Prognosis in Patients With Low Left Ventricular Ejection Fraction After Myocardial Infarction

Importance of Exercise Capacity

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Robert Lisbona, MD, and Allan Sniderman, MD

The measurement of left ventricular ejection fraction (LVEF) plays a key role in many strategies for managing patients after acute myocardial infarction. We tested the hypothesis that exercise capacity 1 month after myocardial infarction provides additional information in patients with a low LVEF and therefore assists in risk stratification. One hundred fifteen patients, with documented myocardial infarction and LVEF less than 35% by gated radionuclide scan 1 month after acute myocardial infarction, were followed up for 2 months to 7 years. Exercise capacity was estimated from a treadmill test 1 month after infarction. Using the Cox proportional hazards model, exercise capacity was a significant predictor of death or reinfarction. The relative risk of death, based on a comparison between the lowermost quintile (<4 METS) and uppermost quintile (>7 METS), was 3.5 (95% confidence interval, 1.1–9.7); the relative risk in the fourth, third, and second quintile was 2.7, 2.1, and 1.6, respectively. In a multivariate analysis, the observed effect of a good exercise capacity was independent of LVEF. These data indicate that in patients with a low LVEF after myocardial infarction, useful prognostic information can be obtained from exercise testing. (Circulation 1989;80:1636-1641)

In recent years, major efforts have been made to identify patients who, after hospital discharge following myocardial infarction, remain at high risk for recurrent cardiac events. Several approaches to detect patients at risk have proven of value; these include exercise testing,1 screening for ventricular arrhythmias,2 determination of left ventricular function at rest,3 and coronary arteriography.4 As a consequence, several strategies for the selection of patients for revascularization have been proposed.5-7

It is generally agreed that the risk of death in the first year after infarction is an inverse function of left ventricular ejection fraction (LVEF).8 Indeed, it has been suggested1,5 that patients with LVEF less than 35% should not undergo further investigation in the absence of symptoms because their prognosis is uniformly bad. On the other hand, some strategies6,7 advocate coronary arteriography in such patients primarily because their mortality is high and because surgery has been shown to improve survival in selected groups.9

In chronic heart disease, the correlation between exercise capacity and ventricular function is poor.10,11 Moreover, we have observed that several patients after infarction tolerate exercise well despite a low LVEF. This observation stimulated the hypothesis that exercise capacity is an independent marker of risk within the subgroup of patients after infarction who have a low LVEF.

In this study, we followed up a group of patients with radionuclide-determined LVEF less than 35% for 2 months to 7.6 years to observe whether exercise capacity predicted death or nonfatal reinfarction. The results support the use of exercise testing to better identify high-risk patients within this specific subgroup.

**Methods**

The Cardiology Followup Centre was established at the Royal Victoria Hospital in September 1979. The objective was to provide a standardized followup so that factors important to outcome could be evaluated. The patients less than 66 years of age, admitted with a documented myocardial infarction,
free of life-threatening comorbid illness, and living within geographic proximity to the hospital were eligible for follow-up. Patients were seen at 1, 3, 6, and 12 months after admission and yearly thereafter for 5 years. At each visit, patients were interviewed by a trained nurse and examined by a cardiologist. At the first visit, and yearly thereafter, a gated radionuclide scan was obtained. At all except the 1-year visit, the patients underwent a treadmill exercise test unless in overt heart failure.

The diagnosis of myocardial infarction was made according to World Health Organization criteria and was further classified as Q and non-Q wave infarction.

Two events, reinfarction and death, were chosen as the relevant outcomes. The risk factors studied were age, sex, Q wave and non-Q wave infarction, postinfarction angina, LVEF, exercise capacity, and aortocoronary bypass surgery. These variables were chosen because they are commonly used to evaluate prognosis after myocardial infarction. However, we chose to treat surgery as a covariate rather than as an outcome because of the possibility that the exercise test itself would influence treatment decisions; the analysis was also performed with patients censored (withdrawn alive) at the time of surgery.

Radionuclide Scan

Equilibrium gated blood pool studies were performed as previously reported.12 After labeling red blood cells with 20 mCi 99mTc pertechnate, data were acquired in 16 frames of 64×64 matrices for a total accumulation of 5 million counts in the left anterior oblique and anterior positions.

Exercise Testing

Exercise testing was performed according to the modified Bruce protocol.13 Medications were not discontinued, and the tests were limited by symptoms or significant ST depression. Estimated oxygen consumption was determined from a regression equation derived from the data of Sullivan and McKirnan,14 who measured oxygen consumption in men after infarction who performed the modified Bruce protocol: METS = [(1.71×exercise time)/3.5] + 4.67.

Statistical Analysis

Analysis was performed using BMDP statistical software (BMDP, University of California). The Cox proportional hazards model (BMDP-2L) was used to estimate the survival function. For the estimation of relative risk, the regression coefficient was exponentiated after multiplying it by the difference between the median value of the index quintile and the lowermost (reference) quintile.15 We used a backward procedure (p=0.10 to enter, p=0.15 to remove) for the stepwise regression; all variables were initially entered and then removed in hierarchical fashion if they did not contribute additional prognostic information at that step. Survival curves were constructed according to the Kaplan-Meier product-limit method (BMDP-1L).

Results

Between September 1979 and July 1987, 614 patients entered the follow-up program. Of these, 115 had an LVEF of less than 35% at their 1-month visit. Ten patients, however, did not perform an exercise stress test because of overt congestive heart failure, and 10 had undergone coronary artery bypass surgery before the scheduled 1-month stress test. These patients were excluded from the Cox model survival analysis but not from the follow-up group. Median follow-up in the overall group was 2.4 years. Fourteen patients did not return to the Followup Centre, and we were able to determine the survival status of 10.

The clinical characteristics of the 95 patients who underwent exercise tests showed many similarities with those who had undergone surgery while in the hospital and with those in heart failure who were unable to exercise (Table 1). However, patients with congestive heart failure had a higher incidence of prior infarction and a somewhat lower ejection fraction and were followed for a shorter period. Most had suffered Q wave infarcts. One in five patients underwent aortocoronary bypass surgery at some time during the follow-up period. The mean LVEF was 25% (range, 7–35%) and was only slightly lower (mean, 21%±8) among patients with clinical heart failure. Thirty percent of the patients who were studied in the Cox model analysis had an ejection fraction of 20% or less. Mean exercise capacity was 5.4 METS (range, 1.9–8.6 METS). In the patients who performed a stress test, there was no relation between exercise capacity and ejection fraction. The exercise test data in these patients are given in Table 2. With exercise, 17 patients experienced angina, 13 had 2 mm ST depression or greater, and five had complex ventricular arrhythmia (multiform premature ventricular complexes or salvos).

Twenty-eight patients died during the follow-up period, and 15 sustained a second myocardial infarction (four of whom died in the immediate period after myocardial infarction and three subsequently). Of the 10 patients who could not exercise at 1 month because of heart failure, seven died in the first year, and all died by the third year.

The stepwise regression procedure is summarized in Table 3. Among these competing variables, exercise capacity was selected as the best predictor of death. Based on a comparison of lowermost and uppermost quintiles of exercise capacity (<4 METS vs. >7 METS), the (unadjusted) relative risk of dying was 3.5 (95% confidence interval, 1.1–9.7) (Figure 1). The relative risk in the fourth, third, and second quintile was 2.7, 2.1, and 1.6, respectively. The results were similar when second events (death or reinfarction) were examined as the outcome of
TABLE 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Included*</th>
<th>Congestive heart failure</th>
<th>Early surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>95</td>
<td>10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56±8</td>
<td>57±8</td>
</tr>
<tr>
<td>Male sex</td>
<td>82 (85)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Prior infarction</td>
<td>18 (19)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Prior congestive heart failure</td>
<td>3 (3)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Q wave</td>
<td>83 (86)</td>
<td>9 (90)</td>
</tr>
<tr>
<td>Angina†</td>
<td>13 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Surgery</td>
<td>21 (22)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>27 (28)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>27 (28)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>25±6</td>
<td>21±8</td>
</tr>
<tr>
<td>Follow-up (mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>Range</td>
<td>2 to 80</td>
<td>3 to 43</td>
</tr>
</tbody>
</table>

Continuous values are mean±SD. Values in parentheses are percentages.

*Patients included in Cox model survival analysis.
†Angina during the first month after infarction.

TABLE 2. Exercise Test Data for 95 Patients Undergoing 1-Month Exercise Test

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
<th>Range</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise capacity (METS)</td>
<td>5.4±2</td>
<td>1.9–8.6</td>
<td></td>
</tr>
<tr>
<td>Peak heart rate</td>
<td>130±22</td>
<td>84–175</td>
<td></td>
</tr>
<tr>
<td>Peak systolic blood pressure (mm Hg)</td>
<td>143±23</td>
<td>95–205</td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>17 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>26 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST depression ≥1 mm</td>
<td>25 (26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST depression ≥2 mm</td>
<td>13 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple premature ventricular contractions</td>
<td>11 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiform</td>
<td>3 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salvos</td>
<td>2 (2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Numbers in parentheses are percentages.

TABLE 3. Stepwise Regression

<table>
<thead>
<tr>
<th>Order of removal of variables</th>
<th>Improvement*</th>
<th>Model†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable removed</td>
<td>Log likelihood</td>
<td>$\chi^2$</td>
</tr>
<tr>
<td>None</td>
<td>-82.9107</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>-82.9266</td>
<td>0.03</td>
</tr>
<tr>
<td>Q/non-Q wave</td>
<td>-83.0828</td>
<td>0.31</td>
</tr>
<tr>
<td>Angina</td>
<td>-83.2680</td>
<td>0.37</td>
</tr>
<tr>
<td>Age</td>
<td>-83.4930</td>
<td>0.45</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>-84.01</td>
<td>1.04</td>
</tr>
</tbody>
</table>

Remaining in model

| Variable       | Coefficient‡ | SE§ | $p$ ||
|----------------|--------------|-----|--||
| Male sex       | 0.785        | 0.49| 0.13||
| Exercise capacity (METS) | -0.266 | 0.13| 0.03||

*All variables listed are initially entered in the model; terms are eliminated in stepwise fashion if the improvement $\chi^2$ suggests they do not significantly ($p<0.15$) improve prediction at that step.
†Tests the goodness of fit of the model (including all terms remaining at that step) to the data.
‡The log of the hazard ratio per unit change in the variable.
§Standard error of the coefficient.
||Tests the hypothesis that the coefficient is zero.
interest. The analysis was repeated with the inclusion of medications in the model, but this addition did not improve prediction ($p>0.2$). When patients were censored (withdrawn alive) at the time of surgery, the coefficient for METS was $-0.289$ ($p=0.025$); the stepwise process results were similar to those in Table 3.

The effect of exercise capacity proved to be independent of LVEF when both exercise capacity and LVEF were forced in the multivariate model (Table 4). The absolute level of ejection fraction did not predict survival in this group with LVEF less than 35%.

The prognostic value of the other exercise test variables compared with exercise capacity is shown in Table 5. Because many of these variables are correlated, stepwise (competing) regression was not performed. Exercise capacity was the most useful variable, and its prognostic value was only slightly improved after adjusting for the other exercise test variables. Four of the 5 patients with complex ventricular arrhythmias died early, and the risk in this setting was therefore high. Similarly, patients who stopped exercise before reaching a high heart rate did poorly. ST depression, however, did not identify patients at risk of death.

Finally, the total event rate, that is, nonfatal myocardial infarction or death, is shown in Figure 2. In the first year, almost 20% of the patients suffered either a nonfatal infarction or died. The second year was practically free of events, but from year 2 on, another 20% suffered a second event. Thus, although adverse events in the first year after discharge, the patients remained at high risk beyond the first year.

**Discussion**

Our study indicates that the estimation of exercise capacity provides useful prognostic information in patients with low LVEF after myocardial infarction.
infarction. Patients who had an exercise capacity of less than 4 METS showed a 3.5-fold greater risk of dying than those with an exercise capacity of more than 7 METS. Moreover, the effect of exercise capacity was independent of measured LVEF in these patients.

Impaired exercise capacity may result from several mechanisms, including residual ischemia, left ventricular dysfunction, and impaired peripheral adaptation to exercise. As an overall measure of cardiorespiratory status, it is not surprising that patients with a poor exercise capacity manifest a poor long-term prognosis and that the information gained from the estimation of exercise tolerance is independent of measured LVEF. The importance of exercise capacity has been addressed by others.16–18 To our knowledge, however, this is the first study that examines the prognostic importance of exercise capacity in patients with a low LVEF, with follow-up beyond 1 year.

Initial evaluation based on LVEF alone is one proposed management strategy after myocardial infarction. This implies that patients with a low LVEF should not be further investigated because their outcome is said to be uniformly poor.1,5 By contrast, our data suggest that further prognostic stratification is possible in these patients, and this view is consistent with the strategies described by the joint task force of the American Heart Association and American College of Cardiology6 and by Ross et al.7

Because it is not our policy to perform routine coronary angiography in patients who have suffered a myocardial infarction, the extent of coronary disease within the entire group was not determined. It is possible, therefore, that the extent of coronary disease might have been a better predictor of survival than exercise capacity alone. Accordingly, it would be improper to conclude that exercise capacity is the best possible indicator of outcome in this patient group. On the other hand, our purpose was to examine, prospectively, whether high and low risk could be distinguished within this specific group by a simple, widely available test without the expense and risk demanded by routine coronary angiography. Similarly, our patients did not undergo routine Holter monitoring, and therefore, the presence of complex ventricular extrasystoles was not assessed. In this regard, it should be noted that in the patients described by Ross et al,7 although ventricular arrhythmias predicted mortality in the overall group, detection of these arrhythmias did not improve prognostic stratification in the subgroup with low LVEF.

Nevertheless, the limitations of our study must be recognized. Coronary angiography or thallium imaging was performed only in selected patients, and in most cases, we had no certain measure of residual ischemia. Because the accurate interpretation of ST segment shifts after infarction is difficult, we used exercise capacity as the primary measure of exercise performance. We did not measure oxy-

![Graph of proportion of patients event free in the whole cohort.](http://circ.ahajournals.org/doi/fig/10.1161/01.CIR.80.6.1640)
gen consumption but estimated it from exercise
time; the equation was, however, derived from data
from male patients after infarction. In addition,
several patients underwent surgery during the follow-
up period. Surgery was not associated with improved
survival in these patients and was eliminated early
from the stepwise model. Furthermore, the results
were the same when patients were censored (with-
drawn alive) at the time of surgery.

Finally, we believe that the 5-year survival data
are of interest. Although patients with markedly
impaired left ventricular function are at substantial
risk after hospital discharge, the longer-term sur-
vival rate documented here argues against any
tendency to therapeutic nihilism. Also, although the
data support the concept of increased risk during
the first year after discharge, they also show that
the risk does not disappear thereafter. Given the
progressive nature of coronary disease, this should
not be unexpected.

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