Long-term prognostic significance of M mode echocardiography in young men after myocardial infarction

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Abstract

Objective—To evaluate the power of measurements of left ventricular size and function for predicting long term (82 month) mortality by performing echocardiography in 97 men who had survived an acute myocardial infarction. Setting—University hospital specialising in cardiology. Participants—97 consecutive male patients who had survived a myocardial infarction.

Main outcome measures—The additive prognostic value of functional measurements to that provided by primary risk factors (smoking habits and lipoprotein levels), radiological heart size, exercise capacity, and number of major coronary arteries with haemodynamically significant stenoses was evaluated. An echo index was calculated from three echocardiographic variables (yielding one score point each: left ventricular diameter at the end of diastole (LVDD) \( \geq 5.7 \) cm, left ventricular fractional shortening \( \leq 24\% \), and E point-separation (EPSS) \( \geq 10 \) mm).

Main outcome—17 cardiac deaths occurred during follow up.

Results—Univariate analysis showed that treatment with loop diuretics for heart failure (P < 0.01), LVDD (P < 0.01), left ventricular diameter at the end of systole (LVSD) (P < 0.001), left atrial diameter (P < 0.001), fractional shortening (P < 0.05), and echo index (P < 0.001) were all associated with cardiac death. Angiographically determined regional wall motion disturbances (P < 0.005) and angiocardiographic ejection fraction (P < 0.001) were also associated with cardiac death, as was the number of major coronary arteries with significant stenosis (P < 0.05). When all significant echocardiographic variables from univariate analysis were entered into Cox proportional hazards survival analysis, LVDS and left atrial diameter contributed independently to the prediction of cardiac death. If angiographic data were also entered into the model, the echo index made an independent contribution to the prediction of cardiac death.

Conclusions—Among young male patients with a previous myocardial infarction, a simple M mode echocardiographic examination can identify high and low risk patients and improve the prediction of cardiac death made from clinical information, exercise test, chest x ray and angiographically determined ejection fraction.

Keywords: myocardial infarction; M mode echocardiography; prognosis; young age

The long-term prognosis for young male postinfarction patients is favourable, although the mortality is much higher in healthy counterparts. The outcome for patients who survive an acute myocardial infarction depends on the amount of damaged myocardium, as reflected by the left ventricular ejection fraction, and the number of significant coronary artery stenoses. However, the invasive nature of such measurements limits their application as routine investigations. Radionuclide methods are valid but expensive for measuring ejection fraction and require intravenous injections of isotopes. Already over a decade ago, echocardiography was judged to be a useful alternative to cardiac catheterisation or radionuclide investigations for evaluating left ventricular size and function. Consequently, van Reed et al found that two dimensional echocardiography was of similar prognostic value to radionuclide ventriculography for evaluating patients after an acute myocardial infarction. This is even more true today, since current echocardiographic equipment has a considerably better signal to noise ratio and creates images that allow better endocardial delineation.

The ability of M mode echocardiography to provide information regarding global left ventricular size and function is limited in patients with coronary artery disease because of its unidirectional nature, and because regional dysfunction may affect some measurements. However, M mode echocardiography has a unique time resolution and is well suited for measuring systolic time intervals and mitral as well as aortic root motion. Atrial and ventricular diameters can also be measured, as long as one is aware of the limitations of such measurements. It is therefore not surprising that several studies have found echocardiography to be useful in predicting mortality after an acute myocardial infarction, and among patients with congestive heart failure. However, to the best of our knowledge, the long term prognostic value of measuring systolic and diastolic left ventricular function...
by echocardiography in young patients who have suffered from myocardial infarction has not been determined.

The purpose of this study was to determine the long term prognostic information of left ventricular function in a consecutive series of men who suffered from myocardial infarction before the age of 45 years. Primary and secondary risk factors as well as angiographic findings were included in the analysis to evaluate the independent contribution of echocardiography in predicting reinfarction and cardiac death in these patients.

Methods
During a period of two years and four months, all survivors of a definite myocardial infarction under the age of 45 years who lived in Stockholm County were referred to the Department of Medicine, Danderyd Hospital, for non-invasive and invasive cardiological investigations, metabolic evaluation, and clinical follow up as part of a comprehensive clinical and metabolic research programme. Details of the study population have been reported earlier. A total of 153 men satisfied the criteria for definite myocardial infarction during the study period. Sixteen patients died outside hospital, and 10 died in hospital. Of the 127 patients who survived the acute myocardial infarction, 107 (84%) were examined by M mode echocardiography, 101 of whom had echocardiographic recordings of acceptable quality. Four of these patients were excluded from this study because they dropped out of the follow up programme (n = 2) or because of the presence of other severe diseases (n = 2). Of the 20 patients not examined with echocardiography, three died before the examination, one moved out of the catchment area, and 16 were not examined with echocardiography for other reasons. A total of 97 patients was thus included in the present study.

PRINCIPLES OF TREATMENT AND FOLLOW UP
After discharge from the referring hospitals, all patients were seen by a cardiologist within two weeks and then at regular intervals during the follow up period. All patients were followed for a mean of 82 months. Treatment with β blockers was not given routinely in this group of young postinfarction patients, but was prescribed individually according to the local policy of the referring units. In most patients, the indication for β blocker treatment was cardioprotection after myocardial infarction. Only cardioselective β blockers (metoprolol or atenolol) were used. Only patients with a history of incapacitating exertional angina despite optimum medication were referred for coronary bypass grafting. When deciding whether a patient should undergo revascularisation, the information from echocardiography did not affect the decision, nor did it affect medication. Principles for patient recruitment and general treatment have been described previously in detail.

CLINICAL VARIABLES AND PRIMARY RISK FACTORS
The clinical variables used in the prognostic evaluation were age, sex, New York Heart Association (NYHA) functional class, type and location of the infarction, and primary risk indicators. Serum cholesterol and triglyceride concentrations were recorded. Details regarding the lipoprotein analysis have been presented in detail earlier. The metabolic investigation was performed three to six months after the infarction, when the patients were considered to be in a stable clinical and metabolic state. The use of loop diuretics for clinical heart failure was recorded.

M MODE ECHOCARDIOGRAPHY
M mode echocardiography was performed with a Hoffrel instrument, equipped with a 2-25 MHz M mode transducer, 6-12 weeks after the myocardial infarction. Recordings were considered acceptable if >50% of the echocardiographic variables could be measured. The average of five consecutive cardiac cycles. In patients with irregular cardiac rhythm, an average of eight cycles was used. In the present study, most of the echocardiographic recordings were made by one experienced cardiologist, though some were also made by another experienced cardiologist according to the American Society of Echocardiography criteria. Initial QRS activity together with aortic valve opening and closure were used to measure left ventricular pre-ejection period (PEP) and left ventricular ejection time (LVET), from which PEP/LVET was calculated. Left ventricular fractional shortening during systole (FS%) was calculated as 100 × (LVDD-LVDS)/LVDD, where LVDD = left ventricular diameter at the end of diastole and LVDS = left ventricular diameter at the end of systole. E point-septal separation (EPSS) was measured from the E point of the anterior mitral leaflet to the interventricular septum. An echo index was calculated from three echocardiographic variables (yielding one score point each if: left ventricular diameter at end of diastole (LVDD) was ≥5.7 cm, left ventricular fractional shortening (FS%) was ≤24%, and E point-septal separation (EPSS) was ≥10 mm). One technician performed all digitised measurements from the posterior aortic wall. By means of a digitiser (Summagraphics) and a personal computer (486 DX), with software developed for the purpose, we evaluated aortic root motion (fig 1). The atrial emptying index was calculated from the posterior aortic wall motion as an estimate of early left ventricular filling properties, reflecting the first one third filling fraction. This index represents the first one third (rapid phase) of left atrial emptying divided by total left atrial emptying. In case of atrial fibrillation, the initial QRS activity was used to mark the end of the passive filling.

CHEST X RAY
Radiological heart size according to Jonsell was calculated in the 79 patients investigated,
EXERCISE TEST
A symptom limited exercise test was performed on a bicycle ergometer six to eight weeks after the myocardial infarction. The work load was set to 20 watts at the beginning of the test, with an increase in work load of 10 watts every minute. The exercise test was stopped when pronounced angina pectoris, severe dyspnoea, fatigue, or serious ECG changes appeared. Exercise-induced ischaemic ST segment depression was considered to be present if the ST segment was horizontal or down sloping and depressed by \( \geq 1 \text{ mm} \) (0-1 mV) 0-08 s after the QRS complex. The ECGs were analysed by one of the authors without knowledge of follow up or coronary angiographic findings.

ANGIOGRAPHIC PROCEDURES
Coronary and left ventricular angiography were performed within three months from the echocardiographic examination in 89 of the 97 patients. No clinical event or deterioration appeared during the time interval between the echocardiographic examination and angiography in any patient. Of the remaining eight patients, five declined catheterisation and one died before angiography. In two patients, angiography was considered unethical (uraemia in one and severe peripheral atherosclerosis in one). The coronary angiography was performed by the percutaneous transfemoral technique and recorded on 35 mm cine film (6-6 inch mode). Both coronary arteries were examined in the right anterior oblique and left anterior oblique views. The left coronary artery was visualised in the posterior-anterior and lateral projections and in a left anterior oblique projection with cranio-caudal angulation. Additional views were taken when necessary for better visualisation of non-tangential or overlapping segments. Angiograms were routinely obtained before and after the administration of sublingual glyceryl trinitrate. All angiograms were interpreted by one experienced angiographer without knowledge of the clinical outcome or the echocardiographic results. Significant coronary artery stenosis was considered to be present if the luminal diameter was reduced by more than 50%. Patients were then allocated to traditional coronary artery disease categories according to the number of major coronary arteries having significant stenosis. Patients were classified as having multivessel coronary disease when two or three major coronary arteries had a significant stenosis. Ejection fraction was calculated for each patient, using the area-length method. Severe wall motion abnormality was defined as a segmental dyskinetic or akinetic wall motion.

DEFINITION OF END POINTS
The criteria for non-fatal reinfarction were identical to those for the primary infarction. A fatal reinfarction was diagnosed when the patient died within four weeks of being admitted for a new infarction, or after admission to hospital with chest pain, pulmonary oedema, syncope, or shock, when death occurred before the detection of increased enzyme levels or development of conclusive electrocardiographic changes. Fatal reinfarction was also diagnosed when the patient was found dead outside hospital, if other causes of death could be ruled out and if a clinical or forensic necropsy report stated that there was a fresh coronary artery thrombosis or myocardial necrosis. In patients dying suddenly, the cause of death was considered cardiac if extracardiac reasons could be excluded. Referral for revascularisation was based on clinical symptoms of severe angina refractory to medical treatment.
STATISTICAL ANALYSIS
Means and standard deviations are given unless otherwise stated. Categorical data were evaluated using the $\chi^2$ test with Yates correction. Group differences in continuous variables were assessed by two-tailed $t$ tests. Coefficients of skewness and kurtosis were used to test deviations from a normal distribution. Values of total triglycerides were accordingly logarithmically transformed to achieve a distribution not significantly different from normal before significance testing. The prognostic power of the different variables was evaluated using Cox proportional hazards survival analysis for different end points. The follow-up period in patients who underwent bypass surgery was terminated (censored) at the time of the surgical intervention to exclude a confounding effect on the analysis of endpoints. Univariate analysis of the relationships between all variables and the different cardiac events was performed. Subsequently, a stepwise selection process was performed and variables entered ($P < 0.01$) or removed ($P > 0.15$) from the regression equation based on a computed significant probability (maximised, partial likelihood ratio). A subset of variables that had significant independent correlations with the time of occurrence of cardiac events was identified. In a basic model, these steps were first performed in each of three blocks of variables as presented in table 3. Secondly, in an intermediate model, the analysis was performed with significant variables in the first block (clinical characteristics, chest X ray, and exercise test) and echocardiographic variables. Thirdly, the significant variables were analysed together with angiographic variables. Life table curves according to Kaplan-Meier were calculated.$^{31}$ The curves were compared using log-rank statistics.$^{24}$

ETHICS
Before the study, informed consent was obtained from all subjects, and the study protocol was approved by the regional ethics committee of the Karolinska Institute.

Results

BASIC CHARACTERISTICS
The age range of the patients was 30–44 years (mean 40 years). Most of the patients (80%) had Q wave myocardial infarctions (46 anterior, 31 inferior). At the time of the echocardiographic examination 69% were in NYHA class I, 61% were treated with a $\beta$ blocker, and 24% were treated with oral loop diuretics because of clinical manifestations of heart failure.

CLINICAL OUTCOME
The mean follow up time for surviving patients was 6 years, 10 months. Seventeen patients died, 13 developed a non-fatal reinfection, and 21 were submitted to bypass surgery because of incapacitating exertional angina despite optimal medication. No patient was referred for percutaneous transluminal coronary angioplasty. The mean time from initial evaluation to death was 2 years, 3 months (range 2–75 months). Age, location, type of infarction, and lipoprotein concentrations did not differ between patients with and without subsequent cardiac death, as shown in table 1.

ANGIOGRAPHIC DATA
Eighty-nine patients (92%) underwent coronary and left ventricular angiography. Eight patients had no significant coronary stenosis, 37 had one vessel disease, 29 had two vessel disease, and 15 had triple vessel disease (table 1). Left main stenosis was not present in any patient. Patients who suffered cardiac death had more wall motion abnormalities and a lower ejection fraction at baseline (table 2). Thirty-eight patients had left ventricular segments with akinetic or dyskinetic wall motion abnormalities.

ECHOCARDIOGRAPHIC DATA
Echocardiographic data from patients with and without cardiac death during follow up are presented in table 2. Left atrial diameter, LVDD, LVDS, fractional shortening, PEP/LVET, and echo index were all significantly related to cardiac death (table 3). After any one of these variables was entered into the regression model in multivariate analysis, nearly all the others became non-significant, indicating that echocardiographic variables...
were closely interrelated in their impact on survival. Patients with an echo index of 2 or 3 had a hazard ratio of 4.7 (95% confidence interval 1.67–13.51). LVDS was closely related to cardiac death and, in combination with left atrial diameter, was the only variable to enter the model in a stepwise regression. No echocardiographic variable was significantly related to non-fatal myocardial infarction during follow up. When clinical characteristics were entered into the intermediate model, use of diuretics showed a global $\chi^2$ of 10, which increased to 18.7 on the addition of the echo index (table 4). When the number of major vessels with significant stenosis was entered in the final model, the addition of the echo index increased the global $\chi^2$ value (table 5).

Table 3 Echocardiographic predictors of survival. Cox regression analysis summarizes the univariate and multivariate analyses for prediction of cardiac death. The first column shows univariate results. The second column shows the result of the first step of Cox proportional hazards model, where the most significant covariate (within each group of variables) has been entered. Only patients with complete angiographic data are included in the analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate $\chi^2$</th>
<th>P value</th>
<th>Step 1 within each block Global $\chi^2$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.5</td>
<td>0.05</td>
<td></td>
<td></td>
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<tr>
<td>Cholesterol</td>
<td>2.8</td>
<td>0.09</td>
<td></td>
<td></td>
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<tr>
<td>Exercise capacity</td>
<td>1.2</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina at exercise</td>
<td>1.8</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST±1 at exercise</td>
<td>1.9</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart size (ml/m²)</td>
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<td>0.006</td>
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<td></td>
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<td>Treatment loop diuretics</td>
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<td>0.002</td>
<td>10.0</td>
<td>0.003</td>
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<td>Echocardiography</td>
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<td></td>
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<tr>
<td>Echo index</td>
<td>13.2</td>
<td>0.0003</td>
<td>+LVDS 12.3</td>
<td>0.002</td>
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<tr>
<td>LVDD</td>
<td>8.5</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVDS</td>
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<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF</td>
<td>2.5</td>
<td>0.1</td>
<td></td>
<td></td>
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<tr>
<td>FS</td>
<td>3.8</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial emptying index</td>
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<td>0.9</td>
<td></td>
<td></td>
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<tr>
<td>Angiography</td>
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<td></td>
</tr>
<tr>
<td>Severe WMA</td>
<td>8.2</td>
<td>0.004</td>
<td>+0–3 vessel 13.8</td>
<td>0.001</td>
</tr>
<tr>
<td>0–3 vessel disease</td>
<td>4.5</td>
<td>0.03</td>
<td></td>
<td></td>
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<tr>
<td>EF</td>
<td>9.4</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0–3 vessel disease = number of major coronary arteries with ≥50% luminal diameter reduction.

Other abbreviations as in table 2.

Table 4 Intermediate model (including echocardiographic variables). Prediction of cardiac death. The variables of the first block (basic characteristics) were entered first and all echocardiographic variables were then entered or removed.

<table>
<thead>
<tr>
<th>Global $\chi^2$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1 Use of loop diuretics</td>
<td>10.0</td>
</tr>
<tr>
<td>Step 2 + echo index</td>
<td>18.7</td>
</tr>
</tbody>
</table>

Table 5 Final model (including angiographic variables). Predictors of cardiac death. The variables from all three blocks were first entered including all angiographic variables; echo index was then entered or removed.

<table>
<thead>
<tr>
<th>Global $\chi^2$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1 Severe wall motion abnormalities</td>
<td></td>
</tr>
<tr>
<td>0–3 vessel disease</td>
<td>13.8</td>
</tr>
<tr>
<td>Step 2 + echo index</td>
<td>20.7</td>
</tr>
</tbody>
</table>

0–3 vessel disease = number of major coronary arteries with ≥50% luminal diameter reduction.

SURVIVAL CURVES AND ESTIMATES
Patients were stratified according to LVDS by means of the median value of 39 mm. Cumulative survival rate according to LVDS at baseline is shown in fig 2—mortality with LVDS above median (log-rank, $P < 0.01$). Patients were also stratified by different echo indices, as presented in fig 3. An echo index of 3 identified a small high risk group ($n = 13$), while an echo index of 2 identified patients with intermediate risk ($n = 24$). An echo index of 0–1 identified a larger low risk group ($n = 54$). Stratification by combining LVDS above or below the median (39 mm) and ejection fraction above or below the median (59%) identified a group at very high risk, where 7-year survival was only 55% (LVDS >39 mm and ejection fraction <63%), versus 91% in those with LVDS <39 mm and angiographic ejection fraction ≥ 63% (log-rank, $P = 0.0001$).

Discussion
In this study we examined whether variables reflecting left ventricular function could provide prognostic information during the long term follow up of relatively young patients with myocardial infarction. Primary and secondary risk factors, exercise test data, and coronary angiographic findings were entered into the analysis for evaluating the independent additional contribution of left ventricular function.

The results show the reliability of a simple M mode echocardiographic examination for
Long-term prognostic significance of M mode echocardiography in young men after myocardial infarction

Determining prognosis after a myocardial infarct at a young age. Our results confirm previous evidence of the prognostic importance of left ventricular ejection fraction. However, our study shows that even when angiographically determined ejection fraction data are available, the echo index provides an independent contribution to mortality prediction during follow up. The reason for the combined influence of ejection fraction and echo index on survival needs further consideration. The ejection fraction provides a quantitative and reliable assessment of left ventricular function, but there are limitations inherent in the technique: it evaluates only global systolic function and provides no insight into the role of regional wall motion abnormalities and no information on diastolic dysfunction of the ventricle; furthermore, angiographically measured ejection fraction does not separate forward flow from regurgitant flow emanating from mitral insufficiency, which is common after a myocardial infarction. The ejection fraction does not provide quantification of left ventricular volume but is merely a measure of the fraction of end diastolic volume ejected with each heart beat. Another study has indicated that ventricular end systolic volume might be an even more sensitive guide to prognosis than ejection fraction. This notion is supported by the present study, in which end systolic diameter was one of the best single prognostic variables obtained from echocardiography.

The value of M mode echocardiography in the assessment of long term prognosis in consecutive survivors of myocardial infarction has been examined in a previous study. However, no one has evaluated the prognostic information from echocardiography in a consecutive unselected series of patients with myocardial infarction at young age recruited from a well defined geographical region.

Studies have shown that treatment with angiotensin converting enzyme inhibitors improves survival in patients with low ejection fraction, even when asymptomatic. It is therefore important to identify these high risk patients with simple non-invasive methods. It is also important to identify low risk patients in whom invasive procedures are not mandatory. Our study supports the findings of Keren and coworkers who showed that the echo index may be useful in determining prognosis. An echo index of < 2 identified a low risk group of 54 patients (56%). Even in patients without cardiomegaly or treatment with loop diuretics, 27% had an echo index of > 1. Thus our data suggest that application of this simple echo index identifies a large group of patients at low risk for cardiac death during long term follow up. The anatomical information obtained by M mode echocardiography is limited by the small size of the investigated myocardium. Furthermore, ischaemic heart disease does not affect the ventricle uniformly. This may explain the poor prognostic information obtained from left ventricular fractional shortening compared to ejection fraction in the present study.

Some studies have indicated that E point-septal separation (EPSS) is the M mode index that shows the best correlation with left ventricular ejection fraction and may be less affected than fractional shortening by abnormal wall motion. However, in our study this index did not emerge as the strongest prognostic indicator. The same observation was made in the postinfarction study by Berning and coworkers but in contrast to their study, we found left ventricular diameter at end systole (LVDS) to be a strong prognostic predictor. The reason for this discrepancy is not clear. In accordance with the present study, Wong et al have recently shown that LVDS and fractional shortening are significant predictors of long term mortality in univariate analyses. In multivariate analysis, LVDS remained a significant predictor of mortality in their study, consistent with our findings. In the study by Berning et al, patients were recruited (median age 60 years for men, 65 years for women) and follow up time was much shorter (one year) as compared to ours. In addition, among older patients, other causes of death than those relating to the myocardial infarction (“specific mortality”) are more frequent. Angiographic disease severity differs between younger and older patients, with a higher prevalence of single vessel disease or normal coronary arteries in the younger group. In addition, we found that the survival curves continue to separate over the long term. This could be due to a progressive remodelling process. Recent studies have shown that treatment with an angiotensin converting enzyme inhibitor can reduce long term mortality in patients with left ventricular dysfunction after a myocardial infarction.

Today, by evaluating left ventricular function with two dimensional echocardiography, both ejection fraction and regional wall motion abnormalities can be determined in most patients. Since the echocardiographic equipment available to us at the time of the present study did not allow accurate measurement of ejection fraction, we used angiographically determined measurements of ejection fraction and wall motion abnormality as a substitute for two dimensional echocardiography. Subsequent studies have shown the prognostic value of wall motion analysis from two dimensional echocardiography for risk stratification after acute myocardial infarction. However, no study has included angiographic ejection fraction measurement in the prognostic analysis.

Diastolic function has been shown to be closely related to exercise capacity after a myocardial infarct. However, indices of diastolic left ventricular function were not closely related to cardiac death in the present study. This finding is in accordance with other studies.

Our study indicates that in young male patients with myocardial infarction, M mode echocardiography is comparable to angiography and superior to most clinical and routine investigations (chest x ray, exercise test) in predicting cardiac death. Multivariate analysis also suggests that simple M mode
echocardiographic measurements do add to the prognostic data obtained from patient characteristics, ECG, and exercise test. Even in the presence of angiographically determined ejection fraction, the echo index made an independent contribution to the prediction of long-term mortality.

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