Low-Dose Dobutamine Echocardiography Detects Reversible Dysfunction After Thrombolytic Therapy of Acute Myocardial Infarction

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Background. Dysfunction after thrombolytic therapy of acute myocardial infarction (MI) may be reversible. Early after myocardial infarction, both reversible and irreversible injury may be manifested by regional wall motion abnormalities. Improved wall thickening during dobutamine infusion (dobutamine-responsive wall motion) may accurately identify reversibly injured segments.

Methods and Results. To determine whether dobutamine-responsive wall motion accurately detects reversible postischemic dysfunction irrespective of infarct location, multistage (baseline, 4 and 12 μg·kg⁻¹·min⁻¹, and peak) dobutamine echocardiography (DE) was performed within 7 days of thrombolytic therapy. Resting echocardiography was repeated ≥4 weeks after MI, and reversible dysfunction was defined as improved wall motion. The accuracy of dobutamine-responsive wall motion was compared with that of signs of early reperfusion, non-Q-wave MI, and peak creatine kinase (CK). Sixty-three patients underwent DE without complications. Follow-up echocardiograms were done in 51 (81%) of these patients, and wall motion improved in 22 (41%). Dobutamine-responsive wall motion during all stages of DE was very specific for reversible dysfunction (90% to 93%) but sensitive (86%) only when hemodynamics were not altered (low dose, 4 μg·kg⁻¹·min⁻¹). Non-Q-wave MI and a low peak CK (<1000 IU/mL) were also specific (89% to 93%) but less sensitive (64% [P=.16] and 55% [P<.05], respectively). Signs of early reperfusion did not identify postischemic dysfunction. Low-dose dobutamine-responsive wall motion and non-Q-wave MI independently identified reversible dysfunction, but only dobutamine-responsive wall motion was sensitive in all infarct locations. Non-Q-wave MI was sensitive only in anterior infarction.

Conclusions. Multistage dobutamine echocardiography can be performed safely early after thrombolytic therapy. Low-dose dobutamine-responsive wall motion accurately detected reversible dysfunction in all infarct locations. Dobutamine-responsive wall motion and non-Q-wave infarction may be very useful for accurately identifying reversible dysfunction early after thrombolytic therapy for acute MI. (Circulation 1993;88:405-415)

Key Words • myocardium • inotropic agents • myocardial contraction • reperfusion

Acute myocardial infarction results in regional wall motion abnormalities that can be reversible or fixed depending on collateral blood flow during coronary occlusion, the timing of reperfusion, and the magnitude of blood flow after reperfusion.¹,² Thrombolytic therapy increases the probability of early reperfusion and may increase the probability of reversible dysfunction.³

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Early after myocardial infarction, it may be difficult to differentiate reversible from fixed dysfunction. Serial echocardiograms after thrombolytic therapy have shown that areas of reversible dysfunction may not recover for days to weeks.⁴ Since prognosis correlates with ventricular function after myocardial infarction,⁵ early and accurate identification of reversible dysfunction may be very helpful for patient management.

In animal models, β-adrenergic stimulation improves contraction in areas of reversible postischemic dysfunction, whereas infarcted areas remain unchanged.⁶,⁷ Dobutamine may also cause myocardial function to deteriorate when myocardial work load is increased in segments with restricted coronary flow.⁸ Patients admitted for thrombolytic therapy of acute myocardial infarction have a high prevalence of coronary disease in the infarct zone.¹⁰ Thus, the dose of dobutamine and the related hemodynamic
alterations may alter the sensitivity of dobutamine echocardiography (DE) for reversible dysfunction after thrombolytic therapy for myocardial infarction.11 Two studies demonstrated that improved wall motion during dobutamine infusion may detect reversible dysfunction after anterior myocardial infarction.12,13 Neither study investigated (1) the optimal dose for increasing wall thickening in regions of reversible dysfunction after myocardial infarction; (2) the specificity of dobutamine-responsive wall motion for reversible dysfunction; (3) the sensitivity of dobutamine-responsive wall motion for reversible dysfunction in inferior, posterior, or lateral infarction; (4) the accuracy of dobutamine-responsive wall motion in patients who were not revascularized; or (5) the potential clinical role for DE in the identification of reversible dysfunction after thrombolytic therapy for acute myocardial infarction.

In the present study, all patients admitted for thrombolytic therapy of acute myocardial infarction irrespective of location were eligible for participation. Reversible dysfunction was defined by improved infarct zone wall motion on follow-up echocardiogram.14 We hypothesized that (1) dobutamine-responsive wall motion will specifically identify reversible postischemic dysfunction irrespective of infarct location and early revascularization, (2) the sensitivity of dobutamine-responsive wall motion for reversible dysfunction will be maximized by infusing doses that do not alter hemodynamics, and (3) DE will complement clinical and angiographic data to more accurately identify reversible dysfunction after thrombolytic therapy of acute myocardial infarction.

Methods

Patient Selection

Between February 1989 and February 1991, 121 patients treated with thrombolytic therapy for acute myocardial infarction were admitted to Indiana University Hospitals. Inclusion criteria were informed consent, prolonged chest pain, peak creatine kinase (CK) >2 SD above normal, ≥1.0 mm ST segment elevation in two or more leads on the initial ECG, and a wall motion abnormality on a baseline two-dimensional echocardiogram. Patients with (1) anterior, inferior, posterior, or lateral infarction; (2) Q-wave or non-Q-wave infarction; and (3) first or recurrent infarction were eligible.

Exclusion criteria were technically difficult echocardiogram, significant valvular disease, referral >7 days after thrombolytic therapy, revascularization before DE, postinfarction angina or infarction complicated by severe hemodynamic instability, uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg), sustained ventricular tachycardia or ventricular fibrillation occurring >24 hours after admission, pregnancy, or history of adverse reaction to dobutamine.

During screening for the study, a detailed history and physical examination were performed, focusing on complications, infarct location, infarction type (Q-wave or non-Q-wave), peak CK, time to peak CK, and time to resolution of chest pain and ST elevation.

Dobutamine Echocardiography

DE was performed between 2 and 7 days after infarction. Patients were positioned in the left lateral decubitus position. Baseline echocardiographic images were obtained with commercially available equipment. The minimum duration of each stage of the infusion was 5 minutes.9 The stages of the protocol were baseline, 4 μg·kg⁻¹·min⁻¹ (low dose), 12 μg·kg⁻¹·min⁻¹ (intermediate dose), and peak dose. Blood pressure and heart rate were recorded at the end of each stage.

The purpose of the peak dose stage was to evaluate patients for inducible ischemia. The end points for the peak dose stage were a dose of 20 μg·kg⁻¹·min⁻¹ for the first 15 patients and 40 μg·kg⁻¹·min⁻¹ for the remaining patients, a heart rate of 130 beats per minute, >2 mm of additional ST segment elevation or depression, angina, significant side effects, new wall motion abnormality, hypertension (systolic blood pressure >220 mm Hg), hypotension (fall in systolic blood pressure of ≥10 mm Hg compared with baseline), ventricular arrhythmia (≥4 consecutive premature ventricular contractions), or sustained supraventricular tachyarrhythmia.15 Patients who developed clinical ischemia were treated with sublingual nitroglycerin and/or esmolol at the investigator’s discretion.16 After the test, the patient was observed with continuous ECG monitoring for an additional 15 minutes.

A Prevue III (Nova-Microsonics, Inc, Mahwah, NJ) acquisition system was used to digitize the images on-line with an ECG R-wave–triggered mechanism according to the previously reported protocol.15 DE images were arranged in a quad screen, continuous loop display so that the baseline, low, intermediate, and peak dose images of each of the four standard views were displayed simultaneously. The completed studies were transferred to 5.25-in floppy disks for permanent storage.

Electrocardiography

Three bipolar leads (CC₅, CM₅, and modified lead II) or the standard 12 leads were monitored during DE. The ECG response was graded as normal, ischemic, or nondiagnostic by an investigator who was blinded to the clinical, echocardiographic, and angiographic data. The criterion for an ischemic response was the development of ≥1.5 mm of additional ST segment elevation or depression during dobutamine infusion.

Coronary Angiography

Coronary cineangiograms were performed by Judkins’ technique. All coronary stenoses were evaluated by a blinded investigator. The infarct artery was identified as the left anterior descending (LAD) or its branches for anterior infarctions and the left circumflex (LCx), right coronary (RCA), or their respective branches for inferior, posterior, or lateral infarctions. The culprit lesion was identified by angiographic criteria for thrombus and/or stenosis severity. The frame and view with the smallest luminal diameter were identified. Percent luminal diameter stenosis was derived by the caliper technique, comparing the diameter of the stenosis with that of the most normal-appearing region proximal to the stenosis. Coronary blood flow was analyzed by Thrombolysis in Myocardial Infarction trial (TIMI) grade. TIMI grade 0 or 1 flow was defined as an occluded artery and grade 2 or 3 as a patent artery.17 Significant lesions were defined as ≥70% diameter stenosis of an epicardial coronary artery or major branch vessel. The decision to perform percutaneous
A. ANT Myocardial Infarction

B. IPL Myocardial Infarction

**FIG 1.** Diagram of infarct zone in patients according to anterior (ANT) (panel A) and inferior, posterior, or lateral (IPL) (panel B) infarct location. LAX, long axis; SAX PM, short axis at papillary muscle level; 4C, four chamber; 2C, two chamber; Sept, septal; Post, posterior; Lat, lateral; Inf, inferior.

transluminal coronary angioplasty (PTCA) or bypass surgery was made by the patient’s private cardiologist without knowledge of the study results.

**Follow-up Two-dimensional Echocardiography**

Follow-up echocardiograms were performed a minimum of 4 weeks after thrombolytic therapy or revascularization.\(^\text{18,19}\) Echocardiographic images were digitized and were stored in the previously described quad screen, continuous loop format.\(^\text{14}\)

**Echocardiogram Analysis**

All interpreters were blinded to the clinical and study data. Two investigators analyzed the digitized baseline and follow-up echocardiograms. Baseline images from the DE were used to assess the initial extent of left ventricular (LV) dysfunction.\(^\text{18}\) Then, follow-up images were paired with the corresponding baseline images and directly compared.

Two other investigators analyzed each stage of digitized DE images by direct comparison with baseline and preceding stages. Digitized DE images were arranged in a quad screen format so that the baseline, low dose, intermediate dose, and peak dose images of each view were simultaneously displayed in the left upper, right upper, right lower, and left lower quadrants, respectively. Videotape recordings were not routinely used for analysis but were made available to the interpreters.

The LV was divided into 16 segments.\(^\text{15}\) The previously described semiquantitative scoring system (1, normal; 2, hypokinesis; 3, akinesis; 4, dyskinesis) was used to analyze each study.\(^\text{14}\) Normal wall motion was defined as ≥5 mm of endocardial excursion and systolic wall thickening. Hypokinesis was defined as <5 mm of endocardial excursion and reduced thickening. Akinesis was defined as near absence of endocardial excursion or thickening. Dyskinesis was defined as paradoxical endocardial excursion away from the lumen of the left ventricle or systolic wall thinning.

Infarct zones were constructed according to theoretical maximal risk area rather than the extent of dysfunction (see Fig 1).\(^\text{15}\) The apical inferior and apical lateral segments were overlap segments, since these segments can be perfused by anterior (LAD) or posterior (LCx or RCA) arteries. The infarct zone for both anterior and inferior, posterior, or lateral infarction consisted of nine segments. The anterior infarct zone was used to analyze infarctions with ST elevation in precordial leads V\(_1\) through V\(_4\) and inferior, posterior, or lateral if ST elevation did not occur in leads V\(_1\) through V\(_4\).

Global and regional infarct zone wall motion score indices (WMSI) were calculated for all stages of DE and follow-up two-dimensional echocardiograms. In addition, the extent of dysfunction was derived from the percentage of infarct zone segments with normal wall motion. WMSI was derived by the standard formula:

\[
\text{WMSI} = \frac{\text{sum of the segment scores}}{\text{no. of segments scored}}
\]

A WMSI of 1.00 indicated normal wall motion. Infarct zone indices of 1.00 to 1.49, 1.5 to 1.99, and ≥2.00 were indicative of mild, moderate, and severe dysfunction, respectively. Inadequately visualized segments were not scored. An individual study was defined as technically difficult if more than two segments of the infarct zone could not be visualized.
Improved segmental wall motion during DE or at follow-up was defined as (1) endocardial excursion and wall thickening (score 1 or 2) in areas of akinesis or dyskinesis (score 3 or 4) at baseline or (2) normalization (score 1) of endocardial excursion and wall thickening in areas of hypokinesis (score 2) at baseline. A change from dyskinesis (score 4) to akinesis (score 3) was considered to be unchanged segmental wall motion.

Reversible dysfunction was defined as improved wall motion in more than two contiguous infarct zone segments at follow-up and a decrease of >0.22 in infarct zone WMSI. All other possibilities were defined as fixed dysfunction.

Dobutamine-responsive infarct zone wall motion at any stage of DE was defined as improved contraction in more than two contiguous segments of the infarct zone compared with baseline and a decrease of >0.22 in infarct zone WMSI. All other possibilities were defined as dobutamine-unresponsive infarct zone wall motion.

Statistical Methods

Continuous data were expressed as mean±SD. Continuous clinical, echocardiographic, and catheterization data were compared by one-way ANOVA and the Bonferroni-corrected t test to test the significance of different pairs of mean values. Repeated-measures ANOVA and the Bonferroni-corrected t test were used to analyze changes in hemodynamics and regional wall motion during DE. χ² analysis or Fisher's Exact Test was used to compare categorical clinical, echocardiographic, and angiographic data. Multiple logistic regression analysis was used to determine independent indicators of reversible postischemic dysfunction. Statistical significance was defined as P≤.05.

Results

Patient Data

We enrolled 63 (52%) of the 121 patients admitted to Indiana University hospitals for thrombolytic therapy of acute myocardial infarction. Twenty-one patients (18%) were ineligible because of complications. Thirty-three patients (27%) were eligible, but either the patient or private cardiologist did not consent. Four patients (3%) were excluded because of technically inadequate images.

The 63 enrolled patients included 54 men and 9 women. The mean age was 54±11 years. Medical treatment included β-blockers in 30 patients and calcium channel blockers in 15. Pulmonary congestion within the first 24 hours and a pericardial rub occurred in 14 and 6 patients, respectively. Chest pain recurred before hospital discharge in 15 patients, but only one had a secondary increase in CK. Twenty-seven patients had anterior and 36 inferior, posterior, or lateral infarction. Q-wave infarction occurred in 39 and non-Q-wave in 24 patients. The mean peak CK was 2289±1628 IU/mL. Thirty-seven patients were treated with tissue plasminogen activator, 25 with streptokinase, and 1 with anistreplase plasminogen streptokinase activator complex. The mean interval from onset of chest pain to thrombolysis was 2.6±1.3 hours. CK peaked within 16 hours of pain in 42 patients, chest pain resolved within 12 hours in 41, and ST elevation resolved within 16 hours in 21.

Follow-up echocardiograms were obtained in 51 (81%) of the 63 patients, and only 4 (<10%) had been readmitted for recurrent ischemia before that study. The reasons why the other 12 patients did not have follow-up echocardiograms were death (2) and failure (7) or inability (3) to return to the medical center. There were no differences between these 12 patients and the 51 patients with follow-up echocardiograms. The mean peak CK and baseline infarct zone WMSI were similar, as were the numbers with dobutamine-responsive infarct zone wall motion (2), peak CK <1000 IU/mL (5), and non-Q-wave infarction (6). Four of the 12 underwent PTCA or bypass surgery before discharge.

Baseline and Follow-up

Two-dimensional Echocardiograms

All baseline and follow-up echocardiograms were interpreted by two echocardiographers in a blinded manner. The two observers agreed on the location of the wall motion abnormality in 98% of the baseline studies (62/63). The two observers agreed on the extent of the wall motion abnormality (±1 segment) in 92% (58/63). Intraobserver variability was assessed in one reader. The location of the wall motion abnormality and the number of segments (±1) scored as abnormal (score of ±2) were similar in 94% (60/63).

Interobserver and intraobserver variabilities were also assessed on the follow-up echocardiograms. The two echocardiographers concordantly scored 94% (48/51) of the follow-up echocardiograms as being improved or unchanged. The number of segments with improved wall motion was similar (±1) in 90% (46/51). Intraobserver variability was again assessed in one reader. Ninety-four percent (48/51) of the studies were scored as being qualitatively improved or unchanged. The number of segments with improved wall motion was again similar (±1) in 90% (46/51) of the patients.

Follow-up echocardiograms were performed 2±1 months after infarction. Fig 2 is a plot of baseline and follow-up infarct zone WMSI of these 51 patients. Overall mean infarct zone WMSI decreased (P<.01) from baseline to follow-up because 22 (41%) of the
TABLE 1. Echocardiographic Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n=22)</th>
<th>Group 2 (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL WMSI</td>
<td>1.56±0.28</td>
<td>1.71±0.30</td>
</tr>
<tr>
<td>BL IZ WMSI</td>
<td>1.85±0.38</td>
<td>2.10±0.38*</td>
</tr>
<tr>
<td>ANT MI</td>
<td>1.91±0.48</td>
<td>2.37±0.33*</td>
</tr>
<tr>
<td>IPL MI</td>
<td>1.78±0.25</td>
<td>1.92±0.31</td>
</tr>
<tr>
<td>BL IZ WMSI&lt;2.00</td>
<td>14 (64)</td>
<td>10 (34)</td>
</tr>
<tr>
<td>% Normal muscle in IZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F/U WMSI</td>
<td>1.28±0.25†</td>
<td>1.71±0.30‡</td>
</tr>
<tr>
<td>F/U IZ WMSI</td>
<td>1.41±0.35†</td>
<td>2.12±0.40‡</td>
</tr>
<tr>
<td>F/U BL IZ WMSI</td>
<td>−0.43±0.14</td>
<td>0.01±0.12‡</td>
</tr>
<tr>
<td>% Normal muscle in IZ</td>
<td>71±22</td>
<td>32±21‡</td>
</tr>
</tbody>
</table>

BL, baseline; WMSI, wall motion score index; IZ, infarct zone; ANT, anterior; IPL, inferior, posterior, or lateral; MI, myocardial infarction; F/U, follow-up. Values are mean±SD or n (%).

*P<.05 vs group 1; †P<.01 vs BL; ‡P<.001 vs group 1.

patients had reversible dysfunction (>0.22 decrease in infarct zone WMSI). The 22 patients with reversible dysfunction will be identified as group 1 and consisted of 11 patients with anterior infarction and 11 with inferior, posterior, or lateral infarction. The 29 patients with fixed dysfunction will be identified as group 2 and consisted of 12 with anterior infarction and 17 with inferior, posterior, or lateral infarction. In group 1 (see Table 1), the percentage of infarct zone segments with normal wall motion markedly increased (P<.01 versus baseline), and mean infarct zone WMSI markedly decreased (P<.01 versus baseline), whereas there were no changes in group 2.

The baseline echocardiogram was different in patients with reversible dysfunction. Baseline mean infarct zone WMSI was lower (P<.05) in group 1, but the prevalence of mild to moderate infarct zone dysfunction (infarct zone WMSI <2.00) was similar in groups 1 and 2. The baseline echocardiogram did not differentiate group 1 from group 2 because the prevalence of mild to moderate dysfunction was too low in anterior infarction and too high in inferior, posterior, or lateral infarction.

**Coronary Angiography**

Forty-nine of the patients with follow-up echocardiograms underwent coronary angiography, including 21 of the 22 group 1 and 28 of the 29 group 2 patients. Coronary angiography was performed within 3 days of the baseline echocardiograms in all patients. The culprit lesion was in the LAD territory in 23, the LCx territory in 7, and the RCA territory in 19. Thirty-two patients had single-vessel coronary artery disease. Three had two-vessel coronary artery disease involving the RCA and LCx territories. Nine patients had two-vessel coronary artery disease involving both the LAD and RCA/LCx territories. Five patients had three-vessel coronary artery disease. Angiographic data failed to differentiate group 1 from group 2. The mean residual stenoses of the infarct artery were 74±25% and 77±23%, respectively. The infarct artery was patent in 19 (90%) and 21 patients (75%, P=NS), respectively. A significant residual stenosis of the infarct artery remained in 17 (81%) and 20 patients (71%, P=NS), respectively.

Thirteen group 1 (59%) and 9 group 2 (31%) patients (P=NS) were revascularized before hospital discharge.

Sixteen patients underwent PTCA of the infarct artery, and 6 patients underwent coronary artery bypass surgery. PTCA was successful in 15 of 16 patients. In one patient, PTCA of the LAD was complicated by acute pulmonary edema and a secondary increase in CK. All coronary bypass operations were uncomplicated. The clinical data of the 22 patients who were revascularized were very similar to those of the 29 who were not. Peak CK was similar (2477±1700 versus 2260±1704 IU/mL), along with the prevalence of non-Q-wave infarction (8 versus 10) and the incidence of recurrent chest pain before discharge (5 versus 5). The only difference was that fewer (P=.05) revascularized patients were treated with β-adrenergic blocker therapy (6 versus 17).

Patients were revascularized on the basis of angiographic factors alone. Only 1 of the 10 patients with infarct artery occlusion was revascularized. All 9 patients with residual stenosis between 90% and 99% were revascularized. Only 11 of the 20 patients with residual stenosis between 70% and 89% were revascularized. Only 1 of the 10 patients without residual stenosis was revascularized. The patient had multivessel coronary artery disease and underwent coronary bypass surgery.

Residual stenosis and revascularization had only a minor effect on the incidence of reversible dysfunction. In the 10 patients without residual stenosis, reversible dysfunction occurred in 4. The one who was revascularized had fixed dysfunction. In the 20 patients with residual stenosis between 70% and 89%, dysfunction was reversible in 10. Seven of the 11 who were revascularized and 3 of the 9 who were not revascularized (P=NS) demonstrated reversible dysfunction. Despite revascularization in all 9 of the patients with residual stenosis between 90% and 99%, only 5 demonstrated reversible dysfunction. In the 10 patients with occluded infarct arteries, only 2 demonstrated reversible dysfunction. One of the 2 patients was revascularized.

**Clinical Data**

Clinical data were remarkably similar in groups 1 and 2. The mean ages were 55±11 and 54±11 years, respectively. Similar numbers of patients had prior myocardial infarction (5 versus 5) and antecedent angina (8 versus 10). A vast majority of patients in each group were treated with aspirin, heparin, and nitrates. Eleven and 13 patients, respectively, were treated with β-adrenergic blockers. There were similar incidences of pulmonary congestion during the first 24 hours (3 versus 9) and chest pain before hospital discharge (2 versus 8). A secondary increase in CK occurred in only 1 patient.

Signs of early reperfusion did not differentiate group 1 from group 2 (see Table 2), but signs of reduced infarct size were much more common in group 1. Mean peak CK was markedly (P<.001) lower. The prevalences of low peak CK (<1000 IU/mL) and non-Q-wave infarction were much (P<.01) higher in group 1.

The sensitivities of non-Q-wave infarction and peak CK <1000 IU/mL for reversible dysfunction were 64% (14/22) and 55% (12/22), respectively. Both criteria were very specific at 86% (25/29) and 90% (26/29), respectively. Non-Q-wave infarction and peak CK <1000 IU/mL were sensitive only in anterior infarction (91% [10/11] and 73% [8/11], respectively). Specificity was 92% (11/12) for both markers. In the 28 patients with inferior, posterior, or lateral infarction, specificities...
TABLE 2. Clinical Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n=22)</th>
<th>Group 2 (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak CK</td>
<td>1392±1091</td>
<td>3112±1702*</td>
</tr>
<tr>
<td>Peak CK &lt;1000 IU/mL</td>
<td>12 (55)</td>
<td>3 (10)*</td>
</tr>
<tr>
<td>Non-Q-wave MI</td>
<td>14 (64)</td>
<td>4 (14)*</td>
</tr>
<tr>
<td>Interval to thrombolysis (hrs)</td>
<td>2.6±1.4</td>
<td>2.7±1.3</td>
</tr>
<tr>
<td>Peak CK &lt;16 hrs</td>
<td>15 (68)</td>
<td>21 (72)</td>
</tr>
<tr>
<td>Resolution CP &lt;12 hrs</td>
<td>15 (68)</td>
<td>17 (59)</td>
</tr>
<tr>
<td>Resolution ST Elev &lt;16 hrs</td>
<td>8 (36)</td>
<td>9 (31)</td>
</tr>
</tbody>
</table>

CK: creatine kinase; MI: myocardial infarction; CP: chest pain; ST, ST segment; Elev, elevation. Values are mean±SD or n (%). *P<.01 vs group 1; †P<.01 vs group 1.

were 82% (14/17) and 88% (15/17), respectively, but sensitivities were lower (P<.05 versus anterior) at 36% (4/11) for both markers.

Revascularization did not affect the accuracy of non-Q-wave infarction and a peak CK <1000 IU/mL for reversible dysfunction. In group 1, non-Q-wave infarction and a peak CK <1000 IU/mL occurred in 7 (78%) and 5 (56%), respectively, of the 9 group 1 patients who were not revascularized and 7 (54%) and 7 (54%), respectively, of the 13 who were revascularized. In group 2, non-Q-wave infarction and a peak CK <1000 IU/mL occurred in only 3 (15%) and 3 (15%), respectively, of the 20 who were not revascularized and only 1 (11%) and 0 (0%), respectively, of the 9 who were revascularized.

Dobutamine Infusion

The interval from myocardial infarction to DE was 5±2 days (range, 2 to 7 days). The mean dose of the peak stage or stress portion of the protocol was 23±10 μg·kg⁻¹·min⁻¹ (range, 12 to 40 μg·kg⁻¹·min⁻¹). End points for this stage were anginal chest pain in 7, an induced wall motion abnormality in the noninfarct zone in 12, maximum dose in 10, heart rate >130 in 8, severe nausea in 1, accelerated junctional rhythm in 3, ST elevation in 16, and ST depression in 6. There were no episodes of unstable supraventricular arrhythmias or ventricular tachycardia or fibrillation. Typical angina occurred in 7 patients, but rapidly resolved with sublingual nitroglycerin (2) or esmolol (5). The mean peak dose of dobutamine was 22±10 μg·kg⁻¹·min⁻¹ in group 1 and 24±10 μg·kg⁻¹·min⁻¹ in group 2 (P=NS). ST segment elevation or depression occurred in 12 group 1 patients (55%) and 18 group 2 patients (62%; P=NS).

Dobutamine Echocardiogram Interpretation

Intraobserver and interobserver variabilities were also assessed for the low-dose stage of the DEs. The two echocardiographers concordantly scored 92% (58/63) of the studies as having dobutamine-responsive or unreversible wall motion. The number of segments with improved wall motion was also similar (±1) in 89% (56/63) of the patients. Intraobserver variability was also assessed in one reader. The studies were concordantly scored as dobutamine-responsive or unresponsive in 95% (60/63). The number of segments improving was similar (±1) in 92% (58/63) of the patients.

The DE results from groups 1 and 2 are compared in Table 4. During the low-dose stage, mean infarct zone WMSI markedly decreased (P<.01 versus baseline) and the percentage of infarct zone segments with normal wall motion markedly increased (P<.01 versus baseline). During the intermediate-dose stage, mean infarct zone WMSI remained lower (P<.01 versus baseline) and the percentage of infarct zone segments with normal wall motion higher (P<.01 versus baseline). In contrast, both mean infarct zone WMSI and the mean percentage of infarct zone segments with normal wall motion in group 2 remained unchanged (P=NS versus baseline) at all doses. At all stages of DE, mean infarct zone WMSI was lower (P<.01) and the mean percentage of infarct zone segments with normal wall motion greater (P<.01) in group 1 patients.

The main purpose of the peak-dose stage was to determine whether patients had inducible wall motion abnormalities. This stage was minimally useful for the detection of reversible dysfunction because infarct zone WMSI reverted to baseline values. Mean infarct zone WMSI was similar to baseline in group 1 and slightly higher than baseline in group 2 (see Table 3).

Fig 3 is a plot of infarct zone WMSI of groups 1 and 2 patients at baseline and at low dose. In group 1 patients, overall mean infarct zone WMSI markedly decreased from baseline to low dose, because 19 of the 22 had dobutamine-responsive wall motion. In contrast, overall mean infarct zone WMSI did not change in group 2 patients from baseline to low dose, because dobutamine-responsive wall motion occurred in only 3 of the 29.

The dose of dobutamine had a dramatic effect on the incidence of dobutamine-responsive wall motion in group 1 patients but did not alter the incidence in group 2 patients (see Table 3). In group 1, dobutamine-responsive infarct zone wall motion occurred in 19 patients (86%) at low dose, 12 (55%) at intermediate
Dose, and 8 (36%) at peak dose. All patients whose infarct zone wall motion deteriorated from low dose to intermediate dose or peak dose had >70% residual stenosis of the infarct artery. In contrast, dobutamine-responsive infarct zone wall motion occurred in 3 Group 2 patients (10%) at low dose, 2 (7%) at intermediate dose, and 3 (10%) at peak dose. Infarct zone wall motion in the three patients responding during low dose deteriorated at intermediate dose or peak dose. All three had >70% residual stenosis of the infarct artery. The three patients with dobutamine-responsive wall motion at peak dose differed from the three responding at low dose. Responding segments were located in the border instead of at the center of the infarct zone.

The sensitivities and specificities of the stages of DE for reversible dysfunction and the respective hemodynamics are listed in Table 4. The sensitivity of dobutamine-responsive infarct zone wall motion was significantly greater for the low dose stage than for the intermediate dose (P<.05) and peak dose (P<.01) stages. Dobutamine-responsive infarct zone wall motion was very specific for reversible dysfunction at all doses (P=NS). Alterations in hemodynamics impaired the sensitivity of dobutamine-responsive wall motion for reversible dysfunction but have no effect on specificity.

Dobutamine-responsive infarct zone wall motion during low-dose DE was superior to the other markers because patients with reversible dysfunction were identified irrespective of infarct location. In anterior infarction, the sensitivity and specificity were 73% (8/11) and 92% (11/12), respectively. In inferior, posterior, or lateral infarction, the sensitivity and specificity were similar at 100% (11/11) and 88% (15/17), respectively.

Revascularization did not alter the accuracy of dobutamine-responsive infarct zone wall motion during low-dose DE for reversible dysfunction. In group 1, dobutamine-responsive wall motion occurred in all 9 patients who were not revascularized and 10 of the 13 (77%) who were revascularized. In group 2, dobutamine-unresponsive wall motion occurred in only 1 (5%) of the 20 who were not revascularized and only 2 (22%) of the 9 who were revascularized.

Multiple Logistic Regression Analysis

Univariate indicators of reversible postischemic dysfunction after thrombolytic therapy for acute myocardial infarction were dobutamine-responsive wall motion at any dose, non-Q-wave infarction, and a peak CK <1000 IU/mL (see Table 5).

Multivariate analysis revealed that only dobutamine-responsive infarct zone wall motion during low-dose DE
and non-Q-wave infarction were independent indicators of reversible postischemic dysfunction. Dobutamine-responsive infarct zone wall motion during low-dose DE was the most accurate (88%, 45/51) indicator of reversible dysfunction. Although non-Q-wave infarction was not an effective criterion alone because of reduced accuracy in inferior, posterior, or lateral infarction (64% [18/28] versus 91% [21/23] in anterior infarction, P=.05), it was very complementary to low-dose DE. Ninety-two percent of the patients (47/51) were correctly identified by the following algorithm: (1) non-Q-wave infarction or dobutamine-responsive infarct zone wall motion during low-dose DE in anterior infarction and (2) dobutamine-responsive infarct zone wall motion during low-dose DE alone in inferior, posterior, or lateral infarction. The algorithm predicted reversible dysfunction in all 22 patients (22/22) in group 1 with a specificity of 86% (25/29).

**Discussion**

**Regional Function After Thrombolytic Therapy of Acute Myocardial Infarction**

Acute coronary occlusion is the cause of acute myocardial infarction. Collateral blood flow during coronary occlusion, the timing of reperfusion, and the magnitude of blood flow after reperfusion determine whether postischemic dysfunction is reversible or fixed. Thrombolytic therapy increases the probability of early reperfusion and may increase the probability of reversible dysfunction. During the acute phase, it may be difficult to differentiate reversible from fixed dysfunction. Several studies have shown that reversible postischemic dysfunction may not completely recover for weeks after reperfusion. Although global measurements have often failed to demonstrate time-dependent improvement in ventricular function after infarction, serial echocardiography has shown that regional dysfunction is reversible in up to 40% of patients treated with thrombolytic therapy. Echocardiography is most effective in evaluating regional function because both wall motion and wall thickening can be evaluated.

In this study, infarct zone wall motion improved at follow-up in 22 of 51 patients (43%). This percentage of patients with reversible dysfunction is compatible with previous studies. The group of patients with reversible postischemic dysfunction (group 1) was clearly different from those with fixed infarct zone dysfunction (group 2). Infarct size was smaller by peak CK and infarct zone WMSI and the prevalence of non-Q-wave infarction much higher.

**Indicators of Reversible Dysfunction in the Infarct Zone**

Non-Q-wave infarction and a low peak CK have been shown in previous studies to correlate with smaller infarct size. The correlation is strong in anterior infarction but weak in inferior, posterior, or lateral infarction. In this study, both non-Q-wave infarction and a peak CK <1000 IU/mL were very specific indicators of reversible dysfunction. Both markers identified the same patients and were limited by insensitivity in inferior, posterior, or lateral infarction.

The baseline echocardiogram did not differentiate reversible from fixed dysfunction. Although mean infarct zone WMSI was smaller in patients with reversible dysfunction, the prevalence of mild to moderate dysfunction (infarct zone WMSI <2.00) was too low in anterior infarction and too high in inferior, posterior, or lateral infarction to differentiate group 1 from group 2.

Multistage DE was performed as early as 2 days after thrombolytic therapy of acute myocardial infarction without complications. Unlike other imaging modalities, safety was maximized by convenient imaging in the coronary care unit, cardiac catheterization laboratory, or stress laboratory. Dobutamine-responsive wall motion was the most accurate indicator of reversible postischemic dysfunction. Dobutamine-responsive wall motion during any stage of DE was very specific for reversible dysfunction but was sensitive only at low dose.

The hemodynamic alterations produced by the higher doses of dobutamine probably caused the dose-related decrease in sensitivity. Intermediate and peak doses of dobutamine increased heart rate, systolic blood pressure, and double product. Heart rate, blood pressure, and double product have been shown to correlate with myocardial oxygen consumption. Animal studies have shown that wall thickening in dysfunctional myocardial regions lacking flow reserve will not increase during dobutamine infusion if oxygen demand increases. The study patients had the expected high prevalence (78%) of severe residual stenosis (≥70%) of the infarct artery. Thus, the increased myocardial oxygen demand of intermediate and peak doses of dobutamine probably caused many patients with reversible dysfunction and residual stenosis of the infarct artery to fail to respond to the inotropic effects.

Although univariate analysis revealed that dobutamine-responsive wall motion during all stages of DE, non-Q-wave infarction, and peak CK <1000 IU/mL indicated reversible dysfunction, only dobutamine-responsive wall motion during low dose and non-Q-wave infarction were independent indicators. The potential clinical utility of DE for identifying reversible dysfunction early after thrombolytic therapy was demonstrated by the finding that dobutamine-responsive wall motion during low dose identified reversible dysfunction irrespective of infarct location or classification (Q-wave or non-Q-wave).

Dobutamine-responsive wall motion did complement clinical data to enhance the identification of reversible postischemic dysfunction after thrombolytic therapy of acute myocardial infarction. Although non-Q-wave infarction or a low peak CK (<1000 IU/mL) identified 14 of the 22 patients with reversible dysfunction, the added wall motion data from low-dose DE in patients with
anterior Q-wave infarction and all patients with inferior, posterior, or lateral infarction resulted in identification of all of the patients (22/22) without altering specificity (86%).

Comparison With Previous Studies

Pierard et al.\textsuperscript{12} compared dobutamine echocardiography with positron emission tomography (PET) scanning for the detection of viable myocardium in 17 patients treated with thrombolytic therapy for acute anterior myocardial infarction. Their criteria for viable myocardium in the infarct zone were both improved wall motion and PET viability at 9±7 months after infarction. Echocardiographic images were stored only on videotape, and dobutamine was infused at 10 μg·kg\textsuperscript{-1}·min\textsuperscript{-1}. In subgroup 1, all five patients with dobutamine-responsive infarct zone wall motion and normal perfusion and glucose uptake by PET demonstrated normal uptake by PET and improved wall motion at follow-up. Interestingly, four of the five patients had non-Q-wave infarction. In subgroup 2, six patients demonstrated ischemia in the infarct zone by PET. Dobutamine-responsive wall motion occurred in five of the six. All patients had Q-wave infarction. At follow-up, one patient demonstrated both improved wall motion and PET viability. A second patient demonstrated improved wall motion without perfusion or glucose uptake by PET. A third demonstrated PET viability without improved wall motion. In subgroup 3, six patients demonstrated infarction by PET with dobutamine-unresponsive wall motion. All had Q-wave infarction. Wall motion was unchanged at follow-up in all six patients, but follow-up PET revealed perfusion and glucose uptake in two patients.

The authors concluded that persistent ischemia was the reason why the majority of the second subset of patients did not improve at follow-up. The data also imply that the metabolic viability detected by PET may not always indicate reversible dysfunction. In animal models, myocardial regions become incapable of functioning if a threshold percentage of transmural irreversible injury is exceeded.\textsuperscript{26} Thus, PET imaging may detect metabolic activity in regions incapable of functioning because of the extent of transmural infarction. Finally, analysis of videotaped echocardiographic images without direct comparison may have contributed to the discordant follow-up data.

Recently, Barilla et al.\textsuperscript{13} published a second study investigating the sensitivity of low-dose (5 to 10 μg·kg\textsuperscript{-1}·min\textsuperscript{-1}) DE for identification of viable myocardium after anterior myocardial infarction and prediction of the extent of improvement after revascularization. Inclusion criteria were non-Q-wave infarction or treatment with a thrombolytic agent. Exclusion criteria were prior Q-wave infarction or treatment with β-adrenergic or calcium channel blocking agents. Sixteen of the 21 patients enrolled had non-Q-wave infarction. Wall motion in the infarct zone improved during dobutamine infusion in all patients except one of the five patients with Q-wave infarction. Although the authors concluded that low-dose DE identified viability and predicted magnitude of recovery after revascularization, the study group was restricted to patients with small infarcts. Thus, the specificity of their findings was not assessed.

Although the data from both studies demonstrate that dobutamine-responsive wall motion may be sensitive for reversible posts ischemic dysfunction in anterior infarction, neither study determined (1) the optimal dose of dobutamine for stimulating reversibly dysfunctional myocardium, (2) the specificity of dobutamine-responsive wall motion for reversible dysfunction, (3) the accuracy of dobutamine-responsive wall motion for reversible dysfunction in inferior, posterior, or lateral infarction, (4) the accuracy of dobutamine-responsive wall motion for reversible dysfunction in patients who are not revascularized, or (5) the potential clinical role for DE in the identification of reversible dysfunction after thrombolytic therapy for acute myocardial infarction.

The data from this study focused on these five questions. Dobutamine-responsive wall motion was specific for reversible dysfunction at all doses but was sensitive only when hemodynamics were not altered. Dobutamine-responsive wall motion during low dose was equally accurate in detecting reversible dysfunction in anterior and inferior, posterior, or lateral infarction. As in the study of Barilla et al., dobutamine-responsive wall motion accurately (77%) predicted the extent of recovery in patients who were revascularized. Our data also demonstrated that dobutamine-responsive wall motion accurately (97%) predicted the extent of recovery in patients who were not revascularized. These data indicated that the segments responding to the inotropic effect of dobutamine were regions of reversible posts ischemic myocardial dysfunction.

In the important subgroup of patients with Q-wave anterior or inferior, posterior, or lateral infarction, dobutamine-responsive wall motion also accurately identified reversible dysfunction. Thus, low-dose DE enhanced the detection of reversible dysfunction after thrombolytic therapy of acute myocardial infarction.

The techniques of echocardiographic image acquisition and analysis used in this study may have contributed to the consistent accurate detection of reversible dysfunction by DE irrespective of infarct location. Online side-by-side digital acquisition may have ensured that the echocardiographic images to be compared were similar. Direct side-by-side comparison of images during analysis may have facilitated the evaluation of subtle changes in wall thickening or motion.\textsuperscript{27}

The techniques that have been used to identify viable myocardium after acute coronary occlusion and reperfusion include PET scanning,\textsuperscript{28,29} single-photon emission computed tomography (SPECT) \textsuperscript{30,31} TI scanning,\textsuperscript{28,29} and \textsuperscript{34}SPECT \textsuperscript{111}In anti-myosin antibody,\textsuperscript{32,33} and \textsuperscript{99m}Te-pyrophosphate scanning.\textsuperscript{34} PET scanning has become the gold standard for detecting metabolic viability. The data from Pierard et al.\textsuperscript{12} demonstrate that presence of metabolic activity may not always correlate with reversible dysfunction. Large direct comparative studies will be needed to define the cause of discordant results.

Study Limitations

Although treatment with β-adrenergic blockers may alter the response to dobutamine, the accuracy of dobutamine-responsive wall motion for reversible dysfunction was similar in patients treated or not treated with β-adrenergic blocker therapy. Since β-adrenergic blocker therapy reduces mortality after acute myocardial-
dial infarction, it would be unethical to withhold treatment with β-blockers.

The population was referral based, and enrollment in the study was dependent on the consent of the patient and primary physician. Exclusion of eligible patients because of nonconsent may introduce a bias. Nonconsent was a major cause of patient exclusion only before general acceptance of the protocol. Thus, the bias resulting from exclusion because of nonconsent was probably small. The bias of excluding patients with technically inadequate images was minimal. Although the results of this study may not be directly applicable to a primary care setting or echocardiographic laboratories without on-line digitizing equipment, the excellent safety profile warrants more widespread evaluation of the accuracy of DE for detecting reversible postischemic dysfunction.

Patient dropout and recurrent ischemia may reduce the detection of reversible postischemic dysfunction after myocardial infarction. Follow-up echocardiograms were obtained in 51 (81%) of the 63 patients who underwent DE. The rate of detection of reversible dysfunction was minimally altered by the dropout of these 12 patients because they were representative of the entire group. Clinical events indicative of recurrent ischemia were infrequent (<10%) before follow-up echocardiography. Thus, recurrent ischemic events probably did not reduce the detection of reversible dysfunction in the study patients.

Regional function was analyzed qualitatively. Since quantification of wall motion remains unperfected, qualitative analysis incorporating estimation of both wall thickening and motion remains the current standard, with minimal interobserver variability.

In this study, PET scanning for metabolic activity was not performed. Thus, any comparison of our results with PET data is inferential and limited by multiple uncontrollable biases. Only a large comparative study of PET and DE will determine whether metabolic activity by PET scanning is a more accurate and cost-effective marker of reversible dysfunction than dobutamine-responsive wall motion.

Conclusions

DE was safely performed early after thrombolytic therapy for acute myocardial infarction. Dobutamine-responsive wall motion at all doses was specific for reversible dysfunction but was sensitive only at low dose. The decrease in sensitivity at higher doses correlated with increases in heart rate and systolic blood pressure. The clinical parameters of non-Q-wave myocardial infarction and a low peak CK were specific but were sensitive only in anterior infarction. Only dobutamine-responsive wall motion during low-dose DE was sensitive in both anterior and inferior, posterior, or lateral infarction. Dobutamine-responsive wall motion was also accurate in patients who were and were not revascularized on the basis of angiographic criteria. Low-dose DE and the ECG (non-Q-wave myocardial infarction) may be very useful for early and accurate identification of reversible dysfunction after thrombolytic therapy for acute myocardial infarction.

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