Prognostication in 3-Vessel Coronary Artery Disease Based on Left Ventricular Ejection Fraction During Exercise Influence of Coronary Artery Bypass Grafting

Phyllis G. Supino, EdD; Jeffrey S. Borer, MD; Edmund M. Herrold, MD, PhD; Clare Hochreiter, MD

Background—Previous data indicate that left ventricular ejection fraction (LVEF) provides prognostic information among patients with coronary artery disease (CAD), but the value of such testing specifically for defining benefits of coronary artery bypass grafting (CABG) may relate to severity of exercise-inducible ischemia measured noninvasively before surgery.

Methods and Results—To determine the independent prognostic importance of preoperative ischemia severity for predicting outcomes of CABG among patients with extensive CAD, we monitored 167 stable patients with angiographically documented 3-vessel CAD (average follow-up of 9 years in event-free patients) who previously had undergone rest and exercise radionuclide cineangiography. Their course was correlated with data obtained during initial radionuclide testing, coronary arteriography, and clinical evaluation at study entry. Fifty-two patients received medical treatment only, and 115 underwent CABG (44 early [≤1 month after initial study]). Multivariate Cox model analysis indicated that change (ΔLVEF) in LVEF from rest to exercise during radionuclide study was the strongest independent predictor of major cardiac events (P=0.003) before surgery and also predicted magnitude of CABG benefit (P=0.04). Patients with ΔLVEF ≥8% or less derived significant survival-prolonging and event-reducing benefit from CABG performed ≤1 month after initial testing (P<0.02 for cardiac death and P=0.008 for cardiac events), early CABG versus medical-treatment-only patients); similar benefits were absent among patients with ΔLVEF more than −8%, and among those in whom CABG was deferred.

Conclusions—Assessment of ischemia severity based on LVEF response to exercise enables effective prognostication among patients with 3-vessel CAD and defines the likelihood of life-prolonging and event-reducing benefits from CABG. (Circulation. 1999;100:924-932.)

Key Words: prognosis ■ ischemia ■ coronary disease ■ grafting

Left ventricular ejection fraction (LVEF) during exercise provides prognostic information among clinically stable patients with coronary artery disease (CAD). However, few studies have assessed the predictive value of exercise LVEF among patients with disease specifically involving all 3 major coronary systems, and none has examined the independent prognostic value of change (ΔLVEF) in LVEF with exercise in this population. Moreover, the relative effects of CABG and of nonsurgical therapy on long-term outcome among subpopulations with equivalent pretherapy exercise responses are poorly understood, precluding optimal application of test results in patient management. Finally, no publication has examined the prognostic implications of early versus delayed surgery or the interaction between ischemia severity and the time between ischemia assessment and CABG.

Elucidation of these relationships is important. Trials of CABG performed without reference to pretherapy exercise left ventricular (LV) performance or timing of surgery disagree regarding benefits of surgery among patients with 3-vessel disease, although several investigations suggest greater life prolongation from surgery if any exercise-inducible ischemia is present before operation than in its absence. LVEF during exercise, as measured by echocardiograms, myocardial perfusion scintigrams when 99mTc-labeled radionuclides are used, or radionuclide cineangiograms, increasingly is used in the management of patients with CAD. Therefore, prognostic precision is needed from such testing to optimize management and to reduce healthcare expenditures.

Accordingly, we analyzed data from a cohort of 167 clinically stable patients who between 1979 and 1983 were entered in a prospectively designed, long-term follow-up study. At study entry, these patients had angiographically confirmed 3-vessel CAD and underwent rest and exercise radionuclide cineangiography for determination of ischemia

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severity by LVEF analysis. Our objectives were to determine cardiac mortality and event reduction from CABG compared with medical therapy among patients with similar LV performance characteristics at study entry and to determine whether the impact of CABG is influenced by the magnitude of preoperative ischemia severity or the interval between the definition of ischemia and surgery. In addition, we sought to define the relative prognostic value of ΔLVEF, other exercise and radionuclide-based findings, selected clinical risk descriptors, and coronary angiographic characteristics during nonsurgical follow-up.

Methods

Patient Population

The study population was drawn from 324 consecutive patients with angiographically confirmed 3-vessel CAD (without associated left main coronary artery stenosis) who underwent maximal, symptom-limited exercise radionuclide cineangiography at The New York Hospital between August 1979 and August 1983 within 1 year of cardiac catheterization and who had no known myocardial infarction (MI) between catheterization and radionuclide study. Patients were excluded if they had prior CABG (51 patients), unstable angina or MI ≤30 days before radionuclide study (64 patients), hemodynamically important primary valvular heart disease (7 patients), cardiomyopathy (2 patients), or left bundle-branch block (1 patient). In addition, patients were excluded if LVEF at rest was <30% at initial study (32 patients); this characteristic confers major independent risk for adverse cardiac outcomes.16–20 potentially confounding results in the less dysfunctional majority.

After these exclusions, 167 patients remained and were allocated into several subgroups. Of the 167 patients, 52 remained free from CABG throughout their entire follow-up. This cohort ("medical-treatment only") served as the control group for comparison with the remaining 115 patients, all of whom underwent CABG, 105 without treatment only) served as the control group for comparison with the CABG throughout their entire follow-up. This cohort ("medical-treatment only") served as the control group for comparison with the remaining 115 patients, all of whom underwent CABG, 105 without CABG, 51 with CABG, and 10 after intercurrent MI. Patients who underwent surgery were assessed in a group combining the 52 medical-treatment-only patients and of the early and late CABG subgroups were contrasted independently with the experience of the 52 medical-treatment-only patients. In addition, the prognostic implications of LV performance were assessed in a group combining the 52 medical-treatment-only patients with the 47 others who underwent late CABG but had not yet had surgery >3 months after initial study or reached a study end point before CABG. The latter grouping ("expanded medical treatment") enabled confirmation of results from the smaller medical-treatment-only group and increased statistical power for evaluation of baseline clinical, proangiographic efficiency of different descriptors during nonsurgical follow-up. As in earlier studies,2,3,21,22 3 months was selected as the minimum initial period of medical therapy after radionuclide testing.

Procedures

Radionuclide Cineangiography

Gated equilibrium radionuclide cineangiography was performed according to our standard procedures, at rest and during symptom-limited supine bicycle exercise, after intravenous administration of 10 to 30 mCi of 99mTc.23,24 Exercise studies were initiated at 25 W; load was generally increased by 25-W increments every 2 minutes until angina, dyspnea, or exercise-limiting fatigue occurred. Heart rate and rhythm were monitored continuously during exercise; blood pressure was recorded at ~2-minute intervals.

Coronary Arteriography

Selective arteriography was performed in all patients as part of their clinically mandated evaluation. Lesions were considered hemodynamically important when they caused ≥50% reduction of coronary luminal diameter. Lesions were classified as proximal if they were proximal to the first septal perforator in the left anterior descending artery (LAD), proximal to the first obtuse marginal branch in the circumflex artery, or in the proximal half of the right coronary artery in the AV groove. Gensini scores25 were calculated to index lesion severity, location of lesions, and adequacy of collateral circulation.

Clinical Characteristics

Baseline data included age at radionuclide study, sex, history of MI, chronic use of antianginal medications, and history of hypertension and diabetes. Severity of angina was graded according to New York Heart Association (NYHA) criteria.26

Coronary Artery Bypass Grafting

Patients underwent CABG at various intervals after radionuclide study. During the period when most operations were performed (1979 to 1983), standard procedure at our institution involved hemodilution prime and moderate systemic hypothermia, with cold cardioplegic arrest for myocardial preservation during the period of cross-clamping. Most CABG patients (86%) received between 2 and 4 grafts. The great majority were saphenous veins; internal mammary artery grafts were used in 3% of patients. Adequacy of revascularization was indexed to the number of graft anastomoses divided by the number of major vessels/branches with hemodynamically important lesions.27

Follow-Up

Clinical course was assessed by periodic telephone interview or questionnaire mailed to the patient, family member, or patient’s physician, supplemented by medical chart review (protocol approved by Cornell University Medical College). During each follow-up, vital status and occurrence of nonfatal cardiac events, hospitalizations, and cardiac revascularization (CABG or PTCA) were recorded. Nonfatal MI was inferred from clinical history, corroborated whenever possible (82% of patients) by ECG, enzyme evidence, or physician report. The decision to undertake CABG was made by the patients and their physicians and was not dictated by research protocol. Patients lost to follow-up were tracked via the Pension Benefit Information Research Services or the National Death Index at the National Center for Health Statistics. Death certificates were obtained whenever possible from state departments of health. Cause of death was determined from death certificates, chart review, or contact with the decedent’s family and/or physician. Deaths were considered cardiac if they occurred proximate to MI, were due to congestive heart failure, or were known to have been sudden or if cause could not be defined. Mean follow-up of event-free patients was 8.9±2.0 (range 2.2 to 13.6) years. Of the 167 patients in the study population, 162 (97%) were followed up to death, MI, or ≥5 event-free years. The status of 32 patients who had not undergone surgery was not precisely known on January 1, 1994, after which no additional data were entered; all but 3 of these had been followed up for ≥8 years.

Statistical Analysis

Baseline differences (continuous variables) among the early CABG, late CABG, and medical-treatment-only subgroups were examined by 1-way ANOVA followed by Tukey’s studentized range test when ANOVA indicated significant global intergroup variation; ordinal and categorical baseline variables were compared by the Kruskal-Wallis or χ2 tests. Survival curves were constructed by the Kaplan-Meier product-limit estimate method28 and compared by the log-rank test (Mantel Cox)29 to contrast the clinical course of non-CABG (medical-treatment-only) and CABG patients. Events considered in these analyses included cardiac deaths alone and major cardiac events (deaths and nonfatal MI), including those perioperative to CABG. When applicable, patient experience was censored at the
time of preoperative MI, repeat CABG, PTCA, or documented noncardiac death. To examine the effect of preoperative MI and permit statistical evaluation of the postoperative course of all patients, a secondary analysis disregarded preoperative events among patients with intercurrent MIs. Separate comparisons were conducted for subgroups categorized according to time of operation (early versus late) and relative ischemia severity at baseline. We used the Cox proportional hazards model to evaluate differences in the relative hazard of major cardiac events among the medical-treatment-only versus CABG subgroups by stratifying the population according to 3 ranges of baseline ischemia severity, defined as 10% increments in ΔLVEF (ie, twice the published standard error of the LVEF determination) around our median ΔLVEF value. Finally, log-rank test comparison of Kaplan-Meier survival curves was performed to screen baseline variables for their univariate relation to initial cardiac event (death or nonfatal MI) in the expanded-medical-treatment subgroup; again, censoring occurred at documented noncardiac deaths and revascularizations. Variables screened are listed in Tables 1 and 2; data were not included in primary analysis unless evaluable in ≥90% of the population. For univariate screening,

TABLE 1. Baseline Clinical and Coronary Anatomic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Expanded-Medical-Treatment Patients (n=99)</th>
<th>Medical-Treatment-Only Patients (n=52)</th>
<th>Early-CABG Patients (n=44)</th>
<th>Late-CABG Patients (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age, y*</td>
<td>57.7±9.9</td>
<td>56.8±9.8</td>
<td>58.9±8.1</td>
<td>58.4±9.6</td>
</tr>
<tr>
<td>Male sex*</td>
<td>86 (87%)</td>
<td>92 (81%)</td>
<td>39 (89%)</td>
<td>66 (93%)</td>
</tr>
<tr>
<td>Average NYHA angina class*‡</td>
<td>2.0±0.7</td>
<td>1.9±0.8</td>
<td>2.3±0.8†</td>
<td>2.1±0.6</td>
</tr>
<tr>
<td>History of MI*</td>
<td>57 (58%)</td>
<td>33 (63%)</td>
<td>20 (43%)</td>
<td>34 (48%)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>36 (44%)</td>
<td>20 (51%)</td>
<td>15 (41%)</td>
<td>29 (43%)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>14 (17%)</td>
<td>9 (23%)</td>
<td>4 (11%)</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>Chronic use of antianginal medication*</td>
<td>64 (66%)</td>
<td>97 (81%)</td>
<td>44 (93%)</td>
<td>71 (66%)</td>
</tr>
<tr>
<td>β-Blockade</td>
<td>16 (16%)</td>
<td>9 (18%)</td>
<td>5 (12%)</td>
<td>12 (17%)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>63 (65%)</td>
<td>37 (72%)</td>
<td>35 (81%)</td>
<td>44 (62%)</td>
</tr>
<tr>
<td>Nitrates†</td>
<td>82 (85%)</td>
<td>42 (84%)</td>
<td>40 (93%)</td>
<td>62 (87%)</td>
</tr>
<tr>
<td>Proximal 3-vessel CAD*</td>
<td>14 (14%)</td>
<td>6 (12%)</td>
<td>8 (18%)</td>
<td>10 (14%)</td>
</tr>
<tr>
<td>Proximal LAD involvement†</td>
<td>46 (46%)</td>
<td>19 (37%)</td>
<td>26 (59%)</td>
<td>38 (54%)</td>
</tr>
<tr>
<td>Average Gensini score*§</td>
<td>65.5±37.0</td>
<td>56.1±34.6</td>
<td>78.5±39.9†¶</td>
<td>74.6±35.0†¶</td>
</tr>
<tr>
<td>Average revascularization index</td>
<td>…</td>
<td>…</td>
<td>0.78±0.3</td>
<td>0.72±0.23</td>
</tr>
<tr>
<td>Internal mammary artery graft</td>
<td>…</td>
<td>…</td>
<td>1 (0.02%)</td>
<td>2 (0.03)</td>
</tr>
</tbody>
</table>

Total population was 167 patients.

*Variables screened for prognostic significance; †P<0.10, ‡P<0.05, §P<0.005, global¶, vs medical-treatment-only¶ patients.

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=167)</th>
<th>Expanded-Medical-Treatment Patients (n=99)</th>
<th>Medical-Treatment-Only Patients (n=52)</th>
<th>Early-CABG Patients (n=44)</th>
<th>Late-CABG Patients (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest LVEF,* %</td>
<td>47.3±9.0</td>
<td>46.3±8.4</td>
<td>46.4±8.4</td>
<td>48.6±8.7</td>
<td>47.1±9.6</td>
</tr>
<tr>
<td>Exercise LVEF,* %</td>
<td>39.0±10.7</td>
<td>39.0±10.3</td>
<td>41.3±10.8</td>
<td>39.0±11.3</td>
<td>37.4±10.0</td>
</tr>
<tr>
<td>ΔLVEF,* ‡±%</td>
<td>−8.3±7.3</td>
<td>−7.2±7.7</td>
<td>−5.2±7.7</td>
<td>−9.7±6.2**</td>
<td>−9.7±6.4**</td>
</tr>
<tr>
<td>Duration of exercise, min</td>
<td>7.2±2.3</td>
<td>7.4±2.3</td>
<td>7.6±2.6</td>
<td>7.0±2.4</td>
<td>7.2±2.0</td>
</tr>
<tr>
<td>Exercise load, W</td>
<td>70.2±29.6</td>
<td>72.7±31.8</td>
<td>72.5±33.4</td>
<td>65.1±26.7</td>
<td>71.7±28.3</td>
</tr>
<tr>
<td>HR at rest, bpm</td>
<td>68.7±11.9</td>
<td>70.0±12.2</td>
<td>70.7±12.9</td>
<td>66.2±10.6</td>
<td>68.8±11.8</td>
</tr>
<tr>
<td>Exercise HR,* bpm</td>
<td>107.1±16.8</td>
<td>109.6±17.9</td>
<td>109.0±17.8</td>
<td>102.3±16.1</td>
<td>108.6±16.2</td>
</tr>
<tr>
<td>ΔHR, bpm</td>
<td>38.4±15.5</td>
<td>39.6±16.4</td>
<td>38.4±16.2</td>
<td>36.1±13.4</td>
<td>39.8±16.2</td>
</tr>
<tr>
<td>SBP at rest,* mm Hg</td>
<td>147.6±20.7</td>
<td>148.1±22.4</td>
<td>147.3±19.1</td>
<td>145.8±18.9</td>
<td>148.9±23.0</td>
</tr>
<tr>
<td>Exercise SBP,*‡#</td>
<td>175.7±23.3</td>
<td>179.7±21.7</td>
<td>181.1±21.7</td>
<td>165.3±24.6†***</td>
<td>178.2±21.9‡††</td>
</tr>
<tr>
<td>ΔSBP, mm Hg#</td>
<td>28.1±20.1</td>
<td>31.6±19.7</td>
<td>33.8±19.6</td>
<td>19.5±19.1§**</td>
<td>29.3±19.7†‡†</td>
</tr>
<tr>
<td>Rest HR-SBP double product</td>
<td>10 149±2362</td>
<td>10 394±2520</td>
<td>10 427±2471</td>
<td>9625±1837</td>
<td>10 271±2543</td>
</tr>
<tr>
<td>Exercise HR-SBP double product*†#</td>
<td>18 937±4475</td>
<td>19 813±4425</td>
<td>19 887±4767</td>
<td>17 026±4258‡**</td>
<td>19 425±4073‡††</td>
</tr>
<tr>
<td>ΔHR-SBP double product‡#</td>
<td>8788±4007</td>
<td>9419±4099</td>
<td>9460±4391</td>
<td>7401±3685†***</td>
<td>9154±3744</td>
</tr>
</tbody>
</table>

HR indicates heart rate; SBP, systolic blood pressure.

All values are averages (mean±SD).

*Variables screened for prognostic significance; †P<0.10, ‡P<0.05, §P<0.01, ||P<0.005, ¶P<0.001, global‡#, vs medical-treatment-only‡¶ patients, vs early-CABG patients‡†.
TABLE 3. AAR and 5-Year Cardiac Event Rates Among Patient Subgroups

<table>
<thead>
<tr>
<th>Event</th>
<th>Expanded-Medical-Treatment Patients (n=99)</th>
<th>Medical-Treatment-Only Patients (n=52)</th>
<th>Early-CABG Patients* (n=44)</th>
<th>Late-CABG Patients**‡ (n=71)</th>
<th>All CABG Patients***‡ (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death,§ AAR (5-y rate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔLVEF &gt;0%</td>
<td>0.0% (0.0%)</td>
<td>0.0% (0.0%)</td>
<td>0.0% (0.0%)</td>
<td>0.0% (0.0%)</td>
<td>0.0% (0.0%)</td>
</tr>
<tr>
<td>ΔLVEF 0 to −7%</td>
<td>1.2% (7.0%)</td>
<td>1.4% (10.0%)</td>
<td>0.0% (0.0%)</td>
<td>2.7% (10.3%)</td>
<td>1.5% (6.1%)</td>
</tr>
<tr>
<td>ΔLVEF &gt; −8%</td>
<td>0.7% (4.8%)</td>
<td>0.8% (6.1%)</td>
<td>0.0% (0.0%)</td>
<td>2.3% (8.5%)</td>
<td>1.3% (5.2%)</td>
</tr>
<tr>
<td>ΔLVEF ≤ −8%</td>
<td>3.1% (15.0%)</td>
<td>4.3% (22.0%)</td>
<td>0.5% (0.0%)</td>
<td>1.7% (10.6%)</td>
<td>1.2% (6.2%)</td>
</tr>
<tr>
<td>All patients</td>
<td>1.6% (8.7%)</td>
<td>1.9% (11.9%)</td>
<td>0.3% (0.0%)</td>
<td>1.9% (9.8%)</td>
<td>1.2% (5.8%)</td>
</tr>
<tr>
<td>Cardiac death or MI, AAR (5-y rate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔLVEF &gt;0%</td>
<td>1.7% (6.2%)</td>
<td>0.9% (0.0%)</td>
<td>0.0% (0.0%)</td>
<td>0.0% (0.0%)</td>
<td>0.0% (0.0%)</td>
</tr>
<tr>
<td>ΔLVEF 0 to −7%</td>
<td>3.0% (12.3%)</td>
<td>2.8% (15.6%)</td>
<td>0.0% (0.0%)</td>
<td>2.7% (10.3%)</td>
<td>1.5% (6.1%)</td>
</tr>
<tr>
<td>ΔLVEF &gt; −8%</td>
<td>2.5% (10.3%)</td>
<td>1.9% (9.4%)</td>
<td>0.0% (0.0%)</td>
<td>2.3% (8.5%)</td>
<td>1.3% (5.2%)</td>
</tr>
<tr>
<td>ΔLVEF ≤ −8%</td>
<td>9.8% (41.3%)</td>
<td>6.9% (32.5%)</td>
<td>1.4% (3.6%)</td>
<td>3.0% (14.7%)</td>
<td>2.3% (10.3%)#</td>
</tr>
<tr>
<td>All patients</td>
<td>5.2% (23.9%)</td>
<td>3.5% (18.0%)</td>
<td>0.9% (2.3%)</td>
<td>2.7% (12.5%)</td>
<td>2.0% (8.4%)</td>
</tr>
</tbody>
</table>

*Denotes initial postoperative events; †excludes postoperative events (2 cardiac deaths) among 10 patients with preoperative MI; ‡includes 1 perioperative MI and 1 periprosthetic death; §includes 7 deaths (4 after MI, 3 sudden) as initial events during medical follow-up and 10 deaths (5 after MI [1 periprosthetic], 1 due to congestive heart failure, 2 sudden, and 1 of unknown cause) without intercurrent event after CABG; ¶comprises patients from subgroups 1 (ΔLVEF >0%) and 2 (ΔLVEF 0 to −7%). AAR (5-y rate)=1.4 (7.2% [deaths]§, 2.5% [events]§) with inclusion of postoperative experience of 8 patients with intercurrent (preoperative) MI.

ΔLVEF was partitioned at its statistical median and again at 0; univariate survival analysis also was performed post hoc on the subset of patients with relatively severe (≥70% luminal diameter narrowing) stenoses to determine whether ΔLVEF provided prognostic information beyond that given by coronary anatomy alone. Other continuous variables were partitioned either according to previously validated prognostic cutpoints or, when cutpoints had not been defined previously, according to their statistical medians or in tertiles, as appropriate. Variables found to be statistically significant or that manifested a trend toward significance in univariate analysis were entered into a forward stepwise multivariate Cox regression model to examine their independent value in predicting cardiac risk. Variables entered into the Cox model were partitioned according to the same cutpoints used for univariate analyses to render hazards approximately proportional across strata. To equalize risk exposure among groups, all time-dependent analyses were indexed to the date of initial radionuclide study. The criterion for statistical significance was P<0.05.

Results

Baseline Characteristics

Clinical and Arteriographic Variables

Most patients had angina (NYHA functional class II or III); the majority reported long-term use of antianginal medications (Table 1) for some period before testing. Approximately half the patients had a history of MI before initial study. Fewer had hypertension; diabetes was relatively uncommon. Proximal involvement of all major vessels was present in relatively few patients; half had significant LAD involvement. Among CABG patients, 75% of hemodynamically important lesions were bypassed. Baseline clinical and coronary anatomic characteristics of the 52 medical-treatment-only patients were similar to those of the 44 early and 71 late CABG patients, except that average Gensini score was higher among CABG patients than among medical-treatment-only patients (P<0.005), whereas angina severity was higher among early CABG than among medical-treatment-only patients (P<0.05). Both adequacy of revascularization and use of internal mammary artery grafts were similar in early and late CABG patients.

LVEF, Blood Pressure, Heart Rate, and Exercise Tolerance

LVEF at rest reached or exceeded the lower limit of normal in most (60%) of the patients. LVEF increased with exercise in 12% of the patients. Among those in whom LVEF failed to rise, a fall of ≥8% (ejection fraction units) with exercise occurred in the majority. This value, −8%, was the statistical median of the distribution of ΔLVEF in the expanded-medical-treatment subgroup. Despite equivalent exercise duration and load during initial testing, baseline ΔLVEF fell further (P<0.001) during exercise among patients who subsequently underwent either early or late CABG than among those who never underwent surgery. Other baseline differences included lower average peak exercise systolic blood pressure and exercise heart rate–blood pressure double product (P<0.005 for both variables) and smaller average changes from rest to exercise in systolic blood pressure (P<0.005) and heart rate–blood pressure double products (P<0.05), primarily among early CABG versus medical-treatment-only patients. (See Table 2.)

Ischemia Severity and Effect of Bypass Grafting

Table 3 summarizes the average annual risks (AARs) and 5-year rates of initial cardiac events and causes of cardiac deaths during medical follow-up or of initial events after CABG. When the clinical course of patients who underwent CABG (early or late) was compared with the experience of the medical-treatment-only patients (Figure 1), the non-CABG patients progressed both to cardiac death and to major cardiac events somewhat more rapidly than the surgically treated patients, although these differences were not statistically significant (P=NS for cardiac death, P<0.10 for cardiac events). However, when patients were stratified according to preoperative ischemia severity, significant intra-
group differences in CABG effect were observed. Outcome in patients without severe ischemia (ΔLVEF more than −8%) who did not undergo surgery was relatively benign despite the presence of 3-vessel disease and was indistinguishable from that in CABG patients who had a comparable degree of ischemia before surgery (Figure 1). When the nonseverely ischemic patients were further stratified post hoc according to magnitude and direction of ΔLVEF (ie, >0% versus 0% to −7%), more deaths and major cardiac events were observed when ΔLVEF was 0% to −7%. However, CABG did not alter the expected natural history of the minimally or modestly ischemic subgroups. In contrast, among patients with ΔLVEF of −8% or less, CABG improved expected outcome (4-fold mortality rate reduction [P=0.02], 3-fold event rate reduction [P=0.01]; Table 3; Figure 1). CABG also produced significant life-prolonging (P<0.05) and event-reducing (P<0.02) benefit when the analysis included the postoperative course of 8 severely ischemic patients who suffered intercurrent MI before operation (Table 3). Cox model analysis revealed a statistically significant (P=0.04) direct relation between preoperative ischemia severity and benefit from CABG (Figure 2). Relative hazards were approximately equivalent among medical-treatment-only versus CABG patients with no or relatively mild ischemia at initial study and rose 5-fold among the most severely ischemic medical-treatment-only patients versus CABG patients.

Timing of Operation and Effect of Bypass Grafting

The interval between initial testing and operation also influenced outcome. Early CABG patients uniformly underwent operation ≤1 month after initial radionuclide study; for late CABG patients, this hiatus averaged 14.5 months. Events were less frequent in early than in late CABG patients: AARs of cardiac death and major cardiac events were 6-fold and 3-fold lower, respectively, among early CABG patients (P<0.04 for cardiac death, P<0.06 for cardiac events; Table 3; Figure 3). Among early CABG patients, no cardiac deaths (and only 1 nonfatal MI, at 3 years) occurred until >5 years after surgery. In contrast, among late CABG patients who underwent surgery without intercurrent event between radionuclide study and operation, 1 nonfatal MI and 6 cardiac deaths occurred within 5 years of follow-up. When the

Figure 1. Medical therapy (Med R) vs CABG (combined early and late CABG subgroups): relation of preoperative ischemia severity to outcome (top, cardiac deaths; bottom, cardiac events).

Figure 2. Relation of baseline ischemia severity to CABG benefit (combined early and late CABG subgroups). P value reflects differences among cardiac event hazard ratios (H/R) (death or MI) derived from non-CABG vs CABG patients, stratified according to 3 sequential 10% increments of ΔLVEF at initial study (−2% to −7% [82 patients], midpoint −2.5% [H/R=1.60%]; −8% to −17% [77 patients], midpoint −12.5% [H/R=2.94%]; and −18% to −27% [15 patients], midpoint −22.5% [H/R=4.95%]). H/R among patients with ΔLVEF 3% to 12% at initial study has been estimated as ≤1 rather than directly calculated, because all CABG patients in this subgroup were event-free and only 1 comparably nonischemic medical-treatment-only patient had an event (a nonfatal MI) late (>7 years) after initial study. MED Rx indicates medical treatment.
postoperative experience of patients with intercurrent events was included in analysis, the advantage of early operation was even more pronounced ($P=0.02$ for cardiac death; $P=0.04$ for cardiac events).

Early CABG patients also suffered 6-fold fewer cardiac deaths ($P<0.05$) and 4-fold fewer major cardiac events ($P<0.02$) than medical-treatment-only patients (Table 3; Figure 4). The influence of early CABG depended on the preoperative severity of exercise-induced LV dysfunction. When the effects of early CABG were evaluated separately among patients without severe preoperative ischemia ($\Delta LVEF$ more than $-8\%$), CABG produced no life-prolonging or event-reducing benefit. When the nonseverely ischemic patients were further stratified to separately examine the course of those with $\Delta LVEF >0\%$ and $\Delta LVEF 0\%$ to $-7\%$ at initial study, CABG produced no survival benefit in either subgroup, although major cardiac events tended downward ($P<0.07$) among patients with $\Delta LVEF 0\%$ to $-7\%$ (Table 3). Among patients with $\Delta LVEF >0\%$, no cardiac deaths occurred in medical-treatment-only or CABG patients, and only 1 nonfatal MI occurred, 7 years after initial study, in a non-CABG patient. In contrast, significantly fewer cardiac deaths ($P<0.02$) and total cardiac events ($P=0.008$) occurred among patients with severe preoperative ischemia ($\Delta LVEF \geq 8\%$ or less) who underwent early CABG than among similarly ischemic patients who remained surgery-free throughout follow-up (Figure 4). AARs of cardiac death and events among severely ischemic early CABG patients were reduced 9-fold and 5-fold, respectively, compared with corresponding medical-treatment-only patients (Table 3); these differences were maintained throughout follow-up (Figure 4).

The effect of CABG was less apparent when operation was deferred $>1$ month after ischemia had been defined (Table 3; Figure 4). For late CABG patients without MI between initial radionuclide study and operation, CABG did not prolong life compared with medical therapy alone, although severely ischemic ($\Delta LVEF \geq 8\%$ or less) patients tended ($P=0.09$) to have fewer major cardiac events when they underwent CABG late than did comparably ischemic medical-treatment-only patients (Table 3; Figure 5). This apparent surgical advantage is approximately half of that achieved in parallel early CABG patients and was abolished when analysis included the postoperative experience of the 10 late CABG patients with MI between initial study and operation.

### Prognostic Indexes

As among the medical-treatment-only patients, univariate analysis in the expanded-medical-treatment group identified a relationship between $\Delta LVEF$ at initial study and the likelihood of subsequent cardiac death or nonfatal MI ($P<0.01$; Figure 5). $\Delta LVEF$ also significantly ($P=0.03$) predicted this outcome when analysis was restricted to the 53 patients with $\geq 70\%$ stenoses.

Among the 16 patients whose LVEF increased with exercise, only 2 nonfatal MIs and no cardiac deaths occurred during follow-up. The AAR of major cardiac events in this subgroup was almost 2-fold less than among the 32 patients whose LVEF either was unchanged or fell $\leq 7\%$ with exercise and $>5$-fold less than among the 51 patients whose LVEF fell $\geq 8\%$ with exercise ($P<0.01$; Figure 5; Table 3). Major cardiac events were unrelated to absolute LVEF at rest, blood pressure, exercise heart rate, exercise tolerance, or clinical variables (including age, MI history, and long-term use of antianginal medications) but were related to CAD severity (by Gensini score; $P<0.03$) and tended to be related to absolute LVEF at peak exercise ($P=0.06$). By multivariate analysis, $\Delta LVEF$ was the most potent independent predictor of initial major cardiac events ($P=0.003$), followed by Gensini score ($P=0.02$). Absolute exercise LVEF added no independent information. $\Delta LVEF$ remained predominantly and independently predictive even when clinical, hemodynamic, and exercise tolerance data were forced into the model on a post hoc basis.

### Discussion

Our data indicate that the benefit of CABG among patients with 3-vessel CAD varies directly with the direction and magnitude of $\Delta LVEF$ measured before operation. Thus, these data can facilitate management decisions. Although no previous investigators have undertaken this analysis, our data are consistent with and extend those of 2 previous reports in which preoperative LVEF with exercise was used to identify patients likely to benefit from CABG. Jones and coworkers found that the concomitant presence of 3-vessel or left main...
disease and a positive exercise radionuclide angiogram (either $\Delta$LVEF $\leq 0\%$ or exercise-induced worsening in wall motion or increase in end-systolic volume $\geq 20$ mL with exercise) predicted CABG-associated benefit at 3 years among patients with mildly to markedly subnormal LVEF at rest. The prognostic value of the LVEF exercise response was not evaluated among those with 3-vessel disease alone, and the influence of ischemia severity on prognosis was not examined. In a later report, Jones$^{13}$ extended these findings through 4 years, additionally widening the range of LVEF at rest for study inclusion.

The present study indicates that among patients with CAD and sufficient exercise-inducible ischemic dysfunction to benefit from CABG, benefit diminishes as the interval between definition of ischemia and operation increases, presumably due to widespread CAD progression during the interval. No previous study has evaluated this issue.

Figure 4. Medical therapy versus early and late CABG: preoperative ischemia severity vs outcome (cardiac death [top] and cardiac events[bottom]). Med $R_s$ indicates medical treatment.

Figure 5. Relation of baseline ischemia severity to initial cardiac events (death or nonfatal MI) in the expanded medical treatment group.

Our data also indicate a significant relation between LVEF exercise response and subsequent outcome among clinically stable, nonsurgical patients with angiographically confirmed 3-vessel CAD and normal or near-normal LVEF at rest. $\Delta$LVEF strongly predicts major cardiac events in this population whether 3-vessel disease is defined as $\geq 50\%$ or $\geq 70\%$ luminal narrowing. Our results are consistent with previous reports of prognostic value of the LV exercise response ($\Delta$LVEF$^1,6$ or absolute exercise LVEF$^3$) in this population$^{1,3,6}$ and also among medically treated patients with 1- or 2-vessel CAD and LV dysfunction at rest$^{32,33}$ and those not stratified for CAD severity.$^2-5$ Most previous studies of 3-vessel disease have dichotomized patients,$^1,6,7,32,33$ although some also analyzed exercise LVEF as a continuous variable; the majority demonstrated that those with ischemia have poorer outcomes than those without.$^1,6,7,32$ Our results confirm these findings by demonstrating a direct relation between the magnitude of LVEF exercise response and likelihood of cardiac events, including cardiac death. Thus, our observations indicate that for a patient with 3-vessel disease whose LV performance is normal or near normal at rest, prognosis can be inferred relatively precisely from the direction and magnitude of $\Delta$LVEF. Moreover, the present study indicates that among patients with clinically stable 3-vessel disease, the prognostic value of a single determination of $\Delta$LVEF maintains its significance for many years, during a more prolonged period than can be inferred from earlier studies. The present findings are at variance with 2 investigations$^7,8$ that failed to identify a relation between exercise-induced LV dysfunction and outcome in patients with 3-vessel disease. However, 1 of these studies$^7$ involved only 53 patients and a relatively short median follow-up (22 months); the other failed to analyze the effect of ischemic dysfunction alone, instead prespecifying a compound ECG-LVEF-exercise tolerance–based criterion that was absent in all 42 study patients.$^8$

Patient selection and other design differences preclude direct comparison between the present study and the 3 large randomized trials of CABG.$^9-11$ None of the CABG trials
assessed exercise-inducible ischemia at study entry in all patients. However, available exercise ECG data suggest different distribution of ischemia severity at entry among the different trials,\textsuperscript{9,34} whereas post hoc analysis of the available sample in 1 trial found that surgical benefit in patients with 3-vessel disease and preserved LV function was related to preoperative exercise ECG results.\textsuperscript{14,35} Therefore, consistent with the suggestion of Bonow and Epstein,\textsuperscript{34} the interaction between baseline ischemia severity and surgical benefit observed in the present study may help to explain the discordant findings among the CABG trials regarding patients with 3-vessel CAD.

The present results suggest that 3-vessel disease does not necessarily require surgery for beneficial alteration of natural history. Without operation, patients with minimal or modest exercise-induced ischemic dysfunction can expect prolonged survival with relatively low risk of intercurrent MI. Such patients are relatively common even among those referred to a large tertiary care center. However, the progressive nature of CAD suggests the prudence of periodic reevaluation of clinically stable patients. Our results provide no insight into the appropriate intertest interval, and additional study is needed.

The present study used radionuclide cineangiography for assessment of LVEF. However, the prognostic implications of \( \Delta \)LVEF are likely to be applicable to results obtained with other techniques, including echocardiography\textsuperscript{15} and myocardial perfusion scintigraphy with \( \text{\textsuperscript{99Tc}} \)-based radionuclides,\textsuperscript{16} which are now frequently used to measure LVEF during exercise. Nevertheless, direct application of these data with other techniques requires determination of the precision of the alternative methods in emulating radionuclide cineangiographic LVEF.

**Study Limitations**

Our findings are limited by the relatively modest size of the cohort and number of end points observed. Cardiac deaths were few and attributed to various causes (Table 3) among medically treated patients, precluding prediction of this outcome alone. Prognostic influences were defined only for relatively broad LVEF ranges and intervals between testing and operation. Relatively few patients who underwent surgery manifested a minimal fall or a rise in LVEF with exercise, which limits the statistical power for detecting treatment differences among those with little or no ischemia. Allocation to medical or surgical therapy was determined by the patient’s physician, which would potentially bias the results. However, CABG and non-CABG patients were comparable on most baseline variables; where differences existed, baseline morbidity was greater among CABG patients than medical-treatment-only patients. Thus, baseline differences are unlikely to account for surgical benefits among CABG versus non-CABG patients. Patients were enrolled in the present study based on referral for exercise radionuclide cineangiography; our cohort is not a consecutive series of patients with 3-vessel disease referred to this hospital or seen by any referring physician, which suggests possible unintentional selection bias. However, previous research in this laboratory\textsuperscript{27} has not disclosed any important clinical, arteriographic, or survival differences between patients undergoing radionuclide cineangiography and comparable patients in our institution not undergoing such testing. Therefore, our study patients probably reasonably represent the general population with anatomically similar disease.

Of necessity in an investigation designed for long-term follow-up, initial study was performed >10 years ago, when most patients in our institution received saphenous vein grafts during CABG; current practice favors internal mammary artery plus vein grafting for 3-vessel disease.\textsuperscript{36} These differences, and newer refinements in surgical technique, may affect the quantitative extrapolation of our results. Study is required to determine precisely the prognostic value of preoperative exercise LVEF response among patients who undergo surgery in the present day. Nonetheless, our results indicate that even with vein bypasses, CABG produces natural history benefit for patients with 3-vessel disease and functionally severe ischemia; this benefit and its direct relation to \( \Delta \)LVEF are likely to be similar or greater with internal mammary artery grafting. Conversely, the present data indicate that absence or minimal abnormality in the LVEF exercise response predicts a benign natural course without surgery; these results should be unaffected by newer surgical techniques. However, our middle group, manifesting moderate exercise-induced ischemic dysfunction, requires additional study, because trends toward CABG benefit may reach significance with application of more effective surgical therapies.

Finally, for reasons previously stated, patients were excluded from this evaluation if LVEF was \(<30\%\) at rest. Patients manifesting this characteristic represent \(<10\%\) of those seen in our laboratory.\textsuperscript{3} They also were excluded if they had previously undergone surgery or had nonischemic cardiac comorbidity or life-limiting noncardiac disease (\(<40\%\) of evaluable patients). Therefore, although our results should be applicable to the majority of patients with 3-vessel CAD, additional study is needed to extrapolate our results to the more severely compromised patient.

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