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Significance of Persistent Left Ventricular Dysfunction During Recovery After Dobutamine Stress Echocardiography

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Objectives. **This study sought to determine the duration of new or worsening left ventricular regional wall motion abnormalities (RWMAs) after dobutamine stress echocardiography (DSE) and their relation to the extent of coronary artery disease (CAD).**

Background. **Despite extensive reports on DSE, little is known about the duration of new or worsening RWMAs during recovery. We hypothesized that the persistence of RWMAs during recovery may be associated with the extent of CAD and therefore ischemia.**

Methods. **Sixty-five consecutive patients with positive results on DSE and angiographically documented CAD were studied. Each patient underwent 12-lead electrocardiography and two-dimensional echocardiography at rest, during dobutamine infusion and continuously during recovery to assess the recovery time of ischemic myocardial regions.**

Results. **All patients had at least one ischemic region during DSE. Complete resolution of RWMAs occurred within 25 min in patients with multivessel CAD, within 20 min in those with two-vessel disease and within 15 min in those with single-vessel disease ($p < 0.001$). The greater the wall motion score index at peak stress, the longer the duration of RWMAs into the recovery phase ($p < 0.01$). RWMAs persisted long after normalization of each patient's symptoms, electrocardiographic (ECG) changes, heart rate and rate–pressure product during recovery.**

Conclusions. **We demonstrated that normalization of left ventricular RWMAs occurs after resolution of symptoms and ECG changes during recovery. The time to recovery is related to the extent of CAD and myocardial ischemia as well as to the presence or absence of collateral circulation. These findings may represent stunned myocardium after brief period of ischemia.**

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Dobutamine stress echocardiography (DSE) has been shown to be a sensitive method for detection of myocardial ischemia that produces reversible regional wall motion and systolic wall thickening abnormalities (1–3). The diagnostic accuracy of the test in detecting coronary artery disease (CAD) has been extensively evaluated (4–7). However, there is limited information regarding the persistence and duration of newly induced regional wall motion abnormalities (RWMAs) during the recovery period after DSE.

RWMAs may persist during recovery after treadmill exercise stress echocardiography (8,9), but little is known of the temporal relation between their persistence and symptoms, electrocardiographic (ECG) changes and extent of ischemia (10).

This study therefore sought to determine the duration of RWMAs during the recovery period after DSE and relate this to the extent of underlying coronary artery lesions and ischemic burden.

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Methods

Patients. The study included 65 consecutive patients with positive results on DSE and angiographically documented CAD who were referred for assessment of the presence and extent of myocardial ischemia. All cardioactive medication (beta adrenergic or calcium channel blocking agents) was withdrawn at least 48 h before DSE.

Cardiac catheterization. The presence of CAD was established during routine coronary angiography using the Judkins technique. Coronary stenoses were expressed as percent diameter reduction. A >70% reduction was considered to be significant. Twenty-one patients (32%) had single-vessel disease; 22 (34%) had two-vessel disease; and 22 (34%) had three-vessel disease (Table 1). The right coronary artery was involved in 40 patients, the left main coronary artery in 3, the left anterior descending coronary artery in 45 and the left circumflex coronary artery in 37. The presence of collateral circulation was seen in 31 patients (48%) (Table 1).

Dobutamine stress echocardiography. Each patient underwent two-dimensional echocardiography using a Toshiba 160 SSH ultrasound system (Manor Court, Manor Royal, Crawley, West Sussex, UK), in the left recumbent position. Standard tomographic views of the left ventricle (parasternal long- and short-axis and apical four- and two-chamber views) were obtained at rest and continuously during dobutamine infusion.

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Abbreviations and Acronyms

ANOVA = analysis of variance
CAD = coronary artery disease
DSE = dobutamine stress echocardiography (echocardiographic)
ECG = electrocardiogram, electrocardiographic
LBBB = left bundle branch block
RWMAs = regional wall motion abnormalities
WMSI = wall motion score index

Imaging was continuously recorded on 0.75-in. videotapes and was digitized on-line using a separate black-and-white output in a quad-screen format (ImageView DCR version 1.61, Nova MicroSonics) every 3 min and during recovery. Recording was completed only after all ischemic regions had returned to baseline. Digital imaging was also obtained at 5-min intervals during recovery to facilitate simultaneous and synchronized analysis of each myocardial region throughout. The 12-lead electrocardiogram (ECG) (Case 15, Marquette) was monitored throughout, and blood pressure (cuff sphygmomanometer) was recorded at rest and at 1-min intervals during dobutamine infusion and recovery. Some chest electrodes were slightly displaced to optimize echocardiographic windows.

An infusion line was placed in the right or left antecubital vein. Dobutamine was administered by incremental infusion doses using an infusion pump (5, 10, 15, 20, 30 and 40 mg/kg/body weight per min) at 3-min intervals. Failure to achieve a minimal heart rate of 90% of maximal predicted levels for age was followed by a bolus administration of 0.6 mg of atropine at the end of the dobutamine protocol (with a maximum of 1.2 mg).

The dobutamine stress test was continued regardless of the occurrence of new or worsening RWMAs until maximal heart rate was achieved. Severe chest pain or symptomatic hypotension not reversible with atropine were also additional end points of the stress test. DSE results were considered *positive* when new or worsening RWMAs were detected in one or more segments. The presence of a biphasic response (improved contraction at low dose with subsequent deterioration at high dose) was also considered positive on DSE. For RWMAs analysis, an 11-segment protocol of the four tomographic views of left ventricle was used (11). RWMAs were graded by two observers (I.K., P.N.) at different time periods to achieve intraobserver variability of wall motion. Each segment was scored as follows: 1 = *normal*; 2 = *hypokinetic*; 3 = *akinetic*; and 4 = *dyskinetic*. For semiquantitative analysis of RWMAs, a total wall motion score index (WMSI) was used: WMSI = (Sum of total score/Number of segments visualized). As a measure of the magnitude of reversible ischemia during the stress test, the *ischemic score* was used: Ischemia at peak stress − Ischemia at rest. The greater the difference between peak and rest scores the greater the ischemic burden.

ECGs were analyzed according to standard criteria (12), and ST segment depression >0.1 mV 60 ms after the J point was considered an ECG indication of ischemia.

Statistical analysis. Results are expressed as mean value ± SD. The Student two-tailed *t* test and chi-square analysis were used, and significance was derived from statistical tables. Comparisons between groups were performed using analysis of variance (ANOVA) (factorial) and the Kruskall-Wallis test for nonparametric values. Multiple comparisons among groups (one-, two- and three-vessel disease) and the various times during recovery were performed using the Scheffé correction. Linear regression analysis was performed to correlate the duration of RWMAs with the ischemic score and WMSI. $p < 0.05$ was considered significant.

Results

Patient cohort (Table 1). Sixty-five consecutive patients (54 men, 11 women; mean [±SD] age 63 ± 9 years, range 33 to 79) with positive results on DSE were studied. No patient was excluded because of inadequate imaging. There were 22 patients with previous coronary artery bypass graft surgery; 8 with previous coronary angioplasty; and 39 (60%) with a previous myocardial infarction. Thirty-seven patients (57%) developed chest pain, and 9 (14%) complained of dyspnea. The duration of dobutamine stress was 21 ± 3 min, and patients achieved 89 ± 12% of the predicted maximal heart rate. The WMSI was 1.33 ± 0.42 at rest and increased to 1.62 ± 0.42 at peak stress

Table 1. Baseline Patient Characteristics

	1 VD (n = 21)	2 VD (n = 22)	3 VD (n = 22)	Total (n = 65)
Age (yr)	61.4 ± 9.1	64.5 ± 8.8	63.1 ± 10.3	63 ± 9
Angina	13	12	12	37 (57)
Breathlessness	4	2	3	9 (14)
Previous infarction	12	15	12	39 (60)
Normal rest wall motion	9 (43)	7 (32)	10 (45)	26 (40)
Rest wall motion score index	1.2 ± 0.28	1.5 ± 0.5	1.27 ± 0.4	1.33 ± 0.42
Rest heart rate (beats/min)	74.7 ± 13.0	73.7 ± 20.9	66.2 ± 13.8	71.5 ± 16.6
Systolic blood pressure (mm Hg)	137.9 ± 18.3	138.5 ± 26.8	140.7 ± 16.6	139.1 ± 20.8
Diastolic blood pressure (mm Hg)	86.8 ± 12.4	82.6 ± 16.8	84.6 ± 9.5	84.7 ± 13.2
Collateral channels	8	12	11	31 (48)

Data presented are mean value ± SD or number (%) of patients. VD = vessel disease.

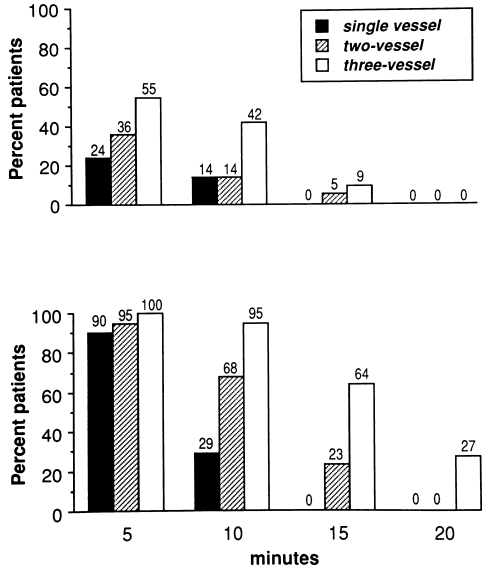

Figure 1. ECG changes (**top**) and RWMAs (**bottom**) during recovery. The ECG changes resolved faster than did the RWMAs in each category of CAD. Similarly, the greater the number of diseased vessels the longer the persistence of RWMAs ($p < 0.01$).

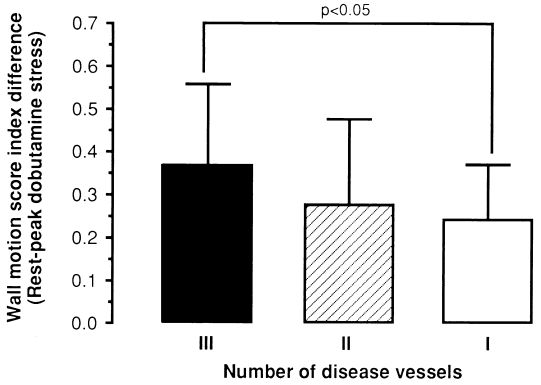

Figure 2. WMSI differences between rest and peak stress were greater in patients with three-vessel than in those with single-vessel disease.

($p < 0.01$). All patients had digitized on-line images at 5, 10, 15 and 20 min during recovery in all four standard echocardiographic views.

ECG findings. A positive ECG response with ST segment depression diagnostic of ischemia occurred in 30 (46%) of 65 patients with positive results on DSE. Five patients (8%) had left bundle branch block (LBBB) on the rest ECG, and one developed transient LBBB during stress. T wave abnormalities were observed in 21 patients, and cardiac rhythm disorders, such as node rhythm, first-degree atrioventricular block, bigeminy and multiform ventricular extrasystoles, were detected in 9 patients. In no instance was the stress test discontinued. During recovery, ischemic ECG changes normalized faster than RWMAs in all patients (Fig. 1). No patient had ECG changes >15 min into recovery.

RWMAs (Table 2). Hemodynamic responses during stress, independent of the number of diseased vessels or the presence of collateral channels, was similar in all patients. No new or further ventricular dysfunction occurred during recovery. Only 3 of 39 patients with rest RWMAs developed a biphasic response during the course of dobutamine infusion indicative of reversible ventricular dysfunction.

In the 21 patients with single-vessel disease, the WMSI increased from 1.2 ± 0.28 to 1.45 ± 0.27 (difference of 0.25 ± 0.13, $p < 0.001$). All regions returned to rest values within 10 min. Persistent RWMAs were seen in 19 patients (90%) at 5 min and in only 6 (29%) at 10 min.

In the 22 patients with two-vessel disease, the WMSI increased from 1.5 ± 0.49 to 1.79 ± 0.48 (difference of 0.28 ± 0.22, $p < 0.0001$). All regions returned to rest values within 20 min. Persistent RWMAs were seen in 21 patients (95%) at 5 min, in 15 (68%) at 10 min and in only 5 (23%) at 15 min.

In the 22 patients with three-vessel disease, the wall motion score index increased from 1.27 ± 0.4 to 1.63 ± 0.44 (difference of 0.36 ± 0.19, $p < 0.0001$). All regions returned to rest values within 25 min. Persistent RWMAs were seen in all patients at 5 min, in 21 (95%) at 10 min, in 14 (64%) at 15 min and in 6 (29%) at 20 min.

The wall motion score and WMSI at peak stress as well as the difference between rest and peak stress were higher in patients with three-vessel than in those with single- and

Table 2. Patient Characteristics at Peak Stress

	1 VD (n = 21)	2 VD (n = 22)	3 VD (n = 22)	Total (n = 65)
Stress duration (min)	20.6 ± 3.9	20.9 ± 2.6	21.7 ± 2.6	21.1 ± 3.1
Time to recovery (min)	6.4 ± 2.3	10 ± 3.8	14.1 ± 4.8	10.2 ± 4.9*†
Angina	13	12	14	39 (60)
ECG changes	8	9	13	30 (46)
Peak wall motion score index	1.45 ± 0.27*	1.79 ± 0.5*	1.63 ± 0.44*	1.62 ± 0.43*†
Wall motion score difference	2.71 ± 1.45	2.95 ± 2.54	3.95 ± 2.06	3.22 ± 2.1†
Wall motion score index difference	0.25 ± 0.13*	0.28 ± 0.22*	0.36 ± 0.19*	0.29 ± 0.19*†
Peak heart rate (beats/min)	144.3 ± 21.2*	142.7 ± 13.5*	135.6 ± 21.3*	140.8 ± 19.1*
Systolic blood pressure (mm Hg)	154.1 ± 21.1*	144.3 ± 24.0*	162.8 ± 21.2*	153.8 ± 23.1*
Diastolic blood pressure (mm Hg)	84.1 ± 16.7	81.9 ± 17.7	88.4 ± 13.2	84.8 ± 16

*$p < 0.001$ versus rest values. †$p < 0.01$ versus one-, two- and three-vessel disease (VD). Data presented are mean value ± SD or number (%) of patients.

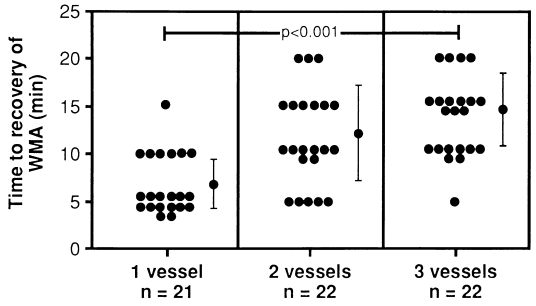

Figure 3. Time to recovery was greater in patients with three-vessel than in those with single- and two-vessel disease ($p < 0.001$ by multiple comparison among the three groups). WMA = wall motion abnormalities.

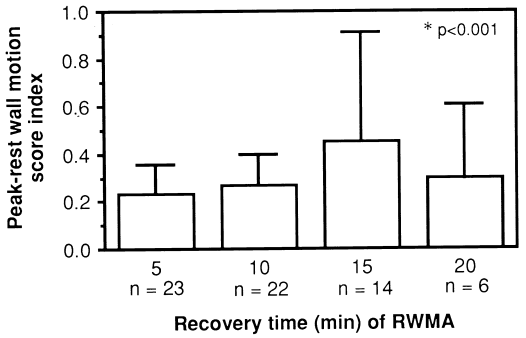

Figure 4. Extent of myocardial ischemia, expressed as the difference in WMSI between peak stress and rest dobutamine infusion, was greater in patients with prolonged recovery (>15 min). *$p < 0.001$ by multiple comparison among the four time periods during the recovery phase.

two-vessel disease ($p < 0.05$) (Fig. 2). Similarly, the time to recovery was longer in patients with two- and three-vessel than those with single-vessel disease (Fig. 3). However, no relation was found between duration of ventricular dysfunction during recovery and duration of dobutamine infusion or extent of myocardial dysfunction at rest.

RWMAs persisted for at least 5 min into the recovery period in 90% of all patients. There was no difference in the number of diseased vessels at 5 min. In only three patients (two with single-vessel and one with two-vessel disease and good collateral channels) did RWMAs return to rest values in <5 min (range 2 to 4 min). However, from the fifth minute onward, the time to recovery was consistently longer in patients with three-vessel than in those with single- and two-vessel disease ($p < 0.01$) (Fig. 1 and 3). Five patients with three-vessel disease and five without collateral channels had persistent RWMAs for up to the 25th minute of the recovery period, which persisted despite a decrease in heart rate, systolic blood pressure and rate–pressure product, similar to the rest levels.

There was good correlation between the duration of RWMAs during recovery and the severity of the wall motion score and WMSI ($p < 0.008$) (regression curve: Recovery time = $14.67 + 0.31 \times$ Score). Figure 4 shows that the greater the difference in WMSI between peak and rest dobutamine stress, the longer the duration of RWMAs into the recovery period ($p < 0.001$, ANOVA factorial and Kruskall-Wallis test). In six patients with an overall WMSI difference that was lower at 20 min than at 15 min, five had three-vessel disease, and one had no collateral channels.

The presence of collateral channels was generally associated with earlier reversibility of RWMAs, whereas their absence was linked to delayed recovery. There was no difference between patients with or without collateral channels with regard to the incidence of persistent RWMAs at minute 5 of the recovery phase. However, at minute 10 of the recovery period, persistent RWMAs were present in 16 patients (52%) with and 26 (76%) without collateral channels ($p = 0.01$). At minute 15, the respective values were 3 (15%) of 20 patients and 11 (69%) of 16 ($p = 0.001$), and those at minute 20 were 0 and 5 (31%) of 16 ($p = 0.007$), respectively.

Interobserver variability. Of 715 myocardial regions analyzed in 65 patients, concordance between observers with regard to rest wall motion was reached in 691 (97%). At peak dobutamine stress, agreement was reached in 673 regions (94%). During recovery, agreement between observers with regard to normalization of ischemic segments was reached in 659 (92%).

Discussion

To our knowledge, this is the first study to demonstrate that the extent of myocardial ischemia is related to delayed recovery of RWMAs after DSE. This delayed resolution of left ventricular dysfunction was prolonged in patients with multivessel CAD as well as in patients with no documented collateral channels. New or worsening RWMAs were still present despite the prompt resolution of heart rate, systolic blood pressure and rate–pressure during recovery.

Prolonged ischemia. Stress echocardiography is now widely used for the diagnosis of CAD by detecting regional myocardial dysfunction during systole. The majority of studies to date have reported on the induction ventricular dysfunction during the course of stress. However, there is little information on the immediate post-stress period, and little is known about the significance of RWMAs during the recovery phase. Delayed recovery of left ventricular systolic function after submaximal exercise treadmill testing has been described (13,14). Homans et al. (13), showed that dogs with partial coronary stenoses developed RWMAs after treadmill exercise. Schneider et al. (14) used radionuclide ventriculography to show that delayed functional recovery after submaximal exercise was primarily related to the extent of CAD. More recently, Vatterott et al. (15) found persistent RWMAs after exercise but, unfortunately, did not provide any angiographic data. Conversely, Brown et al. (16) failed to identify persistent RWMAs on radionuclide ventriculography after termination of exercise.

It is possible that RWMAs can be missed on radionuclide ventriculography because the extent of wall thickening cannot be accurately appreciated. Perfusion studies may show persistent defects several minutes or hours after discontinuation of

stress, but precise timing is difficult because of the lack of continuous imaging. Positron emission tomographic studies have suggested (17) that patients with CAD may demonstrate prolonged metabolic alterations for at least 1 h after exercise, but again, continuous imaging is difficult.

Stress echocardiography is ideally suited for the continuous recording of wall motion after discontinuation of stress. In our study we were able to correlate the persistence of ventricular dysfunction after cessation of stress with the severity of ischemia because the recovery phase in patients with more extensive RWMAs at peak stress was more prolonged.

Myocardial stunning. Myocardial stunning usually refers to postischemic ventricular dysfunction after restoration of perfusion (18). Delayed recovery of RWMAs may also represent myocardial stunning (18,19). However, demonstration of reperfusion is crucial to separate prolonged ischemia from stunning itself (20).

Myocardial stunning has been observed in experimental animal models with temporarily induced coronary artery occlusion followed by reperfusion (13,20). It is also possible that a similar phenomenon may occur in animals when myocardial ischemia is demand driven in the setting of subtotal coronary stenosis (21). There is sufficient evidence that stunned myocardium can occur in humans after thrombolytic therapy for acute myocardial infarction (22,23) or temporary coronary artery occlusion induced by angioplasty (24). Whether the presence of persistent myocardial dysfunction after stress testing in demand-driven ischemia equals myocardial stunning is very difficult to establish and would require demonstrating normal myocardial reperfusion at a time when absence of contraction continues in the same myocardial region. Importantly, none of our patients demonstrated worsening ventricular dysfunction during the 30-min observation period of the recovery phase. Because we did not attempt to assess myocardial perfusion in this study, we purposely avoided using the term myocardial stunning. Although myocardial stunning may be multifactorial and may depend not only on the extent and severity of myocardial ischemia at peak stress but also on the duration of stress and the severity of rest myocardial dysfunction, we failed to demonstrate such a link.

Pathophysiologic considerations. According to the ischemic cascade, RWMAs precede ECG changes and last longer after their resolution. In our study, 53% of patients had no ECG changes despite positive results on DSE. Ischemic ECG changes were present in 46% of patients and normalized earlier than RWMAs (Fig. 1). The rapidity with which ST segment changes normalized after stress may reflect prompt restoration of regional blood flow (21).

The sensitivity of the ECG for detecting ischemia depends on the position of the recording leads, the degree of blood flow reduction and the extent of ischemic myocardium (25–27). The duration of ST segment depression after exercise has been used to predict severity of CAD, but despite high specificity it has only moderate sensitivity (28). In our study the majority of ischemic ECG changes had returned to normal within 10 min, and only three patients with two- and three-vessel disease had persistent abnormalities up to the minute 15.

Limitations of the study. Although monitoring of wall thickening during recovery was performed continuously after discontinuation of the dobutamine infusion, regional measurement of wall thickening was not attempted. Instead, a side by side comparison of each individual segment was performed at fixed time intervals in an attempt to demonstrate appreciable changes in wall motion from one stage to the next. Although subtle changes in wall motion between stages might have been missed, we could ascertain significant wall thickening changes over a prolonged time into the recovery period. Additionally, this side by side analysis showed very good agreement between observers with regard to assessment of recovery of an ischemic segment.

Estimation of CAD severity was performed by visual assessment. Quantitative assessment of minimal lumen diameter might have provided a better estimate of stenosis severity but is more difficult to perform in patients with multivessel disease and not customary in routine clinical practice. In addition, multiple lesions along the same coronary artery may have different hemodynamic significance for stenosis severity than a single lesion. Perhaps an intracoronary flow wire should have been used to measure coronary flow and flow reserve for each lesion. However, we were able to demonstrate a link between the extent of ventricular dysfunction after stress and time to recovery.

Conclusions. We demonstrated that delayed recovery of RWMAs correlates well with severity of myocardial ischemia after DSE in patients with known CAD as well as with number of diseased vessels. Careful observation during the recovery period may add to better assessment of the extent and severity of ischemia in patients with CAD. Whether this delayed recovery represents a form of myocardial stunning after reversible ischemia remains unclear. Simultaneous perfusion studies may be necessary to distinguish ischemic recovery from stunning.

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