28/29 (97%)	11/30 (37%)	14/17 (82%)	16/33 (48%)

Data are presented as number (%) of patients. Abbreviations as in Table 2.

R-R Thallium-201

		Viable	Nonviable	TOTAL
MCE	Viable	60	5	65
	Nonviable	17	27	44
	TOTAL	77	32	109

° agreement 80%

DE (any improvement)

		Viable	Nonviable	TOTAL
MCE	Viable	41	15	56
	Nonviable	11	26	37
	TOTAL	52	41	93

° agreement 72%

(DE biphasic)

		Viable	Nonviable	TOTAL
MCE	Viable	29	27	56
	Nonviable	4	33	37
	TOTAL	33	60	93

° agreement 67%

Figure 4. Observed agreement on viability among the three modalities. DE = dobutamine echocardiography; MCE = myocardial contrast echocardiography; R-R = rest-redistribution.

revascularization, function in the revascularized territory was significantly altered, in contrast to the nonrevascularized territory in the same patients (respective change in wall motion score index from baseline: -1.03 ± 0.99 vs. -0.05 ± 0.12, $p = 0.0007$). Based on the definition of recovery of function, 14 (56%) of the 25 revascularized regions recovered. By comparison, none of 12 nonrevascularized territories showed functional improvement ($p < 0.001$). Viability for a given region mandated the presence of two or more viable segments. Table

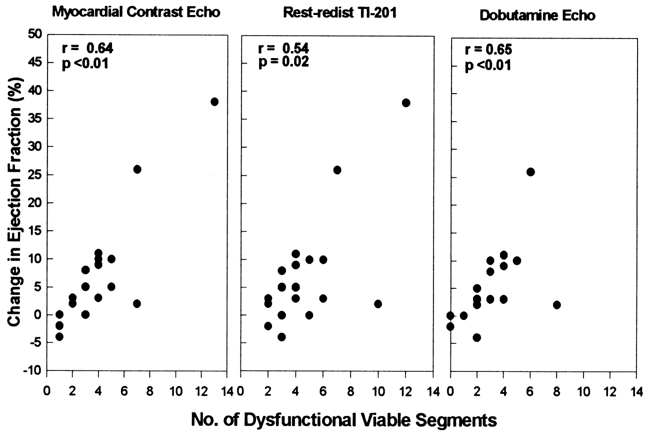


Figure 5. The relation of change in ejection fraction after revascularization to the number of dysfunctional viable segments with MCE (PI ratio >0.25), Tl-201 (≥60% uptake at rest or redistribution) and any contractile reserve during DE. Echo = echocardiography.

4 shows the sensitivity, specificity and predictive accuracy for all three modalities.

Analysis by patients. Of the 18 patients studied, 11 had significant recovery of function. Wall motion score index was 2.42 ± 0.78 at baseline and decreased to 1.96 ± 0.87 after revascularization ($p = 0.0026$). Also, ejection fraction increased from $38 \pm 13.7\%$ to $45 \pm 13\%$ ($p = 0.0029$). Thallium-201 uptake increased from $73 \pm 8\%$ before revascularization to $78 \pm 7\%$ after revascularization ($p = 0.03$). Table 4 shows the sensitivity, specificity and predictive values for all three modalities. Overall, the results were similar to those of the regional function analysis. The sensitivity and specificity for biphasic response were 80% and 71%, respectively. Myocardial contrast echocardiography, Tl-201 scintigraphy and any improvement during DE detected all 11 patients who had recovery of function but low specificities (range 29% to 43%; Table 4).

The relations of change in ejection fraction (baseline to late follow-up) to the number of dysfunctional segments judged to be viable by the three modalities are shown in Figure 5. A significant relation was observed with all the modalities (Spearman rank correlation coefficient range 0.54 to 0.65). Significance was maintained even with exclusion of the two subjects with the largest increments in ejection fraction. A significant change in ejection fraction for individual patients was defined

Table 4. Sensitivity, Specificity and Accuracy for Predicting Recovery of Contractile Function: Analysis by Vascular Territory and by Patients

	Vascular Territory			Patients		
Imaging Modality	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
DE (biphasic)	9/11 (82%)	9/11 (82%)	18/22 (82%)	8/10 (80%)	5/7 (71%)	13/17 (76%)
DE (any improvement)	10/11 (91%)	7/11 (64%)	17/22 (77%)	10/10 (100%)	3/7 (43%)	12/17 (71%)
MCE (visual score)	13/14 (93%)	5/11 (45%)	18/25 (72%)	11/11 (100%)	2/7 (29%)	13/18 (72%)
MCE (PI ratio >0.25)	13/14 (93%)	7/11 (64%)	20/25 (80%)	11/11 (100%)	3/7 (43%)	14/18 (78%)
Tl-201 (R-R ≥60%)	14/14 (100%)	4/11 (36%)	18/25 (72%)	11/11 (100%)	2/7 (29%)	13/18 (72%)

Data are presented as number (%) of patients. Abbreviations as in Table 2.

as ≥9% (±2 SD), based on a study of variability from our institution (14). There were six patients who had such an improvement, and none had significant worsening. All six patients had at least four viable segments by Tl-201 or MCE and more than three viable segments by DE (Fig. 5), using either any improvement or biphasic response.

Discussion

The present study demonstrates that MCE, similar to Tl-201 scintigraphy and DE, can be used in the evaluation of hibernating myocardium. Not surprisingly, the highest concordance among the three modalities was observed between MCE and Tl-201 scintigraphy, the two techniques that assess rest myocardial perfusion. The use of MCE, rest-redistribution Tl-201 tomography or any contractile reserve had a high sensitivity with a moderate to low specificity for predicting recovery of function. The presence of limited contractile reserve (biphasic response) improved the specificity for recovery of function. Importantly, the three methods identified all patients with a significant increase in ejection fraction.

Myocardial contrast echocardiography and myocardial hibernation. In myocardial hibernation, several studies have demonstrated that myocardial blood flow is either significantly reduced or coronary reserve is severely impaired (16,18,19). Recently, MCE has developed into a sensitive method for the assessment of myocardial perfusion (15,20). The echogenic microbubbles have the same rheology as red blood cells and can opacify the myocardium at flow rates as low as 15% of normal (21–23). With a severe reduction of anterograde flow, collateral channels play an increasingly essential role in maintaining cellular viability. Myocardial contrast echocardiography has been demonstrated to be an important technique to delineate the microcirculation and to assess the presence and distribution of collateral channels that may not be evident on angiography (9,24).

Myocardial contrast echocardiography has been used for the evaluation of residual myocardial viability in patients who have had an acute myocardial infarction. Sabia et al. (9) demonstrated that in patients undergoing coronary angioplasty 2 to 5 weeks after myocardial infarction, the presence of intact microcirculation by MCE was related to myocardial viability. Later studies from the same laboratory (10) reported similar conclusions after acute infarction. However, other investigators (25) noted that some patients with acute infarction did not recover contractile function despite adequate contrast opacification. Very recently, MCE was found to have a specificity of 46% for functional recovery in the acute infarct setting (26).

Unlike acute coronary syndromes, a paucity of data exists on the use of MCE in hibernating myocardium. The only report in the published literature is a study by deFilippi et al. (12) using sonicated Renografin-76 and semiquantitative analysis, where MCE was found to have a high sensitivity with a lower specificity (98% and 52%, respectively). In the present study, sonicated albumin was used as the MCE agent because it has no effect on myocardial blood flow (27) and provides more uniform microbubble size. To correct for variability in myocardial opacification, a PI ratio corrected for background intensity was used (25,28), a similar approach to that of Tl-201 SPECT, where counts are normalized to the area with the highest uptake. A PI ratio >0.25 provided a sensitivity of 89% and a specificity of 57% for recovery of function. It is interesting that in a recent study from our institution (29), a ratio of >0.3 identified collateral perfusion and correlated significantly with regional shortening fraction.

The presence of myocardial perfusion by MCE in akinetic or severely hypokinetic segments that fail to recover function after revascularization is not unexpected. A minimal perfusion has to be present for cell survival; however, it may not necessarily be sufficient for contraction. We observed perfusion in 54% of akinetic and dyskinetic segments, although only 34% recovered. Furthermore, contractility is likely to remain depressed when a relatively large amount of fibrous tissue is present, although perfusion has increased. Vanoverschelde et al. (18) previously documented profound ultrastructural changes, including loss of myofibrillar content in regions with myocardial perfusion and metabolic activity by positron emission tomography.

Relation of MCE to rest-redistribution Tl-201 scintigraphy. Myocardial uptake of Tl-201 depends on coronary blood flow characteristics as well as on cellular viability. Several studies have demonstrated the utility of Tl-201 scintigraphy in the evaluation of myocardial viability (3–5). Although earlier studies have demonstrated a high accuracy in the prediction of recovery of function, more recent investigations have shown that the specificity is lower, similar to the present findings (4,16,30). Although Tl-201 uptake indicates the presence of viable myocardium, it may not predict recovery of function after revascularization. Using rest-redistribution Tl-201 SPECT, thallium-201 uptake may not distinguish between hibernating hypoperfused myocardium and regions with varying degrees of subendocardial scarring but without a reduction in rest flow.

There are no previous studies comparing MCE with myocardial scintigraphy in patients with myocardial hibernation. We have previously demonstrated in an animal model of coronary stenosis that myocardial perfusion by MCE correlated well with Tl-201 uptake by tomography (22). In the present study, a high concordance in the assessment of viability was observed (80%) between these two perfusion modalities. Overall prediction of recovery of function was similar with both techniques, including the subgroups of akinetic and hypokinetic segments at baseline. With recent developments in myocardial contrast agents that can opacify the myocardium through intravenous administration, the potential for the use of MCE in the assessment of perfusion and viability is promising.

Myocardial contrast echocardiography and high dose DE. Evidence that the hibernating myocardium exhibits contractile reserve in response to inotropic stimulation has been well documented (6–8,19,31,32). An increasing inotropic stimulation leads to depletion of energy stores resulting in ischemia

(31,32). Recently, the use of high dose, in addition to low dose, dobutamine has unmasked differences in contractile reserve (8,32,33) that had significant implications on the prediction of recovery of function after revascularization (8). Four types of responses of the dysfunctional myocardium to dobutamine could be differentiated, of which a biphasic response was the most predictive of recovery of function (8). In the present study, using a similar protocol and a different patient group, the observed accuracy of DE was similar to that reported previously (8,16). The presence of a biphasic response showed the highest specificity (83%) with a sensitivity (68%) lower than with MCE and Tl-201 scintigraphy. Using any improvement in function during dobutamine resulted in a higher sensitivity (91%) and a lower specificity (66%). These results further corroborate those of deFillipi et al. (12), who compared low dose dobutamine to MCE with sonicated renographin.

Study limitations. Patients with acute coronary syndromes were excluded; however, the possibility of silent recurrent ischemia resulting in dysfunction cannot be completely ruled out. The presence of a wall motion abnormality on two separate occasions before revascularization further supported hibernation as the underlying mechanism of dysfunction. Adjacent segments in a particular patient may behave similarly. The sole use of segmental analysis may therefore overemphasize differences. To minimize this drawback, which is commonly found in the published literature on myocardial viability, we have also analyzed the data using combined segments in a vascular territory and performed an analysis by patients.

We evaluated patients ≥6 weeks after revascularization with all patients having their follow-up by 3 months. The likelihood of recovery after 3 months is possible; however, the recovery rate observed is already high. Furthermore, a longer follow-up interval may result in increased incidence of restenosis or occlusion of saphenous vein grafts. Thus, the timing of follow-up in the present study is likely the most appropriate. All patients remained asymptomatic and the repeat rest Tl-201 studies showed a significant increase in uptake after revascularization, further supporting that in the majority of patients significant restenosis reducing rest perfusion is unlikely.

Anatomic misalignment could have accounted for some of the discrepancy between echocardiographic modalities and scintigraphic studies. However, the 80% concordance rate noted between MCE and Tl-201 favors a minimal contribution of this limitation. Many factors are known to influence myocardial contrast intensity. Albunex bubbles are 4 to 6 μm in diameter and thus allow for a more uniform effect of size. The gains were adjusted before each study and were not altered during the protocol. To correct for interindividual variability, we used the PI ratio corrected for background. Finally, the results observed in this series need further confirmation in a larger number of patients.

Clinical implications. This study has important clinical implications. With the use of imaging modalities that predominantly assess rest perfusion (MCE and rest-redistribution Tl-201 scintigraphy), the prediction of recovery of function in patients with suspected hibernation is similar, yielding a high sensitivity and a lower specificity. This predictive accuracy is also similar to that achieved when any contractile reserve is present during DE. A higher specificity for predicting recovery of function is observed when a biphasic response was observed (induction of ischemia at high dose dobutamine) in patients with suspected hibernation. Importantly, all modalities were capable of identifying patients with hibernating myocardium who increased their ejection fraction after revascularization by ≥9%. With the availability in the near future of intravenous contrast agents that can opacify the myocardium, the simultaneous assessment of perfusion and function may be feasible at rest and during stress in the same setting. Whether this approach would allow a better selection of patients for coronary revascularization in this high risk group remains to be determined.

We acknowledge Helen A. Kopelen, RDMS, Tracy Ferrando, RDCS, Gerardo Villareal-Levy, MD, and Nasser Lakkis, MD, for their help in patient recruitment and coordination. We also thank Nicholas Kutka, MD, for his coordination of the scintigraphic studies at the Veterans Affairs Medical Center; E. O'Brian Smith, PhD, for his helpful statistical review and recommendations; Miguel A. Quiñones, MD, for his review of the manuscript; and Ms. Eula Landry for her secretarial assistance.

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