Noninvasive Screening Criteria for Enhanced 4-year Survival After Aortocoronary Bypass Surgery

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SUMMARY Two thousand one men with coronary heart disease (CHD) who were enrolled in the Exercise Testing Registry of the Seattle Heart Watch had symptom-limited maximal exercise tests at the initial clinical examination and follow-up surveillance of subsequent mortality for 4.1 ± 1.6 years. When subdivided into three mutually exclusive subgroups, 636 patients did not have exertional myocardial ischemia, left ventricular dysfunction or cardiomegaly; 885 without cardiomegaly had only exertional myocardial ischemia; 480 had left ventricular dysfunction by either cardiomegaly and/or two noninvasive exertional criteria, with or without exertional myocardial ischemia. Three hundred thirty-one men had aortocoronary bypass surgery, while 1670 remained unoperated for at least 4 years. Only 34% of the operated patients who had left ventricular dysfunction, as defined, showed a marked improvement in 4-year survival rates (p < 0.01). Differences in the annual CHD mortality rates in relation to surgical treatment in the other two groups were not statistically significant. Restricting the analysis to a subset of patients who had invasive studies did not alter the conclusion. Accordingly, we suggest the use of noninvasive criteria to aid preliminary screening of patients for invasive studies and surgical treatment.

WHETHER SURVIVAL is prolonged after aortocoronary bypass surgery is controversial.1,2 We recently reported noninvasive predictors of sudden cardiac death in men with coronary heart disease (CHD) who were unoperated, and the question arose whether these predictors would be useful for initial screening of patients who might clinically be considered candidates for the necessary invasive studies, and if the findings were appropriate, for aortocoronary bypass surgery.3 We emphasize that the purpose of such screening, which can be accomplished on the initial workup in clinic or office practice, is to identify men with CHD who are at greater risk for diminished survival and who might, if treated surgically, live significantly longer. The purpose of this study is not to determine whether surgical treatment is superior to medical treatment in properly randomized patients with equivalent pathophysiologic findings after the necessary invasive diagnostic tests are obtained. The results suggest, however, that noninvasive screening criteria may aid the detection of a substantial subset of patients who are more likely to live longer if treated surgically. Comparison of these subgroups is not, therefore, dependent upon comparability of invasive findings observed in the resting state, but comparability of the functional limitations of cardiac patients at symptom-limited maximal exercise.

Materials and Methods

Data on 2001 men with a clinical diagnosis of CHD were selected from the Seattle Heart Watch Registry3-6 on the basis of the initial clinical findings, response to maximal exercise and subsequent follow-up status. The clinical diagnosis of CHD was based on a history of: 1) typical angina pectoris upon exertion or emotion, relieved by rest or nitroglycerin; 2) myocardial infarction with appropriate electrocardiographic changes or enzyme responses or both; 3) cardiac arrest treated by ventricular defibrillation; or 4) various combinations of these syndromes, with or without associated hypertension.

Data on 186 other men with a diagnosis of “arteriosclerotic heart disease” unsupported by any of the above criteria were excluded. This decision was justified by the subsequent evidence of a much lower cardiac mortality rate during follow-up. Data on another 97 men with CHD were also excluded because the records of the initial examination or exercise tests were incomplete, making it impossible to classify them by the functional criteria stated below. Data on 530 women with CHD were omitted because only 29 CHD deaths among them have been reported. Since 1971, when the registry was established, 206 men have been withdrawn: 75% of them could no longer be located by mail or by telephone; others requested to be withdrawn; rarely, a patient was withdrawn by request of his physician. The percentages of withdrawals for the first 6 years were 1.3, 3.7, 2.9, 1.6, 0.6 and 0.2%, respectively.

Cardiomegaly was determined by physical and usually chest x-ray examination by the participating physicians; quantitative measurements of heart size were not obtained. The responses to the exercise testing were reported by the physicians on printed forms. Continuous electrocardiographic data on 1127 pa-

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tients (56.3%) were also obtained from computer-averaged consecutive samples of 100 QRS-T complexes in a single precordial lead (V_6 to inferior right scapula), which had been continuously transmitted by telephone in analog format before, during and for 5 minutes after exercise testing from any of 15 remote testing sites. Sequential quantitative measurements of ST<sub>n</sub> voltages 50–90 msec after the nadir of S provided a standardized and objective evaluation of ST depressions that was independent of the clinical interpretations by various physicians.

Invasive diagnostic studies (coronary arteriography and usually left ventriculography) were performed on 669 men, when the responsible physician considered the possible need for bypass surgery. Since there was no established protocol to determine which patients would be studied invasively, this process merely represents the prevailing community practices at that time. The sample selected for this analysis is not limited to the subset of patients with invasive studies (although this is also analyzed below) because it would defeat the purpose of the study: to ascertain the potential value of noninvasive screening criteria. Furthermore, the comparison of medical vs surgical treatment of CHD patients who had invasive studies — most of whom had not had preoperative exercise testing — has already been published. The relevant details of the invasive studies of these patients in the present report are included, when available, to document their status.

Follow-up questionnaires were mailed to each patient every 6 months; the causes of morbidity or mortality were ascertained from the medical records and correspondence with patients and families. Morbidity was defined by admission to a hospital. If this admission was for aortocoronary bypass grafting within 4 years, the patients were subsequently designated as "operated"; otherwise, they remained in the unoperated group. All death certificates and relevant data were reviewed independently by three cardiologists, and deaths were classified as "very sudden cardiac" (within 1 hour of onset of acute symptoms), "sudden cardiac" (within 1–24 hours), "nonsudden cardiac" (more than 24 hours after the onset of cardiac symptoms), "procedural" (as a consequence of diagnostic catheterization or cardiac surgery), and "noncardiac" (death from any other cause). Annual mortality rates were computed on the basis of elapsed time from initial examination and testing to the date of death or to the latest follow-up evaluation of the survivors. Noncardiac deaths were treated as censored observations at the time of death, as were the withdrawn cases who were lost to follow-up.

To evaluate the role of exercise testing in screening for subsets of patients in which surgery may be most beneficial, all patients were initially included in the analysis. After we compared the overall CHD mortality of all operated patients with that of all unoperated patients, the patients were divided into three functional subgroups.

Based on prior data of mortality predictors in unoperated CHD patients, a three-way functional classification of the patients was formulated as follows:

1) The first group consisted of patients with neither exertional myocardial ischemia nor left ventricular dysfunction as defined below, and without cardiomegaly.

2) The second group consisted of patients with only myocardial ischemia (in the absence of left ventricular dysfunction), manifested subjectively by chest pain on symptom-limited maximal exercise testing and objectively by "ischemic" horizontal or downsloping ST depression ≥ 1 mm at least 1 minute after such exertion, by an accentuated ST depression associated with digitalis treatment, or by ST elevation ≥ 1 mm for at least 1 minute after such exertion, or by both chest pain and abnormal ST responses.

3) The third group consisted of patients with left ventricular dysfunction manifested by cardiomegaly (before exercise testing), by a duration of symptom-limited maximal exercise < 3 minutes in stage I of the Bruce protocol (i.e., aerobic capacity < 4 mets or multiples of the resting oxygen uptake), by a peak systolic pressure < 130 mm Hg during such exertion, or by a combination of any two or all three of these criteria, regardless of whether the criteria for exertional myocardial ischemia were also fulfilled.

We then compared the annual cardiac mortality rates between operated and unoperated patients within each subgroup. Significance of differences were defined by nonoverlapping, simultaneous confidence intervals (based upon Bonferroni’s inequality*). Significance of differences in baseline characteristics for these subgroups was assessed by the chi-square test for discrete variables and t tests for continuous variables.

In addition to the analysis that included all patients, another analysis was performed, again comparing the survival experience of operated and unoperated patients within the subgroups, but this time restricting consideration to patients who had subsequent arteriography and at least one vessel feasible for grafting. This was done to see if including unoperated patients without invasive studies biased the results, since it was possible that these patients might have been different from those who had invasive studies. Although this restriction reduces the sample to 508 patients, it allows us to see if both mortality analyses give the same results. Variations in the time course of survival rates for the functional groups in this analysis are evaluated by life table methods.

Using Cox’s regression analysis, we also assessed the role of exercise tests in screening for subgroups in which surgery may be most beneficial. This is a way of testing for the effect of surgery on survival while adjusting for other covariates that may also affect survival, and also uses the variable amounts of follow-up available on the patients. Analyses were performed to see if the use of exercise indicators of left ventricular dysfunction as covariates in this model showed an effect of surgery better than the use of exercise in-
Results

CHD Events in Relation to Initial Functional Classification

The distribution of 2001 men with clinical CHD in relation to the initial functional classification and to the subsequent annual incidence of death from cardiac causes is presented in Table 1. The 636 men (31.8%) with neither exertional myocardial ischemia nor left ventricular dysfunction, as defined in this study, had the lowest annual cardiac mortality rate: 11.7 per 1000 men at risk. The 885 men (44.2%) with exertional myocardial ischemia had an insignificantly higher annual cardiac mortality rate: 22.4 per 1000 men at risk.* The 480 men (24.0%) with left ventricular dysfunction, with or without associated myocardial ischemia, had the highest annual cardiac mortality rate: 56.1 per 1000 men at risk (p < 0.01).

The annual incidence of cardiac morbidity, defined by hospital admissions for acute myocardial infarction or sudden cardiac arrest with resuscitation by ventricular defibrillation, was 68 and 71 per 1000 men at risk in the latter two groups, but only 38 per 1000 men at risk (p < 0.01) in the first group.

Several resting and exercise variables show highly significant (p < 0.001) differences between these functionally classified groups of men with CHD (Table 2). Since these include age, it is likely that the other pathophysiologic differences reflect changes in the severity of cardiac impairment associated with the natural history of CHD. This is also shown by the increasing average number of coronary arteries with at least 70% stenosis in the three groups, as well as by the decline in ejection fraction of the left ventricle at rest in the third group.

Differences in Subsequent Clinical Management and Cardiac Mortality

Of the 2001 CHD men initially examined and exercised, 1670 (83.5%) remained unoperated for at least 4 years, and 331 (16.5%) had aortocoronary bypass surgery. Within about 4 years of follow-up, 188 cardiac deaths were reported in the unoperated men vs 30 in the operated men. These numbers included 17 procedural deaths — two from diagnostic cardiac catheterization and 15 in-hospital operative deaths. There was no significant difference in the annual cardiac mortality rates of 27.5 vs 20.2 per 1000 men at risk in these two major groups defined by type of therapy (Table 3). Since the operation was performed between 1971–1974, the operative mortality of 4.3% reflects the limitations of the early surgical experience. This contrasts with the operative mortality of 0.7% for 283 patients at the university hospital during the last 2 years (Miller DW Jr: personal communication, 1978).

Differences in Subsequent Cardiac Mortality in Relation to Initial Functional Differences and Clinical Management

The subsequent clinical management has no major effect on the incidence of cardiac mortality, but there is a significantly greater mortality risk in the slightly older and functionally more impaired patients who have left ventricular dysfunction (Table 1).

How does aortocoronary bypass surgery affect this relationship? To examine this question, the annual cardiac mortality rates for the three functionally classified groups subdivided in relation to absence or presence of surgical treatment are shown in Figure 1. Patients in both subgroups with exertional myocardial ischemia show virtually identical annual mortality rates from cardiac causes — about 22 per 1000 men at risk, whether or not they are operated. Those

<table>
<thead>
<tr>
<th>Initial classification of all men in relation to cardiac size and responses to maximal exercise</th>
<th>Initial prevalences (n, %)</th>
<th>Subsequent annual CHD mortality ratio/1000 men at risk (Confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neither exertional myocardial ischemia nor left ventricular dysfunction</td>
<td>636, 31.8</td>
<td>11.7 (6.5, 19)</td>
</tr>
<tr>
<td>Only exertional myocardial ischemia (i.e., chest pain with exercise and/or abnormal ST displacement)</td>
<td>885, 44.2</td>
<td>22.4 (16, 31) NS</td>
</tr>
<tr>
<td>Left ventricular dysfunction (i.e., cardiomegaly, exercise test duration &lt; 180 seconds and/or maximal exercise systolic pressure &lt; 130 mm Hg), with or without exertional myocardial ischemia</td>
<td>480, 24.0</td>
<td>56.1 (41, 75) p &lt; 0.01</td>
</tr>
<tr>
<td>Total</td>
<td>2001, 100.0</td>
<td>26.2</td>
</tr>
</tbody>
</table>
who have neither myocardial ischemia nor left ventricular dysfunction have even lower mortality rates, but the absence of any deaths in only 22 patients who were operated makes it impossible to demonstrate a reliable statistical difference. In contrast, the annual cardiac mortality rate of 70.3 per 1000 unoperated men at risk is significantly higher \((p < 0.01)\) than the corresponding rate of 21.2 per 1000 men at risk in the surgically treated patients with left ventricular dysfunction \((33.8\%\) of all operated patients).

Multivariate analyses by Cox's regression model show that surgical therapy is predictive of survival when examined together with presence or absence of cardiomegaly and the exercise variables indicative of

### Table 2. Initial Characteristics of Three Subgroups of Coronary Heart Disease Classified by Noninvasive Criteria

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>Neither manifestation ((n = 636))</th>
<th>Only myocardial ischemia ((n = 885))</th>
<th>Left ventricular dysfunction ((n = 480))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(p)</td>
<td>(p)</td>
<td>(p)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.3 ± 7.9</td>
<td>&lt;0.001</td>
<td>52.7 ± 7.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (em)</td>
<td>177 ± 7</td>
<td>&lt;0.01</td>
<td>176 ± 7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.9 ± 11.7</td>
<td>&lt;0.01</td>
<td>80.3 ± 12.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Relative weight (%)*</td>
<td>104 ± 13</td>
<td>NS</td>
<td>104 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>244 ± 49</td>
<td>&lt;0.001</td>
<td>260 ± 50</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>126 ± 16</td>
<td>&lt;0.001</td>
<td>131 ± 19</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>35 NS</td>
<td>30 NS</td>
<td>NS</td>
<td>35</td>
</tr>
<tr>
<td>One or more risk factors (%)</td>
<td>48 NS</td>
<td>45 NS</td>
<td>NS</td>
<td>47</td>
</tr>
<tr>
<td>Cardiomegaly (%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>29</td>
</tr>
<tr>
<td>Prior myocardial infarction (%)</td>
<td>53</td>
<td>—</td>
<td>47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormalities on resting ECG (%)</td>
<td>52</td>
<td>—</td>
<td>47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximal exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (sec)</td>
<td>475 ± 126</td>
<td>&lt;0.001</td>
<td>386 ± 126</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Est. (\dot{V}O_2) max (ml/(kg × min))</td>
<td>26.6 ± 7.0</td>
<td>&lt;0.001</td>
<td>21.6 ± 7.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FAI (%)</td>
<td>17 ± 19</td>
<td>&lt;0.001</td>
<td>28 ± 21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>160 ± 19</td>
<td>&lt;0.001</td>
<td>147 ± 22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>178 ± 25</td>
<td>&lt;0.001</td>
<td>172 ± 25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR × SBP × 10⁻²</td>
<td>287 ± 57</td>
<td>&lt;0.001</td>
<td>255 ± 59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR1 (%)</td>
<td>9 ± 10</td>
<td>&lt;0.001</td>
<td>15 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVI (%)</td>
<td>14 ± 17</td>
<td>&lt;0.001</td>
<td>23 ± 17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>STB (mV) at 50–69 msec after S nadir (Number with computer analysis)</td>
<td>-0.110 ± 0.171</td>
<td>&lt;0.001</td>
<td>-0.221 ± 0.201</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Chest pain with exercise (%)</td>
<td>—</td>
<td>&lt;0.001</td>
<td>74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postexertional ST depression (%)</td>
<td>—</td>
<td>&lt;0.001</td>
<td>66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exertional ventricular arrhythmia (%)</td>
<td>9</td>
<td>&lt;0.001</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Number coronary artery(ies) ≥ 70%</td>
<td>0.9 ± 0.9</td>
<td>&lt;0.001</td>
<td>1.7 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>59 ± 14</td>
<td>NS</td>
<td>60 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number studied</td>
<td>116 (18.2%)</td>
<td>—</td>
<td>352 (30.8%)</td>
<td>—</td>
</tr>
</tbody>
</table>

\(p\) values relate to data in adjacent columns.

*Percentage relationship of observed to predicted body weight where the latter in kg equals \(-60.7 + 0.79 \times \) (height in centimeters). Abbreviations: FAI = functional aerobic impairment; HRI = heart rate impairment; LVI = left ventricular impairment; \(\dot{V}O_2\) max = maximum oxygen consumption.

### Table 3. Subsequent Cardiac Mortality

<table>
<thead>
<tr>
<th>Clinical management</th>
<th>n</th>
<th>%</th>
<th>Length of follow-up (years)</th>
<th>Deaths</th>
<th>Mortality*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Annual rates per 1000 men at risk</td>
<td>95% confidence intervals</td>
<td></td>
</tr>
<tr>
<td>Unoperated</td>
<td>1670</td>
<td>83.5</td>
<td>4.1 ± 1.6</td>
<td>188</td>
<td>27.5</td>
</tr>
<tr>
<td>Operated</td>
<td>331</td>
<td>16.5</td>
<td>4.5 ± 1.7</td>
<td>30</td>
<td>20.2</td>
</tr>
</tbody>
</table>

*Includes catheterization and in-hospital operative deaths.
ventricular function (table 4). Recognizing and adjusting for the importance of cardiomegaly and two exercise indicators of myocardial ischemia (chest pain and ST depression) as covariates, the effect of the surgery variable is not significantly predictive of survival. Conversely, when the presence or absence of cardiomegaly and the values of two exercise indicators of left ventricular dysfunction (maximal systolic pressure response and exercise duration) are used as covariates, the surgery variable is highly significant in predicting survival. Thus, adjusting for the ischemia variables does not demonstrate a significant effect of surgery in regard to survival, even when simultaneously adjusting for the non-exercise indicator of LV dysfunction, cardiomegaly. However, adjusting for cardiomegaly and the exercise indicators of left ventricular dysfunction magnifies the effect of surgery so that the surgery variable becomes statistically significant. When this analysis also includes each patient's resting ejection fraction as another independent variable, it is strongly related to survival ($p < 0.001$), but adjusting for ejection fraction when the other non-invasive variables of left ventricular dysfunction are already included does not alter the result that surgery is predictive of survival only when these criteria of left ventricular dysfunction are taken into account.

To further test the validity of this observation, the sample was reduced to 452 men with either exertional myocardial ischemia or left ventricular dysfunction, by the noninvasive criteria already described, and with invasive studies indicating both 70% or more stenosis of one or more coronary arteries and distal vasculature deemed feasible for bypass surgery. Of these, 289 were on the basis of the clinical judgment and recommendations of the responsible physicians and acceptance or not by the patients. Differences in resting, exercise and invasive cardiac variables in these four subgroups are shown in table 5. The patients who were operated had significantly greater relative weight, i.e., percentage of weight per unit of height, slightly higher systolic pressure and smaller ventricular volumes at rest. The operated patients with exertional myocardial ischemia also had more extensive vascular disease than the unoperated patients (table 5); however, when we compare the average number of diseased arteries in the two operated groups, there is no significant difference ($p = 0.33$). Two possibly important differences are that men with

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**Table 4. Multivariate Survival Analyses (Cox’s Regression Model) Showing the Differential Effects of Surgery on Survival When Adjustments are Made for Exertional Left Ventricular Dysfunction vs Exertional Ischemia (Whether or Not Cardiomegaly is Present)**

<table>
<thead>
<tr>
<th>Types of covariates included</th>
<th>Variable</th>
<th>Coefficient</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence or absence of cardiomegaly and exercise indicators of myocardial ischemia</td>
<td>Cardiomegaly</td>
<td>1.306</td>
<td>$8.4 \times 10^{-13}$</td>
</tr>
<tr>
<td></td>
<td>Chest pain</td>
<td>0.176</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td>ST depression</td>
<td>-0.012</td>
<td>0.739</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>-0.311</td>
<td>0.131</td>
</tr>
<tr>
<td>Presence or absence of cardiomegaly and exercise indicators of ventricular dysfunction</td>
<td>Cardiomegaly</td>
<td>0.929</td>
<td>$4.59 \times 10^{-3}$</td>
</tr>
<tr>
<td></td>
<td>Maximum systolic</td>
<td>-0.017</td>
<td>$2.29 \times 10^{-11}$</td>
</tr>
<tr>
<td></td>
<td>blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total duration</td>
<td>-0.0028</td>
<td>$1.1 \times 10^{-3}$</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>-0.747</td>
<td>$2.4 \times 10^{-4}$</td>
</tr>
</tbody>
</table>
left ventricular dysfunction treated surgically have higher ejection fractions and smaller left ventricular volumes at rest ($p < 0.01$). Hence, they have more impairment of function at symptom-limited exercise without proportional cardiac enlargement. When noncardiac causes of death are treated as cen-
sored observations at the time of death, life-table analyses of survival rates show a significantly higher survival rate of 93.8% at 4 years of follow-up (fig. 2) among the operated patients than the 67.5% survival rate of the unoperated patients with noninvasive functional manifestations of left ventricular dysfunction. The corresponding difference between unoperated and operated men in the exertional ischemia functional classification is not significant.

If the procedural death rate were reduced from 4.6% in the group of patients with exertional myocardial ischemia, the operative group would have a higher survival rate than the unoperated medically treated patients. This difference might become statistically significant after several years of follow-up surveillance. Life-table analyses using deaths from all causes (not shown) instead of just cardiac deaths gave similar results.

**Discussion**

This study of community practice in the Seattle area from 1971–1975 reflects the combined experiences of several groups of physicians, cardiologists and cardiac surgeons involved in the care of patients with CHD. Accordingly, it reflects several biases:

1) The period of time represents the early experience with bypass surgery before the operative mortality diminished to its present low levels. A greater operative mortality may obscure any subsequent reduction in late mortality that may result from revascularization. Nevertheless, statistically significant differences emerge, despite the relatively small number of operated patients with data available for analyses.

2) Not all the operative cases in this community are included, since only about 25% initially had multistage treadmill tests of symptom-limited maximal exercise as well as invasive diagnostic studies necessary for surgery. Omission of many patients with unstable angina pectoris or preinfarction angina because they were confined to bed for observation, study and often surgery without allowing time for recovery to a stable cardiovascular status for subsequent evaluation by exercise testing conceivably biases the results in favor of better-risk patients for surgery. Yet the sampling of patients who had exercise tests did not exclude all high-risk patients, because two patients died during the subsequent arteriographic examination. We emphasize that exercise testing to symptom-limited maximal effort is not recommended in acutely ill, unstable or nonambulatory patients until reasonable criteria for possible myocardial infarction have been excluded, and the patient has been allowed progressive amounts of ambulation to prepare him for exercise testing. Use of the low-level testing protocol initially is recommended under these conditions.

3) Not all unoperated patients had invasive arteriographic and ventriculographic studies. Since morphologically significant vascular lesions have been reported in some asymptomatic men with ischemic ST depression during exercise testing, some patients with significant disease may not have been evaluated invasively as early as they should have. Nevertheless, by the method of selection (i.e., clinical manifestations of CHD that can be elicited by a careful review of the history), all men in this study were functionally classified by clinical examination and noninvasive exercise testing to their functional limits, though the morphologic details about the severity and distribution of vascular and myocardial lesions at rest were not uniformly obtained. Since the evaluation is based on these noninvasive screening criteria (representing the limits of left ventricular function), demonstration of a significant difference in 4-year survival rates is valid when a subset of patients who had invasive studies as an additional basis for evaluation also show similar differences in cardiac mortality.

Despite the lack of predetermined study protocol, this study has some unique strengths. In fact, the lack of a protocol for selection of patients for surgery provides a broad base of clinical experience with ambulatory patients, which contrasts with the substantial proportion of exclusions often encountered with rigorously defined protocols. First, all ambulatory CHD patients can be classified initially by available and repeatable noninvasive criteria with respect to the functional severity of the underlying pathophysiology,
which is consistent with the natural history of this chronic vascular disease. Second, the majority had exertional myocardial ischemia, but only a minority progressed to significantly impaired left ventricular functional limits. Third, the follow-up permitted assessment of subsequent mortality risks from CHD and, therefore, of effects of surgical treatment on survival.

Fourth, when aortocoronary bypass surgery is performed, there is no significant reduction in the annual CHD mortality rates, or increase in survival rates for the first 4 years in patients who manifest the commonly accepted clinical indication for surgical treatment — exertional myocardial ischemia with exercise testing. Fifth, only 34% of the operated CHD patients who initially manifest left ventricular dysfunction have significantly reduced mortality or improved survival. In another analysis of a matched-pair cohort, the group with improved survival (two-vessel disease) represents 34% (97 of 287) of the total cases. Thus, the subset of surgically treated patients identified on the basis of noninvasive criteria represents a proportion as large as that identified by comprehensive analysis of invasive data. Sixth, although final evidence of statistical benefit in regard to survival of surgical intervention of patients with neither exertional myocardial ischemia nor left ventricular dysfunction is lacking, in part due to the small number of these patients available, the absence of any mortality to date suggests that surgical treatment carries little risk. Prolonged follow-up for another 5–10 years may show significant differences in survival rates.

Seventh, with a change in clinical orientation and greater use of and reliance on differences in functional cardiovascular limits elicited by noninvasive exercise testing, which can easily and safely be done in office practice, serial exercise testing may indicate the optimal time for the necessary invasive studies and, when indicated, surgical intervention in many of these patients. This hypothesis is worthy of further evaluation. Eighth, multivariate analyses strongly suggest that indicators of exertional left ventricular dysfunction are more important than indicators of exertional myocardial ischemia in identifying subsets of patients in whom surgical intervention may significantly improve 4-year survival. These functional limits are apparent noninvasively by readily available, simple methods that are appropriate for clinical use, even in office practice.

The conclusion of McIntosh and Garcia — that, despite a low operative mortality rate and low rate of graft closure and high incidence of relief from anginal pain, previously published reports of surgical treatment do not suggest that life is prolonged in the majority of operated patients — is partially substantiated by two-thirds of the operated men in this study. Concomitantly, the opinion of Hurst that coronary bypass surgery prolongs the lives of carefully selected subsets of patients with coronary atherosclerotic heart disease is substantiated in one-third of the patients.

A major consideration, therefore, is how to achieve cost-effective selection of patients for necessary invasive studies, and when feasible, coronary bypass grafting. This study suggests that subsets of patients who most need to be protected against a greater CHD mortality risk may now be more readily identified for surgical treatment.

It is also important to consider other noninvasive methods of evaluation. ECG-gated radionuclide cineangiograms often (i.e., 17 of 23 patients, or 74%) show an improvement in ejection fraction in response to exercise (but not rest) after coronary revascularization that correlates with symptomatic improvement postoperatively in patients with coronary artery disease. Yet the investigators emphasize that "no aspect of the patient's initial presentation or preoperative cineangiogram obtained either at rest or during exercise was predictive of postoperative symptomatic status or postoperative myocardial dysfunction either at rest or during exercise." Thus, the limitations of that more expensive and less frequently available method of assessing left ventricular function contrast with the predictive power of noninvasive criteria presented in this study.

Not only is there more effective intraoperative myocardial protection and a gratifying reduction in the current operative mortality and postoperative morbidity compared with that of the early years of this operation, hemodynamic responses to progressive levels of exercise in the upright posture are improved. In contrast to the fall in stroke volume at all levels of activity from rest to maximal exertion after clinically successful aortocoronary bypass surgery previously reported by McDonough and associates, two recent case reports from this laboratory demonstrate correction of exertional hypotension, increased stroke volume and cardiac output with exercise, and improved sequential wall contraction of the left ventricle at rest after aortocoronary bypass surgery. After revascularization in patients with exertional hypotension due to obstructive coronary artery disease, 20 of 23 patients (93%) have shown a positive blood pressure response to exercise as well as an increase in heart rate and in pressure-rate product, and a fall in functional aerobic impairment from 46% to 6%.

Further improvement in the survival rate may now result from more appropriate preoperative selection of patients together with more effective intraoperative preservation of the myocardium.

In conclusion, we hypothesize that use of clinical and noninvasive exercise predictors of cardiac death provides important guidelines to indicate the optimal time to select men with clinically manifest CHD for the necessary invasive arteriographic and ventriculographic studies needed to ascertain the vascular and ventricular indications for and feasibility of aortocoronary bypass surgery. This hypothesis should be

*Although six examples of exertional hypotension and postexertional cardiac arrest from ventricular fibrillation have occurred in men with CHD, all were successfully defibrillated without myocardial infarction, brain damage or death. Over 20,000 tests using the Bruce protocol have been performed in the Seattle community without a fatality.
evaluated by the large-scale national cooperative studies now in progress to assess independently the efficacy of these criteria for prolongation of survival by means of surgical intervention in more appropriately selected patients.

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