

# Recovery of Ventricular Function after Myocardial Infarction in the Reperfusion Era: The Healing and Early Afterload Reducing Therapy Study

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**Background:** Patients with reduced left ventricular function and ventricular enlargement after myocardial infarction are at significantly greater risk for congestive heart failure and death. Nevertheless, recovery of ventricular function occurs in a significant proportion of patients after myocardial infarction, and modern reperfusion strategies have been associated with increased recovery of function.

**Objective:** To determine the extent and predictors of recovery of ventricular function after anterior Q-wave myocardial infarction in the reperfusion era.

**Design:** Subgroup analysis of the Healing and Early Afterload Reducing Therapy study.

**Setting:** 35 medical centers in the United States and Canada.

**Patients:** 352 patients with Q-wave anterior myocardial infarction.

**Intervention:** Placebo for 14 days, followed by full-dose (10 mg) ramipril until day 90; low-dose (0.625 mg) ramipril for 90 days; or full-dose ramipril for 90 days. All patients underwent reperfusion therapy.

**Measurements:** Echocardiography was performed on day 1 (before randomization), day 14, and day 90 after myocardial infarction. Left ventricular volume and ejection fraction were measured and wall-motion analyses were performed at all three time points in 249 patients and at baseline in an additional 12 patients who died during follow-up. Echocardiographic and nonechocardiographic predictors of ventricular recovery were examined.

**Results:** By day 90, 55 of 252 (22%) patients who had abnormal ejection fraction and wall-motion abnormalities on day 1 demonstrated complete recovery of function (ejection fraction in the normal range and infarct segment length of 0%), and an additional 36% (91 of 252 patients) demonstrated partial recovery of function. At 90 days, 53% (132 of 249) of patients had greater than 5% improvement in ejection fraction, whereas only 16% (39 of 249) had a decrease in ejection fraction of more than 5%. The majority of functional improvement occurred by day 14 after infarction. Of various clinical and echocardiographic measures obtained on day 1, peak creatine kinase level was the strongest independent predictor of subsequent recovery of ventricular function in multivariate analysis. Each 100-unit increase in peak creatine kinase was associated with a 4.3% decreased odds of recovery ( $P < 0.001$ ) after adjustment for ejection fraction on day 1, extent of akinesis or dyskinesis, treatment regimen, Killip class, age, and sex.

**Conclusion:** Significant myocardial stunning with subsequent improvement of ventricular function occurred in the majority of patients after Q-wave anterior myocardial infarction. A lower peak level of creatine kinase, an estimate of the extent of necrosis, is independently predictive of recovery of function. Early functional assessment (day 1 after acute myocardial infarction) had limited ability to predict recovery of ventricular function.

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A minority of patients experience progression to clinically significant left ventricular dysfunction and enlargement after myocardial infarction (1). However, patients with worsening left ventricular function after myocardial infarction are at significantly greater risk for congestive heart failure and death (2, 3). Advances in the care of acute myocardial infarction over the past decade—particularly the use of mechanical and pharmacologic reperfusion therapies—have reduced the risk for left ventricular dysfunction (4) and improved morbidity and mortality after myocardial infarction (5).

Improvements in left ventricular function can be

apparent shortly after myocardial infarction and have generally been attributed to recovery from myocardial stunning (6). However, the great heterogeneity in patients after myocardial infarction underscores the importance of identifying factors that influence the progression and regression of left ventricular dysfunction.

The Healing and Early Afterload Reduction Therapy (HEART) trial (7) was a randomized, double-blind study of the hemodynamic effects of early versus delayed administration of three regimens of ramipril, an angiotensin-converting enzyme (ACE) inhibitor, after myocardial infarction. Patients were followed by performing

serial echocardiography within the first 24 hours after myocardial infarction and at 14 and 90 days after myocardial infarction. Patients treated with ramipril experienced significant improvements in ejection fraction at 14 days after myocardial infarction, but all echocardiographic measures of ventricular size and function were similar in the three treatment groups by 90 days (7). The present analysis assessed clinical and echocardiographic predictors of recovery of ventricular function in the 88% of patients in HEART who underwent reperfusion therapy (65% received thrombolysis alone, 15% had percutaneous transluminal coronary angioplasty alone, and 8% had both).

## METHODS

### Patients

The HEART study enrolled 352 patients with acute anterior Q-wave myocardial infarction. Patients with ST-segment elevation or new Q waves in two or more contiguous leads were also eligible. Patients underwent echocardiography within 24 hours after myocardial infarction (before randomization [day 1]) and at 14 and 90 days after myocardial infarction. Patients were randomly assigned to receive one of three dosing regimens of ramipril: placebo for 14 days, followed by full-dose (10 mg) ramipril; low-dose (0.625 mg) ramipril for 90 days; or full-dose ramipril for 90 days. Thus, by day 14, all patients were treated with ACE inhibition. Inclusion and exclusion criteria and details of the titration scheme and patient characteristics are described elsewhere (7).

Serial echocardiographic data from days 1, 14, and 90 were available in 249 patients. Baseline data were available for an additional 12 patients who died during follow-up. Patients with day-1 echocardiograms of insufficient quality and those who were alive at 90 days but for whom echocardiograms at this time point were not available were excluded from analysis. Of the 352 patients enrolled in the study, 48 did not have echocardiograms of sufficient quality for analysis, and 18 (including 13 who died) did not have all three echocardiograms. We also excluded 25 patients who did not receive reperfusion therapy.

### Echocardiographic Analysis

Echocardiographic measurements were made in triplicate by using a Nova Microsonics (Mahwah, New

Jersey) workstation, as described elsewhere (7). The echocardiographic reader was blinded to treatment assignment. Endocardial borders from end-diastolic and end-systolic frames were digitized manually, and left ventricular volumes were assessed by using the Simpson rule method. Infarct segment length was assessed by manually tracing the akinetic or dyskinetic segment and was expressed as a percentage of the endocardial perimeter. The reproducibility of the echocardiographic measurements is reported elsewhere (7).

### Statistical Analysis

Patients were categorized into three groups according to degree of recovery of left ventricular function. Patients were categorized as having 1) complete recovery of function if functional abnormalities observed on day 1 improved to normal (left ventricular ejection fraction  $> 0.55$  and absence of regional akinesis or dyskinesis), 2) partial recovery of function if ejection fraction improved and the extent of regional akinesis or dyskinesis decreased from day 1, or no 3) recovery if neither of these criteria was fulfilled or death occurred before 90 days. Left ventricular enlargement (remodeling) was defined as an increase in ventricular end-diastolic volume between day 1 and day 90 and was treated as a continuous variable. Univariate and multivariate logistic regression were used to assess relationships between day 1 values and recovery of function.

Values are expressed as the mean ( $\pm$ SD). A *P* value less than 0.05 was considered statistically significant. Stata statistical software (Stata Corp., College Station, Texas) was used for analyses.

## RESULTS

### Baseline Characteristics and Left Ventricular Enlargement

Clinical and echocardiographic data were obtained on day 1 before randomization (Table 1). Included and excluded patients differed significantly only with regard to age ( $59.4 \pm 12.3$  years vs.  $64.2 \pm 12.9$  years;  $P = 0.001$ ). Patients with partial recovery had lower ejection fraction and larger volumes than did those with no recovery or complete recovery, and patients with full recovery had shorter infarct segments than did those with partial recovery or no recovery (Table 1). Fewer patients in the complete recovery group than in the partial or no recovery groups were diabetic, but this differ-

**Table 1. Baseline Characteristics of Patients by Recovery Group\***

Characteristic	No Recovery (n = 96)	Partial Recovery (n = 98)	Complete Recovery (n = 55)	P Value
Male sex, %	84	73	82	0.15
Age, y	58.9 ± 12.4	59.0 ± 12.0	57.7 ± 11.2	>0.2
Diabetes, %	22.9	20.4	10.9	0.18
Killip class I, %	80.2	79.6	77.8	>0.2
Previous myocardial infarction, %	14.7	16.5	7.2	>0.2
Hypertension, %	32.3	41.2	40.7	>0.2
Thrombolysis, %	84.3	82.6	81.8	>0.2
Angioplasty, %	28.1	26.5	21.8	>0.2
Both thrombolysis and angioplasty, %	9.4	8.3	2.6	0.16
Baseline echocardiographic values				
Ejection fraction	0.551 ± 0.086	0.481 ± 0.094†	0.540 ± 0.085‡	<0.001
End-diastolic volume, mL	99.7 ± 32.3	110.9 ± 39.9	99.6 ± 29.9	0.05
End-systolic volume, mL	45.2 ± 19.9	59.1 ± 30.6†	46.6 ± 19.0‡	<0.001
Length of akinetic or dyskinetic segment, %	25.2 ± 12.2	29.6 ± 8.8§	23.8 ± 9.6	0.001
Treatment group, %				
Placebo, then full-dose ramipril	32	31	33	
Low-dose ramipril	35	32	33	
Full-dose ramipril	32	36	34	>0.2
Time to reperfusion therapy, h	3.8 ± 3.4	3.5 ± 2.6	4.0 ± 7.5	>0.2

\* Values with the plus/minus sign are the mean ± SD.

†  $P < 0.001$  compared with the complete recovery group.

‡  $P < 0.001$  compared with the partial recovery group.

§  $P < 0.04$  compared with the complete recovery group.

||  $P = 0.002$  compared with the partial recovery group.

ence was not statistically significant. The recovery groups did not significantly differ with regard to other baseline characteristics or in the distribution of drug treatment.

### Recovery of Left Ventricular Function

On day 1, only 9 of 261 (3.4%) patients had normal ventricular function (ejection fraction > 0.55 and no akinesis or dyskinesis). The change in left ventricular ejection fraction varied widely and improved by day 90 in 171 of 261 (66%) patients (Figure 1). The mean change in ejection fraction during this time was  $0.045 \pm 0.098$ . Most of this change occurred in the first 14 days (mean change in ejection fraction from day 1 to 14,  $0.038 \pm 0.091$ ); minimal additional change occurred between days 14 and 90 (Table 2). Of the 252 patients with abnormal left ventricular function on day 1 (ejection fraction < 0.55 or any akinesis or dyskinesis), 13% had complete recovery of ventricular function by day 14 and 22% of patients had complete recovery by day 90. An additional 36% of patients had partial recovery of function by day 90, defined as improvement in ejection fraction from day 1 values and shortening of the akinetic or dyskinetic segment. The remaining patients had functional deterioration (decrease in ejection

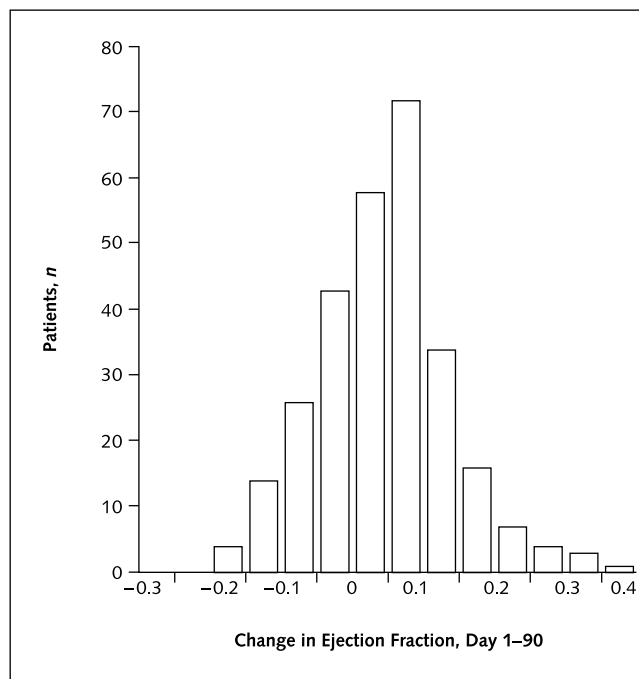
fraction or increase in the length of the infarct segment from day 1; 103 patients) or died (12 patients). At 90 days, 53% (132 of 249) of patients had greater than 5% improvement in ejection fraction from baseline, but only 16% (39 of 249) had a decrease in ejection fraction greater than 5%. The length of the infarct segment decreased in the group as a whole from  $27.0\% \pm 10.9\%$  at day 1 to  $19.1\% \pm 13.1\%$  at day 14 and  $16.9\% \pm 13.7\%$  at day 90.

We previously reported a statistically significant increase in ejection fraction from day 1 to 14 in patients receiving full-dose (10 mg) ramipril (7), although ejection fraction did not differ among the groups by day 90. In the current analysis, we found no differences in the percentage of patients with full recovery of function by day 14 or day 90 according to treatment group. In addition, recovery groups did not differ in time to reperfusion (Table 1) or the proportion of patients who recovered according to type of reperfusion therapy.

### Predictors of Recovery of Function

Baseline clinical characteristics, including age, sex, and Killip class, did not predict recovery of function. In contrast, peak creatine kinase level (which occurred a mean of  $27 \pm 17$  hours after onset of symptoms), a

**Figure 1. Distribution of change in ejection fraction from day 1 to 90.**



crude assessment of the extent of necrosis, and left ventricular function on day 1 (ejection fraction and extent of akinesis or dyskinesis) were significant predictors of recovery of function in univariate and multivariate analyses. The percentage of patients with complete recovery of function decreased as the creatine kinase quartile increased ( $P$  for trend  $< 0.001$ ) (Figure 2). In a multiple logistic regression analysis that included peak creatine kinase level, baseline ejection fraction, infarct segment length, Killip class, age, sex, and drug therapy, peak creatine kinase level remained the strongest independent

predictor of recovery. Each 100-unit increase in creatine kinase level was associated with a 4.3% decreased odds of full recovery ( $P = 0.001$ ).

**Left Ventricular Enlargement and Recovery of Function**

Overall, left ventricular enlargement (remodeling) was inversely related to improvement in ejection fraction over 90 days ( $r = -0.27$ ;  $P < 0.001$ ). Nevertheless, during this time, ejection fraction improved by  $4.5\% \pm 9.5\%$  despite an increase in end-diastolic volume of  $5.6 \pm 25.7$  mL. The majority of this change occurred in the first 14 days after myocardial infarction. Patients who recovered function demonstrated the least enlargement. Left ventricular volume decreased by  $7.6 \pm 18.4$  mL from day 1 to day 90 in patients with complete recovery of function, compared with an increase of  $9.4 \pm 26.3$  mL in all other patients ( $P < 0.001$ ).

Left ventricular enlargement of any degree was observed in only 26% of patients with complete recovery. However, a dissociation between ejection fraction and ventricular enlargement was observed in many individual patients; 32% had increased end-diastolic volume between day 1 and day 90 (mean,  $19.9 \pm 15.2$  mL) despite improvement in ejection fraction and shortening of the infarct segment.

**DISCUSSION**

Morbidity and mortality in the months and years after myocardial infarction have been shown to be directly related to the extent of the resulting ventricular dysfunction (8). Our findings show that in the setting of aggressive reperfusion and pharmacologic strategies, many patients with myocardial infarction have substan-

**Table 2. Echocardiographic Variables throughout the Study**

Variable	Day 1 (n = 261)	Day 14 (n = 255)	Day 90 (n = 249)
Ejection fraction (change from day 1)	0.517 $\pm$ 0.097	0.558 $\pm$ 0.094 (0.038 $\pm$ 0.091)	0.566 $\pm$ 0.96 (0.045 $\pm$ 0.098)
End-systolic volume (change from day 1), mL	51.0 $\pm$ 25.0	49.6 $\pm$ 25.6 (-1.3 $\pm$ 17.8)	49.4 $\pm$ 26.9 (-1.6 $\pm$ 19.9)
End-diastolic volume (change from day 1), mL	103.4 $\pm$ 35.1	109.5 $\pm$ 38.2 (5.7 $\pm$ 23.2)	109.7 $\pm$ 38.3 (5.6 $\pm$ 25.7)
Length of segment with akinesis or dyskinesis (change from day 1), %	27.0 $\pm$ 10.9	19.1 $\pm$ 13.1 (-7.5 $\pm$ 10.9)	16.9 $\pm$ 13.7 (-9.7 $\pm$ 11.8)
Patients with normal function, n (%)*	9 (3.4)	43 (16)†	64 (25)†
Patients with complete recovery of function who did not have normal function on day 1, n (%)	-	34 (13)‡	55 (22)‡
Patients with partial recovery of function who did not have normal function on day 1, n (%)	-	107 (42)‡	91 (36)‡

\* Ejection fraction  $> 0.55$  and no akinesis or dyskinesis.  
 † Proportion of the 261 patients with baseline echocardiograms.  
 ‡ Proportion of the 252 patients with abnormal function at baseline.

tial recovery of ejection fraction after early left ventricular dysfunction. Furthermore, peak creatine kinase level appears to be a strong predictor of functional recovery; the odds of full recovery decrease as peak creatine kinase level increases.

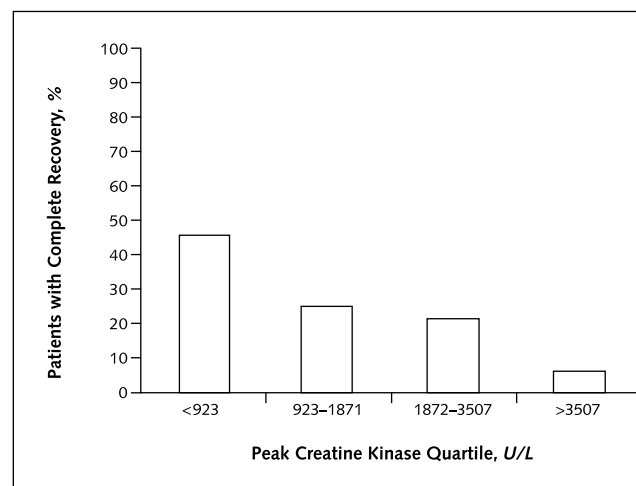
### Recovery of Left Ventricular Function after Myocardial Infarction

The substantial recovery of function that occurred within 90 days after myocardial infarction is one of the most striking findings of our study; 58% of patients had some recovery of function and 23% had complete recovery of function. The extent of functional recovery in our sample, which was greater than that reported in most previous studies, can be explained in part by the fact that ventricular function was first assessed within 24 hours of myocardial infarction. Previous research demonstrating the predictive value of assessment of left ventricular function after myocardial infarction used measurements that were obtained later, such as at hospital discharge, which typically occurs 1 week or more after infarction (9). This finding has important implications about the prognostic value of clinical assessment of left ventricular function early in the course of acute myocardial infarction.

Our findings suggest that the majority of functional recovery occurs within the first 2 weeks after myocardial infarction, although the data do not allow for further discrimination of the time course of recovery in this early period. Nevertheless, other studies of myocardial recovery after myocardial infarction have suggested that recovery occurs relatively early. Sheehan and colleagues (10) demonstrated functional recovery within 3 days of acute infarction treated with thrombolysis in patients who had documented reperfusion, and other investigators have shown functional recovery as early as 24 hours after successful thrombolysis (11), with maximal recovery occurring by 7 days (12).

The majority of patients (88%) in the HEART study underwent reperfusion; 65% had thrombolysis alone, 15% had primary angioplasty alone, and 8% had both. Reperfusion therapy was not mandated by the study protocol, and patients who did not undergo reperfusion therapy appeared to be healthier overall at baseline than the majority of patients who underwent reperfusion therapy. Patients who did not receive reperfusion

**Figure 2. Percentage of patients with complete recovery of function by increasing quartile of peak creatine kinase level.**



To convert U/L to  $\mu\text{kat/L}$ , divide by 60.  $P$  for trend < 0.001.

therapy had significantly lower peak creatine kinase levels (1194 U/L [19.9  $\mu\text{kat/L}$ ] vs. 2664 U/L [44.4  $\mu\text{kat/L}$ ];  $P = 0.001$ ), better ejection fraction on day 1 (0.55 vs. 0.52;  $P = 0.04$ ), and greater overall recovery of function (42% vs. 23% of patients;  $P = 0.01$ ) compared with patients who had reperfusion therapy. We believe that these data reflect selection bias against reperfusion therapy in patients who were healthiest at the time of their infarction. The success of reperfusion was not systematically assessed, but early reperfusion in HEART study patients probably contributed to the high rate of functional recovery seen. Contrast echocardiography assessment has shown that on average, 28% of myocardium can be salvaged with reperfusion after anterior myocardial infarction (13).

Although direct measures of myocardial perfusion were not available, the pattern of early ventricular dysfunction after myocardial infarction and subsequent functional improvement suggests that myocardial stunning is the most likely explanation for the observed reversible myocardial dysfunction. Myocardial stunning is typically defined as reversible myocardial dysfunction in regions of normal myocardial perfusion (14). After myocardial infarction, regional dysfunction can be seen in areas of the myocardium that are destined to improve; because these regions are usually adjacent to the infarct

zone, initial assessments of the infarct size often overestimate the true infarct region (12, 13).

Although echocardiography has an important role in the immediate post-myocardial infarction period, the dramatic change in cardiac function that can occur within 2 weeks of myocardial infarction argues against using early measures (within 24 hours) of left ventricular function to predict long-term risk. Our data indicate that of such early measures, peak creatine kinase level is a more robust predictor of functional recovery. Our observation that the majority of functional recovery occurs by day 14, in conjunction with data from other studies suggesting that improvement is likely to occur earlier (10, 12), suggests that hospital discharge (usually 5 to 10 days after myocardial infarction) or an early follow-up visit may be the ideal time for prognostic assessment.

#### Peak Creatine Kinase Level as a Predictor of Recovery

Previous studies have shown that the best predictor of ventricular enlargement and long-term dysfunction after myocardial infarction is infarct size (15). Because assessment of infarct size is not practical in the routine clinical setting, cardiac markers are typically used as surrogate measures (16). Integrated creatine kinase or creatine kinase-MB areas under the curve have been proposed as reasonable clinical estimates of myocardial damage (17). However, peak creatine kinase levels are much more widely available and have been shown to correlate with  $\alpha$ -hydroxybutyrate dehydrogenase levels, a more accurate assessment in patients undergoing early thrombolysis. Moreover, in the setting of prompt thrombolysis, assessment of total creatine kinase release that used area-under-the-curve methods was no better than peak creatine kinase level in predicting left ventricular function (18).

Some studies have shown overestimation of infarct size according to markers after thrombolysis compared with findings on histologic examination (19–22), but others have demonstrated similar relationships between enzymatic release and left ventricular function in patients receiving streptokinase or placebo (18). Peak creatine kinase level has correlated with in-hospital (but not later) mortality in the setting of thrombolysis (23). Our findings suggest that peak creatine kinase level is also related to recovery of ventricular function after myocardial infarction and may be a more important predictor

of functional recovery than other early clinical or echocardiographic measures. As additional cardiac markers are used with greater frequency, the predictive value of these markers, although probably similar to that of peak creatine kinase level, will need to be examined.

It is not surprising that both ventricular enlargement and recovery of function are inversely related to peak creatine kinase level. More interesting, however, is the fact that left ventricular dilatation occurs despite recovery of function in a substantial number of patients, suggesting a dissociation between ventricular enlargement and function in which morphologic changes in the ventricle occur even if ventricular function improves to within the normal range. This dissociation underscores the role of ventricular enlargement as a physiologic adaptation to loss of stroke volume and as a means of improving ventricular function, albeit at the expense of increased ventricular size. Whether patients who experience remodeling despite improvement in ventricular function are at increased long-term risk remains to be determined.

#### Limitations

Although the HEART study was initially designed to investigate the difference between early and late initiation of ACE inhibitor therapy after myocardial infarction, all patients received ACE inhibitors after 14 days. We previously reported significant improvements in left ventricular function in patients receiving active therapy during the first 14 days, although the differences between treatment groups in almost all echocardiographic assessments were minimal by 90 days. Thus, ultimate extent of functional recovery did not differ according to drug treatment group, although this finding may reflect the limited power of our relatively small sample. The effect of ACE inhibitors on left ventricular enlargement and clinical outcome has been well characterized in longer-term, placebo-controlled studies (24–26).

Of note, the major difference between the HEART study and other trials involving patients with myocardial infarction was the high proportion of patients who received reperfusion therapy early in the course of infarction. Although we do not have data on the patency of infarct arteries for all patients in the study, we observed no appreciable differences in peak creatine kinase level or recovery of ventricular function between patients

with known patency in infarct-related arteries and those in whom the patency of infarct-related arteries was unknown, suggesting that the majority of patients benefited from reperfusion therapy. In addition, we do not know which patients had successful reperfusion, a common problem in clinical practice. Nevertheless, these data suggest that reperfusion alters the relationship between early assessments of left ventricular function and eventual left ventricular function.

Although echocardiography was performed within 24 hours of myocardial infarction and at day 14, we have no echocardiographic data from the interval in between. Therefore, we do not know precisely when the recovery of function seen in the majority of patients in this study occurred, and we cannot exclude the possibility that this recovery occurred very early after myocardial infarction. In addition, we have no data on inferior myocardial infarction, since the HEART study included only patients with anterior myocardial infarction (defined by electrocardiography). We therefore cannot readily extrapolate our findings to myocardial infarction in other locations. Finally, echocardiography was technically inadequate in 14% of patients at baseline. Nevertheless, the quantitative nature of the study required high-quality echocardiograms, and clinically useful echocardiographic studies could probably be performed on more patients after infarction.

## Conclusions

Myocardial infarction and its aftermath remain heterogeneous processes. Some degree of recovery of left ventricular function occurs in most patients. Identifying patients whose ventricles are least likely to recover remains an important clinical challenge because these patients are at greatest risk for subsequent morbidity and death. The results of the HEART study help elucidate the natural history and define the broad range of morphologic and functional sequelae of anterior Q-wave myocardial infarction in the reperfusion era. The degree of improvement in ventricular function seen in the HEART study—which was considerably better than that expected without reperfusion—would probably be even greater if the most modern reperfusion strategies had been used. The finding that peak creatine kinase level is a stronger predictor of recovery of function than early ejection fraction emphasizes the importance of

early measures to limit infarct size. Our findings underscore the limitations of measurement of function early (<24 hours) after myocardial infarction as a predictor of future ventricular function and suggest that clinical evaluations of ventricular function made later after myocardial infarction—perhaps at hospital discharge or an early follow-up visit, and after recovery of stunned myocardium—may more accurately assess long-term risk.

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