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Dobutamine-Atropine Stress Echocardiography for Reversible Dysfunction During the First Week After Acute Myocardial Infarction: Limitations and Determinants of Accuracy

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Objectives. **We sought to compare the accuracy of biphasic and ischemic responses and sustained improvement for reversible dysfunction and to identify causes of false negative and false positive findings.**

Background. **Previous studies have shown that low dose dobutamine echocardiography was accurate for detecting reversible dysfunction after acute myocardial infarction (MI) but did not determine whether accuracy was improved by peak dose findings or influenced by the test interval or clinical or angiographic factors.**

Methods. **Dobutamine-atropine stress echocardiography (DASE) (baseline, low dose [5 and 10 μg/kg body weight per min] and peak dose) and coronary angiography were performed in 115 patients 2 to 7 days after MI (test interval). Segmental wall thickening was analyzed according to the 16-segment model. Sustained improvement and biphasic and ischemic responses included improved wall thickening at low and peak doses, improved wall thickening at the low dose with worsening at peak dose and no change in wall thickening at the low dose with worsening at peak dose, respectively. Follow-up echocardiography was performed at 4 to 8 weeks, and reversible dysfunction was defined as improved wall thickening.**

Results. **Wall thickening improved at follow-up in 305 (44%) of 688 dysfunctional segments. The test interval was 2 days in 16 patients, 3 days in 24, 4 days in 24, 5 days in 12, 6 days in 16 and 7 days in 23. No change at low and peak doses accurately predicted fixed dysfunction (318 [88%] of 360 segments), especially in akinetic and dyskinetic segments (276 [91%] of 303), irrespective of the test interval or clinical and angiographic factors. Ischemic segmental responses also predicted fixed dysfunction (63% [12 of 19 patients]), especially in medically treated compared with revascularized patients (100% [8 of 8] vs. 36% [4 of 11], $p = 0.013$). Both biphasic responses and sustained improvement (77% [179 of 231 segments] vs. 87% [84 of 97], $p = 0.082$) were highly predictive of reversible dysfunction, especially in akinetic segments, irrespective of the test interval or clinical and angiographic factors. The only limitation was reduced accuracy (77% [177 of 222 segments], $p < 0.001$) due to false positive results (16%) in hypokinetic segments.**

Conclusions. **No change and ischemic responses during DASE were specific for fixed dysfunction. Improved wall thickening at the low dose, irrespective of changes at peak dose, was highly predictive of reversible dysfunction. Accuracy was only limited by false positive results in hypokinetic segments and not by the test interval or clinical or angiographic factors.**

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Myocardial dysfunction resulting from acute myocardial infarction (MI) may be reversible or irreversible, depending on myocardial oxygen demand, collateral blood flow and the timing of reperfusion (1,2). Postischemic injury due to early reperfusion or high collateral blood flow is the major mechanism of reversible dysfunction. Recovery is often spontaneous and evolves over the first 4 to 6 weeks (1–5). The mechanism differs from patients with chronic left ventricular dysfunction, in whom 1) reduced coronary blood flow or repetitive ischemia is the major mediator, and 2) recovery occurs only after revascularization (6–10). The determinants of reversible dysfunction are well known in patients with chronic dysfunction (8–12), but clinical and angiographic factors, rest function and the timing of testing may also affect the detection and incidence of reversible dysfunction after acute MI (13).

Dobutamine-atropine stress echocardiography (DASE) is predictive of reversible dysfunction in both patients with acute MI and those with chronic left ventricular dysfunction due to coronary artery disease (14–20), but the predictive value of its multiple responses at low and peak doses is only known in the latter group. Ischemic and biphasic responses are predictive of reversible dysfunction, whereas sustained improvement at low and peak doses is predictive of fixed dysfunction (21). Previous studies have shown that no change and improved wall thickening at the low dose identified fixed and reversible dysfunction, respectively, early after acute MI, but did not 1) deter-

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Abbreviations and Acronyms

CK = creatine kinase
DASE = dobutamine-atropine stress echocardiography
MI = myocardial infarction
ROC = receiver operating characteristic

mine whether changes from low to peak dose improve predictive accuracy; 2) identify the causes of false positive and false negative results; or 3) evaluate whether accuracy was limited by its interval from the onset of acute MI (16–20).

The objectives of the present study of DASE early after acute MI were to 1) compare the predictive values of ischemic responses, biphasic responses and sustained improvement for reversible dysfunction; and 2) identify the causes of false negative and false positive results and the limitations of DASE. To investigate these aims, 115 patients underwent DASE and coronary angiography during the first week after acute MI and follow-up echocardiography 4 to 8 weeks later.

Methods

Patient selection. Between June 1992 and January 1995, 220 patients were admitted to the hospital for acute MI according to the criteria of prolonged chest pain, total creatine kinase (CK) and CK-MB >2 SD above normal and a wall motion abnormality. The study was approved by the Institutional Review Committee. Fifteen patients were excluded because testing was performed >7 days after infarction. Another 67 patients were excluded because of nonconsent (n = 25), technically poor images (n = 2), recurrent hemodynamic instability (n = 20), angina (n = 10) or sustained ventricular arrhythmias requiring intravenous medical therapy (n = 10). The 138 enrolled patients gave written, informed consent and underwent DASE. Twenty-three patients failed to return for follow-up echocardiography.

Dobutamine-atropine stress echocardiography. Patients were studied 2 to 7 days after acute MI with continuous 12-lead electrocardiographic monitoring. Medical therapy was not altered on the day of the test. Dobutamine was stepwise infused at 5, 10, 20, 30 and 40 μg/kg body weight per min (16–20,22). Atropine (0.2 to 0.4 mg every 2 min to a maximum of 2 mg) was infused to achieve peak heart rates >120 beats/min 1) if the heart rate was submaximal at maximal dobutamine, or 2) if cyclic variability in heart rate >10 beats/min, hyperdynamic wall motion (end-systolic left ventricular diameter (<1 cm) or nausea with retching occurred at submaximal doses of dobutamine. Imaging was started and blood pressure measured at 5 min of each stage (22). The dobutamine infusion was increased after imaging at 5 and 10 μg/kg per min and at 5 min thereafter. The stage duration was 5 to 9 min (average 7 min) for 5 and 10 μg/kg per min and 5 min thereafter.

End points for dobutamine infusion were maximal dose, heart rate ≥120 beats/min, limiting chest pain, headaches, nausea with vomiting, ≥2 mm ST segment depression without elevation compared with baseline in two or more leads, systolic blood pressure <90 or ≥240 mm HG, ventricular tachycardia (more than five complexes at cycle lengths <500 ms) or sustained supraventricular tachyarrhythmias (23). Intravenous esmolol (0.1 to 0.5 mg/kg every 2 min up to 1.5 mg/kg) or sublingual nitroglycerin (0.4 mg every 5 min up to three doses), or both, were administered after stopping the infusion if chest pain was severe or did not resolve within 4 min.

Images were digitized on-line with a TomTec R-wave–triggered system at baseline, 5 and 10 μg/kg per min and peak dose (22). Images were digitized from the parasternal long-axis and short-axis planes and apical four-chamber, two-chamber long-axis and short-axis planes and arranged in a quad screen, continuous loop format. Endocardial borders, including the apex, were visualized in all patients. All studies were graded as average or above average in image quality.

Dobutamine echocardiograms were interpreted by two investigators who had no knowledge of the clinical or angiographic data. All stages were directly compared. Videotape recordings were made available. Each stage was analyzed according to the previously described 16-segment model and scoring system (22). Inadequately visualized segments were not scored. Hypokinesia was defined as reduced thickening; akinesia as near or total absence of thickening; and dyskinesia as paradoxic endocardial excursion away from the left ventricle chamber and systolic thinning. Infarction zone segments were identified by the previously described algorithm (Fig. 1) of vascular territories (16). Improved segmental thickening was the induction of wall thickening in akinetic or dyskinetic segments or normalization of wall thickening in hypokinetic segments, but not a change from dyskinesia to akinesia (16). Sustained improvement was improved wall thickening in dysfunctional segments at low and peak doses. A biphasic response was improved wall thickening at the low dose followed by worsening at peak dose. An ischemic response involved hypokinetic segments that did not change at low dose but worsened at peak dose. Scar was reduced wall thickness with moderate to markedly increased echogenicity (24).

In addition to segmental analysis, studies were also analyzed according to the main response or the dysfunctional segments of the infarct-related vascular territory or infarct zone (16,22). A similar response in three or more contiguous segments was the criterion for ischemic responses, biphasic responses and sustained improvement. A mixed response was a combination of biphasic responses and sustained improvement in a sum of three or more segments. All other combinations were considered unchanged. The focus of this study was reversible dysfunction after acute MI, so remote wall motion abnormalities were not analyzed.

Follow-up echocardiography. Follow-up echocardiography was performed 4 to 8 weeks after hospital discharge and digitized as stated earlier (15–20,25). Images were separately analyzed by two investigators who had no knowledge of the clinical, dobutamine echocardiographic or angiographic data.

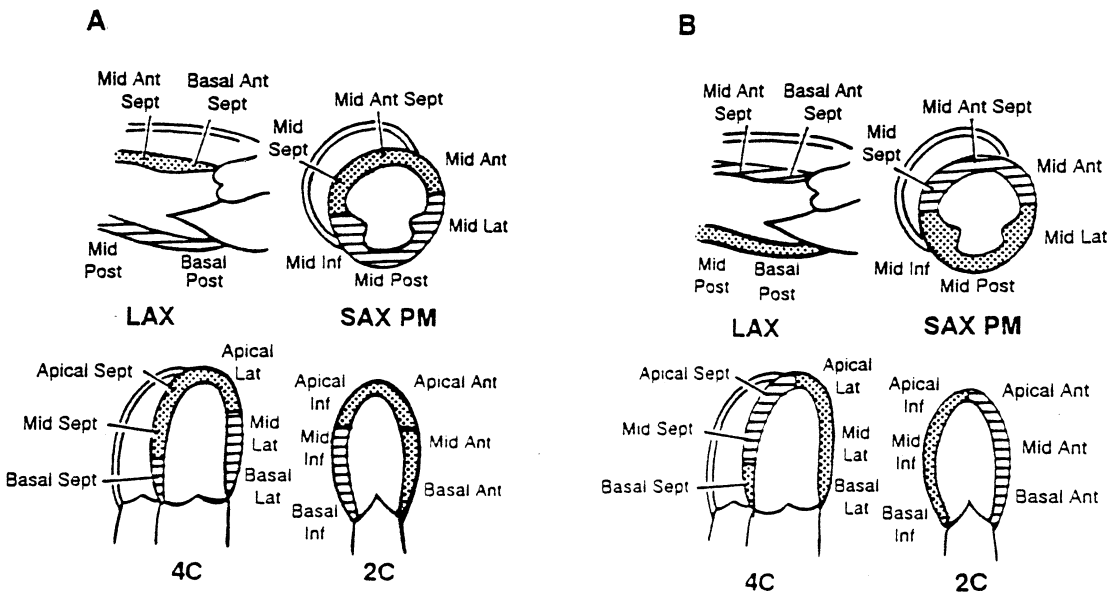

Figure 1. Diagram of infarction zones (**dotted areas**) in patients according to (**A**) anterior (Ant) and (**B**) inferior, posterior or lateral infarction location. LAX = long axis; SAX PM = short axis at papillary muscle level; 4C = four chamber; 2C = two chamber; Sept = septal; Post = posterior; Lat = lateral; Inf = inferior. (Reprinted, with permission, from Smart et al. [16].)

Follow-up images were directly compared with corresponding baseline images. Reversible dysfunction was improved wall thickening at follow-up (16–20). Dyskinetic segments changing to akinetic segments were also evaluated as a criterion for reversibility (16–20,26). Infarct zone dysfunction was defined as reversible if wall thickening improved in three or more segments.

Coronary angiography. Coronary angiography was performed by the Judkin's technique in all patients within the first week after MI. All coronary stenoses were evaluated by an investigator who was unaware of the other data. The culprit lesion was identified by criteria for thrombus or stenosis severity, or both. The frame and view with the smallest lumen diameter were identified. Percent lumen diameter stenosis was derived by the caliper technique. Infarct-related artery stenosis was a lumen diameter stenosis ≥50% and occlusion 100% with Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 or a subtotal occlusion with TIMI flow grade 1 (27). Percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery was performed at the discretion of the patient's cardiologist. Collateral channels were present if the score was ≥2 by the following scale: 0 = none; 1 = minimal with partial filling of the infarct-related artery; 2 = moderate with delayed complete filling; and 3 = abundant with rapid complete filling (28).

Statistical methods. Continuous data were expressed as the mean value ± SD. Continuous data were compared by analysis of variance and the Bonferroni *t* test. Chi-square analysis or the Fisher exact test was used to compare the predictive values of the segmental responses for reversible dysfunction. Computer-driven multiple logistic regression analysis was used to identify independent predictors of reversible dysfunction. Then, stepwise multiple logistic regression analysis and receiver operating characteristic (ROC) analysis were used to determine the incremental value of clinical (step 1), rest echocardiographic (step 2) and DASE data (step 3) in the detection of reversible dysfunction (29). The kappa statistic and the Fisher *z* test were used to assess intraobserver and interobserver variability in a randomly selected series of 100 patients. Statistical significance was set at $p < 0.05$ (two-tailed).

Results

Patient and coronary angiographic data. There were 98 men and 17 women with a mean age of 57 ± 13 years. Twenty patients had a previous MI. Treatment included thrombolytic therapy in 79 patients, angiotensin-converting enzyme inhibitors in 26 and beta-adrenergic blocking agents in 59. Infarction location was anterior in 51 patients. Q waves evolved in 66 patients. Mean peak CK was 2,187 ± 1,965 IU/ml.

The culprit lesion was within the left anterior descending coronary artery in 51 patients (44%), left circumflex artery in 24 (21%) and right coronary artery in 40 (35%). Fifty patients (43%) had multivessel disease (left circumflex and right coronary artery disease in 10, left anterior descending and right coronary artery disease in 16, left anterior descending and left circumflex coronary artery disease in 9 and three-vessel disease in 15) and 23 (20%) had angiographic collateral vessels. The mean stenosis was 79 ± 24%, including 32 patients (28%) with 100% stenosis, 70 (61%) with 50% to 99% stenosis and 13 (11%) with <50% stenosis. Revascularization was done before

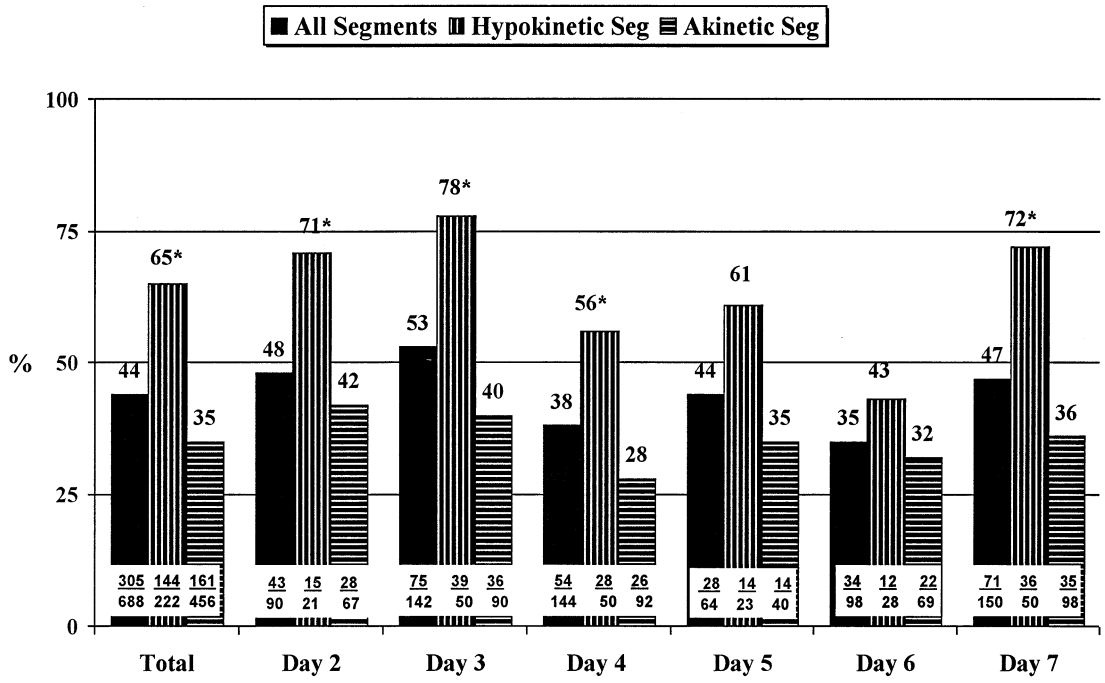

Figure 2. Bar graph of the incidence of reversible dysfunction by segmental function. Reversible dysfunction was not related to the interval from acute MI to baseline DASE in both hypokinetic and akinetic segments.

hospital discharge in 58 patients (50%)—angioplasty in 42 and bypass surgery in 16. The clinical, angiographic and echocardiographic data of the 23 patients without follow-up echocardiograms were similar to the 115 patients with follow up echocardiograms.

Reversible dysfunction by follow-up echocardiography. During the first week after acute MI, baseline echocardiography visualized 1,830 (99%) of 1,840 segments. Of the infarction zone segments 688 (66%) of 1,035 were dysfunctional, including 222 hypokinetic (21%), 456 akinetic (44%) and 10 dyskinetic (1%) segments. Scar was noted in 77 (17%) of the 466 akinetic or dyskinetic segments. Wall thickening improved at follow-up in 305 (44%) of the 688 dysfunctional segments. The majority of hypokinetic segments (65% [144 of 222]) recovered, whereas wall thickening resumed in only 35% (161 of 456, $p < 0.01$ vs. hypokinetic) of akinetic and 0% (0 of 10, $p < 0.01$ vs. hypokinetic) of dyskinetic segments. At follow-up, the 10 dyskinetic segments demonstrated dyskinesia in five and akinesia in five, but almost all (90% [9 of 10]) demonstrated echocardiographic scar. Wall thickening also did not recover in any of the scarred segments (0% [0 of 77]) at baseline. According to the criterion of three or more segments, infarct zone dysfunction was reversible in 65 (56%) of 115 patients at follow-up.

Reversible dysfunction was not related to the interval from acute MI to baseline echocardiography (Fig. 2). According the prospective inclusion criteria of the first week after acute MI, 16 patients were studied at 2 days, 24 at 3 days, 24 at 4 days, 12 at 5 days, 16 at 6 days and 13 at 7 days. Baseline dysfunction was similar irrespective of the interval from acute MI to baseline echocardiography. Reversible dysfunction in both hypokinetic and dyskinetic segments was not related to the interval from acute MI to baseline echocardiography.

Dobutamine echocardiography. Dobutamine echocardiography was performed the same day as baseline echocardiography (4.5 ± 2 days after acute MI). Rest heart rate and blood pressure were 72 ± 14 beats/min and 112 ± 18 mm Hg, respectively. Peak dose was 28 ± 10 μg/kg per min. Atropine was used in 40 patients. Heart rate and blood pressure at peak dose were 115 ± 15 beats/min and 135 ± 28 mm Hg, respectively. Heart rate >120 beats/min (n = 57) or ischemic end points (chest pain or >2 mm ST segment segment deviation, n = 27) were achieved in 84 (73%) of 115 patients.

Segmental data revealed that wall thickening improved at the low dose in 328 (48%) of the 688 dysfunctional segments. Improved wall thickening was more common ($p < 0.01$) in hypokinetic (74% [165 of 222]) than akinetic (36% [163 of 456]) or dyskinetic (0% [0 of 10]) segments. The 328 segments improving at the low dose consisted of 97 with sustained improvement (30%) and 231 with biphasic responses (70%). The prevalence of biphasic responses was similar in hypokinetic (66% [109 of 165]) and akinetic segments (75% [122 of 163]). The only determinant of the pattern of improvement (sustained vs. biphasic) was infarct-related artery stenosis. Responding segments from patients without residual stenosis demonstrated sustained improvement in 75% (30 of 40) and biphasic responses in only 25% (10 of 40). In contrast, biphasic responses were more common in responding segments supplied by infarct-related arteries with residual stenoses 50% to

Table 1. Comparison of Clinical, Rest Echocardiographic and Follow-Up Changes

	Reversible Dysfunction (n = 305)	Fixed Dysfunction (n = 383)	Univariate p Value	Multivariate p Value
Clinical characteristics				
Rest heart rate (beats/min)	71 ± 13	75 ± 15	0.002	NS
Peak CK (IU/ml)	1,694 ± 1,632	2,982 ± 2,276	<0.0001	<0.0001
Peak CK ≤1,500 IU/ml	59 (181)	33 (128)	<0.0001	NS
Non–Q wave MI	50 (153)	30 (113)	<0.0001	0.04
Age (yr)	59 ± 13	56 ± 13	0.01	NS
Gender (female)	17 (52)	10 (40)	0.02	NS
Beta-blocker	56 (171)	44 (167)	0.001	NS
Previous MI	12 (37)	24 (91)	<0.0001	NS
Nonanterior MI	57 (173)	48 (184)	0.03	NS
ACE inhibitor	24 (71)	26 (98)	0.5	NS
Thrombolysis	61 (186)	72 (276)	0.01	NS
Rest echocardiography				
Scar	0 (0)	20 (77)	<0.0001	<0.0001
Hypokinesia	47 (144)	20 (78)	<0.0001	<0.0001
Angiography				
IRA stenosis (%)	78 ± 24	80 ± 23	0.32	NS
Collateral vessels	17 (53)	24 (91)	0.051	NS
Single-vessel disease	59 (180)	49 (186)	0.006	NS
Revascularization	57 (174)	44 (170)	0.001	NS

Data are presented as mean value ± SD or percentage (number) of segments. ACE = angiotensin-converting enzyme; CK = creatine kinase; IRA = infarct-related artery; MI = myocardial infarction.

99% and 100% (77% [156 of 203] and 76% [65 of 85], respectively; $p < 0.01$ vs. no residual stenosis). Ischemic responses were rare in dysfunctional segments. Only 19 (9%) of 222 hypokinetic segments demonstrated no change at the low dose and ischemic responses at peak dose. All 19 segments (100%) demonstrating ischemic responses occurred in patients with >70% infarct-related artery stenosis. Angiographic collateral vessels were most common in ischemic (37% [7 of 19]), unchanged (26% [90 of 341]) and biphasic segments (20% [46 of 231]). Collateral vessels were rare in segments demonstrating sustained improvement (1% [1 of 97], $p < 0.001$ vs. other responses).

Sixty-seven (58%) of 115 patients demonstrated improved infarct zone wall thickening at the low dose in three or more segments. The pattern was sustained in 12, biphasic in 42 and mixed in 13 patients. Only four of the 48 infarct zones that did not change at the low dose demonstrated ischemic responses in three or more dysfunctional segments at peak dose. The main response of the infarct zone also reflected 1) the segmental correlations of mixed, ischemic and biphasic responses with residual stenosis (100% [13 of 13], 100% [4 of 4] and 95% [40 of 42], respectively vs. 89% [39 of 44] for no change and 50% [6 of 12] for sustained improvement, $p < 0.001$) and 2) the correlation of angiographic collateral vessels with ischemic responses, biphasic responses and no change (19% [8 of 42], 50% [2 of 4] and 30% [13 of 44], respectively vs. 0% [0 of 13] for mixed responses and 0% [0 of 12] for sustained improvement, $p < 0.0001$).

Segmental data were used for analysis of the predictive accuracy for reversible dysfunction and the causes of false negative and false positive results. Most patients demonstrated multiple segmental responses during DASE and at follow-up. Multiple segmental responses during DASE were noted in 95 (83%) of 115 patients. The major infarct zone response only reflected 467 (68%) of the 688 segmental responses. Thus, the infarct zone data did not reflect 221 of the segments (32%) or 1.92 ± 1.58 segments/patient (0 in 20 patients, 1 in 35 patients, 2 in 27 patients, 3 in 15 segments, 4 in 7 patients, 5 in 7 patients and 6 in 4 patients).

Identification of reversible dysfunction. Table 1 compares clinical, rest echocardiographic and angiographic factors according to reversible and fixed segmental dysfunction. Univariate clinical predictors of reversible dysfunction were lower rest heart rate, female gender, low peak CK, non–Q wave and nonanterior infarction, beta-blocker therapy and no history of infarction. Thrombolytic therapy and younger age tended to be associated with fixed dysfunction owing to a higher prevalence of akinetic segments. Angiotensin-converting enzyme inhibitor therapy was not predictive of reversible dysfunction. Univariate rest echocardiographic predictors were absence of scar and hypokinesia. Univariate angiographic predictors were single-vessel disease and revascularization. Multivariate predictors were only low peak CK, non–Q wave infarction, absence of scar and hypokinesia.

Figure 3 plots the sensitivity, specificity and positive and negative predictive values of DASE for reversible dysfunction in the 688 dysfunctional segments. The changes at peak dose did not enhance the accuracy of improved segmental wall thickening at the low dose for reversible dysfunction. Biphasic responses and sustained improvement were both specific and

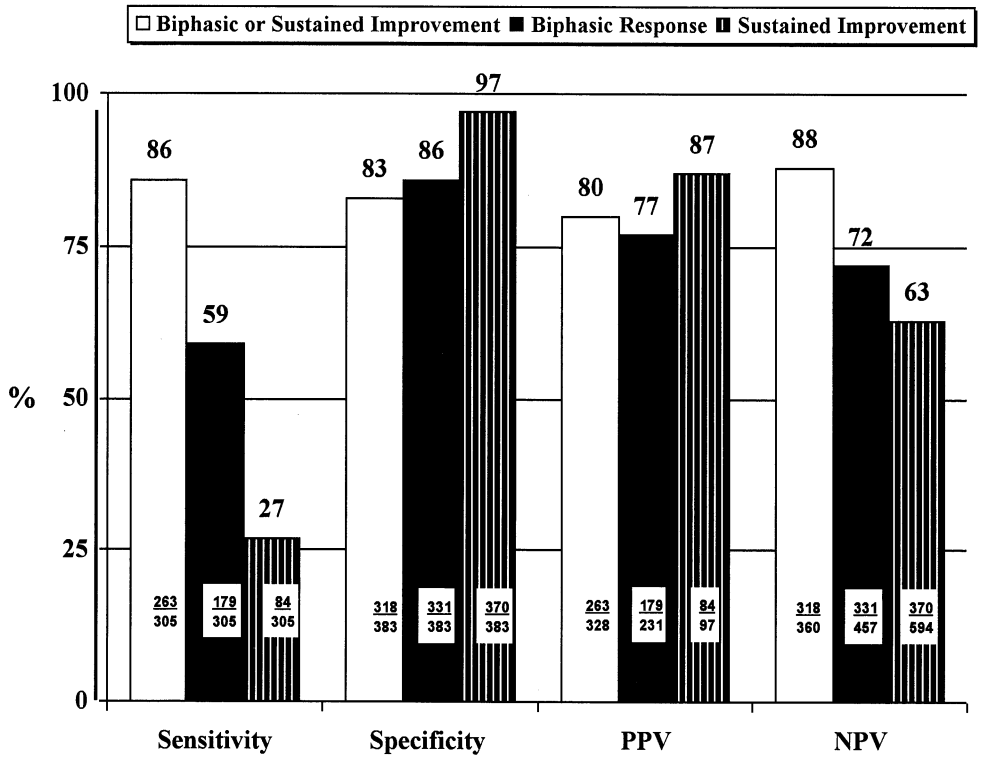

Figure 3. Bar graph of the sensitivity, specificity and positive and negative predictive values (PPV and NPV) of findings during dobutamine-atropine stress echocardiography for reversible dysfunction in the 688 dysfunctional segments. Biphasic responses and sustained improvement were highly specific and positively predictive of reversible dysfunction. Biphasic responses were more common and sensitive than sustained improvement. Improved segmental wall thickening at the low dose, irrespective of changes at peak dose, was sensitive, specific and highly predictive of reversible dysfunction.

positively predictive of reversible dysfunction. Biphasic responses were more sensitive than sustained improvement owing to their greater prevalence. In contrast to these data, ischemic responses in hypokinetic segments predicted fixed dysfunction, especially in medically treated (100% [8 of 8] vs. 36% [4 of 11], $p < 0.05$).

Figure 4 plots the positive and negative predictive values in improved wall thickening and shows no change according to the test interval after acute MI. Improved wall thickening was highly predictive of reversible dysfunction irrespective of the test interval. The positive predictive value was slightly reduced on the fourth day after infarction. Likewise, no change at the low dose was highly predictive of fixed dysfunction irrespective of the test interval.

Table 2 lists the accuracy of improved wall thickening at the low dose and the incidence of true positive, false positive, true negative and false negative results according to baseline dysfunction and clinical and angiographic factors. Dobutamine echocardiography was accurate for reversible dysfunction in all echocardiographic, clinical and angiographic subsets. True

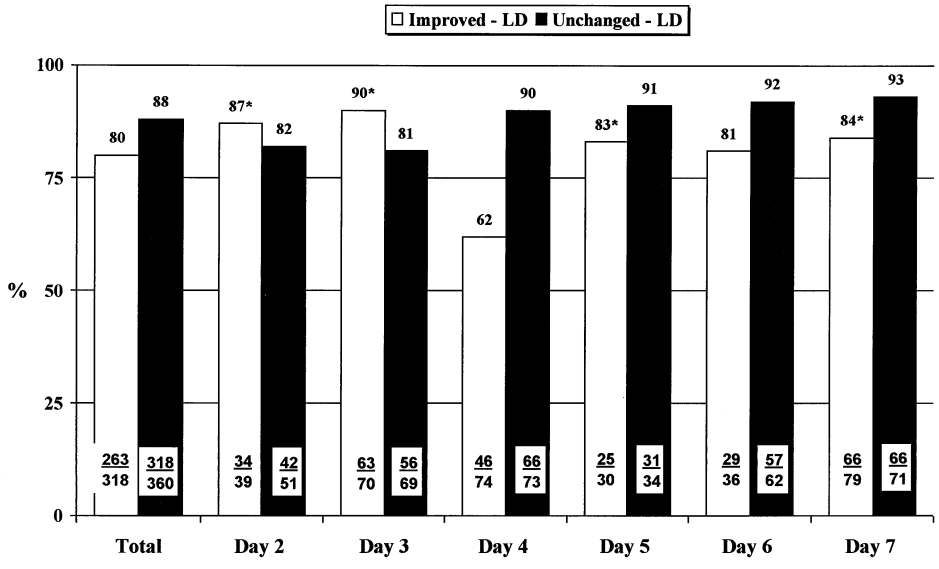

Figure 4. Bar graph of the positive predictive value of improved wall thickening **(open bars)** and the negative predictive value of no change **(solid bars)** at the low dose (LD) according to the test interval after acute MI. Improved wall thickening at the low dose (both sustained improvement and biphasic responses) was predictive of reversible dysfunction, irrespective of the test interval. The positive predictive value was slightly reduced on the fourth day after infarction. Otherwise, there were no differences related to the test interval. No change at the low dose (including ischemic responses at peak dose and no change at low and peak doses) was predictive of fixed dysfunction, irrespective of the test interval. There were no day to day differences in the negative predictive value.

Table 2. Subgroup Analysis of Accuracy for Reversible Segmental Dysfunction

		Dobutamine Echocardiography				
	No. of Segments	Accuracy	True Positive	False Positive	True Negative	False Negative
All segments	688	84 (581)	38 (263)	10 (65)	46 (318)	6 (42)
Hypokinetic segments	222	77 (171)	58 (129)	16 (36)	19 (42)	7 (15)
Akinetic segments	456	88 (400)*	29 (134)	6 (29)*	58 (266)	6 (27)
Dyskinetic segments	10	100 (10)*	0 (0)	0 (0)	(10)	0 (0)
Previous MI	128	84 (108)	21 (27)	8 (10)	63 (81)	8 (10)
No previous MI	560	84 (473)	42 (236)	10 (55)	42 (237)	6 (32)
CK ≥1,500 IU/ml	379	83 (315)	29 (109)	13 (49)†	54 (206)	4 (15)
CK <1,500 IU/ml	309	86 (266)	50 (154)	5 (16)	36 (112)	9 (27)
Beta-blocker	338	84 (284)	43 (147)	9 (30)	41 (137)	7 (24)
No beta-blocker	350	85 (297)	33 (116)	10 (35)	52 (181)	5 (18)
Anterior MI	334	86 (285)	33 (108)	7 (22)‡	53 (177)	7 (24)
Inf, post or lat MI	357	83 (296)	43 (155)	12 (43)	44 (141)	5 (18)
Q wave MI	422	86 (363)	32 (137)	10 (44)	54 (226)	4 (15)
Non–Q wave MI	266	82 (218)	47 (126)	8 (21)	35 (92)	10 (27)
Thrombolysis	462	86 (396)	35 (161)	9 (41)	51 (235)	5 (25)
No thrombolysis	226	82 (185)	45 (102)	11 (24)	37 (83)	7 (17)
Occluded IRA	203	80 (163)§	29 (59)	13 (26)§	51 (104)	7 (14)
Residual stenosis‖	405	85 (344)	41 (167)	9 (36)	44 (177)	6 (25)
No IRA stenosis¶	80	93 (74)	46 (37)	4 (3)	46 (37)	4 (3)
Collateral vessels	144	88 (126)	29 (41)	4 (6)	59 (85)	8 (12)
No collateral vessels	544	84 (455)	41 (222)	11 (59)	43 (233)	6 (30)
Revascularization	344	84 (288)	44 (152)	10 (34)	40 (136)	6 (22)
Medical therapy	344	85 (293)	32 (111)	9 (31)	53 (182)	6 (20)
Single-vessel CAD	366	84 (306)	43 (156)	10 (36)	41 (150)	6 (24)
Multivessel CAD	322	85 (275)	33 (107)	9 (29)	52 (168)	6 (18)

*$p < 0.0001$ versus hypokinetic segments. †$p < 0.01$ versus creatine kinase (CK) <1,500 IU/ml. ‡$p < 0.05$ versus anterior myocardial infarction (MI). §$p < 0.05$ versus no infarct-related artery (IRA) stenosis. ‖Infarct-related artery stenosis 50% to 99%; ¶Lumen diameter stenosis <50%. Data in last five columns are presented as percentage (number) of segments. CAD = coronary artery disease; Inf = inferior; lat = lateral; post = posterior.

positive and true negative responses were directly and inversely related, respectively, to the prevalence of reversible dysfunction. Accuracy was directly related to the severity of dysfunction and was significantly greater in akinetic and dyskinetic segments than in hypokinetic segments ($p = 0.0005$). Accuracy was also greater in segments perfused by arteries without residual stenosis compared with segments with occluded infarct-related arteries ($p = 0.02$). By multivariate analysis, the only independent cause of reduced accuracy was hypokinesia. The causes of false positive responses were hypokinesia ($p = 0.00008$), peak CK ≥1,500 IU/ml ($p = 0.0009$), nonanterior infarction ($p = 0.02$) and infarct-related artery occlusion ($p = 0.04$). By multivariate analysis, the only independent cause of false positive results was hypokinesia. Finally, false negative results were uncommon and not related to any rest echocardiographic, clinical or angiographic factors.

Table 3 lists the stepwise multiple logistic regression analysis and ROC analysis of the incremental value of clinical, rest echocardiographic and DASE findings in the detection of reversible dysfunction after acute MI. Each set of findings incrementally improved the predictive accuracy for reversible dysfunction after acute MI. The clinical findings of a low peak CK level or non–Q wave infarction were moderately predictive of reversible dysfunction after acute MI. The rest echocardiographic findings of no scar and hypokinesia significantly improved the predictive accuracy, but accuracy was only maximized by the addition of dobutamine echocardiographic findings of biphasic responses or sustained improvement.

Comparative analysis—observer variability. Kappa statistic data revealed that intraobserver and interobserver variabilities of baseline, dobutamine-atropine and follow-up echocardiographic interpretations were minimal. There was no variability in the interpretation of infarction zone wall thickening as normal or abnormal. In the 100 patients selected (598 dysfunctional segments), the kappa statistics for interobserver variability of baseline, low dose, peak dose and follow-up segmental readings were 0.745 ($z \pm 25.857$, $p < 0.0001$), 0.741 ($z \pm 25.667$, $p < 0.0001$), 0.702 ($z = 24.659$, $p < 0.0001$) and 0.789 ($z = 26.156$, $p < 0.0001$), respectively. The kappa statistics for intraobserver variability of baseline, low dose, peak dose and follow-up segmental readings were 0.793 ($z = 26.202$, $p < 0.0001$), 0.802 ($z = 26.741$, $p < 0.0001$), 0.780 ($z = 25.950$, $p < 0.0001$) and 0.809 ($z = 26.865$, $p < 0.0001$), respectively. The interobserver reproducibility of segmental readings at baseline, low dose, peak dose and follow-up were 92% (549 segments), 92% (548), 91% (543) and 93% (554),

Table 3. Stepwise Analysis of the Incremental Value of Clinical, Rest and Dobutamine Echocardiographic Variables in the 688 Dysfunctional Segments in Detecting Reversible Dysfunction

		Multiple Logistic Regression		ROC Analysis	
Step	Variable	Incremental Chi-Square	Incremental p Value	Area Under ROC Curve	Incremental p Value
1	Clinical (peak CK <1,500 IU/ml or non–Q wave MI)	74.5	<0.0001	0.684	<0.0001
2	Rest echocardiography (no scar or hypokinesia)	144.3	<0.0001	0.798	<0.0001
3	DASE (biphasic response or sustained improvement)	240.1	<0.0001	0.920	<0.0001

DASE = dobutamine-atropine stress echocardiography; ROC = receiver operating characteristic; other abbreviations as in Table 1.

respectively. The intraobserver reproducibility of segmental readings at baseline, low dose, peak dose, and follow-up were 93% (555 segments), 93% (558), 92% (553) and 94% (560), respectively.

Discussion

Previous studies. *Reversible dysfunction.* Reversible myocardial dysfunction may result from postischemic dysfunction, recurrent ischemia and reperfusion or sustained hypoperfusion, but the major mechanism after acute MI is postischemic injury. Recovery is usually spontaneous, but may not be maximal for 4 weeks or more (14–20,30). The reversibility of dysfunction after acute MI may have important prognostic and management implications (31). Thus, the early differentiation of reversible from fixed dysfunction may be very useful in the clinical management of these patients. Large infarct size or extensive fixed akinesia or dyskinesia confers a poor prognosis, irrespective of the use of revascularization, but prognosis in extensive reversible dysfunction may be improved by early infarct-related artery revascularization (31).

Dobutamine echocardiography. Clinical and angiographic data are poorly predictive (2,16–20,32), but dobutamine echocardiography is highly predictive of reversible dysfunction after acute MI (16–20). Pierard et al. (17) reported that dobutamine echocardiography and positron emission tomography were concordant, sensitive and specific for reversible dysfunction in 17 patients treated with thrombolysis for acute anterior MI. Another study of 51 patients treated with thrombolysis revealed that accuracy was high in both anterior and nonanterior infarctions (16). Other small studies reported a higher sensitivity, especially in patients treated with angioplasty, and a greater specificity than with rest thallium-201 single-photon emission computed tomographic scintigraphy (18–20).

Several important issues regarding DASE for reversible dysfunction early after acute MI remain to be investigated. Its safety has been documented (22), but none have investigated its limitations or the predictive value of the multiple segmental responses from low to peak dose. No change at low dose is very predictive of fixed dysfunction after acute MI, but the predictive values of sustained improvement and biphasic and ischemic responses are unclear (16–20).

Present study. *Reversible dysfunction.* The present study was sufficiently large to investigate the determinants of reversible dysfunction after acute MI. Follow-up echocardiography 4 to 8 weeks after hospital discharge is an established technique for documenting recovery of function and was not confounded by recurrent ischemic events (30).

The interval from acute MI to echocardiography during the first week after acute MI did not influence the incidence of reversible dysfunction. The rates of reversible dysfunction in hypokinetic and akinetic segments and the number and severity of dysfunctional segments were similar throughout the first week after acute MI. Thus, recovery of reversibly injured myocardium mainly occurred after the first week of convalescence.

Clinical and angiographic factors were only moderately predictive of reversible dysfunction after acute MI. Reversible dysfunction was less common in infarct-related artery occlusion, Q wave infarction, multivessel coronary artery disease, peak CK >1,500 IU/ml, previous MI and treatment without beta-blockers. Reversible dysfunction was also less common after thrombolytic therapy, owing to more severe injury (i.e., a greater prevalence of akinetic segments). Angiographic collateral vessels were a marker of residual stenosis rather than reversible dysfunction, consistent with previous data (28). Finally, the data were very consistent with postischemic injury as the major mechanism of reversible dysfunction because revascularization only modestly increased its incidence.

Rest segmental function and morphology by echocardiography were modestly predictive of reversible dysfunction. Most hypokinetic segments recovered and none of the dyskinetic or scarred segments recovered. In the remaining major subset (akinetic segments without scar), reversible dysfunction could only be differentiated from fixed dysfunction by further testing.

Dobutamine-atropine echocardiography. Dobutamine-atropine echocardiography accurately detected reversible dysfunction during the first week after acute MI. Both biphasic

responses and sustained improvement were predictive of reversible dysfunction and no change of fixed dysfunction, irrespective of the test interval. Ischemic responses were uncommon but were predictive of fixed dysfunction, especially in medically treated patients. Again, the major role of postischemic injury in reversible dysfunction after acute MI was implied by the similar predictive values found with revascularization and medical treatment. The similar predictive values of sustained improvement and biphasic responses indicated that the low dose data were adequate to accurately detect reversible dysfunction.

Dobutamine-atropine echocardiography accurately detected reversible dysfunction in subsets with low and high rates of reversible dysfunction and improved the detection of reversible dysfunction compared with clinical, angiographic and rest echocardiographic data. The independent cause of reduced accuracy was rest hypokinesia, due to a high incidence of false positive results. Reversible dysfunction was also common in hypokinetic segments, so testing for reversible dysfunction had limited value. False negative studies were not related to the test interval, baseline dysfunction or clinical or angiographic factors. Accuracy and predictive values were especially high in the important subset of akinetic segments. The high accuracy in infarct-related artery occlusion may have resulted from optimal hemodynamic data or greater retrograde myocardial blood flow (33,34). Testing had no value in dyskinetic segments because none recovered.

The data from this study contrast with those reported by Alfridi et al. (21) in patients with chronic left ventricular dysfunction undergoing revascularization. These investigators showed that biphasic responses predicted reversible dysfunction, but that sustained improvement predicted fixed dysfunction and ischemic responses predicted reversibility. The current study demonstrated that biphasic responses predicted reversible dysfunction, but that sustained improvement also predicted reversibility, whereas ischemic responses predicted fixed dysfunction.

The different results reflect the different mechanisms of dysfunction. Chronic dysfunction that is salvageable by revascularization is mediated by hypoperfusion or repetitive ischemia (21,35–37). In contrast, acute dysfunction that will recover with or without revascularization is mediated by postischemic or reperfusion injury (38–41). Biphasic responses are highly predictive of coronary artery disease, so its high predictive value for reversibility in both chronic dysfunction and acute MI reflects the high prevalence of coronary disease in the two groups (42–44). Sustained improvement is highly predictive of noninfarct-related muscle and the absence of inducible ischemia or coronary disease (42–44). Thus, it was highly predictive of reversibility after acute MI because reperfusion injury rather than myopathy was the major mechanism. In contrast, chronically dysfunctional segments that demonstrate sustained improvement remain fixed because nonischemic myopathy rather than reperfusion injury is the major mechanism. Ischemic responses in dysfunctional segments are also predictive of coronary stenosis (42–44). The moderate predictive value of ischemic responses for reversible dysfunction in the study by Alfridi et al. (21) reflects the greater prevalence of dysfunction due to hypoperfusion or repetitive ischemia in their patients, as well as universal revascularization.

Study limitations. Twenty-three patients were lost to follow-up, but their clinical, angiographic and echocardiographic findings were similar to those of the other study patients. Therefore, lack of follow-up in these patients did not introduce a selection bias. Follow-up angiography was not performed. The goal of the study was to detect reversible dysfunction. There were no clinical signs of restenosis or recurrent ischemia in any patients, so documentation of infarct-related artery patency was not done. Follow-up echocardiography was done before the peak incidence of restenosis (45). Bypass surgery was done in 16 of the 58 revascularized patients. The peak heart rate was (mean ± SD) 115 ± 15 beats/min and beta-blockers were not stopped for the test. Thus, the incidence of biphasic and ischemic responses may have been higher with higher heart rates, but maximal peak heart rates or an ischemic end point was achieved in 73% of patients.

Clinical implications and conclusions. Dobutamine-atropine echocardiography accurately detected reversible dysfunction early after acute MI. Its only limitation was reduced accuracy due to false positive results in hypokinetic segments. False negative results were uncommon and not related to any clinical, echocardiographic or angiographic factor. Reversible dysfunction was common in hypokinetic segments and never occurred in scarred or dyskinetic segments, so testing yielded little clinical benefit in these subsets. Dobutamine-atropine echocardiography was better than rest function and clinical and angiographic data for the early detection of reversible injury, owing to its high accuracy in akinetic segments. No change and ischemic responses were predictive of fixed dysfunction. Sustained improvement and biphasic responses were predictive of reversible dysfunction. The test interval and clinical and angiographic factors did not affect accuracy.

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