Prognosis of Patients with Acute Pulmonary Edema and Normal Ejection Fraction After Acute Myocardial Infarction

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SUMMARY To assess the prognostic importance of resting left ventricular function in survivors of acute myocardial infarction with pulmonary edema, we retrospectively identified 39 consecutive patients who presented with acute pulmonary edema and myocardial infarction. Sixteen patients had radionuclide ejection fractions $10 \pm 2$ days postinfarction of $>0.45$ (group A, mean $0.55 \pm 0.06$), and 23 patients had ejection fractions $\leq 0.45$ (group B, $0.32 \pm 0.06$). There were no significant differences between the two groups for age or sex, but group A patients had a significantly greater incidence of first myocardial infarction predominantly inferior in location. The calculated stroke work index during the acute event was significantly greater in group A than in group B ($33.4 \pm 2.4 \text{ vs } 23.4 \pm 2.0$) ($p < 0.05$). During a follow-up of $9 \pm 3$ months, mortality was not significantly different between the two groups: Four (25%) died in group A and seven (30%) died in group B. In addition, eight patients (50%) in group A were hospitalized for recurrent angina, new myocardial infarction or recurrent pulmonary edema, compared with 11 (48%) in group B (NS). Three deaths in group A were preceded by infarction of the anterior wall of the left ventricle, confirmed at autopsy, and two nonfatal infarctions were anterior by electrocardiography. Four patients in group A had coronary arteriography performed during the follow-up period because of unstable angina, and all had significant ($>70\%$ stenosis) three-vessel disease and two had left main coronary artery disease. Therefore, the predischarge ejection fraction did not predict prognosis for this group of patients.

Patients with acute pulmonary edema in the course of myocardial infarction form a high-risk group despite good resting left ventricular function at discharge. They have a significant incidence of recurrent myocardial infarction and death and, because they have good residual left ventricular function, are excellent candidates for surgical intervention.

THE EARLY and late prognoses for acute myocardial infarction are adversely affected by the occurrence of left ventricular failure. $^1$-$^13$ The manifestation of acute pulmonary edema is particularly lethal. $^1$-$^4$, $^10$ Presumably, pulmonary edema reflects the severity and extent of acute and chronic abnormalities in left ventricular contraction. Thus, pulmonary edema is more common in patients with a history of infarction and in patients with large initial infarctions, which are usually anterior wall infarctions. It is not surprising that in a study by Schelbert et al., $^14$ measuring radionuclide ejection fractions after myocardial infarction, patients with pulmonary edema had severely depressed ejection fractions and no patient had a normal ejection fraction (>$0.52$).

Since January 1980, we have routinely obtained a predischarge radionuclide angiocardiogram for all survivors of acute myocardial infarction. It became apparent that certain patients who had manifested pulmonary edema had an unexpectedly normal or only mildly depressed ejection fraction at the time of discharge. This was distinctly in contrast to other reports. $^12$, $^15$ Possible explanations were either that acute transient abnormalities had occurred in left ventricular function or that acute preload or afterload burdens had existed early after the infarction. Because a good left ventricular ejection fraction at discharge after a myocardial infarction generally predicts a good prognosis, $^8$, $^16$ we postulated that patients with pulmonary edema whose predischarge ejection fraction was within normal limits or only mildly depressed should have a good prognosis.

Accordingly, we retrospectively evaluated the clinical course and determined the morbidity and mortality of 39 consecutive patients with acute myocardial infarction and pulmonary edema who survived for at least 8 days in the hospital and underwent radionuclide angiocardiography.

Methods

Patients

Between January 1980 and March 1981, 39 survivors of acute myocardial infarction had overt pulmonary edema (Killip class III) $^{17}$ during the early postinfarction period and had predischarge ejection fractions determined by radionuclide angiocardiography. They were 45–83 years old (mean 64.9 years). Twenty-eight patients (72%) were men. The ejection fractions were determined $10 \pm 2$ days after infarction.

Acute myocardial infarction was diagnosed when at least two of the following were present: a history of typical prolonged chest pain, evolution of electrocardiographic changes of acute transmural infarction or ST-T changes and characteristic serial elevations of serum enzymes (creatine kinase and MB fraction or lactic dehydrogenase isoenzymes).

Equilibrium-gated radionuclide angiocardiography was performed after injection of 24 mCi of $^{99m}$Tc tagged to human serum albumin. Technetium albumin was the sole agent used for the equilibrium radionuclide angiocardiogram in the course of this study. La-
belonging of red blood cells in vivo has now largely replaced this technique. Despite somewhat greater liver and spleen activity, the usual background levels subtracted in our laboratory are not significantly greater than those for in vivo labeled red blood cells. Although measurement of the distribution of technetium indicates a highly variable proportion in hydrozolized form, the ratio of free to bound is more constant and, in most batches, averaged 0.05 (range 0.003–0.20). Correlation with contrast angiography in our laboratory has been performed with the human serum albumin technique and the results of the latter are consistently higher, but the correlation coefficient is good (0.82). Images were obtained in multiple projections, including at least the 45° left anterior oblique, anterior and 30° right anterior oblique, using a General Electric portable scintillation camera with a “MED III” computer. After equilibration of the radionuclide in the blood pool, 14 frames of 128 × 128 matrix image data, gated by the R wave of the ECG, were acquired from the first three-fourths of the cardiac cycle, acquiring 200,000 counts/frame, which required 5–7 minutes per projection.

Left ventricular ejection fraction was measured with the Muge program, which uses a semiautomatic edge-finding algorithm to place a region of interest on the borders of the left ventricle in each of the 14 frames of the left anterior oblique projection. The program also places a background region of interest over the nearby left lung, subtracts background from each frame and uses the curve of corrected count rate over the left ventricle to compute global left ventricular ejection fraction. Operator intervention was rarely necessary except, at times, in the case of a very large ventricle. Inter- and intraoperator tests of reproducibility of the ejection fraction by this method in our laboratory has been excellent. The method is essentially that of Maddahi et al.18

The clinical records were reviewed for site of infarction, history of myocardial infarction and hemodynamic measurements performed at the time of the acute infarction. The presence or absence of a regurgitant murmur was noted. Patients who had clinically significant mitral or aortic regurgitation were not included in the study.

Twenty-four of the 39 patients had hemodynamic measurements made within 12 hours of admission. Pulmonary arterial wedge pressure was measured through a flow-directed, balloon-tipped catheter19 and cardiac output by thermodilution.20

The patients were divided into two groups, based on ejection fraction. Group A patients had an ejection fraction > 0.45, and group B patients an ejection fraction ≤ 0.45. During the late follow-up period (mean 9 months, range 1–15 months), a new event was defined as death, reinfarction, recurrent angina (New York Heart Association functional class III or IV) or hospital admission for recurrent acute pulmonary edema.

Late follow-up data were obtained from clinical and hospital records in 36 of 39 patients; three patients were followed by telephone interview only. All patients in groups A and B were managed medically, and cardiac catheterization or coronary arteriography was not performed unless unstable angina developed during follow-up.

Statistical analysis was performed using the t test for unpaired data or the chi-square method. The Z test was used for differences in proportions. Survival was analyzed by life-table method.21 Results are expressed as mean ± SD.

Results

Ejection Fractions

In the 39 patients, the ejection fraction obtained 10 ± 2 days after infarction averaged 0.41 ± 0.13 (fig. 1). Sixteen patients had ejection fractions > 0.45 and constitute group A (mean ejection fraction 0.55 ± 0.06). Twenty-three patients had ejection fractions ≤ 0.45 and constitute group B (mean ejection fraction 0.32 ± 0.06). Eleven patients in group A had normal ejection fractions (> 0.52).

Clinical and Hemodynamic Findings (table 1)

Age or sex ratios did not differ significantly between groups A and B. Three patients in group A and six in group B had nonholosystolic murmurs at the apex. No patient was considered to have clinically significant mitral regurgitation. The two groups did not differ significantly with respect to a history of hypertension. However, there were significant differences between the two groups with respect to the site of myocardial infarction and history of myocardial infarction. Group

![Ejection fractions of both groups. LV = left ventricular.](image-url)
TABLE 1. Clinical and Hemodynamic Characteristics of Patients with Myocardial Infarction and Acute Pulmonary Edema

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (EF &gt; 0.45)</th>
<th>Group B (EF ≤ 0.45)</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>n = 16</td>
<td>n = 23</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.8 ± 9.4</td>
<td>66.4 ± 10.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>11/5</td>
<td>17/6</td>
<td>NS</td>
</tr>
<tr>
<td>Location of infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>0</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Anteroseptal</td>
<td>1</td>
<td>2</td>
<td>p &lt; 0.005</td>
</tr>
<tr>
<td>Inferior</td>
<td>11</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Subendocardial</td>
<td>4</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>History of infarction</td>
<td>3 (19%)</td>
<td>19 (83%)</td>
<td>p &lt; 0.005</td>
</tr>
<tr>
<td>Hemodynamic</td>
<td>n = 9</td>
<td>n = 15</td>
<td></td>
</tr>
<tr>
<td>(obtained 6 ± 1.4 hours after admission)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary capillary wedge pressure (mm Hg)</td>
<td>16.8 ± 2.0</td>
<td>17.4 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>104 ± 12</td>
<td>96 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke work index (g-m/m²)</td>
<td>33.4 ± 2.4</td>
<td>23.4 ± 2.0</td>
<td>p &lt; 0.005</td>
</tr>
</tbody>
</table>

Abbreviation: EF = ejection fraction.

B had a significantly greater incidence of anterior and subendocardial infarctions, whereas group A predominately had inferior infarctions. Group B also had a significantly higher percentage of previous myocardial infarctions compared with group A. Hemodynamic measurements were obtained in nine of 16 patients in group A and 15 of 23 patients in group B. Acute pulmonary capillary wedge pressure and mean arterial pressures recorded on admission did not differ significantly. However, the calculated stroke work index was significantly greater in group A than in group B.

Drug therapy in both groups was initiated with digitalis, diuretics or antihypertensive agents alone or in combination. Two patients in group A and three patients in group B required early support of blood pressure with pressor agents. Initial hemodynamic values tended to improve in both groups after therapy but were not uniformly recorded. In general, patients in group A responded rapidly to therapy; 20 patients in group B were taking digitalis at the time of discharge, whereas only three in group A were receiving digitalis therapy.

Late Follow-up (table 2)

During a follow-up of 9 ± 3 months, occurrence of new myocardial events did not differ significantly between the groups (table 2), and survival probability was similar for the two groups (fig. 2).

**Group A**

Four patients in group A died. In three, death was preceded by clinically documented anterior myocardial infarctions. Autopsies confirmed the recent infarctions. One death was an out-of-hospital sudden death.

Five patients had new myocardial infarctions, and in three the infarctions preceded death. Recurrent angina was the most frequent reason for hospitalization (50%) and preceded infarction and death in two patients. Four patients had cardiac catheterization and coronary arteriography in the follow-up period because of severe recurrent angina. All had significant (≥ 70% stenosis) three-vessel disease and two also had left main coronary artery disease. One patient was considered not to be a candidate for coronary bypass surgery because of diffuse distal vessel disease and one patient refused surgery; two others eventually had surgery. One of the patients who had surgery had persistent angina in the postoperative period after development of a new anterior myocardial infarction, and died.

**Group B**

Within 9 ± 3 months after the index episode, 78% of the patients in group B with poor ejection fractions had had a new event, including seven deaths (30%). All deaths were attributed to cardiovascular disease; two were sudden. In two cases, a documented new myocardial infarction had occurred before death.

Of nonfatal events, recurrent pulmonary edema was the most frequent, with 43% of the group requiring another hospitalization. New myocardial infarctions occurred in four (17%), two of which preceded death.

**FIGURE 2. Life-table survivorship.** Numbers in parenthesis represent the number of patients in group A and B, respectively.
Angina pectoris alone as a reason for readmission to the hospital was least common (17%). Five patients underwent catheterization in the follow-up period because of severe recurrent angina or left ventricular failure and two eventually had surgery.

Discussion

The patients in group A were remarkable in that they had unexpectedly normal or only mildly depressed ejection fractions (0.55 ± 0.06). This was in contrast to the study by Schelbert et al.,14 which showed that patients who had manifested overt pulmonary edema in the course of acute myocardial infarction had ejection fractions that were severely depressed (0.33 ± 0.07). In their study, however, the ejection fractions were measured less than 5 days after infarction, compared with more than 10 days in our study. Also, Schelbert et al. showed serial improvement in ejection fractions for 27 patients (54%) during the early postinfarction period. Therefore, the higher mean ejection fraction in our group could reflect the serial improvement described by Schelbert et al., although their data did not reveal whether the subgroup of patients with overt pulmonary edema had a rate of improvement similar to that of the whole group.

A significant number of survivors of acute myocardial infarction with pulmonary edema have good residual left ventricular function. Those who have good residual function (group A) are more likely to have had their first myocardial infarction, predominantly inferior in location.

Our patients could have had severe transient left ventricular dysfunction earlier in the clinical course of infarction, as suggested by the serial studies of Schelbert et al.14 The patients in our group were not studied serially, but serial radionuclide ejection fractions were performed in two similar patients with acute inferior myocardial infarction and pulmonary edema. These two patients showed marked improvement between the acute measurement of left ventricular ejection fraction (0.32 and 0.38 12 hours after admission) and the late value (0.52 and 0.54 10 days after admission).

The possibility that acute mitral insufficiency could account entirely for this disparity in acute clinical presentation and the predischarge ejection fraction is unlikely. The incidence of regurgitation murmurs was no greater in group B than in group A, and no patient with clinically significant regurgitation was included. Another explanation for transient myocardial dysfunction might be acute impedance or afterload burden, either because of increased sympathetic tone or acute hypertension. Acute afterload burdens are possible because group A had a greater mean blood pressure, but individual variation was great. In addition, group B had a significantly lower stroke work index that probably indicated more depressed left ventricular function.

The late prognosis after acute myocardial infarction for any individual patient is influenced by many clinical and laboratory features. However, the left ventricular ejection fraction is a powerful predictor of short- and long-term survival.8,14,16 Nelson et al.4 found that ejection fraction was a more discriminant prognosticator than the severity of angiocardiographic coronary disease or the clinical functional class. Schulze et al.22 found that survivors of acute myocardial infarction with a predischarge radionuclide ejection fraction > 0.40 had an overall good prognosis. The history of first myocardial infarction, inferior location and good residual left ventricular function in group A patients should therefore characterize a low-risk subgroup of survivors of acute myocardial infarction, even if they have a history of pulmonary edema. However, our follow-up of patients showed that morbidity and mortality were similarly high for those with normal and low ejection fractions. More recently, some investigators have shown that the resting left ventricular ejection fraction alone does not completely predict outcome. Corbett et al.23 used exercise radionuclide angiograms to reflect permanently damaged myocardium as "myocardium at risk" during exercise. The exercise measurements proved to be better prognostic indicators. In addition, Silverman et al.24 studied 42 patients within 15 hours of myocardial infarction with thallium-201 scintigraphy and found that this early measurement of the perfusion defect was a significant prognostic indicator. This early study was considered to reflect the permanently injured myocardium as well as "at risk." In our study, the pulmonary edema may also be reflecting "myocardium at risk." Three of the patients in group A who died had ischemia and eventual infarction of the anterior wall of the left ventricle; two nonfatal infarctions were also anterior. In no case was arrhythmia a primary cause of death. Thus, one explanation for the pulmonary edema occurring with the original inferior infarction is that ischemia of the anterior wall with consequent poor function had also occurred but resolved.

These data suggest that patients with myocardial infarction and pulmonary edema form a high-risk group despite good resting left ventricular function. They have severe coronary artery disease and in a medically treated group have a significant incidence of recurrent transmural myocardial infarction and death. The identification of this high-risk subgroup of medically managed patients with good residual left ventricular function is particularly important because they are excellent candidates for surgical intervention.25

References

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