Radionuclide Angiographic Assessment of Global and Segmental Left Ventricular Function at Rest and During Exercise After Coronary Artery Bypass Graft Surgery


SUMMARY Left ventricular ejection fraction (LVEF) was measured by radionuclide angiography at rest and during supine bicycle exercise before and 3 months after coronary artery bypass graft surgery (CABG) in 20 patients with chronic stable angina. The right anterior oblique gated first-pass technique was used to assess LVEF response to maximal exercise (Wmax), while the left anterior oblique equilibrium-gated technique was used to assess LVEF and relative LV volume changes during graded submaximal exercise. Mean LVEF was unchanged at rest after CABG by both the first-pass (60 ± 12% vs 60 ± 12%) and equilibrium-gated (61 ± 13% vs 62 ± 13%) measurements. At Wmax, mean first-pass LVEF was significantly higher postoperatively than preoperatively (63 ± 17% vs 53 ± 17%; p < 0.01), with a higher Wmax (750 ± 182 vs 590 ± 202 kpm/min; p < 0.001) and higher rate-pressure product (302 ± 59 vs 222 ± 57 units; p < 0.001). Similarly, equilibrium-gated LVEF levels during graded exercise, using stepwise regression analysis, were significantly higher postoperatively than preoperatively (p < 0.001); at the highest graded work load, they averaged 63 ± 19% postoperatively and 53 ± 17% preoperatively, with higher work loads (500 ± 190 vs 417 ± 155; p < 0.05) and higher rate-pressure products (271 ± 55 vs 207 ± 53; p < 0.001). The increase in exercise LVEF after surgery was due to a marked decrease in the ratio, relative to resting values, of counts-based end-systolic volumes during submaximal exercise (preoperative 1.91 ± 1.04; postoperative 1.14 ± 0.46; p < 0.01). The five subjects in whom LVEF decreased significantly during exercise postoperatively all had one or more blocked or stenosed grafts. This study documents, by two independent radionuclide techniques, an improved LVEF during exercise at an increased maximal work capacity and rate-pressure product 3 months after successful CABG.

CORONARY artery bypass graft surgery (CABG) relieves the pain of myocardial ischemia and improves quality of life.1,2 Whether surgical treatment of symptomatic coronary artery disease improves ventricular function and prolongs life is controversial.2,3 This study reports the effect of CABG on left ventricular (LV) function assessed by biplane quantitative radionuclide angiography at rest and during sprint maximal and graded submaximal exercise before and 3 months after surgery.

Patients and Methods
The 20 subjects of this study were drawn from the 34 patients admitted to hospital for elective coronary angiography over a 7-month period because of refractory angina pectoris. They had no non coronary heart disease and consented to enter the study. All β-adrenergic blocking medication was withdrawn 48 hours before commencing measurements, and nitrates were withheld for at least 12 hours. Biplane right anterior oblique (RAO) gated first-pass and left anterior oblique (LAO) gated equilibrium radionuclide ventriculography was then performed at rest and exercise on all of these 34 patients in stages on two consecutive days. On the third day, cardiac catheterization and coronary angiography was performed by the standard Judkins method. Thirteen of the original 34 patients did not proceed to CABG: Two had normal coronary arteries, eight minor or anatomically unfavorable disease, two severe inoperable LV dysfunction and one patient declined surgery. One patient withdrew from the protocol after CABG. The remaining 20 patients, who all underwent CABG and completed the study protocol, are the subjects of this study.

Eighteen subjects were male and two were female. Their mean age was 54 years (range 43–67 years). Preoperatively, all patients had New York Heart Association class II–IV angina (table 1) despite adequate medical therapy with nitrates, β-blocking agents and calcium antagonists. Nine patients had ECG evidence of myocardial infarction (eight inferior and one anterior) documented at least 3 months before the time of study. Based on the presence of angiographically significant coronary lesions, defined as greater than 50% luminal narrowing, two patients had one-vessel disease confined to the left anterior descending coronary artery (LAD), three had two-vessel disease and the remaining 15 had three-vessel disease. Two of the patients with three-vessel disease had significant left main lesions (table 1).
Serum creatinine phosphokinase (CPK-MB) was measured 24 hours after CABG and a technetium-99m (99mTc-PYP) myocardial scan was performed on the third postoperative day to exclude perioperative myocardial infarction. Three months after the operation, all patients underwent rest and exercise radionuclide angiography and repeat left-heart catheterization, using a protocol identical to that used preoperatively, to assess LV function and graft patency.

Exercise Protocols

On the first study day, ECG-gated first-pass radionuclide angiocardiography was performed in the 30° RAO projection while the patient was resting. On the second day, the LV response to the highest achievable work load was assessed by performing repeat first-pass imaging immediately after the peak work load (Wmax) of a symptom-limited sprint exercise test designed to determine with maximal precision the highest sustainable steady-state work load. This test was performed supine with an electronically braked bicycle ergometer (Elema Schonander) starting at a work load of 100 kpm/min and increasing work load by 100 kpm/min every minute. Seventy-five percent of Wmax is usually the highest work load that most patients can sustain for the 4-minute period required for successful steady-state gated equilibrium imaging during graded exercise. This protocol provides a valid predictor of the ECG response to more conventional protocols with 3-minute stages. The pre- and postoperative Wmax values were then used to determine as closely as possible three appropriate graded work loads (0.25 Wmax, 0.50 Wmax and 0.75 Wmax) to be used during LAO equilibrium assessment of ventricular response to increasing work loads. A rest period of at least 45 minutes for physiologic recovery was allowed before the second exercise protocol. Equilibrium imaging was then performed for 2 minutes at rest and during the final 2 minutes of all three successive 4-minute levels of graded supine exercise. Symptoms, heart rate, blood pressure and a 12-lead ECG were recorded every minute throughout the exercise period and for 10 minutes after its completion.

Radionuclide Methods

Both gated first-pass (r = 0.91) and gated equilibrium (r = 0.94) radionuclide measurements of LVEF have been validated against contrast angiography in this laboratory. The results obtained by the two techniques at rest correlated strongly with each other (r = 0.95) and were not significantly different in magnitude from each other or from values determined by contrast ventriculography. Cardiac imaging was performed with the patient supine under a single-crystal gamma camera (model GCA-401 Toshiba Company) fitted with a high-sensitivity, parallel-hole collimator and interfaced to a dedicated minicomputer (PDP 11-34, Digital Equipment Corporation). The gamma camera
was fitted with a high-sensitivity collimator, which was covered by a lead shield except for the central cardiac field of view to maximize first-pass counting statistics while minimizing camera dead-time losses. Premedication with 10 mg of stannous pyrophosphate (Mallinkrodt) intravenously was given before first-pass imaging to permit in vivo erythrocyte labeling for later gated equilibrium imaging. First-pass imaging was performed in the 30° RAO projection during bolus injection through an antecubital i.v. line of 25 mCi of 99mTc as pertechnetate. First-pass data were collected using the physiologic list mode of acquisition, in which ECG-gated signals were recorded along with time and position signals to enable subsequent reformatting of an ECG-gated composite cardiac cycle from the LV phase of cardiac transit. Subsequent LAO equilibrium imaging was performed in the best septal LAO projection, with 15° of caudal tilt, using the in-core gate-synchronized mode of computer acquisition. Both the RAO first-pass and LAO equilibrium composite cycles were composed of 20 frames in a 64 × 64 matrix size.

Counts-based LVEF values were determined in identical fashion from the first-pass and equilibrium studies, using computer-assisted variable LV regions of interest (ROIs), assigned to the end-diastolic (ED) and end-systolic (ES) LV images. The free LV edge was computer defined as 30% of peak LV ED activity after smoothing and correction for background counts. Activity in other cardiac chambers was excluded from the two LV ROIs manually. LVEF was calculated from background-corrected ED counts (EDCs) and background-corrected ES counts (ESCs) as 100 × (EDC − ESC)/EDC.

Relative changes in ventricular volumes in diastole and systole and relative stroke volume changes during graded bicycle exercise were estimated by the counts-based volume method with the equilibrium imaging technique previously described. Background-corrected counts in the ED and ES ROIs obtained during all levels of the 2-minute exercise equilibrium imaging were expressed as a fraction of those measured at rest during the equivalent imaging time.

Segmental ejection fraction (SEF) calculations were performed by a computer program that divided the LV ED outline into geometric segments (fig. 1), and calculated SEF values by an equation analogous to that used for LVEF. The LV long axis was defined by that line which bisected the valve plane and also divided the ED LV image into two equal areas, and this was trisected by two perpendicular short axes.

Our first-pass imaging technique provided statistically adequate counts for determining LVEF at rest and exercises, but not always for SEF. Net ED LV counts after background subtraction averaged 2029 ± 800 at rest and 1369 ± 672 at Wmax preoperatively and 1849 ± 609 at rest and 990 ± 465 at Wmax postoperatively. These values are higher than those found with some other first-pass techniques based on a single-crystal camera and are similar to those reported with dual first-pass studies performed on a multicrystal camera.

Measurements of SEF thus derived from the first-pass technique at rest, when net ED LV counts of greater than 500 (and hence ED segment counts of greater than 100) were always obtained, have been validated against RAO contrast ventriculography in our laboratory, and have been found to frequently demonstrate segmental contraction abnormalities not seen on the equilibrium images. In the present study, all patients had net ED LV counts of greater than 500 at rest, but in three of the 20 subjects, net ED LV counts of less than 500 were obtained at Wmax postoperatively. These three subjects were excluded from the first-pass segmental analysis.

To assess quantitatively the effect of patent grafts on exercise-induced wall motion abnormalities, segments were assigned to individual coronary artery territories (fig. 1).

**Statistical Analysis**

Data are expressed as mean ± SD. The mean ± SEM was used for graphic representation in figures. Variables at rest and Wmax before and after CABG were compared with a t test for significance of paired data. Comparison of mean values for preoperative resting LVEF in the patients with and without previous myocardial infarction was performed with the standard t test for the difference of two means. Analysis of responses from rest through graded exercise in the total group before and after surgery, and also in the subgroups of patients with and without prior myocardial infarction, was performed using stepwise regression analysis.

**Results**

**Operative Results and Graft Patency**

Fifty-seven individual grafts were inserted into the 20 patients (average 2.8 grafts per patient). Seven grafts, including five to the left circumflex (LCx) system, one to the LAD and one to the posterior descending branch of the right coronary artery (PDA) were completely occluded at 3 months, giving a graft patency rate of 88%. Another LAD graft in patient 16 was severely stenosed distally, which left a satisfactory graft function rate of 86% (table 1).
Rest and Exercise Electrocardiography

Nine patients had pathologic Q waves due to confirmed myocardial infarction preoperatively. Another patient (no. 20) developed pathologic Q waves postoperatively and had acute inferior myocardial infarction confirmed by the ECG, CPK isoenzymes and 99mTc-PYP myocardial scan performed immediately after CABG.

Preoperatively, 17 of the 20 patients developed chest pain and 17 developed more than 1 mm of ischemic ST-segment depression during exercise testing. Most of these patients had marked degrees of exercise-induced ST depression: four had 1–2 mm, four had 2–3 mm and nine more than 3 mm. Postoperatively, in contrast, only three of the 20 patients developed chest pain and only three developed more than 1 mm of ischemic ST-segment depression during exercise testing. Patient 16, who had both chest pain and ischemic ST depression (4 mm) during postoperative exercise testing, had a severely stenosed single LAD graft.

Work Capacity

Mean Wmax was significantly higher after CABG (750 ± 182 kpm/min) than before (590 ± 202 kpm/min, p < 0.001). Similarly, the mean rate-pressure product attained at Wmax was significantly higher postoperatively (302 ± 59) than preoperatively (222 ± 57) (p < 0.001). Regression analysis demonstrated that the rate-pressure products during graded exercise were also significantly higher postoperatively than preoperatively (p < 0.001) (table 2).

Resting Hemodynamics

LV end-diastolic pressure at rest measured during left-heart catheterization was 19 ± 6 mm Hg preoperatively and 21 ± 7 mm Hg postoperatively (NS).

LVEF

At rest, mean LVEF was not improved after CABG. The mean first-pass LVEF at rest before and after CABG was identical, 60 ± 12%. Mean equilibrium LVEF at rest was also not significantly different, 61 ± 13% before and 62 ± 13% after CABG.

Preoperatively, with sprint maximum exercise, first-pass LVEF fell significantly, from 60 ± 12% at rest to 53 ± 15% at Wmax (p < 0.05). Postoperatively, it increased from 60 ± 12% at rest to 63 ± 17% at Wmax (NS). The difference between the mean first-pass LVEF at Wmax before and after CABG was significant (p < 0.01) (fig. 2).

These findings of increased postoperative LVEF during exercise were confirmed and demonstrated to be present also at lower work loads by the equilibrium LVEF results during graded exercise (fig. 3). Preoperative equilibrium LVEF fell significantly with increasing work loads (p < 0.001). The resting average was 61 ± 13 and the maximum was 53 ± 17 at 0.75 Wmax. Postoperatively, in contrast, equilibrium LVEF was not found to change significantly from the resting level with increasing work loads, with a mean value of 63 ± 19% at 0.75 Wmax. Regression analysis demonstrated a highly significant difference between these preoperative and postoperative equilibrium LVEF responses (p < 0.001). The significant improvement in LVEF levels during graded exercise postoperatively persisted when results were normalized for work load (p < 0.001) and when they were normalized for rate-pressure product (p < 0.001).

Relative LV Volumes and Stroke Volume (fig. 4)

Using the equilibrium method, relative counts-based LV ED volume (EDV) tended to increase progressively with graded exercise before surgery. Postoperatively, EDV tended to increase less, relative to resting values during progressive exercise.
Before operation, relative LV ES volume (ESV) increased markedly with progressive exercise, more so than the relative increase in EDV, resulting in a fall in LVEF during exercise. After CABG, ESV showed little tendency to increase relative to resting values with increasing exercise. At 0.75 Wmax, ESV relative to resting values was significantly lower postoperatively (1.14 ± 0.46 vs 1.91 ± 1.04; p < 0.01).

Relative changes in counts-based stroke volume during exercise before and after CABG are also shown in figure 4. The major change after CABG was at the first work load level, as there was a significantly greater increase relative to the resting value postoperatively (1.28 ± 0.33) than preoperatively (1.12 ± 0.13; p < 0.05).

Effect of Prior Myocardial Infarction (table 3)

Absolute values of mean LVEF at rest at the time of entry to the study were lower in the nine patients with previous myocardial infarction than in the other 11 patients. These differences were statistically significant both in the first-pass data (54 ± 15 vs 65 ± 7; p < 0.05) and in the equilibrium data (54 ± 16 vs 67 ± 7; p < 0.01). However, the response of LVEF to exercise in these two groups before or after surgery were not distinguishable from each other by stepwise regression analysis.

Effect of Graft Patency on Exercise LV Performance

Preoperatively, 16 of 20 patients decreased LVEF significantly (by more than 5% to less than 70%) during exercise by either first-pass or equilibrium techniques. Postoperatively, in contrast, only five patients decreased LVEF significantly during exercise (one only by first-pass measurement at Wmax, one only by equilibrium measurements at 0.75 Wmax and three in both exercise LVEF protocols); all five of these patients (nos. 7, 11, 16, 18 and 19) were among the seven who had one or more obstructed or stenosed grafts (table 4). Patients 11 and 16 had inadequate LAD graft function, patient 19 had PDA and LCx graft obstruction and patients 7 and 18 had isolated LCx graft obstruction (table 1). However, patients 15 and 17, who had obstructed LCx grafts but functioning LAD and PDA grafts, not only had no decrease in LVEF during exercise postoperatively, but they demonstrated a completely normal LVEF increase during exercise of more than 5% in both imaging protocols.

Of the 13 patients with all grafts patent and functioning, none had chest pain or ischemic ECG ST-segment depression during exercise and none had a significant decrease (more than 5%) by either first-pass or equilibrium measurements of LVEF during postoperative exercise testing. However, only six of 13 increased their LVEF normally (by more than 5%) during exercise, while the remainder had a flat response (table 4). Thus, some mild impairment of LV functional reserve persisted in a substantial proportion of patients with anatomically successful grafts and no residual symptomatic or ECG evidence of residual ischemia. The seven patients with no previous myocardial infarction and all grafts functional had the nearest-to-normal mean LVEF responses during exercise; their mean first-pass LVEF increased from 68 ± 7% at rest to 72 ± 9% at Wmax and their equilibrium LVEF increased from 68 ± 4% at rest to 74 ± 7% at 0.75 Wmax. LVEF increased normally in four of seven patients by both first-pass and equilibrium techniques. This compares with the larger average LVEF increase (from 65% at rest to 80% during strenuous exercise) in normal vol-
TABLE 3. Left Ventricular Ejection Fraction at Rest and During Exercise in Patients With and Without Previous Myocardial Infarction

<table>
<thead>
<tr>
<th>Operation status</th>
<th>First-pass LVEF (%)</th>
<th>Equilibrium LVEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Sprint ex (Wmax)</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 patients with previous infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before CABG</td>
<td>54 ± 15</td>
<td>48 ± 15</td>
</tr>
<tr>
<td>After CABG</td>
<td>53 ± 15</td>
<td>56 ± 19</td>
</tr>
<tr>
<td>11 patients without previous infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before CABG</td>
<td>65 ± 7</td>
<td>57 ± 15</td>
</tr>
<tr>
<td>After CABG</td>
<td>66 ± 6</td>
<td>69 ± 12</td>
</tr>
</tbody>
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Abbreviations: CABG = coronary artery bypass graft surgery; Ex = exercise; LVEF = left ventricular ejection fraction; Wmax = maximum exercise work load.

Discussion

This noninvasive study supports the growing evidence that CABG not only alleviates angina, but also produces objective functional improvement, as documented by decreased ECG evidence of exercise-induced myocardial ischemia and improved exercise radionuclide myocardial perfusion images. In our study, radionuclide LV contraction at rest did not improve significantly after CABG, in accordance with reports by other workers who used standard contrast angiography. Stress-induced imbalance between oxygen supply and demand resulting in reversible myocardial ischemia and exercise-induced deterioration of LV function, however, is much more amenable to improvement by CABG. This is confirmed by the findings in our study of substantial, though not always complete, normalization of LVEF response to exercise after successful CABG.

Similar findings of improvement in radionuclide LVEF response to exercise after CABG have been recently reported by two other groups, but our findings were different from those of Freeman et al. Kent et al. found, using equilibrium radionuclide angiography, that coronary revascularization had no significant effect on LV function at rest in 23 patients 6 months after surgery. However, LVEF response to supine bicycle exercise, measured in most subjects only at the same work load as during preoperative exercise testing, improved postoperatively. Because Wmax increased markedly in our patients postoperatively (table 2), Kent's results are comparable to the postoperative improvement in equilibrium LVEF postoperatively at 0.50 Wmax with respect to values at 0.75 Wmax preoperatively (fig. 3). In addition, our equilibrium data at 0.75 Wmax postoperatively indicates that this improvement in exercise LV performance is maintained at increased work loads and substantially increased rate-pressure double products. Newman et al. studied 20 patients using non gated first-pass radionuclide angiography at rest and immediately after erect bicycle exercise. LVEF and exercise-induced wall motion abnormalities improved markedly 4 months after CABG, at increased work loads and increased rate-pressure products levels, only in patients who were asymptomatic postoperatively. Their results are similar to our first-pass results at Wmax. Our results differ from those of Freeman et al., who failed to detect a significant improvement in mean LVEF during exercise after CABG using the equilibrium measurements. The fact that our results are so similar by two independent imaging techniques (figs. 2 and 3) suggests that the difference in our results and those of Freeman et al. may be due to differences in patient selection. A notable feature of the patients in our study appears to be the generally severe degree of preoperative exercise-induced myocardial ischemia; most had more than 2 mm of ST-segment depression preoperatively.

The marked improvement in LVEF during exercise
after CABG in our study differs from the improvement recently reported in patients with angina given nitrate medication\textsuperscript{21, 22} or $\beta$-blocking medication,\textsuperscript{23, 24} both in that it is associated with increased work capacity and in that it is associated with increased maximum rate-pressure product. It seems likely that CABG, but not medical therapy, improves LV performance under these conditions of increased myocardial oxygen requirements, because only CABG actually improves myocardial perfusion during exercise, while medical therapy exerts its beneficial effect on the LVEF response to exercise by reducing myocardial oxygen requirements.

The postoperative improvement in the LVEF response to exercise was related to a greater reduction in the ratio of counts-based LV ESV\textsuperscript{7} during exercise to resting values than of counts-based relative LV ESV after CABG (fig. 4). Newman et al.,\textsuperscript{19} using a radionuclide area-length method to estimate absolute ventricular volumes, reported similar findings 4 months after CABG. Bussmann et al.,\textsuperscript{25} using contrast angiography, also found a marked reduction in absolute exercise ESV with a nonsignificant decrease in exercise EDV after CABG. We found that relative stroke volume showed a normal progressive increase during exercise postoperatively, in contrast to the abnormal preoperative response in which the major increase in relative stroke volume was seen at the first work load, with a tendency to decrease at higher work loads (fig. 4).

Of the seven grafts that were occluded at 3 months, five were grafts to the LCx coronary system. Lower patency rates of grafts to the LCx compared with either the LAD or RCA have been described.\textsuperscript{26, 27} This may be due to greater likelihood of graft kinking when inserted to distal branches of the LCx. Isolated obstruction of LCx grafts, as in four of our subjects, may not be of adverse functional significance if other grafts remain patent, as three of our four patients had no chest pain or ECG evidence of ischemia during postoperative exercise testing, two of whom had completely normal LVEF increases during exercise, by both first-pass and equilibrium techniques, postoperatively. However, all three patients with blocked or stenosed grafts other than isolated LCx obstruction (nos. 11, 16 and 19), together with two of the four patients with isolated LCx graft obstruction, could be distinguished from the patients with all grafts patent and functioning by being the only patients to drop LVEF significantly postoperatively by either first-pass or equilibrium techniques (table 4). Further data are required to determine the clinical value of exercise radionuclide angiography in noninvasively identifying functionally important impairment of graft function.

We did not find significant relationship between exercise-induced changes in SEF and the patency of individual grafts. One reason for this may be the preponderance of three-vessel disease, which may obscure the effect of individual grafts. Also, segments assigned geometrically in two dimensions may include some three-dimensional overlap in the variable perfusion territories of individual coronary arteries. A further consideration is that exercise-induced wall motion abnormalities may only be apparent in the early portion of systole, so that early systolic, rather than end-systolic, SEF measurements may provide a better quantitative index of these local contraction abnormalities.\textsuperscript{28}

This study has shown that successful myocardial revascularization by CABG substantially improves ventricular performance during exercise, at increased work loads and double-product levels and, hence, at increased levels of myocardial oxygen requirement, in patients with stable angina refractory to conventional medical therapy.

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