The Role of Exercise Radionuclide Angiocardiography in Predicting Future Cardiac Events in Patients with Acute Myocardial Infarction

Toshiki Shigeyama, Atsuo Yanagisawa, and Kyozo Ishikawa

Second Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

Left ventricular ejection fraction (LVEF) during exercise radionuclide angiocardiography is a useful prognostic index for patients with acute myocardial infarction (AMI). However, most previous studies were performed before reperfusion therapies (i.e., thrombolysis and coronary angioplasty) were widely used. Therefore, because reperfusion therapy has become a standard therapeutic option, we reexamined the prognostic value of rest LVEF and exercise LVEF determined by radionuclide angiocardiography in patients with AMI at the time of hospital discharge. **Methods:** The retrospective analysis included 419 consecutive patients with AMI who underwent ergometric stress radionuclide angiocardiography before hospital discharge, 44 ± 14 d after the onset of AMI. **Results:** During a mean follow-up of 4.6 y, cardiac events occurred in 101 (24.1%) patients. Cardiac events included recurrent MI (33 patients, 7.9%), unstable angina (49 patients, 11.7%), congestive heart failure (16 patients, 3.8%), and ventricular tachycardia (3 patients, 0.7%). The LVEF at peak exercise was significantly lower in the group with cardiac events (P = 0.0140). However, no significant difference was observed in the rest LVEF between patients with and without cardiac events. On the basis of multivariate analysis using a Cox proportional hazards model, only peak LVEF (P = 0.0246) was found to be an independent predictor of cardiac events. In the patient subsets with a peak LVEF >50% or <50%, the event-free rate was 81.0% versus 62.4% (P = 0.0007), respectively. Regardless of the presence or absence of reperfusion therapy, the lower peak LVEF was associated with a decrease in the event-free survival rate. **Conclusion:** In the current reperfusion era, the lower peak LVEF as measured by radionuclide angiocardiography at the time of discharge is a useful predictor of subsequent cardiac events in patients with AMI.

Key Words: exercise radionuclide angiocardiography; prognosis; left ventricular ejection fraction; myocardial infarction

J Nucl Med 2000; 41:965–972

Received Mar. 1, 1999; revision accepted Sep. 23, 1999.

For correspondence or reprints contact: Kyozo Ishikawa, MD, Second Department of Internal Medicine, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan.

The long-term prognosis for patients with acute myocardial infarction (AMI) has been predicted by exercise electrocardiography, exercise radionuclide angiocardiography, and exercise myocardial scintigraphy (*1–11*). In particular, the left ventricular ejection fraction (LVEF) at rest and at maximum exercise is a useful index for risk assessment or estimation of prognosis after AMI (*5–11*). However, most previous exercise radionuclide angiocardiography studies focusing on long-term prognosis were performed before the era of reperfusion therapy. Thrombolysis, by the intravenous or intracoronary administration of urokinase or tissue plasminogen activator, and direct percutaneous transluminal coronary angioplasty (PTCA) are currently used as reperfusion therapy in the setting of AMI (*12–20*). Recently, intracoronary stent implantation has also been used to treat AMI (*21*). The lower peak LVEF value during exercise radionuclide angiocardiography before hospital discharge has been reported to be a useful predictor of future cardiac events in patients with AMI who underwent thrombolysis (*9*). However, it has also been reported that the peak LVEF cannot be used as an index of prognosis (*10*). Furthermore, to our knowledge, there have been no reports concerning the usefulness of exercise radionuclide angiocardiography in patients with AMI who underwent direct PTCA. Therefore, because reperfusion therapy has become a standard therapeutic option, this study was undertaken to examine the prognostic value of rest LVEF and exercise LVEF by radionuclide angiocardiography in patients with AMI at the time of hospital discharge.

MATERIALS AND METHODS

Study Population

The study group consisted of 419 AMI patients referred to the Nuclear Cardiology Laboratory at Kyorin University Hospital from April 1986 through September 1997 who underwent exercise radionuclide angiocardiography within 2 wk before or after the day of discharge (329 men, 90 women; mean age, 62 ± 10 y; mean hospital stay, 46 ± 15 d) (Table 1). During this period, reperfusion

TABLE 1
Comparison of Patients With and Without Cardiac Events for Each Variable Using Univariate Cox Regression Analysis

Variable	No event (n = 318)	Event (n = 101)	Total (n = 419)	*P*
Sex (M/F)	245/73	84/17	329/90	NS
Age (y)	61 ± 11	63 ± 9	62 ± 10	0.0043
Coronary risk factor				
Systemic hypertension	128 (40)	46 (46)	174 (42)	NS
Diabetes mellitus	53 (17)	27 (27)	80 (19)	0.0062
Serum cholesterol ≥220 mg/dL	103 (32)	50 (50)	153 (37)	0.0014
Cigarette smoking	212 (67)	75 (74)	287 (68)	NS
Site of MI				
Anterior	161 (51)	58 (57)	219 (52)	NS
Inferior	130 (41)	37 (37)	167 (40)	NS
Lateral	27 (8)	6 (6)	33 (8)	NS
Previous MI	24 (8)	20 (20)	44 (11)	<0.0001
Peak CPK activity (IU)	3135 ± 2556	3035 ± 2636	3110 ± 2574	NS
Complication during acute phase				
Congestive heart failure	47 (15)	19 (19)	66 (16)	NS
Cardiogenic shock	45 (14)	15 (15)	60 (14)	NS
Cardiac catheterization data (n = 310)				
Single-vessel disease	132 (54)	29 (43)	161 (52)	0.0413
Multivessel disease	80 (33)	34 (51)	114 (37)	0.0006
Nonobstructive lesions	31 (13)	4 (6)	35 (11)	NS
Radionuclide angiocardiography				
Rest LVEF (%)	56.3 ± 12.1	53.7 ± 15.1	55.6 ± 13.0	NS
Peak LVEF (%)	59.9 ± 13.5	55.5 ± 15.7	58.9 ± 14.2	0.0140
ΔLVEF (%)	3.5 ± 8.7	1.8 ± 7.5	3.1 ± 8.4	NS
Peak work load (W)	66.2 ± 22.6	61.1 ± 20.7	65.0 ± 22.3	0.0018

NS = not significant.
Data are expressed as mean ± SD. Values in parentheses are percentages.

therapy was standard treatment in the coronary care unit of Kyorin University Hospital.

A diagnosis of AMI was based on the following criteria: compatible clinical symptoms, including severe chest pain lasting >30 min that did not improve with sublingual nitrites; the presence of persistent ST segment elevations >2 mm in at least 2 continuous electrocardiographic leads during the acute period; and an increase in the serum creatine phosphokinase (CPK) activity to more than twice the upper limit of normal.

Therapeutic Interventions During Acute Phase and Cardiac Rehabilitation

From the time of admission, patients received intravenous heparin and aspirin orally. Reperfusion therapy was performed in 306 patients within 6 h of the onset of chest pain. Of these patients, 220 patients received thrombolytic therapy. Successful recanalization could not be performed in 19 of 220 patients, and they were monitored by PTCA. Finally, the reperfusion therapy consisted of thrombolytic therapy in 201 patients and PTCA in 105 patients. Thrombolysis was performed by intravenous or intracoronary administration of urokinase or tissue plasminogen activator. When reperfusion therapy was performed during emergent coronary angiography, reperfusion therapy was terminated when a blood flow of at least grade 2 of the Thrombolysis in Myocardial Infarction trial (*13*) was confirmed.

The 113 patients who did not undergo reperfusion therapy included 38 patients who came to the hospital >6 h after onset of chest pain, 12 patients who did not give informed consent for reperfusion therapy, 48 patients in whom spontaneous reperfusion was confirmed during emergent coronary angiography, 8 patients with a recent history of bleeding from gastric ulcers, and 7 patients with renal dysfunction. The patients were discharged after participating in the cardiac rehabilitation program of our institute.

Exercise Protocol

Each patient underwent symptom-limited bicycle ergometer exercise testing. The work load was started at 50 W and increased by 25 W every 3 min. The exercise was terminated at 1 of the following endpoints: moderate angina, >2-mm down-sloping or horizontal ST segment depression, serious arrhythmias, increase in the systolic blood pressure to >200 mm Hg, achieving 85% of the age-predicted maximum heart rate, or moderate dyspnea or fatigue.

Multigated Radionuclide Angiocardiography

Exercise radionuclide angiocardiography was performed on all patients 44 ± 14 d after the onset of AMI. Patients underwent electrocardiographically gated equilibrium blood-pool scintigraphy in the supine position. After intravenous injection of 740 MBq ^{99m}Tc-labeled human serum albumin, data acquisition was performed with a single-crystal γ camera (model GCA-90B; Toshiba, Tokyo, Japan) fitted with a low-energy, all-purpose, parallel-hole collimator and interfaced to a dedicated minicomputer (model GMS-55U; Toshiba) in frame mode. The left anterior oblique projection that best displayed the interventricular septum was used (i.e., approximately 45° with 10° caudal angulation). Data were collected at rest and during the last 2 min of every 3-min increment in exercise. After acquisition, the data were organized into an

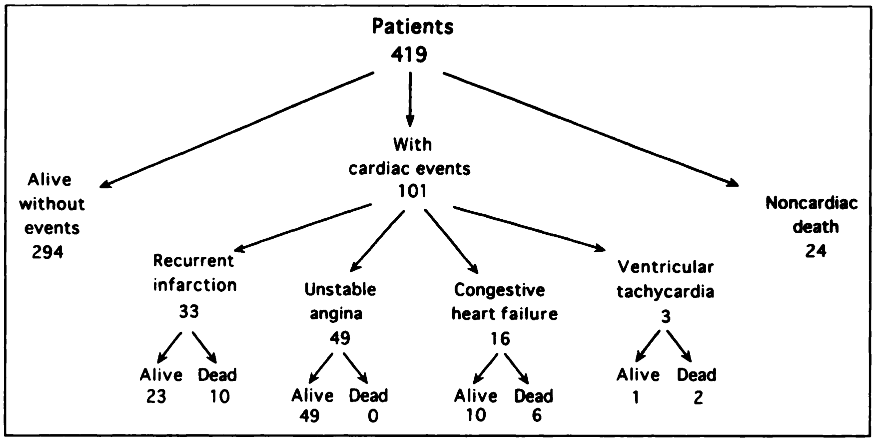

FIGURE 1. Patient follow-up 4.6 y after AMI.

image sequence that included 20 frames per cardiac cycle in a 64 × 64 matrix with a 1.5× zoom. The LVEF was computed from the global time–activity curve using a signal semiautomatic LV region of interest drawn on the functional phase image. Background region of interests was drawn automatically. The rest LVEF and LVEF at peak exercise (peak LVEF) were measured, and the ΔLVEF (peak LVEF − rest LVEF) was calculated.

Coronary Angiography

Coronary angiography was performed on 310 (74.0%) of 419 patients during the acute phase of MI or before discharge. The angiographic findings were quantified on the basis of the American Heart Association classification system (22). A significant coronary stenosis was defined as >75% narrowing. Patients were classified as having single-vessel disease or multivessel disease. Informed consent was obtained from all patients.

Follow-Up Study

Patients were monitored for a mean period of 4.6 ± 3.3 y (1678 ± 1213 d). Survival and the presence of cardiac events were determined from outpatient medical records, by mailed questionnaires, or by telephone contact. Cardiac events included recurrent infarction, unstable angina requiring hospitalization, congestive heart failure, and ventricular tachycardia.

Statistical Analysis

Data are presented as the mean ± SD. A Cox proportional hazards model was used to identify significant predictors of subsequent cardiac events from clinical variables on both a univariate and a multivariate basis. Factors determining the LVEF were analyzed by multiple regression analyses. Event-free survival curves were constructed using the Kaplan-Meier method, and differences between the curves were assessed using the log-rank test.

The diagnostic break point for both rest LVEF and peak LVEF was determined to be 50%, which is very close to the value obtained by subtracting the 2 SDs from the mean LVEF of healthy individuals in our institute (normal values [n = 50]: rest LVEF, 64.8% ± 8.0%; peak LVEF, 70.2% ± 8.9%). The diagnostic break point for ΔLVEF was determined to be 5%, which was derived from the normal value (5.4% ± 4.9%) for our hospital (n = 50). $P < 0.05$ was considered statistically significant. Statistical calculations were performed using StatView for Macintosh, version 4.5 (Abacus Concepts, Inc., Berkeley, CA).

RESULTS

Clinical Characteristics and Cardiac Events

During a mean follow-up period of 4.6 y, 101 (24.1%) of 419 patients had cardiac events (group with cardiac events, Fig. 1). The cardiac events included recurrent infarction (33 patients, 7.9%), unstable angina (49 patients, 11.7%), congestive heart failure (16 patients, 3.8%), and ventricular tachycardia (3 patients, 0.7%). Death associated with cardiac events occurred in 18 patients (4.3%), including 10 patients with recurrent infarction, 6 patients with congestive heart failure, and 2 patients with ventricular tachycardia. Ischemic cardiac events (i.e., recurrent infarction or unstable angina) occurred in 82 (81.2%) of 101 patients with cardiac events. Of 101 patients with cardiac events, 37 patients received emergent PTCA or coronary artery bypass grafting. Of the 419 patients, 318 (75.9%) had no cardiac events (group without cardiac events). Among these patients, 24 patients (5.7%) died of noncardiac events. The cardiac events occurred in 58 (29%) of 201 patients with thrombolysis, 22 (21%) of 105 patients with PTCA, and 21 (19%) of 113 patients without intervention.

When a univariate analysis using a Cox proportional hazards model was performed, significant differences between the groups with and without cardiac events were noted for the following characteristics (Table 1): age (P = 0.0043), diabetes mellitus (P = 0.0062), hyperlipidemia (serum cholesterol concentration >220 mg/dL; P = 0.0014), previous MI (P < 0.0001), single-vessel disease (P = 0.0413), and multivessel disease (P = 0.0006).

Exercise LVEF and Cardiac Events

Both peak LVEF (P = 0.0140) and peak work load (P = 0.0018) during exercise radionuclide angiocardiography were significantly lower in the group with cardiac events than in the group without cardiac events (Table 1). The rest LVEF was lower in the group with cardiac events, although no statistical difference was seen between patients with or without cardiac events. Multivariate analysis using a Cox proportional hazards model showed that age, male gender, hyperlipidemia, and a peak LVEF of <50% were indepen-

TABLE 2
Independent Predictors of Cardiac Events Based on Multivariate Cox Regression Analysis

Variable	Hazard ratio	95% CI	*P*
Age	1.028	1.003–1.053	0.0256
Male	2.008	1.038–3.883	0.0383
Cigarette smoking	—	—	0.1992
Systemic hypertension	—	—	0.1836
Diabetes mellitus	—	—	0.0774
Serum cholesterol ≥220 mg/dL	2.162	1.388–3.367	0.0007
Rest LVEF <50%	—	—	0.4887
Peak LVEF <50%	1.926	1.063–3.490	0.0306
ΔLVEF <5%	—	—	0.6744
Peak work load	0.985	0.973–0.998	0.0224

CI = confidence interval.

dent variables predicting poor prognosis, and an increased peak work load was an independent variable predicting good prognosis (Table 2).

On the basis of multiple regression analyses, the independent factors that determined the peak LVEF were age (P = 0.0014), anterior wall MI (P = 0.0191), history of previous MI (P = 0.0007), peak CPK activity (P < 0.0001), congestive heart failure (P = 0.0001), and PTCA (P = 0.0067) (Table 3). Of these factors, age, anterior wall MI, history of previous MI, peak CPK activity, and congestive heart failure were factors that predicted a reduced peak LVEF. In contrast, use of PTCA was the only factor that predicted an increase in the peak LVEF.

Exercise LVEF and Prognosis

Event-free survival curves were calculated using the Kaplan-Meier method. Cardiac event-free survival rates

TABLE 3
Independent Predictors of Peak LVEF Based on Multiple Regression Analysis

Variable	Coefficient	95% CI	*P*
Age	−0.217	−0.349 to −0.085	0.0014
Sex	—	—	0.3241
Cigarette smoking	—	—	0.1370
Systemic hypertension	—	—	0.2287
Diabetes mellitus	—	—	0.4432
Serum cholesterol ≥220 mg/dL	—	—	0.6046
Anterior wall infarction	−6.000	−11.010 to −0.990	0.0191
Inferior wall infarction	—	—	0.7663
Previous MI	−7.188	−11.311 to −3.064	0.0007
Peak CPK activity	−0.001	−0.002 to −0.001	<0.0001
Congestive heart failure	−7.186	−10.849 to −3.524	0.0001
Cardiogenic shock	—	—	0.8200
PTCA	4.076	1.135 to 7.018	0.0067
Thrombolysis	—	—	0.7100

CI = confidence interval.

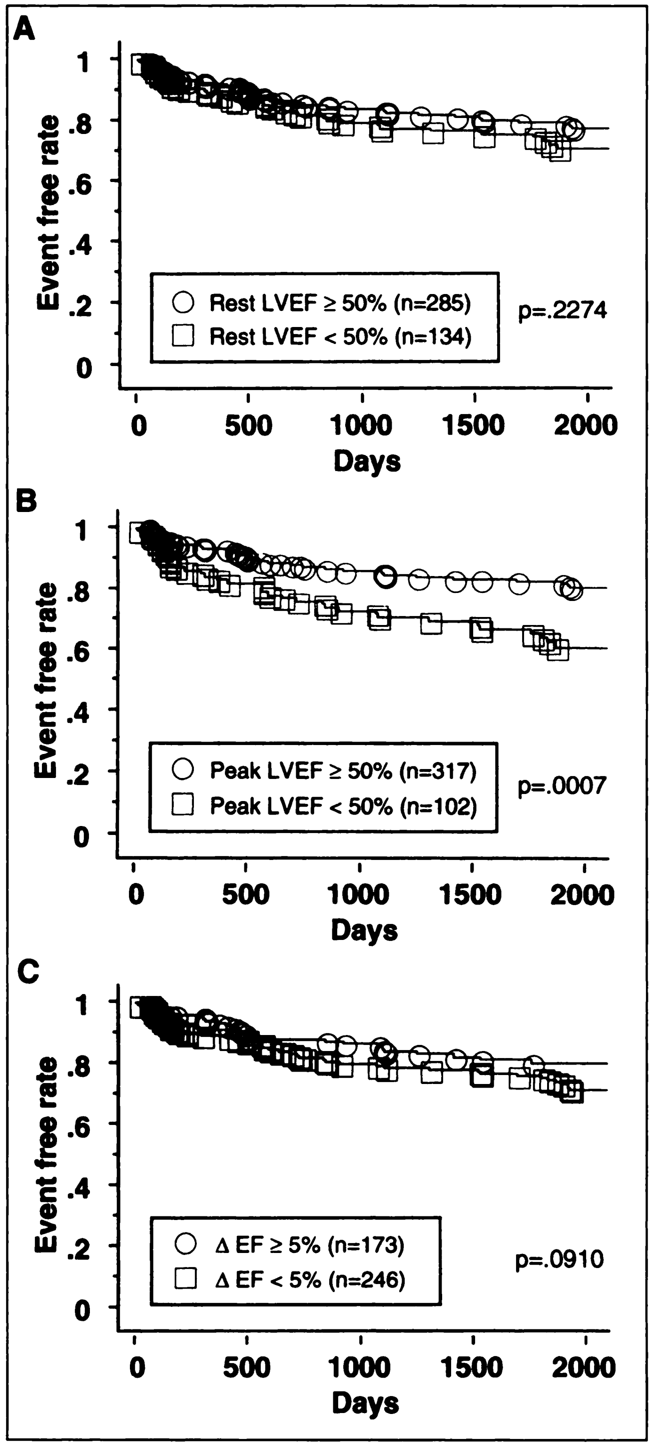

FIGURE 2. Kaplan-Meier event-free survival curves for 419 patients after AMI based on LVEF >50% or <50% (A), peak exercise LVEF >50% or <50% (B), and Δ(peak − rest) LVEF >5% or <5% (C).

were similar between patients with a rest LVEF <50% and those with a rest LVEF >50% (P = 0.2274; Fig. 2A). The event-free survival rate was significantly lower in patients with a peak LVEF <50% (62.4%) than in those with a peak LVEF >50% (81.0%; P = 0.0007; Fig. 2B). No differences were noted in event-free survival rates between patients with a ΔLVEF <5% and patients with a ΔLVEF >5% (Fig. 2C).

In patients who received reperfusion therapy with thrombolysis or PTCA (n = 306), the event-free survival rate was similar between patients with a rest LVEF <50% and patients with a rest LVEF >50% (P = 0.7739; Fig. 3A). However, the event-free survival rate was significantly lower in patients with a peak LVEF <50% than in patients with a peak LVEF >50% (P = 0.0119; Fig. 3B).

Similarly, in patients who did not receive reperfusion therapy, the event-free survival rate was similar between patients with a rest LVEF <50% and patients with a rest LVEF >50% (P = 0.0723; Fig. 4A). In contrast, the event-free survival rate was significantly lower in patients with a peak LVEF <50% than in patients with a peak LVEF >50% (P = 0.0118; Fig. 4B).

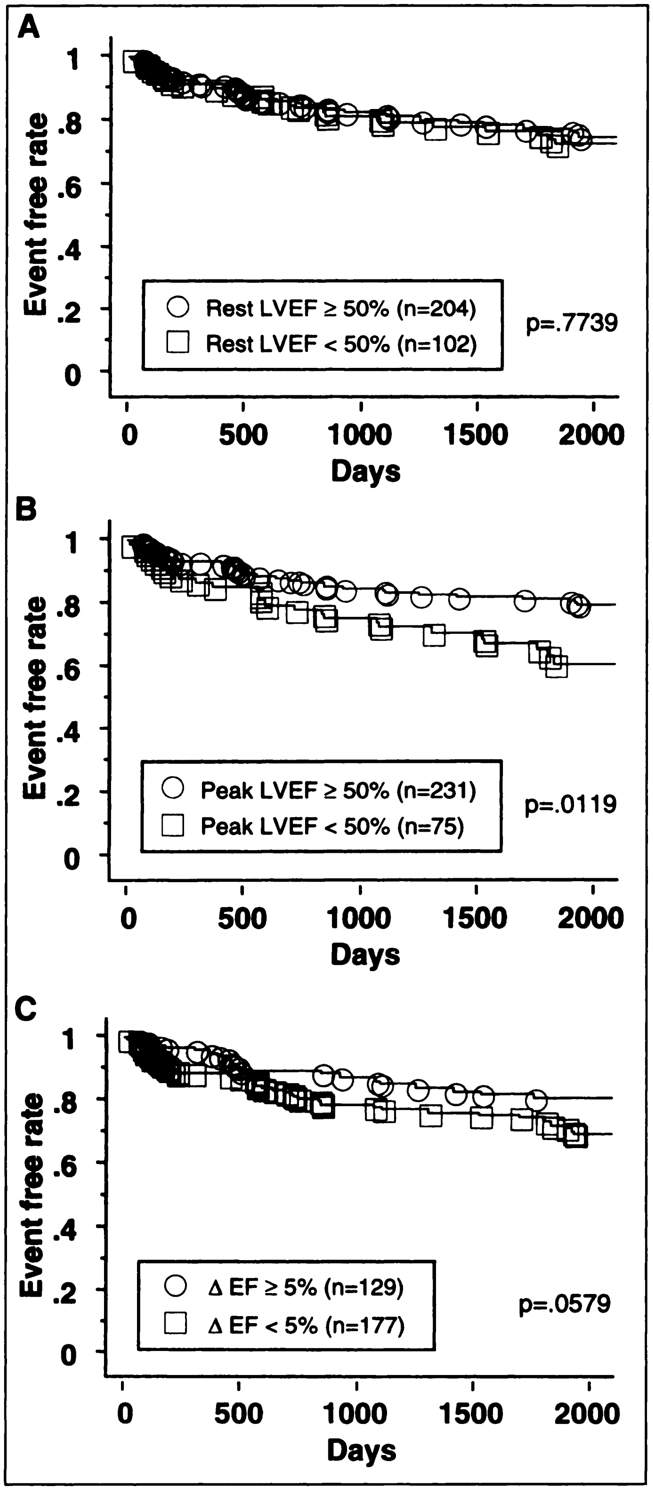

FIGURE 3. Kaplan-Meier event-free survival curves for 306 patients after reperfusion therapy based on rest LVEF >50% or <50% (A), peak exercise LVEF >50% or <50% (B), and Δ(peak − rest) LVEF >5% or <5% (C).

DISCUSSION

The extent of MI and the factors related to LV function are useful indices for determining the prognosis of patients with AMI. Among the factors related to LV function, the rest LVEF and peak LVEF determined by radionuclide angiocardiography have been reported to be useful predictors of cardiac events in patients with AMI (*5–11*). In recent years, the short- and long-term survival rates after AMI have improved markedly with the introduction of thrombolytic therapy and PTCA (*12–20*). However, most studies assessing long-term prognosis based on radionuclide angiocardiography determinations of ventricular function were performed before the era of reperfusion therapy. Because reperfusion therapy has become a standard therapeutic option, we examined the prognostic value of rest LVEF and exercise LVEF determined by radionuclide angiocardiography in patients with AMI at the time of hospital discharge. On the basis of our findings, only the peak LVEF was an independent predictor of prognosis, regardless of the therapeutic interventions during the acute phase.

Rest LVEF and Peak LVEF as Prognostic Factors

The cardiac event-free rate in this study was 24.1%, which is similar to previously reported rates (*19,20*). The peak LVEF was found to be an independent predictor of cardiac events, regardless of whether reperfusion therapy was performed or what type of reperfusion therapy was used. A decrease in the peak LVEF is thought to result from exercise-induced myocardial ischemia. However, the rest LVEF was not an independent predictor of prognosis in this study. Zhu et al. (*9*) performed exercise radionuclide angiocardiography in 96 patients with MI after thrombolytic therapy and reported that only the peak LVEF was a significant predictor of cardiac events over a 3.5-y period.

Two major factors affect the long-term prognosis of patients with MI: the extent of MI and the presence of exercise-induced myocardial ischemia (*9*). Exercise radionuclide angiocardiography has been used to detect the presence and the location of exercise-induced myocardial ischemia (*5–10*). The rest LVEF was reported to be reduced in patients with extensive MI, indicating that the rest LVEF may be a powerful prognostic indicator (*10,11*). Khattar et al. (*11*) determined the prognosis of patients with AMI using rest LVEF and exercise electrocardiography and found that the rest LVEF and exercise duration were independent predictors of prognosis. They suggested that the rest LVEF might

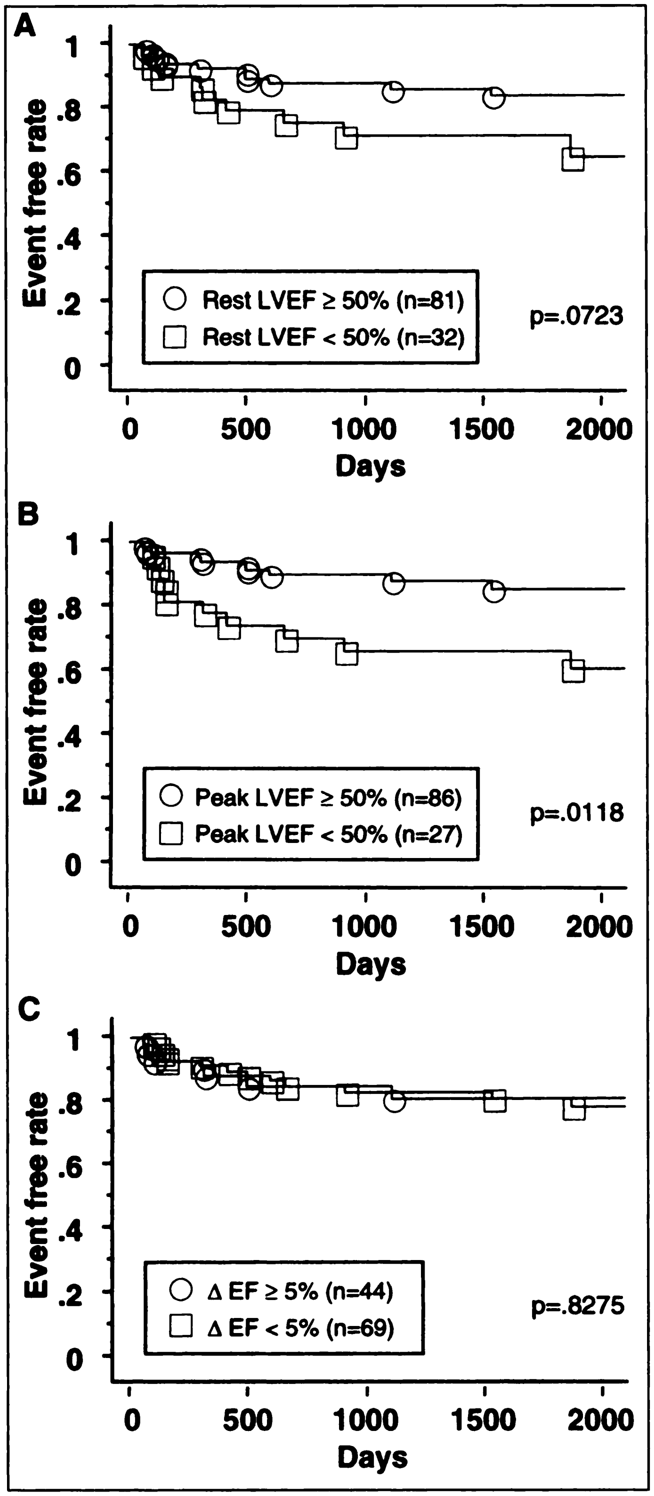

FIGURE 4. Kaplan-Meier event-free survival curves for 113 patients without reperfusion therapy based on rest LVEF >50% or <50% (A), peak exercise LVEF >50% or <50% (B), and Δ(peak − rest) LVEF >5% or <5% (C).

be useful for predicting the development of heart failure and ischemic cardiac events associated with multivessel disease because the rest LVEF represents the function of the left ventricle that is determined by the extent of the MI (*11*). However, in this study, the rest LVEF was not an independent prognostic factor, possibly because only 15.8% of all cardiac events in our study were related to heart failure, whereas 48.5% and 32.7% were associated with unstable angina and recurrent MI, respectively.

Furthermore, the rest LVEF in the group with cardiac events in this study was 53.7% in contrast to 42.0% in the study by Khattar et al. (*11*). It is possible that the rest LVEF was not an independent prognostic factor because our study included only a few patients with cardiac dysfunction. The reason for the lower rest LVEF in the group with cardiac events in the study by Khattar et al. might be related to the fact that they performed exercise radionuclide angiocardiography only 5–8 d after the onset of AMI. During the acute phase of MI, transient reversible contractile dysfunction (stunning) occurs in the ischemic myocardium that has not developed myocardial necrosis (*23*). Because many of the patients in the group with cardiac events had multivessel disease, it can be assumed that extensive stunning occurred, causing a decrease in the rest LVEF. Because exercise radionuclide angiocardiography was performed 44 d on average after the onset of AMI in this study and because the myocardium had time to recover sufficiently from stunning, only a small difference might be observed in the rest LVEF at the time of discharge between the groups with and without cardiac events. Zhu et al. (*9*) performed exercise radionuclide angiocardiography 2 wk after AMI and found no difference in the rest LVEF between the groups with and without cardiac events, which agrees with our results. These observations suggest that the prognostic value of rest LVEF in patients with AMI is largely dependent on when the radionuclide angiocardiography is performed.

Factors Determining Peak LVEF

The peak LVEF was an independent predictor of long-term prognosis in this study. Many factors are thought to affect the peak LVEF. In this study, age, a history of previous MI, anterior wall MI, congestive heart failure, and a high serum CPK activity were associated with a reduction in the peak LVEF at the time of discharge. All of these factors are related to an impairment of cardiac function and to the extent of MI. In addition, they are well-known factors that predict the short-term prognosis after AMI (*24–29*). In contrast, the use of PTCA during the acute phase was the only factor that was associated with an improvement in the peak LVEF. It is possible that recanalization of the coronary artery by PTCA during the acute phase could prevent a reduction in the peak LVEF and reduce the incidence of ischemic cardiac events. This suggestion is in keeping with the open artery hypothesis (i.e., improvement in prognosis by early opening of the infarct-related coronary artery) (*30–32*). Opening of the infarct-related coronary artery may prevent myocardial remodeling and swelling of the ischemic myocardium, thereby improving the diastolic function of the left ventricle (*33*). However, thrombolytic therapy did not improve the LVEF in our study, probably because some patients did not have sufficient opening of the infarct-related coronary artery with intravenous administration of thrombolytic agents.

Other Prognostic Factors

In addition to the peak LVEF, coronary risk factors including hyperlipidemia and male gender were independent predictors of poor prognosis in this study. Martin et al. (*34*) also emphasized the importance of coronary risk factors as determinants of long-term prognosis for patients with MI. These coronary risk factors, which contribute to the progression of arteriosclerosis, do not directly affect cardiac function during the acute phase of MI. However, these coronary risk factors may be involved by accelerating the progression of coronary atherosclerosis. The results of this study lead us to reconsider the importance of strict management of coronary risk factors for the reduction of cardiac events in patients with MI.

Study Limitations

Because our investigation was a retrospective study, technologic advances in the monitoring of cardiac function and therapeutic interventions during the study period could not be avoided (*35*). During the 11 y of the study, thrombolytic therapy has shifted from the use of urokinase to tissue plasminogen activator. In addition, other pharmacologic or catheter interventions used during the acute and chronic phases and operative procedures have also been modified. For these reasons, we could not compare the prognosis between patients with thrombolytic therapy and PTCA.

In addition, the patients included in this study underwent exercise radionuclide angiocardiography at the time of hospital discharge. Elderly patients or those with left main coronary artery disease or severe multivessel disease who could not undergo exercise radionuclide angiocardiography were excluded. Because elderly patients and those with severe coronary artery disease are known to have a poor prognosis and were excluded, the long-term prognosis of the patients in this study may be better than that in studies in which high-risk patients were included. Therefore, the results of this study are applicable to the prediction of prognosis only in patients who are able to undergo exercise radionuclide angiocardiography.

CONCLUSION

The prognostic value of rest LVEF and exercise LVEF by radionuclide angiocardiography at the time of hospital discharge was determined in patients with AMI. On the basis of multivariate analysis of a Cox proportional hazards model, only the peak LVEF was an independent prognostic factor. Regardless of the presence or absence of reperfusion therapy, the lower peak LVEF was associated with a decrease in the event-free survival rate. Therefore, even in the current reperfusion era, the lower peak LVEF determined by radionuclide angiocardiography at the time of hospital discharge can be a useful index for the prediction of subsequent cardiac events in patients with AMI.

REFERENCES

1. Théroux P, Waters DD, Halphen C, Debaisieux J-C, Mizgala HF. Prognostic value of exercise testing soon after myocardial infarction. *N Engl J Med.* 1979;301:341–345.
2. Davidson DM, DeBusk RF. Prognostic value of a single exercise test 3 weeks after uncomplicated myocardial infarction. *Circulation.* 1980;61:236–242.
3. Weld FM, Chu K-L, Bigger JT Jr, Rolnitzky LM. Risk stratification with low-level exercise testing 2 weeks after acute myocardial infarction. *Circulation.* 1981;64:306–314.
4. DeBusk RF, Kraemer HC, Nash E, Berger WE III, Lew H. Stepwise risk stratification soon after acute myocardial infarction. *Am J Cardiol.* 1983;52:1161–1166.
5. Corbett JR, Dehmer GJ, Lewis SE, et al. The prognostic value of submaximal exercise testing with radionuclide ventriculography before hospital discharge in patients with recent myocardial infarction. *Circulation.* 1981;64:535–544.
6. Dewhurst NG, Muir AL. Comparative prognostic value of radionuculide ventriculography at rest and during exercise in 100 patients after first myocardial infarction. *Br Heart J.* 1983;49:111–121.
7. Morris KG, Palmeri ST, Califf RM, et al. Value of radionuclide angiography for predicting specific cardiac events after acute myocardial infarction. *Am J Cardiol.* 1985;55:318–324.
8. Hung J, Goris ML, Nash E, et al. Comparative value of maximal treadmill testing, exercise thallium myocardial perfusion scintigraphy and exercise radionuclide ventriculography for distinguishing high- and low-risk patients soon after acute myocardial infarction. *Am J Cardiol.* 1984;53:1221–1227.
9. Zhu W-X, Gibbons RJ, Bailey KR, Gersh BJ. Predischarge exercise radionuclide angiography in predicting multivessel coronary artery disease and subsequent cardiac events after thrombolytic therapy for acute myocardial infarction. *Am J Cardiol.* 1994;74:554–559.
10. Zaret BL, Wackers FJT, Terrin ML, et al. Value of radionuclide rest and exercise left ventricular ejection fraction in assessing survival of patients after thrombolytic therapy for acute myocardial infarction: results of Thrombolysis in Myocardial Infarction (TIMI) phase II study—The TIMI study group. *J Am Coll Cardiol.* 1995;26:73–79.
11. Khattar RS, Basu SK, Raval U, Senior R, Lahiri A. Prognostic value of predischarge exercise testing, ejection fraction, and ventricular ectopic activity in acute myocardial infarction treated with streptokinase. *Am J Cardiol.* 1996;78:136–141.
12. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet.* 1986;1:397–402.
13. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. *Circulation.* 1987;76:142–154.
14. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. *Lancet.* 1987;2:871–874.
15. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet.* 1988;2:349–360.
16. Wilcox RG, Olsson CG, Skene AM, Lippe G, Jensen G, Hampton JR. Trials of tissue plasminogen activator for mortality reduction in acute myocardial infarction: Anglo-Scandinavian Study of Early Thrombolysis (ASSET). *Lancet.* 1988;2:525–530.
17. AIMS Trial Study Group. Effect of intravenous APSAC on mortality after acute myocardial infarction: preliminary report of a placebo controlled clinical trial. *Lancet.* 1988;1:545–549.
18. White HD, Norris RM, Brown MA, et al. Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. *N Engl J Med.* 1987;317:850–855.
19. Simoons ML, Vos J, Tijssen JG, et al. Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5-year follow-up of a trial conducted by the Interuniversity Cardiology Institute of The Netherlands. *J Am Coll Cardiol.* 1989;14:1609–1615.
20. Every NR, Parsons LS, Hlatky M, Martin JS, Weaver WD. A comparison of thrombolytic therapy with primary coronary angioplasty for acute myocardial infarction. *N Engl J Med.* 1996;335:1253–1260.
21. Garcia-Cantu E, Spaulding C, Corcos T, et al. Stent implantation in acute myocardial infarction. *Am J Cardiol.* 1996;77:451–454.

22. AHA Committee Report. A reporting system on patients evaluated for coronary artery disease: report of the ad hoc committee for grading of coronary artery disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation*. 1975;51:5–40.
23. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation*. 1982;66:1146–1149.
24. Schneider RM, Chu A, Akaishi M, Weintraub WS, Morris KG, Cobb FR. Left ventricular ejection fraction after acute coronary occlusion in conscious dogs: relation to the extent and site of myocardial infarction. *Circulation*. 1985;72:632–638.
25. Bertrand ME, Rousseau MF, Lablanche JM, Carre AG, Lekieffre JP. Cineangiographic assessment of left ventricular function in the acute phase of transmural myocardial infarction. *Am J Cardiol*. 1979;43:472–480.
26. Swan HJC, Forrester JS, Diamond G, Chatterjee K, Parmley WW. Hemodynamic spectrum of myocardial infarction and cardiogenic shock: a conceptual model. *Circulation*. 1972;45:1097–1110.
27. Stone PH, Raabe DS, Jaffe AS, et al. Prognostic significance of location and type of myocardial infarction: independent adverse outcome associated with anterior location. *J Am Coll Cardiol*. 1988;11:453–463.
28. Warnowicz MA, Parker H, Cheitlin MD. Prognosis of patients with acute pulmonary edema and normal ejection fraction after acute myocardial infarction. *Circulation*. 1983;67:330–334.
29. Sobel BE, Bresnahan GF, Shell WE, Yoder RD. Estimation of infarct size in man and its relation to prognosis. *Circulation*. 1972;46:640–648.
30. Kim CB, Braunwald E. Potential benefits of late reperfusion of infarcted myocardium: the open artery hypothesis. *Circulation*. 1993;88:2426–2436.
31. Tiefenbrunn AJ, Sobel BE. Timing of coronary recanalization: paradigms, paradoxes, and pertinence. *Circulation*. 1992;85:2311–2315.
32. Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival: should the paradigm be expanded? *Circulation*. 1989;79:441–444.
33. Levy WC, Cerqueira MD, Litwin PE, et al. A patent infarct related artery improves diastolic filling after thrombolytic therapy: Myocardial Infarction Triage and Intervention (MITI) trial [abstract]. *Circulation*. 1992;86(suppl I):I-455.
34. Martin CA, Thompson PL, Armstrong BK, Hobbs MS, de Klerk N. Long-term prognosis after recovery from myocardial infarction: a 9-year follow-up of the Perth Coronary Register. *Circulation*. 1983;68:961–969.
35. Lavie CJ, Gibbons RJ, Zinsmeister AR, Gersh BJ. Interpreting results of exercise studies after acute myocardial infarction altered by thrombolysis therapy, coronary angioplasty or bypass. *Am J Cardiol*. 1991;67:116–120.