Identification of Hibernating Myocardium With Quantitative Intravenous Myocardial Contrast Echocardiography
Comparison With Dobutamine Echocardiography and Thallium-201 Scintigraphy

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Background—There are currently no data on the accuracy of intravenous myocardial contrast echocardiography (MCE) in detecting myocardial hibernation in man and its comparative accuracy to dobutamine echocardiography (DE) or thallium 201 (Tl201) scintigraphy.

Methods and Results—Twenty patients with coronary artery disease and ventricular dysfunction underwent MCE 1 to 5 days before bypass surgery and repeat echocardiography at 3 to 4 months. Patients also underwent DE (n=18) and rest-redistribution Tl201 tomography (n=16) before revascularization. MCE was performed using continuous Optison infusion (12 to 16 cc/h) with intermittent pulse inversion harmonics and incremental triggering (1:1 to 1:8). Myocardial contrast intensity (MCI) replenishment curves were constructed to derive quantitative MCE indices of blood velocity and flow. Recovery of function occurred in 38% of dysfunctional segments. MCE parameters of perfusion in hibernating myocardium were similar to segments with normal function and higher than dysfunctional myocardium without recovery of function (P<0.001). The best MCE parameter for predicting functional recovery was Peak MCI×β, an index of myocardial blood flow (area under the curve, 0.83). MCE parameters were higher in segments with contractile reserve and Tl201 uptake ≥60% (P<0.05) and identified viable segments without contractile reserve by DE. The sensitivity of Peak MCI×β >1.5 dB/s for recovery of function was 90% and was similar to Tl201 scintigraphy (92%) and any contractile reserve (80%); specificity was higher than for Tl201 and DE (63%, 45%, and 54%, respectively; P<0.05).

Conclusions—MCE with intravenous contrast identifies myocardial hibernation in humans. Prediction of viable myocardium with MCE is best using quantification of myocardial blood flow and provides improved accuracy compared with DE and Tl201 scintigraphy. (Circulation. 2003;107:538-544.)

Key Words: echocardiography ■ perfusion ■ hibernation ■ ischemia ■ cardiovascular diseases

Evaluation of hibernating myocardium has included metabolic and perfusion imaging, as well as assessment of contractile reserve.1,2 Recently, myocardial contrast echocardiography (MCE) using intracoronary contrast administration has emerged as a modality for assessing myocardial perfusion, and it has the potential to predict myocardial viability.3-5 Its underlying basis is that myocardial contrast enhancement depends on an intact microcirculation. Recently, the combination of intravenous MCE and destruction and replenishment contrast intensity curves have allowed for the noninvasive quantification of myocardial blood volume and velocity and, thus, myocardial blood flow.5 Whether these new quantitative MCE parameters help predict myocardial hibernation, are superior to conventional maximal contrast intensity, and are comparable to inotropic reserve and radionuclide imaging with rest-redistribution thallium-201 (Tl201) scintigraphy is currently not known.

Methods

Patient Population
The study population consisted of patients with chronic, stable, ischemic heart disease and rest ventricular dysfunction in the distribution of ≥1 coronary artery stenoses (>70% diameter stenosis) who were already scheduled for coronary artery bypass surgery. Dobutamine echocardiography (DE), MCE, and rest-redistribution Tl201 tomography were performed 1 to 5 days before bypass surgery. Patients underwent repeat 2D echocardiography and DE 3 to 4 months after surgery to assess recovery of function. The Institutional Review Board of Baylor College of Medicine approved the study protocol, and all patients gave written informed consent before enrollment.

Echocardiographic Studies
Echocardiographic imaging was performed in the standard parasternal and apical views (Advanced Technology Laboratories 5000 scanner, 2 to 4 MHz transducer). Regional function was assessed...
according to the 16-segment model of the American Society of Echocardiography and graded from 1 to 5 as previously described. Ejection fraction was quantified with the multiple diameter method. Regional recovery of rest function was defined as improvement in ≥2 grades, and myocardial segments were matched to coronary distributions as previously described.

Myocardial Contrast Echocardiography

Baseline apical 4-chamber, 2-chamber, and long-axis views were obtained using pulse inversion second harmonic imaging (ATL-5000, 2 to 4 MHz transducer). Continuous infusion of contrast agent (Optison) was administered (12 to 16 cc/h) using an infusion pump (Baxter, Model AS50). The infusion rate was adjusted to minimize attenuation, confining it to beyond the mitral valve plane, and to give the best myocardial opacification at the triggering interval of 1:4. Gain settings were optimized and unchanged throughout the protocol. Images from the apical 2-chamber, 4-chamber, and long-axis views were obtained using incremental end-systolic triggering (1:1, 1:2, 1:3, 1:4, 1:6, and 1:8). Images were recorded on videotape and captured on-line on optical disk for later interpretation and quantification.

MCE images were analyzed both qualitatively and quantitatively. Qualitatively, myocardial segments were scored as follows: 0, no opacification; 1, patchy or epicardial opacification only; or 2, homogeneous opacification. Quantitative analysis was performed using a prototype software (HDI laboratory, Advanced Technology Laboratories). Background subtracted myocardial contrast intensity (MCI) was measured at each pulsing interval in each segment. Plots of MCI versus pulsing intervals were constructed and fitted to an exponential function, as described by Wei et al. The derived plateau of MCI (peak MCI), the slope of the MCI ascending curve (β), and the product (peak MCI×β) were calculated. Peak MCI in every segment (n) was also normalized to the segment with the highest peak MCI as follows: peak MCI/peak MCIseg. MCI at the 1:8 gating interval was also evaluated and normalized to the segment with highest contrast intensity to assess whether this parameter would help evaluate myocardial viability, because it is a simpler index to derive.

Dobutamine Echocardiography

Dobutamine infusion was started at a low dose of 2.5 μg · kg⁻¹ · min⁻¹ and increased in 3-minute intervals to 5, 7.5, 10, 20, 30 and 40 μg · kg⁻¹ · min⁻¹. Image display and analysis of the response of dysfunctional segments to DE was performed as previously described. Segments with any contractile reserve during DE were dysfunctional segments to DE was performed as previously described.

Results

Patient Population

The patient population consisted of 20 patients (18 men) with a mean age of 65 years (range, 51 to 73 years) and a mean ejection fraction of 29% (range, 18% to 44%). Fifteen patients had symptoms of heart failure, 9 had a history of distant infarction (>6 months), and 11 had stable angina before surgery. Eighteen patients underwent DE and 16 had scintigraphic studies before revascularization. Complete revascularization was performed with a total of 1 to 4 grafts per patient, and none developed postoperative ischemic events. All patients underwent repeat 2D echocardiography, and 16 had repeat DE 3 to 4 months after surgery; no patient showed evidence of ischemia.

Of the 320 myocardial segments, 65 had normal function at baseline and 255 were dysfunctional (11 were mildly hypokinetic, 129 were severely hypokinetic, 112 were akinetic, and 3 were dyskinetic). Ninety-six abnormal segments (60 hypokinetic and 36 akinetic) recovered function after revascularization (38%).

Relation of MCE With Resting Ventricular Function

Qualitative MCE assessment was feasible in 80% of segments, whereas quantitative MCE was feasible in 74%. Inability to evaluate myocardial perfusion was predominantly seen in basilar segments, mostly because of attenuation. All MCE indexes, including peak MCI, MCI at 1:8, normalized MCI (at peak or 1:8 gating), β, and peak MCI×β decreased with worsening myocardial function (P<0.001 by ANOVA; Figure 1). Similar findings were observed with Tl²⁰¹ uptake, particularly when compared with normalized MCI.

Quantitative MCE, Qualitative MCE, and Recovery of Ventricular Function

Quantitative MCE parameters were highest in normal segments, intermediate in dysfunctional segments that recovered function after revascularization, and lowest in segments without recovery (Table 1). Overall, the value of peak MCI was 1 to 5 dB higher than MCI at 1:8 pulsing interval. However, when normalized, peak MCI and MCI at 1:8 gating yielded almost identical results (Table 1). Thus, normalized peak MCI will be used hereafter in the article. Receiver-operator characteristic curves were generated to assess the prediction of recovery of function for the different MCE parameters. The area under the curve was lowest (0.64) for peak MCI, increased to 0.77 when MCI was normalized (peak or at 1:8 gating), was 0.79 for β, and was highest (0.83) for peak MCI×β. Using the receiver-operator characteristic curves, the best cutoff points for the different parameters were assessed to give a high sensitivity and acceptable specificity, because this is preferable clinically (Table 2). Although the accuracy of peak MCI×β was the highest, there was no statistical difference among the different quantitative MCE parameters. In akinetic segments, the sensitivity for predicting recovery of function was slightly lower, with a higher specificity (Table 2). Prediction of recovery by coronary territory using peak MCI×β revealed a sensitivity and specificity of 90% and 72%, respectively, for the left anterior descending coronary artery and 89% and 51%, respectively.
for right or circumflex coronary artery distribution (non-left anterior descending artery; \(P=\text{NS}\)).

Recovery of function after revascularization was observed in 53% of segments with normal perfusion and in 27% with patchy perfusion, but it was only seen in 5% of segments without perfusion by MCE \((P<0.001)\). The sensitivity and specificity of qualitative homogeneous MCE to detect recovery of function was 81% and 49%, respectively. When any contrast enhancement was used as criterion for perfusion, the sensitivity rose to 99%, with a drop in specificity to 14% \((P<0.001)\). Overall, the accuracy of quantitative parameters in predicting recovery of function was higher than qualitative MCE parameters.

Quantitative MCE Versus Contractile Reserve
Quantitative MCE and contractile reserve before revascularization were evaluated in 169 dysfunctional segments, of which 98 had contractile reserve and 71 did not. All MCE parameters were significantly higher in segments with contractile reserve compared with those without \((P<0.001)\). Of the 71 dysfunctional segments that did not have contractile reserve before surgery, 15 recovered resting function and contractile reserve, 14 recovered contractile reserve only, and the remaining had no improvement in either rest function or contractile reserve. Normalized peak MCI, \(\beta\), and peak MCI×\(\beta\) were highest in segments without contractile reserve at baseline that recovered rest and contractile function, intermediate in segments that recovered contractile reserve only, and lowest in segments without any change in function \((P<0.001)\).

Relation of Quantitative MCE to Tl201 Uptake
In viable segments by Tl201, the mean thallium uptake was 73±9% compared with 50±9% in nonviable segments \((P<0.001)\). Normalized peak MCI was higher in segments deemed viable by Tl201 compared with those without viability.

### Table 1. Quantitative Myocardial Contrast Echocardiographic Parameters in Normal and Dysfunctional Segments With and Without Recovery of Rest Function After Revascularization

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Resting Function</th>
<th>Abnormal Resting Function</th>
<th>Recovery</th>
<th>No Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak MCI, dB</td>
<td>18 (15–21)</td>
<td>14 (12–17)</td>
<td>12 (9–14)*†</td>
<td></td>
</tr>
<tr>
<td>MCI at 1:8 gating, dB</td>
<td>17 (13–20)</td>
<td>12 (10–15)*</td>
<td>9 (7–11)*†</td>
<td></td>
</tr>
<tr>
<td>Normalized peak MCI</td>
<td>0.76 (0.67–0.9)</td>
<td>0.79 (0.7–0.93)</td>
<td>0.60 (0.43–0.75)*†</td>
<td></td>
</tr>
<tr>
<td>Normalized MCI (1:8)</td>
<td>0.80 (0.69–0.94)</td>
<td>0.80 (0.71–0.86)</td>
<td>0.56 (0.43–0.74)*†</td>
<td></td>
</tr>
<tr>
<td>(\beta), s(^{-1})</td>
<td>0.35 (0.18–0.82)</td>
<td>0.36 (0.21–0.59)</td>
<td>0.08 (0.03–0.18)*†</td>
<td></td>
</tr>
<tr>
<td>Peak MCI×(\beta), dB/s</td>
<td>6.8 (3.2–15.9)</td>
<td>4.7 (2.5–7.9)</td>
<td>1.0 (0.4–2.3)*†</td>
<td></td>
</tr>
</tbody>
</table>

Values are median (first and third quartiles).

*\(P<0.05\) vs normal; †\(P<0.001\) vs recovery.
(0.74±0.17 versus 0.62±0.22; P<0.001). Similarly, β and peak MCI×β were higher in segments with viability by Ti201 scintigraphy compared with those without viability (median [first and third quartiles], β: 0.27 [0.1 to 0.5] versus 0.07 [0.02 to 0.2]; peak MCI×β: 2.8 [1.4 to 6.7] versus 0.84 [0.3 to 2.3]; both P<0.001). Modest correlations were found between percent thallium uptake and quantitative MCE parameters (normalized peak MCI: r=0.34, P<0.001; peak MCI×β: r=0.31, P<0.001).

Comparison of MCE, DE, and Ti201 in Predicting Recovery of Function

A high concordance was observed between assessment of viability in dysfunctional segments by MCE and Ti201 maximum uptake. Using the best MCE indicator (peak MCI×β), the concordance was 75%, with a κ of 0.46. The agreement with MCE for viability using a biphasic response during DE was 66% (κ, 0.35) and increased to 70% (κ, 0.4) when any contractile reserve was considered an indicator of viability.

### Table 2. Accuracy of Qualitative and Quantitative MCE in Predicting Recovery of Rest Function in All Dysfunctional Segments and in Akinetic Segments

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Segments</td>
<td>Akinetic Segments</td>
<td>All Segments</td>
<td>Akinetic Segments</td>
</tr>
<tr>
<td>Qualitative MCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any contrast enhance</td>
<td>99</td>
<td>97</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>81</td>
<td>53</td>
<td>49</td>
<td>67</td>
</tr>
<tr>
<td>Quantitative MCE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalized MCI at 1:8 gating ≥0.6</td>
<td>94*</td>
<td>93*</td>
<td>56</td>
<td>67</td>
</tr>
<tr>
<td>Normalized peak MCI ≥0.6</td>
<td>93*</td>
<td>93*</td>
<td>53</td>
<td>61</td>
</tr>
<tr>
<td>Peak MCI×β&gt;1.5</td>
<td>90</td>
<td>88*</td>
<td>63*</td>
<td>73</td>
</tr>
</tbody>
</table>

PPV indicates positive predictive value; NPV, negative predictive value. *P<0.05 vs qualitative MCE.

Figure 2. Myocardial contrast echo parameters in dysfunctional segments in relation to the presence (CR+) or absence (CR−) of contractile reserve during dobutamine before revascularization.
The sensitivity of quantitative MCE was comparable to any contractile reserve during DE and Ti201 and was higher than a biphasic response (Table 3 and Figure 4). The specificity of quantitative MCE was higher than qualitative MCE and Ti201, but lower than biphasic response during DE. When viability was considered as recovery of rest function or contractile reserve after revascularization, sensitivity with most modalities decreased slightly, with an increase in specificity for quantitative MCE and biphasic dobutamine response (sensitivity/specificity, qualitative MCE: 75%/49%; quantitative MCE, 82%/69%; Ti201, 83%/44%; dobutamine biphasic, 55%/94%; Dobutamine any improvement, 71%/52%, respectively).

**Analysis by Patients**

After bypass surgery, ejection fraction increased from 29±8% to 36±13% (P<0.03). A significant relation was seen between the change in ejection fraction and the number of viable segments by MCE (r=0.4 P<0.01). Of the 20 patients studied, 8 had a significant improvement (≥9%) in ejection fraction. All 8 patients had at least 3 viable segments by MCE and Ti201 and at least 2 viable segments by DE. Table 4 shows the sensitivity and specificity of the various methods for predicting an improved ejection fraction of ≥9% with increasing number of viable segments by the respective modality. The best predictive cutoff was lowest for biphasic response (2 segments) and was between 3 and 5 segments for the other modalities.

**Interobserver and Intraobserver Variability**

The interobserver variability for quantification of peak MCI and Ti201 was 8% and 17%, respectively. The intraobserver variability was 7% for quantification of peak MCI and 13% for β.

**Discussion**

The present study demonstrates that in patients with suspected myocardial hibernation, MCE performed with intravenous contrast can be used to evaluate viability. The accuracy of quantitative MCE is higher than qualitative interpretation. The product peak MCI×β, an index of myocardial blood flow, is the best parameter for predicting recovery of function. Quantitative assessment of resting perfusion with intravenous MCE has a similar sensitivity but higher specificity compared with Ti201 scintigraphy and improves the accuracy of DE in predicting recovery of function.
MCE and Myocardial Hibernation

Preservation of microvascular integrity has been associated with myocardial viability. In animal models using intracoronary or left atrial injection of contrast, peak MCI correlates with myocardial blood volume, whereas the rate of increase in contrast intensity is an index of myocardial blood velocity. Several studies have shown that MCE is effective in evaluating myocardial viability in patients after acute myocardial infarction. Fewer studies, however, have evaluated the role of MCE in myocardial hibernation. deFilippi et al and Nagueh et al showed the effectiveness of intracoronary MCE in predicting recovery of function in patients with suspected myocardial hibernation. Using maximal MCI and earlier technology, both studies demonstrated a high sensitivity and moderate specificity for predicting functional recovery. The predictive accuracy was similar to Tl201 scintigraphy. The findings of the present study, the first to use intravenous contrast to assess myocardial hibernation in comparison with available modalities, support these earlier observations and show that the new MCE parameters derived from intravenous contrast have the best accuracy to detect hibernating myocardium.

MCE and Contractile Reserve

Overall, peak MCI and myocardial blood flow were higher in dysfunctional segments with contractile reserve than those without. This observation supports previous studies showing dependence of contractile function on the level of myocardial blood flow at rest. However, similar to previous studies, 21% of dysfunctional segments without contractile reserve improved rest function after revascularization, and an additional 20% improved contractile reserve only. MCE indices of blood flow were, in general, preserved, particularly in the former group of myocardial segments. The reason for the lack of inotropic reserve at baseline in this setting thus cannot be explained by a major reduction in resting blood flow. Possible mechanisms include severe alteration in cardiomyocytes and the interstitium, impairment of myocardial blood flow reserve, or regional alteration in cardioinhibitory cytokines or adrenergic receptors. In these myocardial areas with reversible dysfunction, MCE improves the accuracy of DE in predicting recovery of function.

MCE and Tl201 Uptake

MCE indexes of myocardial blood volume and blood flow were higher in segments defined as viable by Tl201 compared with nonviable segments. Relative myocardial uptake of thallium is determined by capillary volume, myocardial blood flow, and myocardial function. Our results show a good concordance between normalized MCE and Tl201 uptake in relation to regional function. Although the correlations of

| TABLE 3. Accuracy of MCE, DE, and Rest-Redistribution Tl201 in Predicting Recovery of Rest Function After Revascularization |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | Sensitivity, %  | Specificity, %  | PPV, %          | NPV, %          |
|                  | All Segments    | Akinetic Segments | All Segments    | Akinetic Segments | All Segments    | Akinetic Segments |
| Qualitative MCE  | 81              | 53              | 49              | 67              | 53              | 47              |
| Homogeneous      |                 |                 |                 |                 |                 |                 |
| Quantitative MCE | 90              | 88†             | 63†             | 73              | 66†             | 68              |
| Peak MCI ×β1.5   |                 |                 |                 |                 |                 |                 |
| DE               | 63¶             | 58‡             | 87¶             | 89§             | 71§             | 65              |
| Biphasic response|                 |                 |                 |                 |                 |                 |
| Any improvement  | 80              | 69              | 54              | 78              | 47              | 53              |
| R-R Tl201 ≥60%   | 92              | 80              | 45              | 62              | 52              | 51              |

R-R indicates rest-redistribution.

*P<0.05 vs qualitative MCE and Tl201.
†P<0.05 vs qualitative MCE.
‡P<0.05 vs quantitative MCE.
¶P<0.05 vs qualitative MCE, Tl201, and DE any improvement.
§P<0.05 vs MCE, Tl201, and DE any improvement.
#P<0.05 vs MCE and Tl201.

Figure 4. Sensitivity and specificity of the different modalities to predict recovery of rest function after revascularization. Qual indicates qualitative; Quant, quantitative; Imp, improvement; and red, redistribution.
segmenetal Ti^{201} uptake to MCE indices were only modest, the concordance of viability between the 2 techniques was high. Better correlations were previously reported in the myocardial infarct setting. These discrepancies may be explained by the more pronounced regional differences in blood flow in the infarct setting and by other contributing factors that alter Ti^{201} uptake during chronic ischemia.

**Study Limitations**

Several factors can affect contrast intensity and the parameters derived from MCE. Care was taken not to alter the imaging parameters after the initial optimization period. Basilar segments with possible contrast attenuation or poor contrast signal were also avoided. Some discrepancy between echocardiographic and scintigraphic studies may be due to anatomic misalignment of segments, an inherent limitation of studies that attempt to compare different imaging modalities. Left ventricular remodeling, arrhythmia, or survival may improve in patients with viability by MCE, even without functional recovery. These end points need further evaluation in larger studies.

**Conclusions**

Quantitative MCE using intravenous injection of contrast can assess the presence of hibernating myocardium in humans. The product peak MCI/β, an index of myocardial blood flow, is the best parameter for predicting recovery of function, has a similar sensitivity to but higher specificity than Ti^{201} scintigraphy, and improves the accuracy of DE in predicting recovery of function.

**Acknowledgments**

Supported by a grant from the John S. Dunn, Sr, Trust Fund. Dr Shimoni is the recipient of a Research Fellowship Award from the American Society of Echocardiography. The authors thank Jo Ann Rabb for her expert help in preparing this manuscript.

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Circulation. 2003;107:538-544; originally published online January 13, 2003;
doi: 10.1161/01.CIR.0000047211.53448.12
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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