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Long-term Implications of Reocclusion on Left Ventricular Size and Function After Successful Thrombolysis for First Anterior Myocardial Infarction

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Background Successful thrombolysis can prevent left ventricular dilatation after acute myocardial infarction. However, in almost 30% of patients, reocclusion occurs. The aim of this study was to assess the long-term implications of reocclusion on left ventricular size and function.

Methods and Results Fifty-six patients were studied with two-dimensional echocardiography at baseline (2 ± 1.6 days) and 5.0 ± 1.4 years after first anterior myocardial infarction. All patients (a subset of those enrolled in the APRICOT trial) had a patent infarct-related artery when studied <48 hours after thrombolysis and underwent repeat coronary angiography at 3 months. Baseline characteristics were comparable in patients with ($n=17$) and without reocclusion ($n=39$). Left ventricular volume indexes were stable in patients without reocclusion. Patients with reocclusion, however, showed a significant increase in end-diastolic volume index (EDVI; $P=.008$) and end-systolic volume index (ESVI; $P=.039$). Furthermore, patients without reocclusion dem-

onstrated improvement in wall motion score index (WMSI; $P=.0001$) and ejection fraction (EF; $P=.016$), whereas patients with reocclusion did not. After 5 years, patients with reocclusion had significantly larger volume indexes (EDVI, 99 ± 41 versus 76 ± 22 mL/m², $P=.007$; ESVI, 59 ± 40 versus 39 ± 20 mL/m², $P=.017$) and more compromised left ventricular function (WMSI, 1.63 ± 0.33 versus 1.39 ± 0.32 , $P=.013$; EF, $45 \pm 13\%$ versus $51 \pm 11\%$, $P=.077$) than patients without reocclusion. Multivariate analysis identified baseline WMSI and reocclusion as significant independent predictors of left ventricular dilatation.

Conclusions Reocclusion of the infarct-related artery within 3 months of successful thrombolysis is associated with left ventricular dilatation and is detrimental to functional recovery of left ventricular function 5 years after first anterior myocardial infarction. (*Circulation*. 1997;95:111-117.)

Key Words • myocardial infarction • occlusion • thrombolysis • echocardiography • remodeling

Left ventricular remodeling after acute myocardial infarction, resulting in enlargement of the ventricle, is a progressive process beginning in the early phase and continuing for months and years.¹⁻⁴ It occurs predominantly after a large transmural anterior wall infarction^{2,5} and carries an adverse prognosis.^{6,7} There are supporting experimental and clinical data that successful reperfusion of the infarct-related artery can prevent this sequela by limiting infarct expansion.⁸⁻¹⁰ Recent clinical studies have shown that infarct-related artery patency is one of the most important determinants for ventricular remodeling after myocardial infarction.^{4,11,12} Initial success of thrombolysis, however, is followed by reocclusion in almost 30% of patients within 3 months after myocardial infarction.^{13,14} Reocclusion is associated with a more complicated hospital course,¹⁵ impaired short-term recovery of regional and global ventricular function,^{15,16} and an increase in end-systolic volume 3

months after myocardial infarction.¹⁶ Long-term data with respect to reocclusion are limited.¹⁷ Therefore, the aim of this study was to determine the implications of reocclusion on left ventricular size and function 5 years after first anterior myocardial infarction.

Methods

Patient Population

The study population consisted of 56 patients who had been enrolled in the Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis (APRICOT) trial.¹³ The entry criteria and study protocol have been described in detail previously.¹³ In brief, patients younger than 71 years with symptoms of acute myocardial infarction of <4 hours' duration were included if ST-segment elevation of ≥ 0.2 mV was present in two contiguous leads of a standard 12-lead ECG. All patients received intravenous thrombolytic therapy with streptokinase or anistreplase. Coronary angiography was performed within 48 hours of thrombolytic treatment. Only patients with a patent infarct-related artery, as described below, were eligible to enter the study. Then, patients were randomized to receive either coumadin, aspirin, or placebo. After 3 months, repeat coronary angiography was performed to assess reocclusion. A conservative strategy was intended, implying that revascularization procedures were performed only for reasons of recurrent angina refractory to medical therapy. In case of coronary angioplasty within 3 months, the status of the infarct-related artery before angioplasty was used for analysis.

For the present study, only patients with a left anterior descending artery-related myocardial infarction, enrolled in the Free University Hospital, who fulfilled the following criteria were selected: (1) enzymatically proven myocardial infarction, defined

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as creatine kinase elevation exceeding twice the upper limit of normal; (2) both first and second coronary angiography were performed; (3) two-dimensional echocardiography of adequate quality for quantitative analysis was performed during the early hospital phase; (4) reocclusion had occurred in the absence of documented reinfarction; and (5) no Q-wave myocardial reinfarction had occurred during long-term follow-up. Q-wave myocardial reinfarction was defined as recurrent ischemic chest pain accompanied by a rise in cardiac enzymes and appearance of new Q waves on the ECG. Surviving patients were invited to participate in the follow-up investigation, which consisted of a two-dimensional echocardiographic study. Of three patients who died during follow-up, an echocardiogram taken <3 months before death was available for analysis. On the basis of the results of the second coronary angiography, two groups of patients were defined: patients with and without reocclusion.

Coronary Angiography

All coronary angiograms of the APRICOT trial have been examined by an angiography committee, which consisted of three experienced cardiologists blinded to treatment allocation and clinical course of the patients. Decisions were made by consensus. Patency of the infarct-related artery was classified according to the European Cooperative Study Group¹⁸ 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 three cycles; and grade 5, 100% diameter stenosis. Patients with grade 1 to 3 stenosis were eligible for the study. Reocclusion was defined as grade 4 or 5 stenosis at follow-up coronary angiography. Quantitative angiographic analysis of the residual stenosis was performed with a personal computer-based QCA system (QCA-CMS, MEDIS Medical Imaging Systems). End-diastolic cine frames of at least two orthogonal views, clearly demonstrating the stenotic coronary segment, were selected, magnified, and digitized. The boundaries of the selected segment of the coronary artery were detected automatically.¹⁹ A diameter was computed perpendicular to the vessel centerline as the distance between the edges. A computer estimation of the original arterial dimension at the site of obstruction was used to calculate the interpolated reference diameter. The mean percentage diameter stenosis was used for subsequent analysis.

Two-dimensional Echocardiography

The early echocardiographic studies were performed with either an Advanced Technologies Laboratory ADR-4000 or a Hewlett-Packard Sonos 1000 using a 3.0- or 3.5-MHz transducer; follow-up echocardiograms were performed by means of a Hewlett-Packard Sonos 1500 using a 2.5-MHz transducer. All examinations included standard parasternal and apical views and were stored on half-inch VHS videotape for subsequent analysis. Regional wall motion was assessed semiquantitatively by two experienced observers unaware of clinical or angiographic data, using a 13-segment division of the left ventricle.²⁰ Wall motion for each segment was graded visually as 1, normokinesia; 2, hypokinesia; 3, akinesia; and 4, dyskinesia. Wall motion score index was calculated by summing the scores for each segment and dividing by the number of segments analyzed. Left ventricular end-diastolic and end-systolic volumes were determined from apical two- and four-chamber views by use of the Simpson biplane formula according to the recommendations of the American Society of Echocardiography.²¹ Tracing of the endocardial borders was performed on a digitized frame from the technically best cardiac cycle (Image Vue, Nova Microsonics), and volumes were normalized for body surface area. An increase of >20% in end-diastolic volume index (EDVI) from baseline to follow-up was defined as left ventricular dilatation.²²⁻²⁴ Ejection fraction was calculated as (End-Diastolic Volume - End-Systolic Volume) / End-Diastolic Volume.

Statistical Analysis

Data are presented as mean \pm SD. Comparisons between groups for continuous data were made with an unpaired Student's *t* test. Differences between proportions were assessed by χ^2 analysis. Fisher's exact test was used if there was an expected cell value <5. Changes in left ventricular volume and function over time were analyzed by paired Student's *t* test. Statistical significance was defined as a value of $P < .05$. Stepwise logistic regression analysis was performed to determine which variables were independent predictors of left ventricular dilatation.

Results

Study Group

Of 200 patients enrolled in the APRICOT trial in the Free University Hospital, 94 had a left anterior descending artery-related myocardial infarction. Eleven patients of this group underwent no second coronary angiography because of death ($n=2$), coronary surgery within 3 months ($n=1$), or patient refusal ($n=8$). Of the remaining 83 patients, 20 were excluded for aborted infarction ($n=5$), documented reinfarction during hospitalization ($n=4$), death without a second echocardiogram ($n=8$), or Q-wave myocardial reinfarction during follow-up ($n=3$). Furthermore, in 3 patients, the first echocardiogram was of inadequate quality, and 4 patients were lost to follow-up.

Patient Characteristics

All 56 selected patients had a first myocardial infarction. Baseline characteristics of patients with and without reocclusion are shown in Table 1. There were no significant differences between both groups with respect to age, sex, and medication or ventricular volume indexes and ejection fractions. Enzymatic infarct size and wall motion score index, both indicators of the extent of left ventricular dysfunction, were higher in patients who suffered reocclusion, although the difference was not significant. Patients with reocclusion had a higher mean percentage diameter stenosis at first coronary angiography than patients with sustained patency ($P=.0001$). Eleven patients suffered from recurrent angina pectoris before the second coronary angiography; 3 of these had reocclusion and 8 had no reocclusion ($P=NS$). The incidence of non-Q-wave myocardial reinfarction and unstable angina during the mean follow-up period of 5.0 ± 1.4 years was similar (5% and 18%, respectively, in patients with persistent patency versus 6% and 18% in patients with reocclusion). Hospitalization for heart failure had occurred in 3 patients with reocclusion (18%) compared with 1 patient without reocclusion (2.6%; $P=NS$). At the time of follow-up echocardiography, there were no differences in New York Heart Association class; all patients were in class I or II. Revascularization procedures have been performed in 9 (23%) of the 39 patients without reocclusion compared with 4 (24%) of the 17 patients with reocclusion ($P=NS$).

Left Ventricular Volumes

Fig 1 shows the impact of reocclusion of the infarct-related artery on left ventricular volume. In patients without reocclusion, left ventricular volume indexes were stable throughout the study period. EDVI tended to increase from 70 ± 12 mL/m² to 76 ± 22 mL/m², but this change was not statistically significant ($P=.054$). Also, end-systolic volume index (ESVI) remained unchanged, with a baseline value of 37 ± 11 mL/m² and a follow-up value of 39 ± 20 mL/m² ($P=.58$). In contrast, left ventricular volume in-

TABLE 1. Baseline Characteristics

Variables	No Reocclusion (n=39)	Reocclusion (n=17)	P
Age, y	56±10	53±10	NS
Male, n (%)	30 (77)	17 (100)	NS
Hypertension, n (%)	11 (28)	4 (24)	NS
Time to thrombolysis, h	1.8±0.8	2.3±0.9	NS
Peak creatine kinase, U/L	2000±1901	2391±1281	NS
Peak MB fraction, U/L	163±126	184±123	NS
Time to peak, h	12±4	13±4	NS
No. leads with ST elevation*	5.51±1.35	5.12±1.65	NS
No. pathological Q waves†	2.1±1.5	2.4±1.8	NS
Multivessel disease, n (%)	14 (36)	8 (47)	NS
% Diameter stenosis IRV‡	51±12	64±5	.0001
Medication at hospital discharge			
Nitrates, n (%)	3 (8)	1 (6)	NS
β-Blockers, n (%)	28 (72)	11 (65)	NS
Calcium antagonists, n (%)	2 (5)	1 (6)	NS
ACE inhibitors, n (%)	5 (13)	2 (12)	NS
End-diastolic volume index, mL/m ²	70±12	76±14	NS
End-systolic volume index, mL/m ²	37±11	42±11	NS
Ejection fraction, %	48±8	45±6	NS
Wall motion score index	1.55±0.24	1.64±0.21	NS

IRV indicates infarct-related vessel. Values are mean±SD.

*On the ECG before thrombolytic therapy.

†On the ECG at hospital discharge.

‡At first coronary angiography.

dexes increased significantly in patients with reocclusion, EDVI from 76±14 mL/m² to 99±41 mL/m² ($P=.008$) and ESVI from 42±11 mL/m² to 59±40 mL/m² ($P=.039$). The mean percentage change in volume indexes was significantly higher in the reocclusion group than in patients without reocclusion (EDVI, 23% versus 5%, $P=.006$; ESVI, 17% versus 1.4%, $P=.015$). After 5 years, patients with reocclusion had significantly larger EDVIs and ESVIs than patients with sustained patency (EDVI, $P=.007$; ESVI, $P=.017$).

Left Ventricular Function

Fig 2 displays the impact of reocclusion on left ventricular function. In patients without reocclusion, ejection fraction increased significantly from 48±8% to 51±11% ($P=.016$). With reocclusion, there was no change: the baseline value was 45±6%, and the follow-up value was 45±13% ($P=NS$). At long-term follow-up, patients without reocclusion had a higher ejection fraction than patients with reocclusion ($P=.077$).

Patients without reocclusion showed an improvement in regional wall motion: the wall motion score index decreased

significantly from 1.55±0.24 to 1.39±0.32 ($P<.0001$). In contrast, patients with reocclusion showed no change, with a baseline value of 1.64±0.21 and a follow-up value of 1.63±0.33 ($P=NS$). After 5 years, patients with sustained patency had a significantly better regional left ventricular function than patients with reocclusion ($P=.013$).

Predictors of Left Ventricular Dilatation

Left ventricular dilatation, defined as an increase of >20% in EDVI, was evident in 12 (21%) of the 56 patients. Table 2 shows the univariate predictors of left ventricular dilatation. Peak MB fraction, number of leads with ≥1-mm ST elevation, number of pathological Q waves, wall motion score index, ESVI, and ejection fraction at baseline as well as reocclusion were all associated with a greater risk of left ventricular dilatation by univariate analysis. Logistic regression analysis revealed that baseline wall motion score index was more significantly related to ventricular dilatation than reocclusion and the number of Q waves on the ECG. When baseline wall motion score index was used as the first predictor in the multivariate model, reocclusion still added significantly to the predic-

End Diastolic Volume Index

End Systolic Volume Index

Ejection Fraction

Wall Motion Score Index

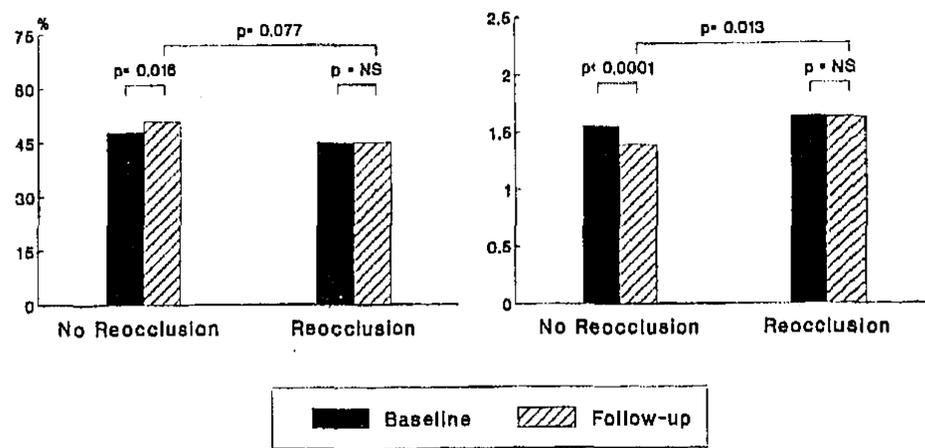
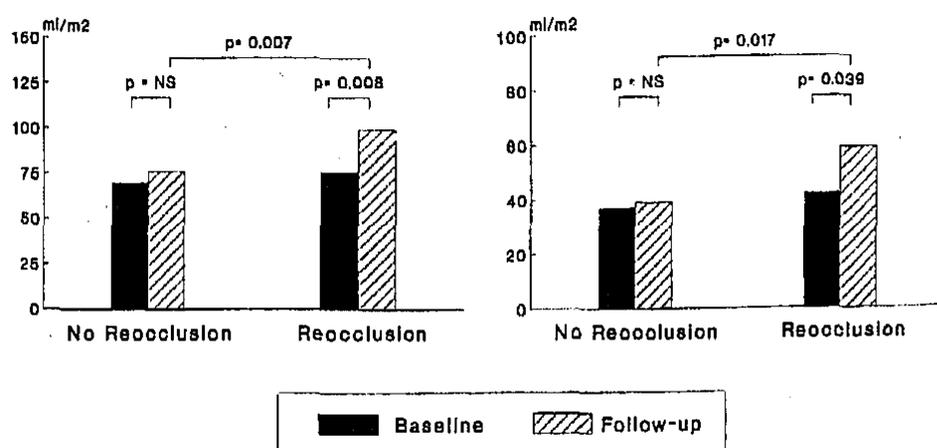


FIG 1. Change in left ventricular end-diastolic and end-systolic volume indexes between baseline and 5 years after myocardial infarction in patients with and without reocclusion.

FIG 2. Change in ejection fraction and wall motion score indexes between baseline and 5 years after myocardial infarction in patients with and without reocclusion.

tion of dilatation. Fig 3 shows the relation between baseline wall motion score index and the risk of left ventricular dilatation in patients with and without reocclusion. For a similar extent of regional dysfunction, the risk of ventricular dilatation was smaller in patients without reocclusion than in patients with reocclusion. Patients with a high wall motion score index at baseline with reocclusion were at the highest risk for left ventricular dilatation.

Discussion

Left Ventricular Dilatation and Patency of the Infarct-Related Artery

The patency status of the infarct-related artery has been identified as one of the most important determinants for left ventricular dilatation after myocardial infarction.^{4,11,12} Previous clinical studies²⁵⁻²⁸ have shown the detrimental effect of an occluded infarct-related artery on left ventricular shape and volume. Forman et al²⁵ studied 79 patients with a first anterior myocardial infarction without thrombolysis using cardiac catheterization within 6 months. Left ventricular aneurysm had developed in 25 (48%) of 52 patients with an occluded left anterior descending artery in contrast to only 4 (15%) of 27 patients with a patent artery.²⁵ Jeremy et al²⁶ demonstrated that at each level of infarct size, patients with an occluded infarct-related artery at hospital discharge had a greater increase in left ventricular volume at 1 month than patients with spontaneous reperfusion of this artery. The beneficial effect of thrombolytic therapy on left ventricular dilatation was shown in the GISSI trial,²⁹ in which end-systolic volume was smaller in patients treated with thrombolysis than in patients assigned to standard care. However, the relation between infarct-related artery patency and ventricular dilatation in that study remained unclear because angiography was not performed. Recent experimental and clinical data indicate that successful reperfusion of the infarct-related artery, even beyond the time frame for myocardial salvage, can prevent or limit ventricular dilatation.^{9,10,12,30-35} The preventive effect of late reperfusion seems to be independent of the limitation of infarct size.^{8,12} Specifically, it has

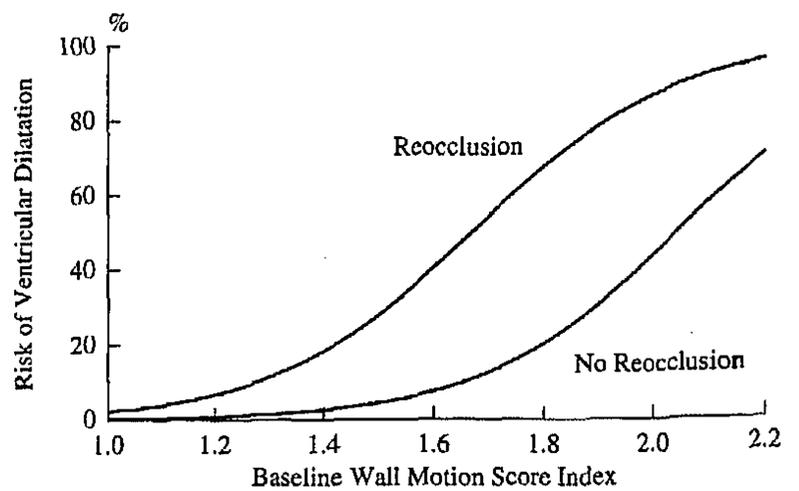


FIG 3. Relation between baseline wall motion score index and the risk of left ventricular dilatation in patients with and without reocclusion. For a similar extent of regional dysfunction, the risk of ventricular dilatation is less in patients without reocclusion than in patients with reocclusion. Patients with a high wall motion score index at baseline with reocclusion are at highest risk for left ventricular dilatation.

been shown that late reperfusion acts by limitation of infarct expansion.^{8,36-38}

Data with respect to the impact of reocclusion after successful reperfusion on left ventricular dilatation are scarce.¹⁶ Meijer et al¹⁶ showed a trend toward dilatation in patients with reocclusion 3 months after myocardial infarction. To our knowledge, no study has evaluated the long-term implications of reocclusion in this respect. Therefore, the current study not only supports the previous findings but extends them in a significant way. Our data demonstrate the importance of sustained patency of the infarct-related artery. This allowed preservation of EDVI and ESVI, whereas reocclusion results in an apparent increase in these parameters. The favorable effect of successful reperfusion on ventricular dilatation appears to be attenuated by reocclusion. This observation may be of prognostic importance because mortality increases progressively with increased left ventricular volumes.⁷

Infarct-related artery patency as such is not the only characteristic that is important with respect to ventricular

TABLE 2. Univariate Predictors of Left Ventricular Dilatation

Variables	No Dilatation (n=44)	Dilatation (n=12)	P
Age, y	55±10	53±11	NS
Male, n (%)	36 (82)	11 (92)	NS
Peak creatine kinase, U/L	2001±1817	2371±1390	NS
Peak MB fraction, U/L	147±107	228±149	<.05
No. leads with ST elevation*	5.19±1.37	6.17±1.59	<.05
No. pathological Q waves†	1.8±1.3	3.3±2.0	<.005
Multivessel disease, n (%)	15 (34)	7 (58)	NS
% Diameter stenosis IRV‡	54±13	60±9	NS
Reocclusion,§ n (%)	9 (20)	8 (67)	<.005
Medication at hospital discharge			
ACE Inhibitors, n (%)	4 (9)	3 (25)	NS
End-diastolic volume index, mL/m ²	71±12	78±17	NS
End-systolic volume index, mL/m ²	37±11	45±13	<.05
Ejection fraction, %	48±8	43±5	<.05
Wall motion score index	1.53±0.23	1.76±0.17	<.005

IRV indicates infarct-related vessel. Values are mean±SD.

*On the ECG before thrombolytic therapy.

†On the ECG at hospital discharge.

‡At first coronary angiography.

§At second coronary angiography.

||At baseline.

dilatation; Leung and Lau³⁹ demonstrated that patients with a minimal lumen diameter <1.5 mm show a significantly greater increase in left ventricular volume than patients with a minimal lumen diameter \geq 1.5 mm. However, their results may be attributable to the expected higher rate of reocclusion in patients with a minimal lumen diameter <1.5 mm. Reocclusion of the infarct-related artery within the first year after thrombolysis might be as high as 25% to 30%^{13,14,40} and is related to the severity of the residual stenosis.^{40,41} In the present study, the percentage diameter stenosis after thrombolysis was not related to left ventricular dilatation by either univariate or multivariate analysis, whereas reocclusion was a significant independent predictor. Also, in patients without reocclusion, there was no relation between the mean percentage diameter stenosis at first coronary angiography and changes in EDVI from baseline to follow-up ($r=.18$, $P=.21$). Future clinical studies are needed to confirm the hypothesis that the occurrence of reocclusion, not the severity of residual stenosis, is related to ventricular dilatation.

Determinants of Left Ventricular Dilatation

Previous clinical studies have evaluated variables that predict an increase in left ventricular volume after myocardial infarction.^{4,11,42,43} In addition to the patency status of the infarct-related artery,^{4,11} the extent of left ventricular dysfunction (as assessed by enzymatic infarct size,⁴³ echocardiography,⁴² ventriculography,¹¹ or radionuclide imaging^{4,44}) and infarct location (anterior⁴) are independently associated with progressive left ventricular dilatation. Other contributing factors are left ventricular end-diastolic pressure,¹¹ baseline left ventricular volume,^{42,43} and transmuralilty.⁴⁵ Our data are consistent with these previous findings. Interestingly, the number of pathological Q waves on the ECG at hospital discharge is a strong univariate predictor of ventricular dilatation. Despite the fact that a Q wave is neither sensitive nor specific for transmuralilty,⁴⁶ a high number of Q waves probably reflects greater transmuralilty and greater infarct size. Jugdutt et al⁴⁷ showed in an experimental study that anterior Q-wave infarction is associated with greater transmuralilty and more remodeling than non-Q-wave infarction. Multivariate analysis of the present data demonstrates that baseline wall motion score index and reocclusion have an additive and independent effect on ventricular remodeling. This suggests that efforts to limit infarct size by achieving reperfusion as early as possible after coronary occlusion must be followed by efforts to maintain patency.

Left Ventricular Function

It has been demonstrated that successful early thrombolysis results in improvement of regional and global systolic function by salvage of jeopardized myocardium.^{48,49} However, the recovery of this salvaged myocardium is significantly impaired by reocclusion.^{15,16,50} Two previous clinical studies,^{15,16} both performed shortly after myocardial infarction, reported that left ventricular function was significantly better in patients without reocclusion than in those with reocclusion. This difference was largely due to recovery of infarct-zone function in patients without reocclusion. The present study shows similar results after a time span of 5 years. Patients with sustained patency show improvement in wall motion score index and ejection frac-

tion, whereas patients with reocclusion do not. Thus, the beneficial salvaging effects of reperfusion over time are attenuated by reocclusion.

Study Limitations

In interpreting our findings, several limitations must be considered. First, the present data were obtained in a selected group of patients, and a certain selection bias cannot be excluded. The requirement for invasive restudy at 3 months and repeat echocardiography at 5 years eliminated some of the highest-risk patients for left ventricular remodeling. Furthermore, the results cannot be applied universally to patients with inferior myocardial infarction. The decision to study only patients with anterior wall infarction was based on the observation that patients at risk for remodeling are predominantly those with a large anterior myocardial infarction.⁵ Another limitation of our study is the small number of patients. It may be too small to detect baseline clinical differences between patients with and without reocclusion, owing to insufficient power. This may be especially important for differences in infarct size, which could influence long-term left ventricular dilatation. Finally, the role of intervening revascularization procedures after the second coronary angiography remains unclear from this study. In one of the four patients who underwent a revascularization procedure in the reocclusion group, it was performed shortly after the second coronary angiography. This patient showed an improvement in regional and global left ventricular function, as well as a decrease in volume indexes. The other three patients (in whom the procedure was performed after a mean of 41 months) all demonstrated a deterioration in ventricular function and an increase in volume indexes.

Clinical Implications

Our findings support the "open artery hypothesis"^{51,52} and emphasize the importance of sustained patency of the infarct-related artery. Because left ventricular function and volume are both important prognostic indicators, the differences that we observed between the groups with and without reocclusion are likely to be of prognostic significance. Our observations underline the importance of prevention and detection of reocclusion. Future clinical studies should address the value of angioplasty or coronary artery bypass surgery in prevention and treatment of reocclusion and determine the optimal timing of these procedures.

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