Evolution of Left Ventricular Dysfunction in Coronary Artery Disease

Serial Cineangiographic Studies Without Surgery

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SUMMARY The evolution of left ventricular dysfunction in 36 patients with coronary artery disease and no interim surgical intervention was studied over a mean interval of 26 months (range 6–71 months). The ejection fraction decreased 0.08 (p < 0.001) on the average in patients with coronary artery disease progression. However, progression of coronary artery disease was not accompanied by a decrease in ejection fraction in every patient. Though deterioration in left ventricular function in the entire group was associated with the presence of new collateral vessels and interim arteriographic total occlusion, collaterals and occlusion did not imply a decline in ejection fraction of 0.10 or more in the individual patients. The ejection fraction tended to fall in patients with progression of arterial disease and no occlusion or interim infarction. Patients with interim myocardial infarction were more likely to have a decrease in ejection fraction of 0.10 or more (p < 0.05). Isolated left anterior descending coronary artery occlusion in five patients resulted in marked segmental contraction abnormalities and a fall in ejection fraction not observed with occlusion of the other major coronary vessels. Progression of muscle damage may result from intrinsic changes induced by primary injury, recurrent ischemic episodes or unperceived infarction. The evolution of dysfunction in association with changes in coronary anatomy, clinical events or as the consequence of primary injury should be considered in the evaluation of the efficacy of therapeutic interventions.

SEGMENTAL AND GLOBAL disorders of left ventricular contraction are frequently observed in patients with coronary artery disease. Though serial coronary cineangiographic studies have shown the appearance of new coronary obstructive lesions, or progression in the severity of obstruction,1,2 little is known regarding the associated changes, if any, in left ventricular function. In single angiographic studies, equivalent degrees of coronary artery obstruction and history of myocardial infarction have been associated with mild-to-severe disorders of left ventricular contraction. There has been recent interest in the effect of aortocoronary artery bypass surgery on left ventricular function. Improvement in ejection fraction and derived indexes of myocardial contractility,3,4 as well as failure to improve resting left ventricular performance,5,6 has been reported.

This study was undertaken to determine the influence of initial angiographic findings, interim clinical events and subsequent angiographic progression of coronary artery disease. For many patients, coronary artery bypass graft surgery was not available after the initial study, and they were managed medically. A second study was done when coronary bypass surgery was available and warranted by the patient’s clinical condition.

Methods

Records of all patients who had undergone serial coronary angiography and left ventriculography without surgical intervention were reviewed. Cases were excluded when arrhythmias or films of inadequate quality precluded accurate left ventriculographic interpretation. Patients with rheumatic or valvular heart disease were also excluded. Patients undergoing catheterization initially had a chest pain syndrome of sufficient severity or frequency and clinical suspicion of coronary artery disease to require referral for coronary arteriography. Restudy was undertaken in most instances because coronary artery bypass surgery was a new mode of therapy available after the initial cardiac catheterization, and medical therapy for angina pectoris had not been satisfactory. Some patients had progressive symptoms despite medical management after a first catheterization showed coronary artery disease not requiring bypass surgery, and were referred for restudy because more than 6 months had elapsed. At least two complete and technically adequate studies were available for 36 subjects, who served as their own controls. Resting right- and left-heart cardiac catheterization were performed after premedication with 10 mg of diazepam and 50 mg of diphenhydramine hydrochloride. At the time of these studies propranolol was used by 30 patients before one or both studies and was discontinued 48 hours before catheterization. Forward cardiac outputs were deter-
mined either by the direct Fick method or duplicate indocyanine green indicator techniques. Left ventriculography and selective coronary cinearteriography were performed by the Sones or Judkins technique using either General Electric or Siemens x-ray image-intensification systems (9- or 6-inch dual field) using a 6-inch field and recording on 16-mm film at 60–100 frames/sec.

Severity of coronary disease was determined by the scoring technique of Friesinger et al. Each of the three major coronary arteries, right, left anterior descending and left circumflex, was given a score from zero to five, with the highest possible score being 15 for total obstruction of all three major vessels. Progression or worsening of coronary disease was defined as at least 20% additional decrease in lumen size or total obstruction of a vessel. The qualification for the presence of disease required an angiographic score of 2 or greater (localized narrowing greater than 50% but less than 90%). An arteriographic score was assigned by at least two observers and concurrence reached. Two separate studies of patients were viewed at one sitting by an observer panel. This facilitated agreement and observer reproducibility because comparisons of the same vessel could be made.

Criteria for the presence of coronary collateral vessels were (1) direct visualization of accessory blood vessels either filling the distal segment of an occluded or severely stenotic artery or subserving the area of myocardium that would ordinarily be supplied by the severely stenotic vessel, and (2) visualization of a coronary artery after injection of contrast material into the contralateral vessel. Angiographic methods used to classify the adequacy or quantity of flow in collateral vessels have not been verified and were not used in this study.

Single-plane, right anterior oblique left ventriculograms were performed with the injection of 40–50 ml of 76% meglumine sodium diatrizoate over 3–4 seconds. All patients were in sinus rhythm. Premature and the first postextrasystolic beats were not used for volume analysis. Left ventricular asynergy and abnormalities of systolic wall motion were assessed by superimposing multiple hemiaxes on the end-diastolic and end-systolic frames. Perpendiculars were drawn from the points that divided the major axis into fourths to the points of intersection of the ventricular outline (fig. 1). Percentage changes in these hemiaxes were determined from the end-diastolic and end-systolic frames. Two observers agreed on the adequacy and outline of the cardiac silhouette.

Ventricular volumes were determined by the Dodge area-length method, assuming the ventricle to approximate an ellipsoid of revolution. Left ventricular stroke volume was obtained by subtracting the angiographically determined end-systolic volume from end-diastolic volume. The ejection fraction was obtained from the ratio of stroke volume to end-diastolic volume. Because differences in ejection fraction of 0.07–0.08 have been reported to represent the margin of reproducibility, we selected an arbitrary value of 0.10 as a significant change in ejection fraction.

The left anterior oblique projection provides information concerning the septal and posterolateral area not visualized in the right anterior oblique view. In studies comparing biplane with single-plane ventriculography, these zones were not asynergic in the absence of corresponding involvement of the anterior, apical or inferior zones in the latter view. Larger ejection fractions are found in the same patient with asynergy when the biplane technique is used compared with the single-plane view. We felt, therefore, that significant declines in ejection fraction would be represented in the right anterior oblique view by changes of 0.10 or more.

The hemodynamics of each patient at each study were compared, including heart rate, systolic blood pressure, cardiac index and left ventricular end-diastolic pressure (LVEDP). Statistical significance of the difference between variables in the two studies was evaluated by appropriate procedures, including paired t test (two-tail), correlation, covariance analysis, chi-square contingency with Yates correction, and Fisher’s exact test for 2 × 2 table.

Results

Clinical Characteristics

The clinical characteristics of the patient group are presented in table 1. The mean age of a group of 30 men and six women at the time of the first study was 46 years (range 27–66 years). Most patients had a prior myocardial infarction and were initially studied because of incapacitating angina. The patients with significant three-vessel coronary artery disease predominated. The mean arteriographic score of 9 at initial study by the technique of Friesinger et al. represents moderately severe coronary artery disease.

Patients were subdivided into those with an ejection
fraction decrease of 0.10 or greater (15 patients, group 1) and those with no or less than 0.10 decrease in ejection fraction (21 patients, group 2). Age at the time of the initial study was unrelated to progression of left ventricular dysfunction (fig. 2). Angiographic studies were performed 6–71 months after the first study (mean 26 months). Trend analysis showed no statistically significant relationship between the time interval and a decrease in ejection fraction (fig. 3).

The hemodynamics of the entire group of patients, including LVEDP, cardiac index, systolic blood pressure and heart rate at the time of each study, were compared. Only mean LVEDP increased, from 10 mm Hg to 13 mm Hg \((p < 0.025)\). Group 1 patients had no significant change in mean LVEDP \((10 \text{ mm Hg to 12 mm Hg})\). In the remaining 21 patients in group 2, however, mean LVEDP increased from 10 mm Hg to 14 mm Hg \((p < 0.025)\).

The history of propranolol used varied at each study. The presence or absence of a change in ejection fraction was not related to prior use of propranolol (table 2).

**Ejection Fraction and Coronary Progression**

The severity of coronary artery disease at the time of the first study was compared with ventriculographic changes found at the second study. No statistically significant correlation for individual patients could be found between the value of the initial ventriculographic score and a subsequent decrease in ejection fraction of 0.10 or more (fig. 4). In addition, no correlation between angiographic score and ejection fraction was found at the time of either study. Between study 1 and study 2, the mean ejection fraction for the entire group of 36 patients fell from 0.61 to 0.54 \((p < 0.001)\), while the mean ventriculographic score increased from 9 to 10.

**Table 2. Relationship of Propranolol Use to Ejection Fraction Change**

<table>
<thead>
<tr>
<th></th>
<th>Decrease in EF (\geq 0.10) ((n = 15))</th>
<th>No decrease in EF (\geq 0.10) ((n = 21))</th>
</tr>
</thead>
<tbody>
<tr>
<td>No propranolol either study</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Propranolol use before first study</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Propranolol use before second study</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Propranolol use before both studies</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
(p < 0.001). The statistical significance of this inverse correlation between ejection fraction and arteriographic score over the interval was determined by covariance analysis (p < 0.05).

Changes in ejection fraction in 28 patients with angiographic coronary arterial progression was compared with ejection fraction in eight patients without progression. In the 28 patients with progression, mean ejection fraction decreased from 0.60 to 0.52 (p < 0.01), while mean ejection fraction was unchanged in the eight patients without progression (fig. 5). The inverse correlation between angiographic score and change in ejection fraction over the interval was even stronger for the patients with progression than for the combined group. The angiographic score in patients without progression did not correlate with changes in ejection fraction during the study.

The magnitude of ejection fraction change as a predictor of coronary arterial progression was evaluated. Fifteen patients (group 1) had an ejection fraction decrease of 0.10 or greater, while 21 patients (group 2) had no or less than 0.10 decrease in ejection fraction. Thirteen of the 15 patients in group 1 (87%) had progression of coronary arterial disease, while 15 of the 21 patients in group 2 (71%) showed progression (p = NS). There was no significant difference in the change of arteriographic score between the two groups (fig. 6). Using a decrease in ejection fraction of 0.10 or more as an indication of progressive disease, a correct diagnosis could be made in 47% of the patients, with 6% false negatives. Using a decrease in ejection fraction of 0.08 or more, the correct diagnosis was made in 61%, with 6% false negatives. Using a decrease in ejection fraction of any magnitude, the diagnostic accuracy improved to 69%, with 17% false negatives. Thus, ejection fraction decreased with an increase in arteriographic score or arteriographic progression. Although the correlation was statistically significant by covariance analysis, it was not strong enough to be used as a reliable indicator of progressive coronary artery disease.

**Ejection Fraction and Myocardial Infarction**

Twelve patients had an interim myocardial infarction. A decrease in ejection fraction of 0.10 was more likely to be present (p < 0.05) in those instances when an interim myocardial infarction had occurred. Eight of 15 patients in group 1 had interim myocardial infarctions, compared with only four of 21 patients in group 2 (fig. 6).

Ten of the 28 patients with angiographic progres-
sion of coronary disease had a history and electrocardiographic evidence of an interim myocardial infarction (fig. 7). In these 10 patients, the mean ejection fraction fell from 0.58 to 0.50, but not significantly. Ejection fraction decreased in six of the 10 patients. Progression of coronary artery disease in the remaining group of 18 patients without evidence of interim infarction was still associated with a statistically significant reduction in mean ejection fraction, from 0.60 to 0.53 ($p < 0.025$).

Six of the 12 patients with a previously documented myocardial infarction between studies had an electrocardiographic abnormality representing an interim change. However, no association could be made between the electrocardiographic change and a decrease in ejection fraction of 0.10 or more.

Ejection Fraction and Collateral Vessels

The presence of new collateral vessels did not influence the outcome of the ejection fraction at the second study. New collaterals were found in 10 of 15 patients in group 1 and in 11 of 21 patients in group 2 (fig. 6). Seven of 13 patients in group 1 with both progression of coronary artery disease and a decrease in ejection fraction of 0.10 or more had antecedent collaterals, while nine of 15 patients in group 2 with progression had collaterals at first study ($p = NS$). Six patients in each group had no collaterals at first study and subsequent progression of coronary disease.

When arteriographic progression was present and new collateral vessels were also identified at the time of the second study (20 patients), a significant reduction in mean ejection fraction ($p < 0.001$) was observed. When arteriographic progression occurred without the appearance of new collaterals (eight patients), no significant reduction in ejection fraction was found (fig. 7).

Ten of the 12 patients with interim myocardial infarction had collateral vessels present at the time of the first study. All of the six patients with total occlusion and an interim myocardial infarction had collateral vessels at first study. At second study only two of the six patients with infarction and occlusion had no new collateral vessels. Neither collaterals before the first study nor collaterals demonstrated at the second study were related to the absence of an interim myocardial infarction ($p = NS$).

Ejection Fraction and Interim Occlusion

Six of 15 patients with a decrease in ejection fraction of 0.10 or more had angiographic evidence of interim total occlusion of a major vessel, while nine of the 21 without this ventriculographic change had a total occlusion at the time of the second study ($p = NS$) (fig. 6). Conversely, of 15 patients with new total occlusion, only six showed major reduction in ejection fraction, and six had both an interim myocardial infarction and demonstrable total occlusion. Four of the six with both interim infarction and total occlusion also had a significant reduction in ejection fraction ($p < 0.001$). Interval occlusion without evidence of an infarction was seen in 53% of occlusion events. There was no relationship to the presence of collaterals at first study, new collaterals at second study or both old and new collateral vessels.

Fifteen of the 28 patients with arteriographic progression of coronary disease had interim occlusion of either the right, left anterior descending or left circumflex coronary artery (fig. 7). Changes in ejection fraction for the group paralleled the angiographic change. Mean ejection fraction fell from 0.60 to 0.53 ($p < 0.01$). Systolic blood pressure, LVEDP, cardiac index and heart rate were not significantly different at the time of each study. Thirteen patients without interim occlusion but with arteriographic progression did not evidence significant changes in ejection fraction.

There were seven patients with isolated occlusion of either the right or left circumflex coronary artery. Two of these patients had declines in ejection fraction of 0.10 or more, but still had ejection fractions greater than 0.50. Interim decreases in the percent of shortening of radii in the areas of distribution of the right coronary artery and the left circumflex coronary artery (fig. 1, $R_{1}$, $R_{5}$ and $R_{6}$) were compared with interim arteriographic progression of coronary disease to 70% or greater obstruction, total occlusion or no luminal change between studies. There was no significant change in radius of shortening for any interim angiographic change in the area of distribution for these vessels. Five patients had isolated total obstruction of the left anterior descending coronary artery at second study. Anterior wall radii of shortening $R_{5}$, $R_{4}$ and $R_{6}$ were considered representative of the right anterior oblique ventriculographic area of distribution of the left anterior descending coronary artery. FL, a representative patient (fig. 8), had an interim occlusion of the left anterior descending coronary artery. A marked decrease in the radii of shortening $R_{5}$, $R_{4}$ and $R_{6}$ was present at the second study (fig. 8). Anterior wall radii of shortening in these five patients were

Figure 7: Influence of specific angiographic changes and interim myocardial infarction on the evolution of left ventricular dysfunction in the subgroup with angiographic evidence of coronary artery disease.
compared with those of the eight patients who had no angiographic evidence of progression of coronary artery disease at the time of the second study. There was no significant difference in shortening of each radius between the two groups at the time of the first study. At the second study no significant change had occurred in the group without progression of coronary artery disease. However, in the group with interim isolated left anterior descending occlusion, the percent shortening of each radius fell significantly in comparison with initial study (fig. 9). In addition, ejection fraction fell 0.10 or more in four of the five patients with interim left anterior descending occlusion alone. The fifth patient had an ejection fraction of 0.30 and a high-grade lesion of the left anterior descending coronary artery at the first study. When the radii of shortening of the two groups determined at the second study were compared, there was a significant difference ($p < 0.05$) for the $R_5$ radius, while the $R_4$ and $R_6$ difference approached significance. The time between studies and the first study angiographic score of the two groups were not significantly different.

### Discussion

The patients in this study were not randomly selected. Factors resulting in the reevaluation should be considered. Most of the patients in this study had a second arteriographic and ventriculographic study because of progressive symptoms or availability of new surgical methods of treatment. An unknown number of patients in whom ventricular function might have deteriorated so as to result in death would not have been available for a second study. Therefore, progression of coronary disease may result in much greater deterioration of ventricular function than that presented in our group of patients. A number of patients with consecutive studies were excluded because of inadequate ventriculographic studies. Patients with no change in their clinical course might not be well represented in the study group but this should not have introduced bias. Clinical symptoms and interim course have not been shown to be predictive of progression of coronary artery disease.2

There was an overall tendency for a decrease in ventricular function with time. Age, severity of coronary artery disease and the actual time between studies were not predictive of clinically significant decreases in ejection fraction.

### Coronary Disease Progression

The mean ejection fraction for the entire group with arterial progression declined significantly. Changes in left ventricular function and progression of arterial disease have been reported in serial studies of coronary atherosclerosis but without reference to ejection fraction or the magnitude of change. In a study of 18 patients with progressive coronary artery disease, 83% had changes that were reported as ventricular dysfunction on left ventriculography.14 Five of eight patients (63%) with arterial progression treated medically were described as having greatly impaired contractility with increased dyskinesis at the repeat study.18 Although a group change in ejection fraction occurred in our patients, angiographic progression of coronary arterial disease or the magnitude of change per se did not discriminate a decrease in ejection fraction of 0.10 or more in the individual patient. These results reflect the disparate anatomic coronary vs ventriculographic findings often observed clinically in single studies. There was a significant association between reduction in ejection fraction and the occurrence of interim infarction, but not with the presence of new collateral vessels or arteriographic total occlusion. Both transmural and nontransmural infarction result in loss of myocardium and alteration of function represented by
segmental contraction and the ejection fraction. Overall ventricular function depends on the extent of the disturbance in segmental contraction. A highly significant correlation has been shown between the relative size of an akinetic or dyskinetic segment and the ejection fraction in the year after infarction. In our study, infarction in the individual patient was the best predictor of subsequent abnormality or deterioration in ejection fraction. The percentage of angiographic abnormalities of the left ventricle in a large group of patients with a previous history of myocardial infarction was higher than in the presence of multivessel involvement alone. Because such patients also had a high 5-year cardiac mortality related primarily to left ventricular dysfunction, an even greater number of patients with infarction and left ventricular dysfunction could have been expected had their survival permitted restudy.

Interim Arterial Occlusion

Segmental changes and overall ejection fraction have been related to the degree of patency of a coronary artery after myocardial infarction. The presence of both angiographic occlusion and infarction has been reported as more likely to be associated with major declines in ejection fraction than moderate-to-severe arterial stenosis and infarction. In comparable groups of patients we have found that individual decreases in ejection fraction of 0.10 or more are significantly associated with infarction and not angiographic occlusion. As a group, patients with interim angiographic occlusion had a significant decline in ejection fraction, but almost half had an interim infarction as well. The occurrence of angiographic occlusion and infarction was not more likely to effect major deterioration in ejection fraction than either event singly or with progression. Group declines in ejection fraction were observed for patients with infarction and progression similar to those with occlusion (0.08 vs 0.07), but the change was not significant for the small group with infarction and arterial progression. Preexisting collaterals or the appearance of new collaterals did not alter this relationship.

Coronary Collaterals

The presence or absence of coronary collateral circulation is not considered a determinant of overall left ventricular function. Moreover, no consistent difference in segmental contraction has been observed in patients with and without collaterals, nor has the quality of collateral vessels correlated with the number of abnormal segments or percent shortening of segments. In a study of progressive arterial disease, a subgroup of nine patients had collateral vessels. Collaterals were felt to be protective because none of the patients subsequently had what was described as abnormal myocardial contractility at the time of the second study. In our patients, the presence or absence of antecedent collaterals did not influence the subsequent decrement in ejection fraction of 0.10 or more.

New coronary collaterals were present in the majority of our patients with an interim fall in ejection fraction of 0.10 or more, but the presence of new collaterals was just as likely when a change of this magnitude had not occurred. New collaterals were associated with a significant decrease in ejection fraction in the group of patients who also had coronary arteriographic progression. In addition, collateral vessels were present at the first study in most of the patients with subsequent infarction and preexisted in all patients with both angiographic occlusion and interim myocardial infarction. Collaterals may have reflected the presence or severity of ischemia at the time of the first study, appearing as a prelude to or a consequence of progression, and did not have a role as a determinant of ventricular function. The small group of patients with arterial progression and no new collaterals did not have significant declines in ejection fraction. Thus, the presence or absence of new collateral vessels was not associated with the relation between arterial progression and ventricular deterioration.

Segmental Dysfunction

Marked deterioration in anterior wall segmental contraction was observed in the five patients with occlusion of the left anterior descending coronary artery. Cardiogenic shock is more prevalent in anterior infarction and the extent of impairment of left ventricular performance if dyssynergy is present has been reported as more extensive if the abnormal segment involved the anterior wall compared with the inferior wall. Although a major decline in ejection fraction (≥ 0.10) was not more likely when total occlusion had occurred, segmental dysfunction in our patients with left anterior descending occlusion was accompanied by a reduction in ejection fraction. Compromise of ventricular function was not as prevalent in patients with progression of coronary disease confined to occlusion of the other two major coronary arteries and is supportive of the relative importance of the left anterior descending coronary artery in the evolution of left ventricular dysfunction.

Patients with coronary arterial progression but without interim infarction or occlusion had a group decline in ejection fraction. In addition, individual deterioration in ejection fraction can be observed without coronary angiographic change. This suggests that events resulting in left ventricular dysfunction might not be perceived clinically or that other factors may participate in the deterioration of left ventricular function. Though good correlation has been shown between ventriculographic findings and the amount of muscle loss determined histopathologically, akinetic and dyskinetic segments are compatible with the presence of histologic and electrographic intact myocardium by biopsy at the time of surgery. Temporal regional disorders of contraction can be induced by ischemia related to atrial pacing. Severity of a lesion with consequent ischemia may be underestimated, or unperceived progression of coronary dis-
ease may occur with recanalization of the coronary artery segment before a second study. Unrecognized infarction may occur without occlusion complicating assignment of the ventriculographic change to an etiologic factor. Recurrent ischemic episodes may result in coalescent myofibrotic changes and eventual asynergy without a frank clinical event.

Progression of muscle damage may occur through intrinsic changes in the architecture of the ventricle induced by the primary injury. Changes in shape, volume and radius of curvature will alter ventricular wall tension and ejection fraction. Although ventriculographic progression can be said to parallel certain clinical and angiographic parameters, exceptions with progression may be a consequence of factors that cannot be measured or that are unknown and should be considered in the study of the evolution of left ventricular dysfunction, especially in the evaluation of therapeutic interventions.

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