

Transient Left Ventricular Filling Abnormalities (Diastolic Stunning) After Acute Myocardial Infarction

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A variety of experimental studies suggest that diastolic left ventricular (LV) function changes after acute myocardial infarction (AMI), but limited data exist on these changes in humans. To assess diastolic filling after AMI, 60 patients underwent Doppler echocardiographic examination within 24 hours of AMI. Of 54 patients who also underwent catheterization, 45 (83%) were successfully reperfused. A subgroup of 17 patients underwent a follow-up Doppler examination at 7 days after infarction, whereas 15 patients with stable exertional angina served as control subjects. There was no significant difference in age, gender, incidence of systemic hypertension or diabetes mellitus, heart rate, mean arterial pressure or severity of coronary artery disease between the infarct and control groups. The infarct group had a lower velocity time integral total (9.9 ± 0.4 cm vs 12.0 ± 0.9 cm, $p < 0.001$), a lower velocity time integral E (5.8 ± 0.3 cm vs 6.8 ± 0.5 cm, $p < 0.01$) and a lower velocity time integral 0.333 (3.5 ± 0.4 cm vs 6.1 ± 0.5 cm, $p < 0.01$) than the control group. In addition, velocity time integral A/total was significantly greater in the infarction group (0.44 ± 0.03 vs 0.35 ± 0.04 , $p < 0.01$) compared to the control group. The follow-up subgroup showed an increase in velocity time integral total ($p < 0.01$), velocity time integral E ($p < 0.05$) and velocity time integral 0.333/total ($p < 0.05$) over the first 7 days after infarction. The final recovery values at 7 days were not significantly different from those of the coronary artery disease group. Patients with initial ejection fractions $< 40\%$ or anterior infarction had the greatest recovery during the 7-day period. In conclusion, LV filling is further impaired during acute infarction

compared to patients with stable coronary artery disease with the predominant impairment in early diastole. After infarction, filling parameters improve over the first 7 days after AMI, suggesting a recovery of diastolic stunning.

(Am J Cardiol 1990;66:897-903)

Acute myocardial infarction (AMI) is well known to produce impaired systolic function, whereas reperfusion may attenuate the measured decline in systolic function.^{1,2} The concept of myocardial stunning has been proposed to explain the delayed recovery in systolic myocardial performance after AMI.³ The impact of AMI and reperfusion on left ventricular (LV) diastolic performance and the possibility of diastolic stunning is less clear. In this regard, it has been shown that transient myocardial ischemia can result in diastolic filling abnormalities in addition to systolic dysfunction.^{4,5} Furthermore, experimental studies have indicated that AMI leads to abnormal LV stiffness or relaxation that may improve with time.^{6,7} The nature and extent of LV diastolic dysfunction in AMI in humans and its potential for recovery remain unsettled. The development of Doppler echocardiography has allowed the noninvasive measurement of diastolic filling, which correlates well with other measures of filling.⁸ Accordingly, this study characterizes Doppler LV filling in patients with AMI compared to patients with stable coronary disease and determines if changes in filling occur during the first 7 days after AMI, which may support the existence of diastolic stunning.

METHODS

These studies were approved by the Human Subjects Review Committee of the University of Michigan Medical School and informed consent was obtained from each patient.

Study group: Pulsed Doppler echocardiograms were performed in 60 patients (51 men, 9 women) within 24 hours of admission with AMI as determined by typical history, standard electrocardiographic changes and an increase in cardiac enzymes. No patient had significant valvular heart disease, evidence of mitral regurgitation

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TABLE I Demographics and Clinical Parameters for Patients in the Coronary Artery Disease Control Group, Patients in Acute Myocardial Infarction Group, and Patients in Follow-Up Subgroup

	CAD (n = 15)	MI (n = 60)	F/U (n = 17)	p Value
Age (mean)	56 ± 9	57 ± 10	58 ± 2	NS
Men	12 (80%)	52 (87%)	12 (71%)	NS
Hypertension	5 (33%)	31 (52%)	9 (53%)	NS
Diabetes mellitus	3 (20%)	14 (23%)	6 (35%)	NS
Extent of CAD				
1 vessel	9 (60%)	33 (55%)	10 (59%)	NS
2 vessels	6 (40%)	17 (28%)	6 (41%)	NS
3 vessels	0 (0%)	4 (7%)	1 (5%)	NS

CAD = coronary artery disease (defined as ≥70% narrowing of a major coronary artery or branch); F/U = follow-up subgroup, MI = acute myocardial infarction group; NS = not significant.

or cardiogenic shock and all were in a sinus rhythm and had a technically adequate study. Ejection fractions were determined in all patients within 24 hours of admission by radionuclide techniques.

The patients ranged in age from 37 to 76 years (mean 57). All patients developed new Q waves during hospitalization. Thirty-one had a history of systemic hypertension and 14 were known to have diabetes mellitus. Thirty-one patients had anterior AMI and 29 had inferior AMI.

Diagnostic catheterization was performed in 54 patients during the first week after infarction (6 patients refused catheterization). Thirty-three patients had 1-vessel disease (defined by a ≥70% narrowing of a major coronary artery or branch), 17 had 2-vessel and 4 had 3-vessel disease. Forty-five of these 54 patients (83%) were successfully reperfused, as determined by an open infarct-related vessel at catheterization.

A subgroup of 17 patients underwent a follow-up Doppler examination 7 days after admission as part of a later phase of patient recruitment. These patients ranged in age from 37 to 76 years (mean 56). Eight patients had inferior AMI while 9 patients had anterior AMI. Serial measurements of systolic function by radionuclide or contrast ventriculography were available in 14 of these patients. There was no difference in age, gender, blood pressure, severity of coronary artery disease, ejection fraction or Doppler filling parameters between these patients and the infarct group as a whole, as listed in Table I.

Control group: Doppler studies were also performed on 15 patients with angiographically documented coronary artery disease (12 men, 3 women). These patients ranged in age from 36 to 74 years (mean 56) and had a history of typical stable exertional angina, ≥70% narrowing of a major coronary artery or large branch, LV ejection fraction of 50% and no evidence of valve disease. No patient had previous myocardial infarction, as determined by history, electrocardiogram and wall motion analysis. Five patients had a history of systemic hypertension and 3 had diabetes mellitus. Nine patients had 1-vessel and 6 had 2-vessel disease.

Doppler studies: Pulsed-wave Doppler examinations of the LV inflow were performed with a 2.5-MHz

TABLE II Hemodynamics and Peak Filling Velocities for Patients in the Coronary Artery Disease Group and the Acute Myocardial Infarction Group

	CAD (n = 15)	MI (n = 60)	p Value
HR (beats/min)	66 ± 2	80 ± 3	NS
MAP (mm Hg)	79 ± 3	85 ± 2	NS
Peak E (cm/s)	56 ± 2	54 ± 2	NS
Peak A (cm/s)	51 ± 4	57 ± 2	NS
Peak E/A	1.1 ± 0.1	1.0 ± 0.1	NS

CAD = coronary artery disease group; HR = heart rate; MAP = mean arterial pressure; MI = acute myocardial infarction group; NS = not significant.

transducer. Using the apical 4-chamber view, the Doppler sample volume (5 mm) was placed in the mitral valve funnel on the LV side of the mitral annulus. The sample volume was placed as parallel to flow as possible to maximize recorded velocity.⁹ The tracings were recorded on a strip chart recorder at a paper speed of 100 mm/s.

A digitizing pad and a microcomputer were used to analyze the Doppler wave forms. Wave form analysis was performed by tracing the modal velocity (darkest portion) of each beat and averaging ≥3 consecutive beats.¹⁰ Peak filling velocities of the early rapid filling wave (E) and the atrial contraction wave (A) as well as the E/A ratio were determined. Velocity time integrals, reflecting the area under the wave form, were computed for the total diastolic cycle (velocity time integral total), as well as for early filling (velocity time integral E), late atrial filling (velocity time integral A) and the first one-third of the diastolic cycle (velocity time integral 0.333).

Statistical analysis: All results are expressed as mean ± standard error of the mean. Comparisons were made between the filling parameters and hemodynamics of the infarct group and the coronary artery disease group. Paired comparisons were also made between the acute and follow-up studies in the 7-day follow-up subgroup. A 2-tailed Student's *t* test was used for all the analyses.

RESULTS

Comparison of initial filling after infarction to control subjects: The coronary artery disease control group was age- and sex-matched to the AMI group. There was no difference in incidence of diabetes mellitus, systemic hypertension or severity of coronary artery disease between the 2 groups as listed in Table I.

Heart rate and mean arterial pressure were not significantly different between groups. Peak early filling (E), late filling velocity (A) and E/A ratio did not differ significantly between the coronary artery disease and acute infarction groups (Table II). However, there were differences between the velocity time integrals in the infarct group and the coronary artery disease control subjects, as shown in Figure 1. There was a significantly lower total filling integral (velocity time integral total) in the infarct group (9.9 ± 0.4 cm vs 12.0 ± 0.9 cm, $p < 0.001$), as well as lower early diastolic filling (velocity time integral E; 5.8 ± 0.3 cm vs 6.8 ± 0.5 cm, $p < 0.01$), and first third velocity time integral ($3.5 \pm$

TABLE III Twenty-Four-Hour Doppler Examination Parameters for Patients in the Acute Myocardial Infarction Group Compared to Patients in the Follow-Up Subgroup

	MI (n = 60)	F/U (n = 17)	p Value
Peak E (cm/s)	53 ± 2	5 ± 5	NS
Peak A (cm/s)	57 ± 2	55 ± 4	NS
Peak E/A	1.0 ± 0.1	0.9 ± 0.1	NS
VTI E (cm)	5.8 ± 0.3	5.1 ± 0.2	NS
VTI A (cm)	4.4 ± 0.2	4.2 ± 0.2	NS
VTI E/A	1.6 ± 0.1	1.4 ± 0.2	NS

VTI = velocity time integral; other abbreviations as in Table I.

0.4 cm vs 6.1 ± 0.5 cm, $p < 0.01$). The proportion of the late filling to total filling, as measured by velocity time integral A/total, was significantly greater in the infarct group (0.44 ± 0.03 vs 0.35 ± 0.04 , $p < 0.01$), whereas velocity time integral E/total and velocity time integral E/A were not significantly different between the 2 groups.

Of the 54 infarction patients who underwent catheterization, 45 were successfully reperfused. There were no significant differences in peak velocities or velocity time integrals on the acute examinations based on whether reperfusion was successful.

Changes in filling during the first week after infarction: The subgroup of 17 patients with follow-up examinations did not differ significantly from the infarct group as a whole in the clinical parameters of age, gender, systemic hypertension, diabetes mellitus, heart rate, blood pressure or severity of coronary artery disease. Furthermore, the follow-up subgroup had similar Doppler indexes on the 24-hour examination compared to the AMI group as a whole (Table III). Heart rate, mean arterial pressure, peak E, peak A and peak E/A were not significantly changed over the first 7 days, as listed in Table IV. There were, however, significant changes in the velocity time integrals over this time.

Figure 2 shows the changes in mean velocity time integrals from the acute to the follow-up examination. The mean total velocity time integral was depressed

TABLE IV Hemodynamics and Peak Filling Velocities for Patients in the Follow-Up Subgroup

	AMI (n = 17)	F/U (n = 17)	p Value
HR (beats/min)	82 ± 3	76 ± 2	NS
MAP (mm Hg)	85 ± 2	83 ± 2	NS
Peak E (cm/s)	50 ± 5	55 ± 3	NS
Peak A (cm/s)	55 ± 4	61 ± 4	NS
Peak E/A	0.9 ± 0.1	1.0 ± 0.1	NS

AMI = 24-hour study for follow-up subgroup; other abbreviations as in Table II.

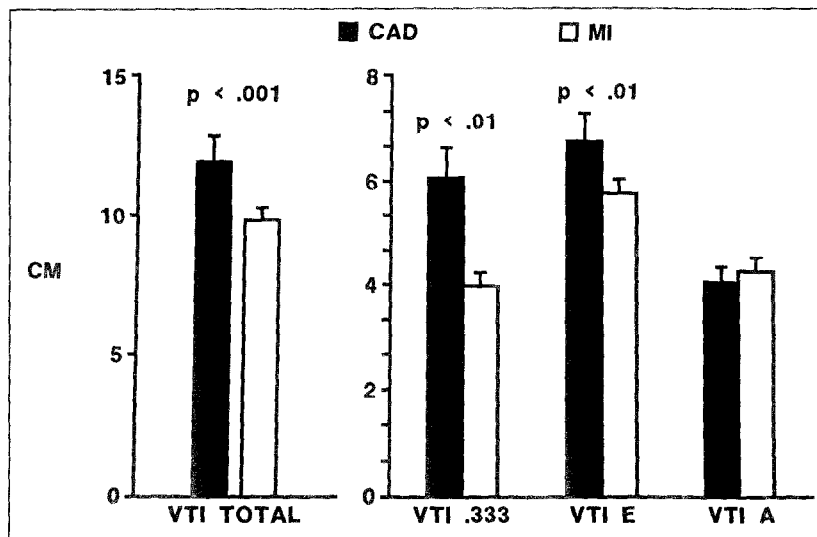
acutely, but recovered by 1 week (8.5 ± 0.7 cm to 11.8 ± 1.1 cm; $p < 0.01$) to that of control subjects. Similarly, early filling, as measured by velocity time integral 0.333, and velocity time integral E were depressed acutely (3.5 ± 0.4 cm and 5.1 ± 0.5 cm, respectively) and showed significant recovery after 7 days (5.2 ± 0.5 cm, $p < 0.01$ and 6.8 ± 0.7 cm, $p < 0.05$, respectively). Again, the follow-up values were not significantly different from coronary artery disease control subjects. There was no significant change in velocity time integral A from acute to follow-up examination.

Velocity time integral A/total was lower at follow-up than it was acutely (0.4 ± 0.02 vs 0.5 ± 0.04), although statistical significance was not quite reached ($p = 0.07$). Velocity time integral 0.333/total increased significantly from the initial study to 7 days (0.42 ± 0.04 vs 0.45 ± 0.03 ; $p < 0.05$) but velocity time integral E/total was unchanged. The peak velocities and velocity time integrals at 7 days were not significantly different from those of the coronary disease control group.

Serial measurements of global systolic function by radionuclide or contrast ventriculography were available in 14 of the 17 patients in the follow-up subgroup. There were no significant changes in ejection fraction from the first to the seventh day after infarction (initial mean $43.1 \pm 2.5\%$ vs a follow-up mean of $45.4 \pm 3.0\%$, $p = 0.57$).

Subgroup analysis was performed in the follow-up patients to compare anterior myocardial infarction versus inferior infarction and ejection fraction $>40\%$ vs

FIGURE 1. Comparison of velocity time integrals of total diastolic filling (velocity time integral total), first third of diastole (velocity time integral 0.333), early filling (velocity time integral E) and late filling (velocity time integral A) in coronary disease control subjects versus acute myocardial infarction group. CAD = coronary artery disease control group; CM = centimeters; MI = acute myocardial infarction group; VTI = velocity time integral.



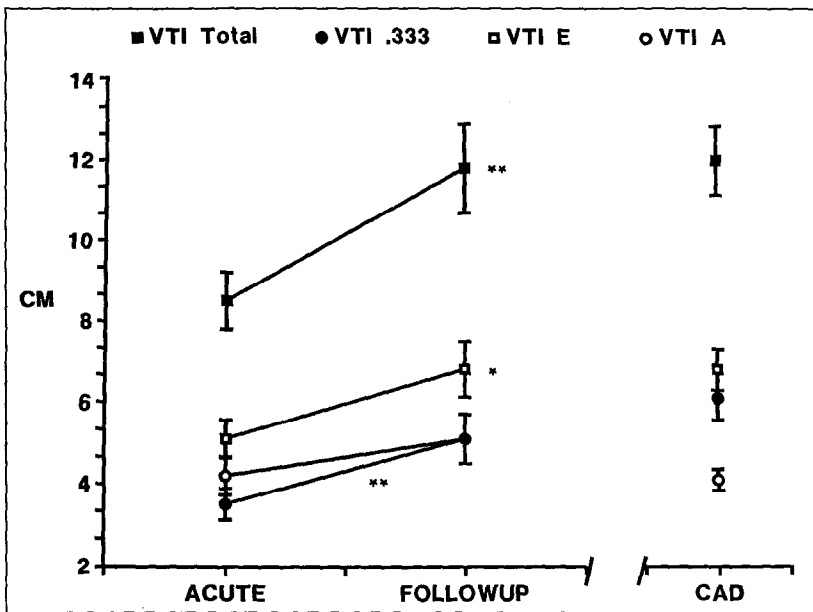


FIGURE 2. Velocity time integrals of total filling (velocity time integral total), first third diastole (velocity time integral 0.333), early filling (velocity time integral E) and late filling (velocity time integral A) at 24 hours and the 7 days after infarction. Values for the coronary artery disease control group are placed on right side of the graph for reference. *p < 0.05 vs 24 hours; **p < 0.01 vs 24 hours.

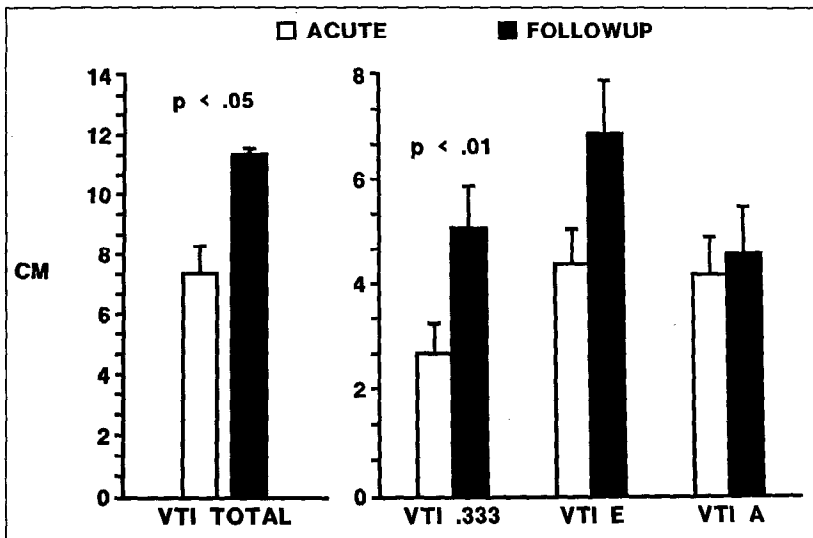


FIGURE 3. Comparison of velocity time integrals between acute and follow-up examinations in the subgroup of patients with anterior myocardial infarction.

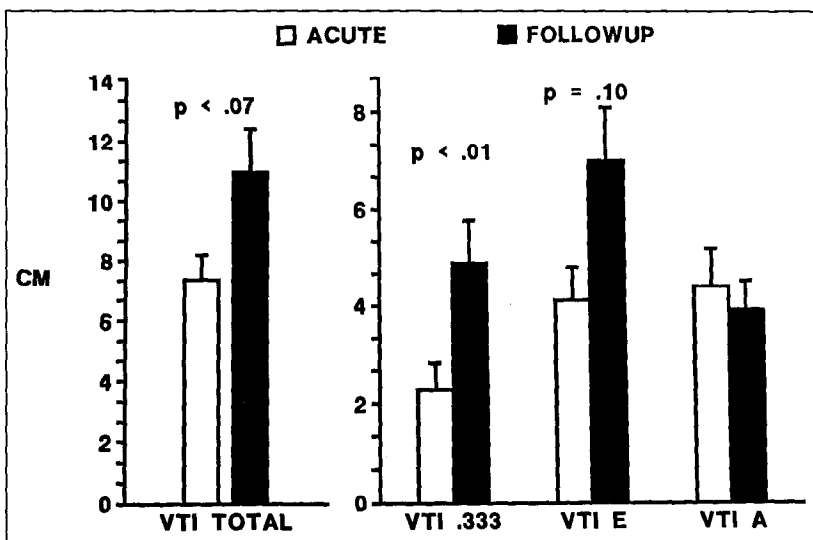


FIGURE 4. Velocity time integrals for the acute and follow-up examinations in patients with initial ejection fraction < 40%.

<40%. There was no significant change in hemodynamics over the week after infarction in the group as a whole, although patients with anterior infarction had a statistically significant change in heart rate over the 7-day follow-up period (89 ± 4 vs 78 ± 3 beats/min respectively, $p < 0.01$). There were no significant changes in peak filling velocities over time, but in patients with anterior infarction, a significant improvement in velocity time integral total (7.4 ± 0.9 cm vs 11.4 ± 1.6 cm, $p < 0.05$) and velocity time integral 0.333 (2.7 ± 0.5 cm vs 5.1 ± 0.8 cm, $p < 0.01$) was seen (Figure 3). The patients with inferior infarction did not show significant changes in peak velocities or velocity time integrals.

Similarly, in the subgroup of patients with initial ejection fraction <40%, there was no change in hemodynamics or peak filling velocities. However, despite the limited number of patients, a significant improvement in early filling as measured by velocity time integral 0.333 (2.4 ± 0.5 cm vs 5.1 ± 0.9 cm, $p < 0.01$) was seen in this subgroup of patients with initially impaired ejection fraction. Velocity time integral total and velocity time integral E showed trends to increase within 7 days, but statistical significance was not quite reached. These results are shown in Figure 4. Patients with initial ejection fractions that were >40% did not show any significant changes in peak filling velocities or velocity time integrals over the first 7 days.

Sixteen of the 17 follow-up patients were successfully reperfused. Because of the high incidence of reperfusion in this group, subgroup analysis to compare filling parameters at follow-up based on reperfusion status was not possible.

DISCUSSION

Alterations in LV filling dynamics may be due to a variety of mechanisms, including changes in myocardial stiffness, impaired LV relaxation, changes in right ventricular loading conditions, pericardial constraints, viscoelastic considerations and nonuniformity, among others.¹¹ Clearly, the determinants of diastolic filling are complex. The aim of this study was not to set apart the impact of these various forces, but to measure LV filling after AMI and the changes that occur in filling over time, as a reflection of possible recovery.

The important new observations from our study are the following: early diastolic LV filling after AMI is decreased, while the atrial contribution to filling is maintained; filling is most impaired initially in patients with anterior infarction or with more severely depressed ejection fraction; and normalization of filling patterns occurs in the first week after AMI.

It is well known that myocardial ischemia can lead to impairment in systolic function, with regional wall motion abnormalities resulting in decreased ejection fraction and increased ventricular volumes.¹² The impact of acute ischemia on diastolic properties has been less well defined. Several investigators have observed an upward shift in the pressure-volume curve with myocardial ischemia as a result of an increase in resistance to LV filling or increased chamber stiffness.^{13,14} These diastolic abnormalities during acute ischemia are further

reflected by impairment in early LV filling after transient coronary occlusion by angioplasty.⁴

Diastolic filling in coronary artery disease: In addition to these findings with acute ischemia, a number of studies have identified abnormal filling patterns in patients with stable coronary artery disease. Radionuclide angiography has shown that patients with coronary artery disease have impaired early peak LV filling rates at rest, independent of systolic function or previous AMI. These filling abnormalities have been shown to normalize after revascularization, either by angioplasty or coronary bypass surgery.^{15,16} Wind et al,⁹ using Doppler echocardiography, showed significantly depressed peak E (early diastolic) velocity in patients with stable coronary artery disease and normal global systolic function as well as an increased percentage of the Doppler LV filling during late diastole. These diastolic LV filling abnormalities persisted 24 hours after successful angioplasty. Thus ischemia, in the absence of AMI, can lead to prolonged abnormalities in early filling, with preservation of late filling due to atrial systole. In this study, diastolic LV filling was equally impaired acutely in patients who had been successfully reperfused and in those who had not. Although this impairment may be reversible, the time course and mechanism of such recovery is not well known.

Diastolic LV filling abnormalities have also been reported in patients with remote AMI. Fuji et al¹⁷ studied 40 patients with previous AMI and found prolonged deceleration and acceleration half-times of transmitral inflow, as well as an increase in late diastolic inflow relative to early filling, suggesting that weeks after AMI, early diastolic filling is impaired, which may be compensated for by atrial systole. Thus, these data, in combination with our own, may suggest that diastolic function initially is impaired after AMI, improves over the first 7 days, but then becomes further impaired as infarct healing and scarring occur. However, additional serial studies in patients after AMI will be necessary to support this hypothesis.

Other factors, such as hypertension, diabetes and mitral regurgitation, have been shown to affect filling dynamics. However, there was no difference in the incidence of these clinical parameters in the infarction patients and the control group.

Impact of reperfusion: The development of thrombolysis has provided the potential to change the natural history of AMI. The post-AMI period has been shown to result in dynamic changes with consequent myocardial remodeling and possible infarct expansion. The impact of thrombolysis and reperfusion on subsequent systolic and diastolic performance has only recently been addressed.^{18,19} Global and regional systolic function may be preserved both in experimental animals and in humans after infarction with reperfusion.^{20,21} However, little is known in humans concerning diastolic performance after acute ischemia and reperfusion. In this regard, our study provides new observations on changes in diastolic filling after reperfusion. Almost all patients in this study underwent successful reperfusion, which may have contributed to the improvement in filling dynamics

over time. The percentage of patients who did not have successful reperfusion was too small to assess the differential impact reperfusion had on diastolic filling in the recovery period.

Few experimental studies have addressed the effect of reperfusion on diastolic performance. Kurnik et al⁶ examined the impact of AMI and reperfusion on myocardial and chamber stiffness in a canine model. They found coronary occlusion led to a decrease in LV systolic function and a concomitant increase in myocardial and chamber stiffness. One hour of occlusion with subsequent reperfusion resulted in improvement in systolic function and decreased stiffness by 1 week. On the other hand, late reperfusion or permanent occlusion resulted in persistent abnormalities in indexes of systolic and diastolic function. Tilton et al⁷ examined LV segmental relaxation in dogs undergoing a 2- or 4-hour coronary occlusion followed by reperfusion. They found that the recovery of diastolic function occurred in the first week after AMI. Thus, the findings of this experimental study concur with our clinical observations, which showed an improvement in diastolic filling over the first week after AMI.

Potential mechanisms: The determinants of diastolic filling are complex and cannot be differentiated in our study. However, 2 major mechanisms of impaired filling in the setting of AMI are decreased myocardial relaxation and increased LV stiffness. Decreased relaxation would be expected to have its greatest impact during early diastole, as the transition from active contraction to active relaxation occurs.²² Impaired relaxation after AMI appears to be due to depletion of adenosine triphosphate stores or changes in intracellular calcium concentration.²³⁻²⁵ Increased stiffness, while it may affect the slope of the pressure-volume curve throughout diastole, would tend to provide the greatest resistance to filling near end-diastole, at maximum ventricular distention.²² This increased stiffness may be secondary to edema formation early after AMI, or developing fibrosis in the late post-AMI course.²⁶ Both of these mechanisms may play a role in contributing to observed diastolic filling abnormalities.

In addition to decreased myocardial relaxation and increased LV stiffness, there are a number of other factors that may also play a role in diastolic filling abnormalities. These include the production of reactive oxygen metabolites, which have been shown to interfere with sarcoplasmic reticulum function, extrinsic factors such as pericardial constraints and right ventricular loading conditions, and temporal nonuniformity of relaxation. Clearly, further investigation will be necessary to delineate the contributions of these multiple factors.

Recent experimental models have shown that post-ischemic reperfused myocardium exhibits abnormalities in diastolic as well as systolic performance, which may be prolonged but which have the potential for recovery.^{7,27} These findings have been proposed to reflect stunning of both systolic and diastolic properties (i.e., sublethal ischemic injury to myocardial cells results in functional abnormalities, which may be reversible once

flow is restored). Our clinical findings are consistent with the hypothesis of stunning of diastolic function after ischemic injury with recovery after reperfusion.

The decrement in total filling observed in this study may also be related to changes in cardiac output, since concomitant changes in systolic performance occur after AMI.²⁷ However, the overall pattern of diastolic filling changed with infarction, with the predominate impact on filling occurring during early diastole, which normalized in the recovery period. This differential change in the pattern of LV filling suggests a concomitant abnormality in diastolic performance. Furthermore, the changes in diastolic filling that occurred during the first week after AMI were not accompanied by improvement in systolic function measured by ejection fraction. Thus, our study supports the concept that perturbations in systolic and diastolic function are tightly interrelated and that ischemia results in a global stunning of myocardial performance with gradual recovery after reperfusion.

Study limitations: Several studies have shown the effect preload can have on filling dynamics.^{28,29} Decreased preload, such as by occlusion of the vena cava or by intravenous nitroglycerin decreases peak early filling, whereas increased preload via volume infusion augments early filling.³⁰ In general, one might expect higher filling pressures after infarction, which would have augmented early filling, which was the opposite of our findings. Thus, it seems unlikely that the changes we observed can be accounted for by changes in preload. However, since invasive hemodynamic correlates were not available in all of our patients, changes in preload affecting early diastolic filling cannot be excluded. Heart rate can also alter diastolic filling. Although there was a trend toward higher heart rates initially after AMI, it was not statistically significant. In the subgroup of patients with anterior AMI, heart rate significantly decreased within 1 week, although the AMI group as a whole, as well as other subgroups, did not have significant changes in heart rate with serial examinations. Thus, it is unlikely that the changes in filling that we observed can be explained by these other factors.

Acknowledgment: We sincerely appreciate the contributions of Dr. Rita C. Pinton and Dr. A. Rebecca Snider to the study. We would also like to thank Mary Sue LeMire and Maria Bajor for their technical assistance during the study.

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