Left Ventricular Function at 3 Months After Successful Thrombolysis

Impact of Reocclusion Without Reinfarction on Ejection Fraction, Regional Function, and Remodeling

Albert Meijer, MD; Freek W.A. Verheugt, MD; Machiel J. van Eenige, PhD; Christ J.P.J. Werter, MD

Background After successful thrombolysis for acute myocardial infarction, reocclusion is observed in about 30% of patients after 3 months and usually occurs without reinfarction. We studied the impact of reocclusion without reinfarction on global and regional left ventricular function and on remodeling during that period.

Methods and Results The patients for this analysis constituted a subset of those enrolled in the APRICOT- trial, which was designed to study the efficacy of antithrombotics on the prevention of reocclusion. Patients were selected who had a left anterior descending- or right coronary artery-related myocardial infarction, had an angiographically patent infarct-related vessel when studied <48 hours after intravenous thrombolysis, and underwent repeat cardiac catheterization at 3 months. Paired contrast ventriculograms of quality sufficient to analyze regional wall motion, global ejection fraction, and ventricular volumes were analyzed in 129 patients. Enzymatic infarct size and baseline left ventricular function as well as other baseline characteristics were similar in patients with (n=34) and without (n=95) reocclusion. Ejection fraction improved in anterior infarction without reocclusion from 47±10% to 54±13% (P=.0001) but not with reocclusion (baseline, 48±13%; 3 months, 48±16%). No improvement was seen in inferior infarction with or without reocclusion. Persistent patency allowed preservation of end-systolic volume index (ESVI) at 3 months (37±14 mL/m²) to baseline level (38±13 mL/m²), with a better chance for improvement of >10 mL/m² without reocclusion in those with baseline values >40 mL/m². After reocclusion, in contrast, ESVI increased from 37±14 to 43±20 mL/m² (P=.08). Comparable mean changes of ESVI in response to persistent patency or reocclusion were seen in anterior versus inferior infarction. Recovery of infarct zone contractility was impaired by reocclusion, both in terms of abnormality of segment shortening and expressed in the number of segments showing abnormal wall motion. In anterior but not in inferior infarction, infarct zone contractility was better with good collaterals to the reoccluded artery compared with poor collaterals.

Conclusions After successful thrombolysis for acute myocardial infarction, reocclusion without reinfarction withholds salvaged myocardium from regaining contractility. This has deleterious consequences for regional and global left ventricular function and for remodeling. To further optimize prognosis in patients after thrombolysis, future research should focus on the prevention of reocclusion and should evaluate revascularization therapy in patients with reocclusion.

Key Words • thrombolysis • occlusions • ventricles

After myocardial infarction, the functional status of the left ventricle is the major predictor of long-term survival. In particular, ejection fractions <40% are associated with a progressive increase in 1-year mortality.1 In the range of ejection fractions <50%, an end-systolic volume of >100 mL, measured at 1 to 2 months after infarction, is an even stronger predictor of mortality.2 Treatment of myocardial infarction should thus be aimed at limitation of infarct size and preservation of end-systolic volume.

Thrombolysis has been shown to improve survival after myocardial infarction3 and also improves left ventricular volume.4 Successful thrombolysis, however, is associated with a risk for reocclusion that averages 10% to 20% before hospital discharge5,6 and was recently reported to occur in almost 30% after 3 months.7,8 Reocclusion occurs without symptoms in about half of the patients but is nevertheless associated with higher mortality rates, impaired recovery of left ventricular function, and a more complicated hospital course.5 To date, no studies have been reported in which the impact of reocclusion observed after 3 months has been related to changes in global and regional ventricular function and to changes of left ventricular volumes during that period in a group of patients that did not sustain recurrent infarction after thrombolysis. For the study of ventricular function, a time window of 3 months is of interest because by then vital myocardium in patients with sustained reperfusion is likely to have completely recovered from stunning. Furthermore, dysfunctioning myocardium in patients with reocclusion will do so because of necrosis or hibernation. We therefore report data on regional and global left ventricular function and remodeling that are derived from patients enrolled in the Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis (APRICOT) trial,7 in which angiographic reocclusion after 3 months in patients with a patent infarct-related vessel at

Received March 9, 1994; revision accepted May 31, 1994.
From the Free University Hospital (A.M., F.W.A.V., M.J.v.E., C.J.P.J.W.) and the Interuniversity Cardiology Institute (A.M.), Amsterdam, The Netherlands.
Correspondence to Freek W.A. Verheugt, MD, FACC, Department of Cardiology, Free University Hospital, PO Box 7057, Amsterdam, the Netherlands 1007 MB.
© 1994 American Heart Association, Inc.
coronary angiography within 48 hours after thrombolysis was the primary end point.

Methods
Study Protocol
The study aimed to assess the relative efficacy of aspirin, Coumadin, and placebo on reocclusion. The study protocol has been described in detail elsewhere. In brief, patients <71 years old who presented with chest pain of <4 hours and >30 minutes' duration and a minimum of 0.2 mV of ST-segment elevation in two contiguous ECG leads, suggestive of acute myocardial infarction, were treated with intravenous thrombolytic therapy with streptokinase or anistreplase. Thrombolytic treatment was followed by intravenous heparin. Cardiac catheterization was performed within 48 hours after the start of thrombolytic treatment. Patients were eligible to enter the study when the infarct-related artery was patent, as described below. Then, patients were randomized to either Coumadin or aspirin 325 mg daily or a matched placebo. Patients with a history of coronary surgery, patients with normal coronary arteries or with significant left main stem stenosis, and those with an occluded infarct-related artery were excluded. After hospital discharge, follow-up lasted 3 months, when a second cardiac catheterization was scheduled to assess patency of the infarct-related artery and left ventricular function. In patients undergoing either coronary surgery or coronary angioplasty, no second ventriculogram was made. A conservative strategy was intended, implying that revascularization was to be performed only for reasons of recurrent ischemia not responsive to medical anti-ischemic treatment. The primary end point was patency of the infarct-related artery at follow-up angiography. For the present analysis of the impact of reocclusion on left ventricular function, only patients enrolled in the Free University Hospital were studied. Surviving patients with a first myocardial infarction who fulfilled the following criteria were selected: 1) the infarct-related vessel was either the left anterior descending or the right coronary artery, 2) ventriculograms were done at both catheterizations and preceded coronary angiography, 3) ventriculograms were of quality sufficient to draw contours and had at least 1 sinus beat preceding the sinus beat that was selected for drawing of contours, and 4) no reinfarction had occurred after thrombolysis. Reinfarction was defined as recurrent ischemic chest pain accompanied by a creatine kinase elevation exceeding twice the upper limit of normal.

Analysis of Coronary Angiograms
The infarct-related artery was identified correlating the coronary anatomy with the distribution of wall motion abnormality on the 30o right anterior oblique and the 60o left anterior oblique ventriculograms. When necessary, coronary anatomy was also correlated with the site of ST-segment elevation on the admission ECG. Residual stenosis severity of the infarct-related artery was classified as grade 0, normal coronary artery; grade 1, <50% diameter stenosis; grade 2, 50% to 90% diameter stenosis; grade 3, 91% to 99% diameter stenosis, complete filling within three cycles; grade 4, 91% to 99% diameter stenosis, no complete filling within 3 cycles; and grade 5, 100% diameter stenosis. Lesions were analyzed from the angiographic view in which the stenosis was most severe. Patients with a grade 1 to 3 stenosis were eligible for the study. Reocclusion was defined as a grade 4 or 5 stenosis at follow-up coronary angiography. Collaterals to the infarct-related vessel in patients with reocclusion were prospectively defined as good quality, poor quality, or absent. Good-quality collaterals filled the reoccluded central epicardial infarct-related vessel partly or completely, whereas poor-quality collaterals filled only side branches. All visual assessments were done by an angiography committee, which consisted of three experienced angiographers who were blinded to the treatment allocation and to the clinical course of the patients. Decisions were made by consensus.

Analysis of Contrast Ventriculograms
End-systolic and end-diastolic contours were drawn on paper and subsequently digitized, both by one observer (C.J.P.J.W.), to eliminate interobserver variability. Ventricular volumes and ejection fraction were calculated by means of the area-length method with a metal ball 5.6 cm in diameter for calibration. End-systolic and end-diastolic volumes were indexed for body surface area and expressed in milliliters per square meter. Quantitative segmental wall motion was calculated by the Stanford system, in which each endocardial site is assumed to move toward a point located at 69% of the distance along a line from the anterolateral aortic valve edge to the apex in the end-systolic frame. By use of the method of Baer et al,11 the ventriculogram in the right anterior oblique projection was divided into five segments: anterobasal, anterolateral, apical, diaphragmatic, and inferobasal. The percentile shortening of each segment was analyzed on a digitizer attached to a computer system. This was done by taking points on the end-diastolic contour at a distance of 0.5 cm. From these points, the system computed polar coordinates to the 69% point and crossing points of these coordinates and the end-systolic contour. The percentile shortening of a coordinate was the difference between the lengths of the end-diastolic and the end-systolic coordinates divided by the length of the end-diastolic coordinate. The shortening of each segment was the mean percentile shortening of all coordinates in that segment. We expressed wall motion abnormality of a segment as the absolute percentage that the shortening of that segment was lower than the lower limit of normal. The definition of asynergy was a difference of at least 5%. Lower-limit-of-normal values were derived from Baer et al. Since this method provides no definition for hyperkinesia, wall motion in the noninfarcted zone was also expressed as the difference between the measured shortening for that segment and the lower-limit-of-normal value. The "central infarct area" was defined as the single segment in the entire infarct area that showed the lowest shortening at analysis of the first ventriculogram of every individual patient. In anterior infarction, the "entire infarct area" was defined as segments 1 to 3, and entire infarct area wall motion was expressed as the mean of these three segments. In these patients, noninfarcted zone wall motion was analyzed as wall motion in the "central contralateral area," defined as the largest shortening in segment or in every individual patient at first ventriculography. In inferior infarction, segments 4 and 5 were analyzed as the entire infarct area and segments 1 to 3 as the contralateral area.

Statistics
Continuous variables are expressed as mean±SD unless stated otherwise. For comparisons between groups, the χ2 and Student's t test were used whenever appropriate. ANCOVA was used where indicated. Only values of P<.1 are reported.

Results
Study Group
Of 284 patients analyzed in the APRICOT trial, 200 were enrolled in the Free University Hospital. For the present analysis, 129 of these patients were selected who fulfilled the criteria described above. Reasons for not fulfilling the criteria were a history of prior infarction in 19 patients, a circumflex artery–related infarct in 24, revascularization in 14, death before repeat study in 1, documented reinfarction in 6, and finally refusal of repeat study or quality insufficient for analysis in 7 patients. In 26 of the 129 patients, paired changes of ventricular volumes could not be calculated because of

Downloaded from http://circ.ahajournals.org/ by guest on November 17, 2017
TABLE 1. Baseline Characteristics of Patients With and Without Reocclusion and Those of the Total Study Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Reocclusion</th>
<th>Reocclusion</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>95</td>
<td>34</td>
<td>284</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>74 (78)</td>
<td>30 (88)</td>
<td>231 (81)</td>
</tr>
<tr>
<td>Age, y</td>
<td>56±9</td>
<td>55±9</td>
<td>57±9</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>22 (23)</td>
<td>8 (24)</td>
<td>57 (20)</td>
</tr>
<tr>
<td>Time to thrombolysis, h</td>
<td>2.0±0.9</td>
<td>2.0±0.8</td>
<td>2.1±1.0</td>
</tr>
<tr>
<td>Anterior myocardial infarction, n (%)</td>
<td>49 (52)</td>
<td>21 (62)</td>
<td>119 (42)</td>
</tr>
<tr>
<td>Inferior myocardial infarction, n (%)</td>
<td>46 (48)</td>
<td>13 (38)</td>
<td>165 (58)</td>
</tr>
<tr>
<td>Enzyme characteristics, U/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak creatine kinase</td>
<td>1575±1586</td>
<td>1767±1609</td>
<td>1512±1431</td>
</tr>
<tr>
<td>Peak MB fraction</td>
<td>126±116</td>
<td>136±111</td>
<td>121±101</td>
</tr>
<tr>
<td>Peak lactate dehydrogenase</td>
<td>900±494</td>
<td>995±527</td>
<td>901±511</td>
</tr>
<tr>
<td>Creatine kinase peak &gt;1000 U/L, n (%)</td>
<td>44 (46)</td>
<td>13 (38)</td>
<td>150 (53)</td>
</tr>
<tr>
<td>Time to peak MB, h</td>
<td>11±6</td>
<td>11±5</td>
<td>11±5</td>
</tr>
<tr>
<td>Study medication, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>36 (38)</td>
<td>10 (29)</td>
<td>102 (36)</td>
</tr>
<tr>
<td>Coumadin</td>
<td>30 (32)</td>
<td>14 (41)</td>
<td>92 (32)</td>
</tr>
<tr>
<td>Placebo</td>
<td>29 (31)</td>
<td>10 (29)</td>
<td>90 (32)</td>
</tr>
<tr>
<td>Other medication at first angioplasty, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>12 (13)</td>
<td>2 (6)</td>
<td>53 (19)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>21 (22)</td>
<td>6 (18)</td>
<td>101 (36)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>63 (66)</td>
<td>26 (76)</td>
<td>195 (69)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>8 (8)</td>
<td>2 (6)</td>
<td>28 (10)</td>
</tr>
<tr>
<td>Catheterization data, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-vessel disease</td>
<td>56 (59)</td>
<td>15 (44)</td>
<td>163 (57)</td>
</tr>
<tr>
<td>Two-vessel disease</td>
<td>26 (27)</td>
<td>12 (35)</td>
<td>80 (28)</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>13 (14)</td>
<td>7 (20)</td>
<td>41 (14)</td>
</tr>
<tr>
<td>No. of asynergic segments (entire infarct area)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior infarction (3 segments)</td>
<td>2.3±0.7</td>
<td>2.1±0.8</td>
<td></td>
</tr>
<tr>
<td>Inferior infarction (2 segments)</td>
<td>1.0±0.7</td>
<td>0.9±0.3</td>
<td></td>
</tr>
</tbody>
</table>

NA indicates not applicable.

failing or inadequate calibration. Seventy patients had an anterior wall myocardial infarction with the left anterior descending coronary artery as the infarct-related vessel, with reocclusion observed in 21. Fifty-nine patients had an inferior wall myocardial infarction, with the right coronary artery as the infarct-related vessel, with reocclusion observed in 13. We compared the groups with and without reocclusion. We also subdivided these groups according to infarct location and to the presence of left ventricular dysfunction, defined as a baseline ejection fraction <50%. The baseline characteristics of these groups are given in Table 1. There were no essential differences between patients with and without reocclusion. Importantly, myocardial enzyme characteristics of the index infarction and ventriculographic indicators of the extent of left ventricular dysfunction were comparable in the two groups. Fourteen patients suffered from angina pectoris that was treated medically; 8 of these had reocclusion and 6 had no reocclusion. The baseline variables in the subgroup selected for the present analysis did not differ from those of the total study group. In the total study group, patients with a circumflex artery–related infarct were counted as inferior infarcts. This accounts for the high number of inferior infarcts in the total study group.

**Changes of Ejection Fraction**

For the whole group of patients without reocclusion, left ventricular ejection fraction increased from 51±10% to 55±11% (P=.0004), whereas there was no increase in patients with reocclusion (baseline value, 52±12%; 3-month value, 51±14%). When subdivided by infarct location (Fig 1A), the improvement of ejection fraction in patients without reocclusion was observed only in the group of patients with anterior infarction. In this group, baseline ejection fraction was lower than in inferior infarction (47±10% versus 55±9%; P=.0001). In anterior infarction without reocclusion, ejection fraction increased to 54±13% (P=.0001). The 3-month value in inferior infarction was
56±8%. When reocclusion had occurred, no increase of ejection fraction was observed in either anterior infarction (baseline value, 48±13%; 3-month value, 48±16%) or inferior infarction (baseline value, 59±7%; 3-month value, 55±1%; \( P=1 \)). When the groups were subdivided by baseline ejection fractions <50% and >50%, an increase of ejection fraction was observed only in the group with baseline ejection fractions <50% and no reocclusion. In this group, ejection fraction increased from 41±6% to 50±12% (\( P<0.00001 \), \( n=40 \), anterior infarction in 31 [78%], inferior infarction in 9 [22%]). When reocclusion had occurred, baseline and 3-month values were 40±8% and 42±12%, respectively (\( P=NS \), \( n=13 \), all anterior infarction). When baseline ejection fractions exceeded 50%, there was no change of ejection fraction without reocclusion (baseline value, 58±6%; 3-month value, 59±8%; \( n=55 \); \( P=NS \)) and there was a trend to a decrease when reocclusion had occurred (baseline value, 60±7%; 3-month value, 56±13%; \( n=21 \); \( P=.08 \)).

**Changes of End-Systolic Volume Index**

End-systolic volume index did not increase in the total group of patients without reocclusion (baseline value, 38±13 mL/m²; 3-month value, 37±14 mL/m²) but tended to increase with reocclusion (baseline value, 37±14 mL/m²; 3-month value, 43±20 mL/m²; \( P=.08 \)).
Responses of end-systolic volume indexes to either persistent patency or reocclusion (Fig 1B) were comparable for both infarct locations. With persistent patency, there was preservation of end-systolic volume index (anterior infarction: baseline value, 41±13 mL/m²; 3-month value, 38±16 mL/m²; P=NS; inferior infarction: baseline value, 35±12 mL/m²; 3-month value, 37±10 mL/m²; P=NS). Small increases of end-systolic volume indexes were observed in both infarct locations with reocclusion (anterior infarction: baseline value, 43±15 mL/m²; 3-month value, 46±23 mL/m²; P=NS; inferior infarction: baseline value, 28±8 mL/m²; 3-month value, 37±12 mL/m²; P=.009). Thus, the final end-systolic volume index of patients with anterior infarction and reocclusion tended to be higher than in those with inferior infarction and reocclusion but was similar for both infarct sites without reocclusion. In patients with baseline ejection fractions <50%, end-systolic volume index changed −4±27 mL/m² (P=NS) without reocclusion and +3±23 mL/m² with reocclusion (P=NS). With baseline ejection fractions >50%, these changes were +1±18 mL/m² (P=NS) and +11±22 mL/m² (P=.06), respectively. In patients with baseline end-systolic volume indexes >40 mL/m², the upper limit of normal (mean±2 SD) for our laboratory, an arbitrary but important decrease of ≥10 mL/m² was observed in 14 of 30 patients without reocclusion but in only 1 of 11 with reocclusion (P<.05). Importantly, in the group with reocclusion, there were more patients with a final end-systolic volume exceeding the prognostically important value of 100 mL (9 of 78 [12%] versus 9 of 29 [31%], P<.01). At baseline, 8 of 77 patients (10%) without reocclusion had an end-systolic volume >100 mL versus 4 of 29 (14%) of those with reocclusion (P=NS).

Changes of End-Diastolic Volume Index

End-diastolic volume index increased significantly both in the total group with reocclusion (baseline value, 78±20 mL/m²; 3-month value, 85±22 mL/m²; P=.04) and in the group without reocclusion (baseline value, 77±17 mL/m²; 3-month value, 81±18 mL/m²; P=.007). In anterior infarction without reocclusion (Fig 1C), end-diastolic volume index increased from 78±18 to 82±18 mL/m² (P=.02). In anterior infarction with reocclusion, there was an increase of end-diastolic volume index from 82±18 to 87±24 mL/m² (P=NS). In inferior infarction without reocclusion, end-diastolic volume index increased from 77±17 to 81±16 mL/m² (P=NS). In inferior infarction with reocclusion, an increase from 71±21 to 80±20 mL/m² (P=.07) was observed. When baseline ejection fraction was <50%, mean increase of end-diastolic volume index was similar without (8±18 mL/m², P=NS) and with reocclusion (7±12 mL/m², P=.1). When baseline ejection fraction was >50%, these increases were 3±15 mL/m² (P=NS) without reocclusion and 6±16 mL/m² (P=NS) with reocclusion. The mean end-diastolic pressures between the two catheterizations were comparable in all groups (anterior infarction, no reocclusion: baseline value, 17±7 mm Hg; 3-month value, 15±7 mm Hg; anterior infarction, reocclusion: baseline value, 17±6 mm Hg; 3-month value, 13±8 mm Hg; inferior infarction, no reocclusion: baseline value, 13±6 mm Hg; 3-month value, 12±7 mm Hg; inferior infarction, reocclusion: baseline value, 15±6 mm Hg; 3-month value, 12±5 mm Hg).

Changes of Regional Wall Motion

In patients with anterior infarction without reocclusion, the increase in wall motion of the central and entire infarct areas was larger than in patients with reocclusion (P=.01 and P=.02, respectively). In addition, the increase of wall motion in the entire infarct area in patients with reocclusion was not statistically significant. The central contralateral wall motion was comparable in patients with and without reocclusion. In patients with inferior infarction, there was a significant increase in motion of the central and entire infarct areas without reocclusion but not with reocclusion. In contrast to anterior infarction, in patients with inferior infarction with and without reocclusion there was a decrease in contralateral segment shortening over time. For both infarct sites, the improvement in regional wall motion without reocclusion was due to both an increase of percentile shortening (Fig 3) and improvement of the number of segments showing asynergy as defined above (Table 2). In anterior infarction, many patients showed involvement of all three segments defined as the entire infarct area at acute ventriculography. After 3 months, this was unchanged with reocclusion but had decreased without. In inferior infarction, this was also observed (although not statistically significant) for the two segments defined as the entire infarct area.

Collaterals: Incidence and Consequences for Regional Wall Motion

All 21 patients with anterior infarction and reocclusion had collaterals to the infarct-related vessel that were of good quality in 12 patients and of poor quality in 9. Two patients with good collaterals had a grade 4 stenosis, and 10 had a grade 5 stenosis. One patient with poor collaterals had a grade 4 stenosis, and 8 had a grade 5 stenosis. All but 1 of the 13 patients with inferior infarction and reocclusion had collaterals. One of these had poor-quality collaterals, and 11 had good-quality collaterals. Both the patient without collaterals and the patient with poor collaterals had grade 5 stenoses. Those with good collaterals had a grade 4 stenosis in 3 and a grade 5 stenosis in 8 patients. In anterior infarction with poor-quality collaterals, there was no increase of entire infarct area wall motion with
reocclusion (baseline value, −16±12%; 3-month value, −16±15%). With good-quality collaterals, in contrast, shortening of the entire infarct zone did improve from −19±9% to −14±13% (P=.007). This improvement, however, tended to be less than that seen in anterior infarction without reocclusion (Table 2). Note that no improvement was seen in inferior infarction with reocclusion and good-quality collaterals (baseline value, −3±11%; 3-month value, −3%±11%).

**Discussion**

Recently we reported that at 3 months after initially successful thrombolysis, angiographic reocclusion was seen in about 30% of patients, irrespective of the antithrombotic agent the patients were assigned to. The present study demonstrates that even reocclusion without reinfarction has deleterious consequences for global and regional left ventricular function, especially in patients with anterior infarction. We found that global ejection fraction increased significantly in patients with persistent patency but not when reocclusion had occurred. In patients with persistent patency, wall motion in the infarct area had improved significantly at 3 months compared with the acute study, thus preserving end-systolic volume. In contrast, when reocclusion had occurred, no recovery of left ventricular ejection fraction was observed. In this group, end-systolic volume increased because of a less pronounced contractile recovery of the infarct area. Fig 1A through 1C shows wide scatters in changes of ejection fraction and ventricular volumes. Nevertheless, the likelihood of a considerable improvement of end-systolic volume index in patients with an enlarged end-systolic volume index at baseline was greater in patients without reocclusion. These observations may be of prognostic importance in that long-term mortality increases progressively with lower values of ejection fraction and with higher values of end-systolic volume.

**Left Ventricular Function and Prognosis After Myocardial Infarction: Influence of Thrombolysis**

The most important prognostic indicator after myocardial infarction is the left ventricular function, expressed as global left ventricular ejection fraction or preferably as end-systolic volume, especially if ejection fraction is <50% or end-systolic volume is >100 mL. In the present study population, infarct size is likely to be the major determinant of end-systolic volume. Infarct size is determined by the amount of myocardium at risk, collateral flow, and the duration of coronary occlusion. Myocardial at risk has been shown to be highly variable but was 53±9% of the left ventricle in anterior infarction and 22±12% in inferior infarction (P<.0001) as measured by $^{99}$Tc sestamibi. It is therefore not surprising that baseline end-systolic volume index was lower in inferior infarction than in anterior infarction. Early thrombolysis has been shown to improve global and regional systolic function by myocardial salvage.

### Table 2. Infarct Zone and Noninfarct Zone Wall Motion With and Without Reocclusion

<table>
<thead>
<tr>
<th></th>
<th>No Reocclusion</th>
<th>Reocclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Angio 1</td>
<td>Angio 2</td>
</tr>
<tr>
<td><strong>Anterior MI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All three segments asynergic, n (%)</td>
<td>21 (43)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Segment shortening relative to LLN, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire infarct area</td>
<td>−20±8</td>
<td>−11±11</td>
</tr>
<tr>
<td>Central infarct area</td>
<td>−36±10</td>
<td>−22±15</td>
</tr>
<tr>
<td>Central contralateral area</td>
<td>24±13</td>
<td>25±15</td>
</tr>
<tr>
<td><strong>Inferior MI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both two segments asynergic, n (%)</td>
<td>13 (28)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Segment shortening relative to LLN, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire infarct area</td>
<td>−3±12</td>
<td>1±12</td>
</tr>
<tr>
<td>Central infarct area</td>
<td>−9±12</td>
<td>−5±12</td>
</tr>
<tr>
<td>Central contralateral area</td>
<td>15±13</td>
<td>11±8</td>
</tr>
</tbody>
</table>

Angio indicates angiography; MI, myocardial infarction; and LLN, lower limit of normal. Asynergic segment is a segment in the infarct area exhibiting shortening of at least 5% below the LLN.
has also been suggested that left ventricular function should be used as the end point in trials that evaluate thrombolytic therapy, since it is assumed to reflect the amount of myocardium salvaged. Our study, however, suggests that in patients with reocclusion, salvaged myocardium does not regain or incompletely regains contractility. Thus, on average, when measured after 3 months, left ventricular function inaccurately reflects the amount of myocardium salvaged by thrombolysis, given an angiographic reocclusion rate of about 30%. Two previous studies reported that among determinants of left ventricular ejection fraction after reperfusion therapy, a diminished baseline ejection fraction was the strongest predictor of subsequent change. However, these results may be explained by the statistical phenomenon of regression to the mean. The present analysis demonstrates that the final ejection fraction is considerably higher than the baseline ejection fraction, particularly when the baseline ejection fraction is low, but only in patients without reocclusion. In a recent study, the impact of in-hospital reocclusion was studied. With repeat angiography at a mean of 7 days after the onset of symptoms, infarct zone function was better in patients without reocclusion, and the recovery of both global and infarct-zone function was significantly impaired by reocclusion. The present study confirms these findings in a patient group with reocclusion without reinfarction, after a time span that allowed stunned myocardium to recover completely. Thus, dysfunctioning myocardium will be either hibernating or simply necrotic.

Left Ventricular Remodeling After Myocardial Infarction: Importance of Vessel Patency

In the acute phase of myocardial infarction, left ventricular volumes are only minimally increased, even in patients with marked wall motion abnormalities. In this phase, there is reduced stroke volume when ≥20% loss of myocardium has occurred, despite acute compensatory mechanisms of an increase in chronotropy, filling pressure, and hypercontraction of the noninfarcted myocardium. An increase in ventricular volume is then necessary to restore stroke volume. Indeed, our data demonstrate that, although there were differences in end-systolic volume in the acute phase between patients with anterior and inferior infarction, baseline end-diastolic volumes were comparable. Ventricular enlargement, therefore, may be viewed as a compensatory mechanism to restore stroke volume after substantial loss of contractile tissue. This enlargement or remodeling of the ventricle may involve both the infarcted region because of infarct expansion and the noninfarcted regions because of eccentric hypertrophy. These compensatory mechanisms, however, occur at the expense of an increased preload and afterload to the left ventricle that may stimulate further ventricular enlargement. A comparison of patients with and without reperfusion demonstrated that ventricular dilatation can be prevented by reperfusion and that if dilatation occurs, the amount of dilatation is proportional to systolic dysfunction. This increase in left ventricular volume occurred between 1 and 6 weeks but has been shown to progress thereafter in some patients. This is in accordance with the findings of indicating that final infarct size, as measured by Tc sestamibi, does not correlate with end-diastolic volume at discharge or at 6 weeks but does correlate at 1 year. In a recent study, ejection fraction, stroke index at 4 days, infarct size, infarct location, and TIMI perfusion grade were significant determinants of progressive ventricular enlargement during a 3-year observation period. Of note, 6 of the 14 patients in this study with progressive dilatation after a first infarction had inferior infarction. The influence of infarct vessel patency on remodeling was stressed in earlier studies that showed that the development of ventricular enlargement after 1 year is larger with an occluded than with a patent infarct-related vessel. Coronary angioplasty has therefore been proposed as a treatment option to prevent ventricular dilatation.

It has been demonstrated that relatively small absolute changes in left ventricular volumes result in marked increases in mortality rate. Death rate increased sixfold with an increase of end-diastolic volume from ≤90 to ≥111 mL/m² and similarly when the end-systolic volume index increased from ≤34 to ≥45 mL/m². Thus, the differences in volumes that we found between the groups with and without reocclusion are likely to be of prognostic significance, especially in patients with anterior infarction, in whom left ventricular function is often depressed. Furthermore, these differences may become larger after a longer period of follow-up.

Relations Among Infarct Site, Ventricular Volumes, and Noninfarcted Zone Function

Compared with patients with inferior infarction, patients with anterior infarction had larger baseline end-systolic volumes and ended up with a lower ejection fraction when reocclusion ensued. Nevertheless, in patients with inferior infarction and reocclusion, the increases of volumes after 3 months were comparable to those seen in patients with anterior infarction and reocclusion. This observation was also made by others in patients with failed thrombolysis. There were differences, however, in contractile behavior of the noninfarcted zone between the two infarct sites. In anterior infarction, the shortening of the central collateralateral segment persisted on the same level, whereas a decrease was observed in inferior infarction. Given the smaller infarct size in patients with inferior infarction, this observation suggests that the primary long-term compensation for loss of contractile function in myocardial infarction is increase of end-diastolic volume. This allows initial hyperkinesia to subside. With larger infarctions, such as anterior infarctions, however, a persisting demand for increased contractility is apparently put on the collateralateral area to keep up stroke volume. Inability to meet this demand, as may be observed in multivessel disease, would consequently lead to further volume increase. Furthermore, this may contribute to the explanation of why ventricular dilatation is progressive in some patients and not in others. It is not unlikely that noninfarcted zone function deteriorates later in time, especially in patients with progressive ventricular enlargement. Gaudron et al found that noninfarcted zone function in patients with progressive dilatation starts to deteriorate progressively after 4 weeks to 6 months after infarction. They speculate that this may be a sequel of the regional hypertrophy per se. However, in their attempt to identify variables associated with progressive enlargement, they
did not analyze the effect of the extent of coronary artery disease or the presence of residual ischemia.

**Reversibility of Asynergy and Dilatation**

Considering similar enzymatic infarct sizes and baseline global and regional left ventricular function in the groups with and without reocclusion, our data suggest that after reocclusion, there is hibernating myocardium in the infarct area in at least a proportion of the patients that may resume contractility on reestablishment of perfusion, assuming that it behaves identically to hibernating myocardium in chronic coronary artery disease. This, however, remains speculative, since we did not study our patients for the presence of viable myocardium in the territory of the infarct-related artery. It has been demonstrated that ventricular dilatation can be reversible. Therefore, we think that in patients with reocclusion after successful thrombolysis, left ventricular dilatation may also be reversed when abolishment of reocclusion results in contractile recovery.

**Limitations of the Study**

Only a selection of patients fulfilling criteria necessary for analysis were studied. Although a selection bias therefore cannot be excluded, the baseline clinical characteristics of the study population were comparable to those of the entire group of patients that were enrolled in the APRICOT trial, and the same limitations apply. Although the data suggest that there is hibernating myocardium in the risk area, this has not been proved. In some patients with reocclusion, the absence of reinfarction may merely indicate lack of initially salvaged myocardium. This seems unlikely to be the case in all patients with reocclusion, however, considering the relatively quick institution of thrombolytic therapy in both the groups with and without reocclusion, the comparable infarct sizes, and the comparable baseline global and regional left ventricular function in these groups. Since uncertainty remains in individual patients, a reliable and affordable diagnostic method is badly needed for determining the presence of viable myocardium in the individual patient.

**Implications**

The present study underscores that at 3 months after myocardial infarction, left ventricular ejection fraction reflects increases of ventricular volumes that originate in regional contractile dysfunction. After successful thrombolysis, this regional dysfunction may relate to reocclusion, which is observed in almost one third of patients after 3 months and occurs without reinfarction in the large majority of patients. Our data suggest that this regional dysfunction may then be in part reversible. Since coronary angioplasty may be safely performed after 3 months after infarction, when almost all patients with reocclusion have collateral supply to the risk area, the value of this intervention should be evaluated in patients with reocclusion. Furthermore, these findings underscore the urgent need to find a strategy that is capable of preventing reocclusion. This will result in better left ventricular recovery and, consequently, prognosis after coronary thrombolysis.

**Acknowledgments**

This study was funded by and conducted under the auspices of the Interuniversity Cardiology Institute of the Netherlands. We gratefully acknowledge Cees A. Visser, MD, FACC, and Jean G.F. Bronzwaer, MD, for critically reading the manuscript, Jan G.P. Thijsse, PhD, for statistical advice, and Tinke Welle for expert secretarial assistance.

**References**


Left ventricular function at 3 months after successful thrombolysis. Impact of reocclusion without reinfarction on ejection fraction, regional function, and remodeling.

A Meijer, F W Verheugt, M J van Eenige and C J Werter

*Circulation*. 1994;90:1706-1714
doi: 10.1161/01.CIR.90.4.1706

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/90/4/1706

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org/subscriptions/