Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction


ABSTRACT  Impairment of left ventricular function is the major predictor of mortality after acute myocardial infarction, but it is not known whether this is best described by ejection fraction or by end-systolic or end-diastolic volume. We measured volumes, ejection fractions, and severity of coronary arterial occlusions and stenoses in 605 male patients under 60 years of age at 1 to 2 months after a first (n = 443) or recurrent (n = 162) myocardial infarction and followed these patients for a mean of 78 months for survivors (range 15 to 165 months). There were 101 cardiac deaths, 71 (70%) of which were sudden (instantaneous or found dead). Multivariate analysis with log rank testing and the Cox proportional hazards model showed that end-systolic volume ($\chi^2 = 82.9$) had greater predictive value for survival than end-diastolic volume ($\chi^2 = 59.0$) or ejection fraction ($\chi^2 = 46.6$), whereas stepwise analysis showed that once the relationship between survival and end-systolic volume had been fitted, there was no additional significant predictive information in either end-diastolic volume or ejection fraction. Severity of coronary occlusions and stenoses showed additional prediction of only borderline significance ($p = .04$ in one analysis), but continued cigarette smoking did remain an independent risk factor after stepwise analysis. For a subset of patients (n = 200) who had taken part in a randomized trial of coronary artery surgery after recovery from infarction, surgical “intention to treat” showed no predictive value. We conclude that for prediction, end-systolic volume is the primary predictor of survival after myocardial infarction, being superior to ejection fraction when ejection fraction is low ($<$50%) or when end-systolic volume is high ($<$100 ml). Treatment of infarction should be aimed at limitation of infarct size and prevention of ventricular dilation.


It is now recognized that the major predictor of long-term survival after recovery from acute myocardial infarction is the functional status of the left ventricle. Left ventricular function has usually been described in terms of the ejection fraction (EF), but it is not clear whether EF is the most meaningful index of left ventricular function in the postinfarction situation. Low EF may, on the one hand, be caused by poor contractile function due to extensive myocardial damage or continuing ischemia, or, on the other hand, to left ventricular dilation caused by infarct expansion and stretching of the myocardial scar. Thus end-systolic volume (ESV) or end-diastolic volume (EDV) might be more meaningful predictors of prognosis than EF, which is merely an arithmetical term based on these two values. In this study we used the Cox proportional hazards model to compare the individual predictive powers of ESV, EDV, and EF, together with other possible angiographic and clinical predictors of cardiac mortality in 605 patients. ESV was found to be the best predictor of prognosis, and standardization of the results for ESV showed that the severity of arterial lesions gave only weak and inconsistent additional predictive power.

Patients and methods

The study group consisted of 605 male patients under 60 years of age who had been investigated at 4 to 8 weeks after recovery from a first (n = 443) or recurrent (n = 162) myocardial infarction. First-infarction patients comprised 83% of consecutive hospital survivors who had been admitted to one coronary care unit between January 1977 and July 1984; patients with recurrent infarction comprised 78% of a combined population of patients from our own coronary care unit (66%) and referred patients (34%) who had been investigated between
PATHOPHYSIOLOGY AND NATURAL HISTORY—MYOCARDIAL INFARCTION

1972 and 1979. The mean age of the patients was 50 ± 7 years
(range 21 to 60). Reasons for exclusion of patients were the
presence of other life-threatening disease, patient refusal to join
the study, or death between discharge from hospital and planned
readmission for investigation. Both series of patients have been
the subject of previous reports, which described the anatomic
and functional determinants of long-term prognosis after first
infarction and the effect of coronary artery surgery on survival
in relatively asymptomatic patients after recurrent infarction.

Informed consent was obtained as described previously. Clin-
ically important information presented here that was not in the
previous studies relates to ESV and EDV, together with in-
creased numbers of patients and a longer follow-up.

Myocardial infarction was diagnosed when at least two of the
following abnormalities were present: (1) characteristic clinical
presentation, (2) development of pathologic Q waves or evolu-
tionary ST and T wave changes on the electrocardiogram, (3) an
increase in creatine kinase above normal levels. Cardiac cath-
eterization was performed at 4 to 8 weeks after infarction.
Selective coronary arteriography was performed by the Judkins
technique and arteries were viewed in multiple projections. Left
ventriculography was performed in the right anterior oblique
position. Ventricular volumes and ejection fraction were calcu-
lated by an integration method with correction factors based on
comparisons between true and calculated volumes of radia-
opaque left ventricular casts made from hearts at autopsy. Norm-
al values for our laboratory were obtained from analysis of left
ventriculograms from 53 male patients under 60 years old (mean
41 ± 10) without coronary or valvular disease: EDV 132 ± 36
ml, ESV 39 ± 15 ml, and EF 71 ± 7%. Ventricular volumes
were not indexed to body surface area in this study because there
is lack of evidence for a relationship between ventricular vol-
umes and body surface area in normal adult subjects, and this
lack of relationship was confirmed by examination of the data
from our own normal subjects. In 33 subjects in whom data on
height and weight were available, the correlation between ESV
and body surface area was r = .37 (r² = .14; p < .05), implying
that only 14% of the variation in ESV was accounted for by
variation in body surface area. Coronary arteriographic findings
were documented by our reporting system, which calculates
myocardial score based not only on the severity of the arterial
stenoses but also on the amount of left ventricular myocardium
supplied by each involved vessel. As before, we divided the
myocardial score into an “occlusion score,” which was the
percentage of left ventricular myocardium judged to have been
supplied by occluded vessels, and a “stenosis score,” which was
the percentage of left ventricular myocardium supplied by arter-
ies showing hemodynamically significant but incompletely ob-
structive lesions (75% to 99% cross-sectional area stenoses).
Both the occlusion and stenosis scores were expressed as per-
centages of the total left ventricular myocardium, whereas the
myocardial score was expressed as a number from 0 to 15. Less
than 5 approximates one-vessel disease, 5 to 10 two-vessel
disease, greater than 10 three-vessel disease.

After cardiac catheterization, all cases were discussed at a
weekly combined cardiology and cardiac surgery conference.
Surgery was offered for (1) all patients with left main coronary
stenosis greater than 75% cross-sectional area, (2) severe angina
(Canadian Cardiovascular Society grade III or IV) despite
medical therapy, and (3) 200 patients (100 after first infarction
and 100 after second infarction) who had no or mild angina and
who had suitable coronary anatomy for insertion of at least two
vein grafts; these patients were randomized to be offered either
coronary artery bypass surgery or medical management as part
of a clinical trial. Ejection fraction and volumes were in general
not considered for decisions on entry of patients into the trials.

Follow-up. Patients were seen every 6 to 12 months at our
clinic and the clinical data were recorded. β-Adrenoceptor
blocking agents were prescribed for angina or hypertension but
were not recommended for all patients. Weight reduction was
recommended for the obese, but specific low-fat diets were
usually not advised. Patients were strongly advised to stop
smoking, and smoking habits and cardiac medication were
recorded at each visit. Regular exercise was also recommended. If
patients developed severe angina, despite medical therapy, car-
diac catheterization was repeated and the need for surgery was
reassessed. For patients who died, mode and circumstances of
death were established from hospital notes or, for the majority
of patients who died outside the hospital, from the patient’s
general practitioner or the next of kin. Deaths were classified as
(1) sudden (instantaneous) if they occurred in the presence of
symptoms with or without confirmation of terminal arrhythmia or
if the patient was found dead having previously appeared to
be in normal health; (2) deaths occurring within 30 days of
recurrence of prolonged chest pain with or without confirmation
of reinfarction; (3) deaths resulting from progressive cardiac
failure; (4) deaths after cardiac surgery; or (5) deaths from
noncardiac causes.

At the time of review (October 1985), only three of the 605
patients had been lost to follow-up; the mean follow-up period
for survivors was 78 ± 32 months (range 15 to 165).

Analysis of data. As before,2 data were stored on a PDP 11
computer. Differences between means were compared by use of
the unpaired t test. Univariate analysis of cardiac mortality in
relation to the catheter findings was performed by the Kaplan-
Meier actuarial method, with analysis of differences between
curves by the Mantel-Haenszel method. Correlations between
EF and ESV were calculated by linear regression, and the slopes
of the regression lines for survivors and cardiac deaths were
compared.11

In addition, a full multivariate analysis of factors affecting
the survival time was carried out with log rank testing and the Cox
proportional hazards (multiple) regression model.12 Factors
subjected to multivariate analysis were EF, ESV, EDV, myo-
cardial score, occlusion score, stenosis score, patient age, status
of index infarction (first or recurrent), cardiac surgery, con-
tinued cigarette smoking, and treatment with β-blockers. To allay
fears that the apparent effects of other prognostic variables had
been created artificially by association with a surgical group, a
stratified analysis also was performed on the levels of surgery.
These levels were surgery as part of the randomized trial, early
elective surgery (within 1 year of infarction), or late elective
surgery (after 1 year). Data were analyzed both with respect to
total cardiac mortality and to the occurrence of sudden cardiac
death as defined above. A second Cox analysis was performed
on the 200 patients who had entered the randomized surgical
trials, including surgical “intention to treat” as a predictor,
regardless of whether or not the patient had actually had sur-
gery. Finally, the log relative risk = β1 (X - X0) + β2 (X2 - X02)
was calculated where X was the value for ESV, X0 was the
normal ESV for our laboratory (39 ml), and β1 and β2 were the
coefficients derived from the proportional hazards model.

Results

Cardiac surgery. Of the 200 patients who entered the
randomized trials of coronary artery surgery, 100 (50 after first
infarction and 50 after recurrent infarction) were randomly
allocated to surgical management. Of these, 89 (49 patients after
recurrent infarction and 40 after first infarction) actually had
surgery; the reasons for nonperformance of surgery were patient refusal,
reinfarction, or death while awaiting operation. Twenty-one patients with left main coronary stenosis and 72 with disabling angina (present at the time of investigation or developing subsequently) had elective coronary surgery. Six patients had left ventricular aneurysmectomy in an attempt to relieve severe cardiac failure or intractable ventricular arrhythmias occurring late after infarction, and two had mitral valve replacement for acute papillary muscle rupture occurring during the index infarct. One patient has had a successful cardiac transplant. Thus a total of 191 (32%) of the 605 patients had cardiac surgery, 89 (15%) having surgery on a trial basis and 102 (17%) as an elective procedure for relief of symptoms.

**Medical management.** During follow-up, the proportion of patients smoking cigarettes was decreased by counseling from 62% to 15%. β-Adrenoceptor blocking drugs were prescribed for 28% of patients. Most patients exercised regularly, but relatively few had any formal rehabilitation or exercise program.

**Total mortality.** One hundred twenty (20%) of the 605 patients died during the follow-up period of 78 ± 32 months, 101 of these deaths being from a cardiac cause. Seventy-one (70%) of these 101 cardiac deaths were sudden, 17 (17%) followed reinfarction or prolonged chest pain, eight (8%) were from cardiac failure, and five (5%) followed cardiac surgery.

**Factors associated with mortality.** A comparison of prognostic factors for patients who survived (n = 485) with those dying of a cardiac cause (n = 101) is shown in table 1. Patients who died had significantly higher ventricular volumes, lower EFs, and higher myocardial scores (overall severity of obstructive coronary lesions) than those who survived. However, the difference in myocardial score comparing survivors with patients who died (8.9 ± 2.9 vs 10.2 ± 2.2) was considerably less than the difference in left ventricular volumes (ESV for survivors 72 ± 36 ml and for cardiac deaths 122 ± 65 ml) and was accounted for by a greater volume of myocardium distal to blocked vessels (occlusion score) and not by a difference in myocardium supplied by significantly stenotic vessels (stenosis score). Age (within the range studied) and the incidence of cardiac surgery were no different between surviving and dying patients. However, continued cigarette smoking significantly worsened the prognosis on univariate analysis, whereas prescription of a β-blocker improved it.

The preliminary analysis (table 2), in which log rank tests linked survival to each of the predictors, showed that ESV ($\chi^2 = 82.9$) had greater predictive power

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**TABLE 1**

Prognostic factors in survivors (n = 485) and patients dying from a cardiac cause (n = 101)

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Survivors (n = 485)</th>
<th>Noncardiac deaths (n = 19)</th>
<th>Cardiac deaths (n = 101)</th>
<th>p value (cardiac deaths vs survivors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (%)</td>
<td>55 ± 13</td>
<td>51 ± 12</td>
<td>44 ± 14</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>72 ± 36</td>
<td>87 ± 38</td>
<td>122 ± 65</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>155 ± 47</td>
<td>173 ± 47</td>
<td>209 ± 73</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Myocardial score (%)</td>
<td>8.9 ± 2.9</td>
<td>9.9 ± 2.6</td>
<td>10.2 ± 2.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Occlusion score (%)</td>
<td>25 ± 20</td>
<td>34 ± 21</td>
<td>34 ± 23</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Stenosis score (%)</td>
<td>38 ± 27</td>
<td>36 ± 20</td>
<td>37 ± 24</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>50 ± 7</td>
<td>51 ± 5</td>
<td>51 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac surgery (%)</td>
<td>156 (32%)</td>
<td>6 (31%)</td>
<td>32 (32%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>13</td>
<td>29</td>
<td>23</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>β-Blockers (%)</td>
<td>30</td>
<td>35</td>
<td>18</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Follow-up (mo)</td>
<td>78 ± 32</td>
<td>51 ± 43</td>
<td>44 ± 35</td>
<td></td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.9 ± 0.1</td>
<td>1.8 ± 0.1</td>
<td>1.9 ± 0.1</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD.
of cardiac death was curved (quadratic). The final proportional hazards model is shown in table 4, and the plot of relative risk (for nonsmokers) with 95% confidence limits for the range of ESV is shown in figure 3. Once this relationship had been fitted there was no additional significant predictive information in either EF or EDV. Results were similar when sudden death rather than total cardiac death was used as the dependent variable in the analysis. When the Cox analysis was repeated on the subset of 200 patients who had entered the randomized trial of surgery, the results again were similar, with surgical “intention to treat” having no predictive value ($\chi^2 = 0.4$, $p = .52$). Further subset analysis of the 83 patients with EFs under 50% who were included in the surgical trials showed no trend toward improved survival as a result of surgery.

Relationship between EF and ESV. Because EF and ESV are clearly related to each other, the relationship

than EDV ($\chi^2 = 59.0$) or EF ($\chi^2 = 46.6$). This is shown in figure 1, in which separation of survival curves with stratification by ESV is greater than the separation with stratification by EF, and in figure 2, which shows that for patients with EF under 50% survival was significantly worse when ESV was above the median value for that group than it was when ESV was below the median value. Five year survival for these groups of patients, with 95% confidence limits, is shown in table 3.

These indexes of ventricular function, in turn, were better predictors of survival than myocardial score ($\chi^2 = 9.7$) or occlusion score ($\chi^2 = 10.0$). Second vs first infarction showed no significant predictive value. Stepwise analysis with standardization for ESV showed no consistent additional predictive value for any other variable apart from smoking. Although in one analysis myocardial score showed a predictive value of borderline significance ($\chi^2 = 4.4$, $p = .04$), this was not a consistent finding in other analyses. However, addition of the square of ESV to ESV in the analysis did show additional predictive value, indicating that the relationship between ESV and the log relative risk

FIGURE 1. Actuarial survival curves constructed by dividing the patients into three groups according to their ESVs (top) or EFs (bottom). Although both methods of classification give highly significant prediction for cardiac mortality ($p < .001$), the separation is wider with classification by ESV than with classification by EF. Numbers after the last data points shown numbers of patients at risk during the last year of follow-up.

FIGURE 2. Actuarial curves constructed for three groups of EF ($\geq 50\%$, 40% to 49%, and $< 40\%$), each group being subdivided according to whether ESV was above or below the median for that group. Predictive value for ESV is apparent only when EF is less than 50%, mortality for patients with EFs of 40% to 49% but ESV below the median being no worse than that for patients with EFs of 50% and above.
TABLE 3
Five year cardiac survival (± 95% confidence limits) for the groups of patients shown in figures 1 and 2

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>5 year survival (% ± SE)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESV&lt;95 ml</td>
<td>437</td>
<td>94 ± 1</td>
<td>.0001</td>
</tr>
<tr>
<td>ESV 95–130 ml</td>
<td>97</td>
<td>78 ± 5</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ESV&gt;130 ml</td>
<td>71</td>
<td>52 ± 6</td>
<td>.97</td>
</tr>
<tr>
<td>EF≥50%</td>
<td>379</td>
<td>94 ± 1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>EF 40%–49%</td>
<td>120</td>
<td>83 ± 4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>EF&lt;40%</td>
<td>106</td>
<td>65 ± 5</td>
<td>.0001</td>
</tr>
<tr>
<td>ESV&lt;55 ml</td>
<td>186</td>
<td>95 ± 2</td>
<td>.318</td>
</tr>
<tr>
<td>ESV≥55 ml</td>
<td>193</td>
<td>94 ± 2</td>
<td>.006</td>
</tr>
<tr>
<td>EF 40%–49%</td>
<td>60</td>
<td>92 ± 4</td>
<td>.012</td>
</tr>
<tr>
<td>ESV&lt;95 ml</td>
<td>60</td>
<td>73 ± 7</td>
<td></td>
</tr>
<tr>
<td>ESV≥95 ml</td>
<td>60</td>
<td>73 ± 7</td>
<td></td>
</tr>
<tr>
<td>EF&lt;40%</td>
<td>60</td>
<td>73 ± 7</td>
<td></td>
</tr>
<tr>
<td>ESV&lt;130 ml</td>
<td>53</td>
<td>79 ± 6</td>
<td></td>
</tr>
<tr>
<td>ESV≥130 ml</td>
<td>53</td>
<td>52 ± 7</td>
<td></td>
</tr>
</tbody>
</table>

between these variables was plotted for individual patients who survived or died from a cardiac cause (figure 4). Correlations between the two variables were reasonably close (r = −.78 both for survivors and for cardiac deaths). However, the slopes of the regression lines were significantly different (t = 4.6, p < .001), indicating that patients who died had higher ESV for a given EF than those who survived; this tendency became apparent only when EF was reduced below 50% or ESV was increased above 100 ml. However, for individual patients ESV varied widely for the same EF; two representative examples are shown in figure 5. A full correlation matrix of the noncategorical variables that were entered into the Cox analysis is given in the appendix.

Discussion

Results of four other studies of prognosis in consecutive series of angiocardiographically defined patients after myocardial infarction1–4 are compared with those of the present study in table 5. All five studies were performed on relatively young patients (mean age 49 to 51 years), and four of the five studies have shown a low cardiac mortality rate with only one cardiac death for every 456 to 500 patient-months of follow-up. This implies an overall cardiac mortality rate of just under 3% per year. As reported previously,3,6 our findings differ from those of Sanz et al.,2 De Feyter et al.,5 and Roubin et al.4 (although they agree with those of Taylor et al.1) in that we found only a weak predictive value for the severity of coronary arterial lesions in comparison with the severity of myocardial damage. There are a number of possible reasons for this difference. First, the studies of Roubin et al.4 and De Feyter et al.5 did not use multivariate analysis; in the present study the coronary arterial lesions were more severe (although not markedly so) in patients who died than in those who survived, but the difference almost disappeared on multivariate analysis. Second, we believe that our scoring system,9 which takes into account not only the severity of the coronary lesions but also the amount of myocardium that these arteries supply, gives a more accurate picture of the overall severity of arterial disease than the terms one-, two-, or three-vessel disease, which were used in the other studies. Third, the present study is larger, has a longer follow-up, and includes more than five times as many deaths as any of the previous studies, giving it much greater statistical power.

The fourth possibility for the lack of predictive value from the severity of arterial lesions in our study is that

FIGURE 3. Estimated relationships between ESV and relative risk of cardiac death over the follow-up period. The risk is relative to that of an individual with an ESV of 39 ml (normal for our laboratory). The risk does not rise steeply until ESV is 3 to 4 SD above normal. Fine lines indicate 95% confidence limits of relative risk. Strictly speaking, this curve applies only to nonsmokers (see text for details).
this effect was negated by the high proportion of patients (32%) who had cardiac surgery. However, for the 15% of patient who had surgery on a clinical trial basis, multivariate analysis showed no effect of surgical “intention to treat,” whereas the remaining proportion of 17% who had surgery for relief of disabling symptoms is no higher than that reported by Roubin et al.4 (10%) or De Feyter et al.3 (13%), given that our period of observation was three times longer than theirs. The lack of benefit from surgery for patients who do not have disabling symptoms supports our previous observations5,6 and those of the Coronary Artery Surgery Study (CASS).13 The subset analysis of patients with low EF did not support the CASS finding of a possible benefit from surgery for these patients,14 but numbers may have been too small for such an effect to be observed.

The most important conclusion from our study is that left ventricular dilation after infarction is the major identifiable risk factor for subsequent cardiac death. Left ventricular dilation results from infarct expansion15 due probably to slippage of the necrotic fibers on one another as the infarct stretches during systole.16 Infarct expansion occurs between 3 days and 2 weeks after infarction,17 and patients showing expansion by 10 to 21 days after transmural infarction may continue to have expansion over a period of 6 to 30 months.18 Infarct expansion would increase left ventricular systolic and diastolic volumes with resultant increase in wall stress, which in turn may act as a stimulus to cardiac hypertrophy. The mechanism of cardiac hypertrophy (remodeling) after infarction is ill understood because infarction is a regional not a global process. However, by analogy with conditions leading to global ventricular dysfunction, it is likely that increases both

FIGURE 4. Relationship between EF and ESV for surviving patients (left) and patients dying of a cardiac cause (right). Correlations are similar (t = −.78) for both groups of patients, but for patients who died the slope of the relationship is significantly steeper than for those who survived (t = 4.6, p < .001).

FIGURE 5. End-diastolic frames from left ventriculograms taken in the right anterior oblique projection of two patients with the same EFs but with markedly different ESVs. EF was 29% in both patients, but the ESV of patient A (top), who died suddenly after 1 month of follow-up, was 230 ml, while that of patient B (bottom), who survives after 103 months, was 117 ml. Myocardium in the aneurysmal region in patient A is thinned as shown by the reduced distance between inner and outer lines. These lines indicate the endocardial and epicardial surfaces at end-systole (dotted lines) and end-diastole (broken lines).
TABLE 5
Comparison of prognostic studies in angiographically defined patients after myocardial infarction

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Unselected cases (%)</th>
<th>Recurrent infarcts (%)</th>
<th>Cardiac surgery (%)</th>
<th>Mean F-U (mo)</th>
<th>Total patients F-U*</th>
<th>Cardiac deaths</th>
<th>F-U for 1 cardiac death</th>
<th>Analysis of prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>605</td>
<td>50 (21–60)</td>
<td>All M</td>
<td>82</td>
<td>27</td>
<td>32</td>
<td>78</td>
<td>47,190</td>
<td>101</td>
<td>467</td>
<td>Multivariate</td>
</tr>
<tr>
<td>Ganz et al.2</td>
<td>259</td>
<td>51 ± 7 (SD)</td>
<td>All M</td>
<td>91</td>
<td>9</td>
<td>3</td>
<td>34</td>
<td>8,806</td>
<td>19</td>
<td>463</td>
<td>Multivariate</td>
</tr>
<tr>
<td>Roubin et al.4</td>
<td>229</td>
<td>51 (27–60)</td>
<td>15% F</td>
<td>89</td>
<td>10</td>
<td>10</td>
<td>24</td>
<td>5,496</td>
<td>11</td>
<td>500</td>
<td>Univariate</td>
</tr>
<tr>
<td>De Feyter et al.3</td>
<td>179</td>
<td>51 (28–65)</td>
<td>10% F</td>
<td>81</td>
<td>8</td>
<td>13</td>
<td>28</td>
<td>5,012</td>
<td>11</td>
<td>456</td>
<td>Univariate</td>
</tr>
<tr>
<td>Taylor et al.1</td>
<td>106</td>
<td>49 (27–66)</td>
<td>26% F</td>
<td>38</td>
<td>26</td>
<td>18</td>
<td>30</td>
<td>3,180</td>
<td>18</td>
<td>177</td>
<td>Multivariate</td>
</tr>
</tbody>
</table>

F-U = follow-up.

in systolic and diastolic stress would lead to regional hypertrophy or remodeling. As an index of left ventricular function, ESV is independent of preload but very dependent on afterload so that the absence of data on afterload at the time that ESV was measured is a limiting factor to our study.

Despite these limitations, ESV was the most significant predictor of prognosis in our study, and the Cox analysis showed no additional information from either EF or EDV. When EF and ESV were compared in individual patients, addition of ESV clearly added prognostic power to stratification of mortality risk by EF alone (figure 2). Most of the cardiac deaths (70%) were sudden, implicating ventricular fibrillation as the mechanism. Presumably increased wall stress leading to increased myocardial oxygen demand is a risk factor for ventricular fibrillation because of reentry of electrical impulses between normal myocardium and fibers in the stretched ischemic scar. It is of interest that the severity of stenoses was not a risk factor in this study, implying that coronary thrombosis, if it preceded late sudden death, could not have been predicted from the presence of stenotic lesions after recovery from the index infarct.

It is possible that other known risk factors, not assessed in this study, might have added extra prognostic information to the ESV measurements. Ventricular arrhythmias detected during 24 hr Holter monitoring constitute a risk factor that is probably additive to the severity of left ventricular dysfunction. Ongoing reversible myocardial ischemia is another risk factor. In our study, patients with severe ongoing symptoms despite medical therapy were managed surgically. No attempts were made to evaluate asymptomatic ischemia, and it is possible that some deaths might have been related to jeopardized myocardium not identified by symptoms. Again it is possible that classification of coronary stenoses on the basis of their eccentricity and irregularity might give better prediction of future coronary thrombosis and cardiac death than classification in terms of cross-sectional area loss, which was used in the present and previous studies. Continued cigarette smoking has been identified in the past as a cause of increased cardiac mortality after recovery from infarction and our results confirm that it is an independent risk factor. Apart from smoking, primary risk factors are probably not important predictors of prognosis once serious myocardial damage has occurred, although it is possible that imbalance between humoral procoagulant and anticoagulant factors might be additional risk factors for recurrent coronary thrombosis and cardiac death.

Identification of cardiac dilation as the major risk factor after myocardial infarction raises the question of how dilation might be prevented. Limitation of myocardial infarct size by reperfusion with an intravenous thrombolytic agent would seem the best strategy at present. In addition, Pfeffer et al. have shown in rats with myocardial infarction and cardiac failure that reduction of left ventricular filling pressures with captopril prevents ventricular dilation and increases survival. It appears that studies involving alterations in blood pressure, heart rate, and contractility during the days and weeks after myocardial infarction in man are needed to assess the effects of interventions on the little-investigated healing phase of myocardial infarction. This includes the processes of infarct expansion, left ventricular dilation, and ventricular remodeling.

We are grateful to the cardiologists who have helped us in this study, to Carol Breed and Margaret Vedder for expert statistical assistance, and to Janice Pillinger for typing the manuscript.
APPENDIX

Correlation matrix of noncategorical variables entered into the Cox analysis

<table>
<thead>
<tr>
<th></th>
<th>EF</th>
<th>ESV</th>
<th>EDV</th>
<th>Myocardial score</th>
<th>Occlusion score</th>
<th>Stenosis score</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF</td>
<td>.78</td>
<td>.45</td>
<td>.28</td>
<td>-.28</td>
<td>-.42</td>
<td>.16</td>
<td>-.20</td>
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<tr>
<td>ESV</td>
<td>.87</td>
<td></td>
<td></td>
<td>.28</td>
<td>.38</td>
<td></td>
<td></td>
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<tr>
<td>EDV</td>
<td></td>
<td></td>
<td></td>
<td>.21</td>
<td>.27</td>
<td></td>
<td></td>
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<tr>
<td>Myocardial score</td>
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<td></td>
<td></td>
<td></td>
<td>.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occlusion score</td>
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<td></td>
<td></td>
<td></td>
<td>.43</td>
<td>.17</td>
<td></td>
</tr>
<tr>
<td>Stenosis score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.34</td>
<td>.02</td>
<td></td>
</tr>
</tbody>
</table>

References

Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction.
H D White, R M Norris, M A Brown, P W Brandt, R M Whitlock and C J Wild

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