Independent Impact of Thrombolytic Therapy and Vessel Patency on Left Ventricular Dilation After Myocardial Infarction

Serial Echocardiographic Follow-up

Aleksandar D. Popović, MD, PhD; Aleksandar N. Nešković, MD; Rade Babić, MD; Velibor Obradović, MD, PhD; Ljubica Božinović, MD, PhD; Jelena Marinković, PhD; Jar-Chi Lee, MS; Ming Tan, PhD; James D. Thomas, MD, FACC

Background It has been shown that successful reperfusion of the infarct-related artery by thrombolysis can prevent left ventricular dilation after acute myocardial infarction; these beneficial effects were detected from several days to several months after infarction. To date, however, no study has shown that these effects can be demonstrated within hours after the onset of infarction. Furthermore, data are scarce on the independent impact of thrombolytic therapy and late vessel patency on ventricular volume and function. The aim of this study was to assess separate effects of thrombolysis and patency of the infarct-related artery on left ventricular size and function by serial two-dimensional echocardiographic examinations.

Methods and Results We evaluated 131 consecutive patients with first acute myocardial infarction by two-dimensional echocardiography in the following sequence: days 1, 2, 3, 7, and after 3 and 6 weeks. Intravenous streptokinase was administered in 81 patients, and 50 patients were treated without thrombolysis. Left ventricular end-diastolic volume, end-systolic volume, and ejection fraction were determined from apical two- and four-chamber views using the Simpson biplane formula and normalized to body surface area. Coronary angiography was performed in 107 patients after a mean of 26.0±20.2 (mean±SD) days after infarction. Patency of the infarct-related artery was assessed using TIMI criteria, with 54 considered patent (TIMI 3) and 53 with TIMI grade <3. On day 1, end-systolic volume was significantly higher in patients not receiving thrombolysis (37.7±15.3 versus 33.0±10.6 mL/m², P=.045). End-systolic volume (ESVi) was significantly higher in patients treated without thrombolysis throughout the study, whereas significant differences in end-diastolic volume (EDVi) were detected from day 3 (P=.041) onward and in ejection fraction (EF) from day 2 (P=.025) onward, all differences becoming progressively more significant with time (6-week values: EDVi, 78.8±25.4 versus 65.9±15.7 mL/m², P=.001; ESVi, 45.4±22.6 versus 33.9±15.1 mL/m², P=.002; EF, 45.1±11.6% versus 50.2±10.1%, P=.018). Patients with an occluded infarct-related artery (TIMI <3) demonstrated highly significant differences at 6 weeks compared with patients with patent vessels (EDVi, 76.8±24.7 versus 65.2±15.6 mL/m², P=.006; ESVi, 44.6±23.3 versus 31.9±12.2 mL/m², P=.001; EF, 45.0±11.6% versus 52.1±9.0%, P<.001), but these differences developed more slowly than that seen among the thrombolytic subgroups. Indeed, multivariate analysis demonstrated that thrombolysis was the major determinant of initial volumes (P=.06, .02, and .09 for EDVi, ESVi, and EF, respectively), while vessel patency was the overwhelming determinant of subsequent changes (P=.003, .0002, and .0024 for EDVi, ESVi, and EF, respectively). Additionally, ventricular volumes were significantly higher and ejection fractions lower in patients with anterior versus inferior infarction, but even adjusting for these differences as well as those associated with age, sex, and initial ventricular volume, the additive and independent impact of thrombolysis and infarct vessel patency persisted.

Conclusions These data indicate that the beneficial effect of thrombolysis on left ventricular size and function can be demonstrated in the earliest phases of acute myocardial infarction and that subsequent changes are mediated primarily through patency of the infarct-related artery. Thrombolytic therapy and late vessel patency thus have an additive and complementary impact in reducing ventricular dilation after myocardial infarction. (Circulation. 1994;90:800-807.)

Key Words • myocardial infarction • thrombolysis • echocardiography

Acute myocardial infarction excludes variable amounts of left ventricular myocardium from function, leading to a decrease in global systolic function. Subsequently, progressive left ventricular dilation occurs, beginning in the early phase of the disease and continuing for months and years, a process known as remodeling.1 Several studies have shown that successful reperfusion of the infarct-related artery by thrombolysis can prevent left ventricular dilation after acute myocardial infarction; these beneficial effects of reperfusion were detected from several days2,3 to several weeks and months after infarction.4,5 To date, however, no study has observed this effect within hours of infarction. Furthermore, data are scarce on the independent impact of thrombolytic therapy and late vessel patency on left ventricular volume and function. This is important because significant numbers of patients who receive
TABLE 1. Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=131)</th>
<th>T+ (n=81)</th>
<th>T− (n=50)</th>
<th>All Data (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55.1±8.8</td>
<td>54.2±9.0</td>
<td>56.5±8.2</td>
<td>54.1±8.8*</td>
</tr>
<tr>
<td>Sex</td>
<td>36F/95M</td>
<td>21F/60M</td>
<td>15F/35M</td>
<td>26F/71M</td>
</tr>
<tr>
<td>Location</td>
<td>55A/76L</td>
<td>29A/52L</td>
<td>26A/24L</td>
<td>56A/41I</td>
</tr>
<tr>
<td>CPK</td>
<td>1092±785</td>
<td>1055±829</td>
<td>1152±712</td>
<td>1094±810</td>
</tr>
<tr>
<td>SBP</td>
<td>141±27</td>
<td>141±24</td>
<td>141±31</td>
<td>140±25</td>
</tr>
<tr>
<td>DBP</td>
<td>86±14</td>
<td>87±13</td>
<td>85±15</td>
<td>86±13</td>
</tr>
<tr>
<td>HTN</td>
<td>39%</td>
<td>39%</td>
<td>39%</td>
<td>40%</td>
</tr>
<tr>
<td>DM</td>
<td>19%</td>
<td>18%</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>Cig</td>
<td>54%</td>
<td>54%</td>
<td>53%</td>
<td>55%</td>
</tr>
</tbody>
</table>

T+ indicates patients receiving thrombolytic therapy; T−, patients treated without thrombolysis; all data represents patients with echo data at all six time points; CPK, peak creatine phosphokinase level (IU); SBP, systolic blood pressure (mm Hg); DBP, diastolic blood pressure (mm Hg); HTN, history of hypertension (0=no, 1=yes); DM, history of diabetes mellitus; Cig, history of tobacco use; A, anterior; and I, inferior. *P<.05.

Thrombolytic therapy may recanalize initially only to reocclude subsequently, whereas many patients who are not treated with thrombolysis may achieve late vessel patency spontaneously. Such data might shed light on the benefits of late recanalization after myocardial infarction.

Therefore, the aim of this study was to assess the complementary effects of thrombolysis and patency of the infarct-related artery on left ventricular size and function by serial two-dimensional echocardiographic examinations from 1 day to 6 weeks after acute myocardial infarction.

Methods

Study Patients

The study group consisted of 131 consecutive patients (95 men and 36 women; age, 55.1±8.8 years, mean±SD) with first acute myocardial infarction admitted to the coronary care unit of Clinical-Hospital Zemun between January 1990 and June 1992 who met the following criteria: (1) age <70 years, (2) chest pain lasting >30 minutes, (3) ST-segment elevation ≥2 mm at least in two ECG leads, and (4) elevation of creatine kinase (CPK) and/or MB isoenzyme. During this period, only 2 patients did not yield quantifiable two-dimensional echocardiographic images, and 97 were studied at all six time points (see below). Eight patients initially enrolled in the study died within 6 weeks, with death occurring on days 1 (3 patients), 2, 3 (2 patients), 6, and 35. Data for these patients were included in the univariate analysis until death.

Study Protocol

Thrombolytic therapy (streptokinase, 1 500 000 U over 1 hour) was administered in 81 patients after a mean of 2.7±1.9 hours from the onset of pain. The remaining 50 patients did not receive thrombolytic therapy because they were admitted late after the onset of pain or had some contraindication for thrombolysis. As shown in Table 1, there was no significant difference in patient age, sex, infarct location, maximal CPK, initial blood pressure, or history of hypertension, diabetes, or cigarette use between the two treatment groups. Also shown are the demographics of the patients with complete echo data, showing no change from the overall group except for a slight reduction in age. An initial echocardiogram was performed after a mean of 9.7±5.4 hours from the onset of pain (8.6±4.6 hours for thrombolysis patients, 11.3±6.2 hours for nonthrombolysis patients; P=.01).

Complete two-dimensional echocardiograms were performed in the following sequence: days 1, 2, 3, 7, and after 3 and 6 weeks. All examinations were performed with an Acuson 126 machine, using a 2.5-MHz transducer; they were stored on half-inch VHS videotape for later analysis.

Left ventricular end-diastolic volume, end-systolic volume, and ejection fraction were determined from apical two- and four-chamber views using the Simpson biplane formula according to the recommendations of the American Society of Echocardiography.6 Tracing of endocardial borders in end diastole and end systole was performed on the Acuson 128 machine in the technically best cardiac cycle. The volumes were normalized for body surface area.

Coronary angiography was performed in 107 patients after a mean of 26.0±20.2 days from infarction, of whom 86 had echo data available at all six time points. It was not performed in the 8 patients who died and in 16 patients who refused. Stenosis of the major coronary artery ≥70% was considered significant. Perfusion of the infarct-related artery was assessed by an experienced angiographer (R.B.) who was blinded to clinical and echocardiographic data, using TIMI criteria.7 One-vessel disease was found in 58 of 107 patients, the rest having two- or three-vessel disease. The infarct-related artery was patent (TIMI grade 3) in 54 of 107 patients and occluded (TIMI grade <3) in the other 53.

Only four patients underwent revascularization during the time of the study: two angioplasties on days 13 and 29 and two coronary bypass operations on days 34 and 40. Each of the thrombolytic (T)/patency (P) subgroups (T+P+, T−P−, T+P−, and T−P+) was represented by one patient who was revascularized. Because of the small number of procedures and the few echo examinations occurring subsequent to them, revascularization was not included in the analysis.

Statistical Analysis

Unpaired t tests were used to assess the univariate effect of thrombolytic therapy, patency of the infarct-related artery, and infarct location on left ventricular size and function at each point of time. ANOVA with repeated measurement was used to assess the independent impact of thrombolysis and vessel patency of left ventricular volume and function. This also supplied data on the timing of the impact, since the between-subjects differences would relate to overall ventricular volumes, whereas the within-subjects differences would relate to volume changes during the 6-week period of observation.

Temporal Analysis

To better utilize the temporal nature of the data, a two-stage linear regression model was used, analyzing in turn each of the systolic function indices. For example, end-systolic volume was modeled as follows.

\[ ESV_{ij \text{a}} = \alpha_{ij \text{a}} + \beta_{ij \text{a}} + \epsilon_{ij \text{a}} \]

where \(i\) represents patient number, \(j\) represents thrombolysis (0=no, 1=yes), \(k\) represents vessel patency at catheterization (TIMI 0 to 2=0; TIMI 3=1), and \(l\) represents infarct location (0=inferior, 1=anterior). \(a\) and \(b\) are, respectively, the intercept and slope for the linear regression of end-systolic volume for each subgroup, \(t\) is the follow-up time, and \(\epsilon\) is assumed to be a randomly distributed Gaussian error term. To convert the temporal sampling to a more normal distribution, the logarithm (base 2) of the day number was used instead of the actual day number. An additional benefit of this was that the intercept of the regression line would closely relate to initial (day 1) volumes, since \(\log(2)=0\). Among the dependent variables analyzed in this way were end-diastolic volume index (EDVI), end-systolic volume index (ESVI), and ejection fraction (EF). The independent (categorical) variables tested in
the analysis were utilization of thrombolytic therapy, TIMI grade, and infarct location, with the slopes and intercepts compared among these subgroups. To rule out any confounding effect of other patient characteristics, the analysis was repeated with age, sex, CPK, and history of hypertension, diabetes, and cigarette use entered as covariates. Additionally, initial ventricular volume was used as a covariate in the slope analysis to determine the extent to which ventricular dilation simply reflected enlargement of already large ventricles.

**Results**

**Change in Systolic Function Over Time**

(Full Group)

Analysis of all patients together demonstrated significant increases in left ventricular end-diastolic volume over the 6 weeks of observation: 62.1±12.9 (mean±SD) to 70.4±20.5 mL/m² (P<.001). Left ventricular end-systolic volume showed a less dramatic though still significant (P=.014) increase, from 34.8±12.7 mL/m² on day 1 to 37.9±18.8 mL/m² after 6 weeks. Ejection fraction showed a slight, nonsignificant increase over the period of observation: 45.1±11.4% to 48.4±10.9% (P=.6).

**Univariate Subgroup Analysis**

Figs 1 to 3 and Tables 2 to 4 display the impact of thrombolysis, patency of the infarct-related artery, and infarct location on left ventricular volume and function.

**Thrombolysis**

End-systolic volume index was already significantly higher in patients treated without thrombolysis on day 1, with this difference growing over 6 weeks (Fig 1, middle; Table 2, left). End-diastolic volume index was similar in patients treated with and without thrombolysis on days 1 and 2 but became significantly higher in patients treated without thrombolysis on day 3; this difference became increasingly significant throughout the study (Fig 1, bottom; Table 3, left). Ejection fraction was higher in patients receiving thrombolysis from admission to the end of the study (Fig 1, top; Table 4, left).

**Patency of the Infarct-Related Artery**

Fig 2 shows the impact of patency of the infarct-related artery on left ventricular volume and function. End-systolic volume index was significantly higher in patients with an occluded infarct-related artery from day 2, remaining higher over 6 weeks (Fig 2, middle; Table 2, middle). End-diastolic volume was similar in both groups until 3 weeks, when significantly higher end-diastolic volumes were detected in patients with an occluded infarct-related artery (Fig 2, bottom; Table 3, middle). Ejection fraction was higher in patients with a patent artery from day 2, and the difference remained significant over the study period (Fig 2, top; Table 4, middle).

**Infarct Site**

Fig 3 displays the impact of infarct location on left ventricular volume and function. Both end-diastolic and end-systolic volumes were significantly higher on day 1 in patients with anterior infarction and steadily increased at each measurement in these patients (Fig 3,
Combined Impact of Thrombolysis and Vessel Patency

At the time of catheterization, 62% of patients who had undergone thrombolytic therapy demonstrated TIMI 3 flow through the infarct related artery compared with only 29% of those who were not thrombolysed ($P=.002$ by $\chi^2$). Nevertheless, a significant subgroup demonstrated discordance between thrombolysis and patency (thrombolysis without patency, 26 patients; patency without thrombolysis, 11 patients). The combined impact of thrombolysis and patency of the infarct-related artery is shown in Fig 4 and Table 5. It can be noted that left ventricular volumes were best preserved in thrombolysis patients with a patent infarct-related artery and to a lesser extent in patients receiving thrombolysis with an occluded artery. Patients who did not receive thrombolytic therapy had higher left ventricular volumes irrespective of the patency of the infarct-related artery, demonstrating that some effects of thrombolysis on left ventricular size may be partially independent of late vessel patency. The same was true for ejection fraction: it was highest in patients treated with thrombolysis and successful reperfusion, lowest in patients treated without thrombolysis and with an occluded artery, and intermediate for the subgroups with discordant thrombolysis and patency data. In the statistics given for Fig 4, the probability values for thrombolysis reflect between-group effects (differences between volume or ejection fraction at all time points); those for patency are for within-group effects (predictive of a significant change over the course of the study).

Temporal Analysis

Thrombolytic therapy, vessel patency, and infarct location were entered into a two-stage regression model to first calculate the intercept and slope of the end-diastolic volume index, end-systolic volume index, and ejection fraction from initial to final examination. The intercepts and slopes then were compared across groups. As shown in Table 6 (top), when thrombolysis and patency were considered together, there was a striking divergence of impact on initial and subsequent volumes. It appears that thrombolytic therapy is the predominant determinant of initial ventricular volume and function, with little contribution of late vessel patency. In sharp contrast, however, it is vessel patency that predicted which patients would suffer subsequent ventricular dilation, with relatively little impact of thrombolysis.

When infarct location was included in the model (Table 6, bottom), it became the dominant univariate predictor of intercept and slope. For example, end-diastolic volume index ($P=.0001$) rose by $3.0\pm0.08$ (mL/m$^3$)/log$_2$(day) for anterior infarcts versus $0.4\pm0.22$ (mL/m$^3$)/log$_2$(day) for inferior ones, with end-systolic volume index ($P=.0001$) demonstrating a slope of $1.83\pm0.47$ versus $0.05\pm0.16$, respectively. Nevertheless, vessel patency remained a highly potent predictor of the change.
TABLE 3. LEFT VENTRICULAR END-DIASTOLIC VOLUME INDEX (mL/m²)

<table>
<thead>
<tr>
<th>Day (n)</th>
<th>All</th>
<th>Yes (81)</th>
<th>P</th>
<th>No (50)</th>
<th>Yes (54)</th>
<th>P</th>
<th>No (53)</th>
<th>Inf (76)</th>
<th>P</th>
<th>Ant (55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (128)</td>
<td>62.1±12.9</td>
<td>61.0±1.1</td>
<td>.221</td>
<td>63.9±2.4</td>
<td>61.7±1.5</td>
<td>.658</td>
<td>62.8±2.0</td>
<td>58.7±1.2</td>
<td>&lt;.001</td>
<td>66.6±2.0</td>
</tr>
<tr>
<td>2 (118)</td>
<td>63.5±13.9</td>
<td>61.9±1.2</td>
<td>.091</td>
<td>66.4±2.8</td>
<td>62.8±1.7</td>
<td>.23</td>
<td>66.2±2.3</td>
<td>59.2±1.3</td>
<td>&lt;.001</td>
<td>69.6±2.2</td>
</tr>
<tr>
<td>3 (116)</td>
<td>65.6±15.6</td>
<td>63.4±1.3</td>
<td>.041</td>
<td>69.6±3.3</td>
<td>64.0±1.8</td>
<td>.135</td>
<td>68.6±2.5</td>
<td>60.3±1.5</td>
<td>&lt;.001</td>
<td>72.8±2.4</td>
</tr>
<tr>
<td>7 (112)</td>
<td>66.9±16.6</td>
<td>64.7±1.5</td>
<td>.05</td>
<td>71.1±3.5</td>
<td>64.7±1.8</td>
<td>.062</td>
<td>71.1±2.9</td>
<td>61.4±1.6</td>
<td>&lt;.001</td>
<td>74.6±2.7</td>
</tr>
<tr>
<td>21 (120)</td>
<td>68.6±19.4</td>
<td>64.7±1.7</td>
<td>.002</td>
<td>75.9±3.7</td>
<td>64.4±2.0</td>
<td>.008</td>
<td>74.7±3.3</td>
<td>61.2±1.6</td>
<td>&lt;.001</td>
<td>79.6±3.1</td>
</tr>
<tr>
<td>42 (112)</td>
<td>70.4±20.5</td>
<td>65.9±1.8</td>
<td>.001</td>
<td>78.6±4.1</td>
<td>65.2±2.2</td>
<td>.006</td>
<td>76.8±3.6</td>
<td>62.1±1.6</td>
<td>&lt;.001</td>
<td>81.9±3.4</td>
</tr>
</tbody>
</table>

Definitions and abbreviations are the same as for Table 2.

in EDVi (P=.0001) and ESVi (P=.0001) and was the dominant predictor of the change in EF (P=.0006). As in the bivariate model, thrombolytic therapy contributed little incrementally to predicting this change.

Interestingly, there was significant interaction between vessel patency and infarct location for the change in end-diastolic volume (P=.0006) and end-systolic volume (P=.0002). For example, full reperfusion dramatically reduced the slope of end-diastolic volume in patients with anterior infarcts (4.79±0.66 versus 1.3±0.48 [mL/m²]/log₂[day]), with relatively less impact (0.84±0.33 versus −0.02±0.27) in inferior infarcts. For end-systolic volume, the slope fell from 3.70±0.66 to −0.05±0.39 (ie, actual regression in end-systolic volume over time) in anterior infarcts, whereas the effect in inferior infarcts (0.40±0.23 versus −0.29±0.20), while still significant, was less dramatic due to the lower risk of ventricular dilation in nonreperfused inferior infarcts.

With respect to the volume and function intercepts, there was a highly significant interaction between thrombolysis, patency, and infarct location. For example, in patients with anterior infarcts who had late vessel patency, volume intercept was dramatically lower in those who received thrombolysis compared with those who achieved patency spontaneously (and likely delayed) for ESVi (51.0±3.9 versus 32.6±1.8 mL/m², P=.0002) and EDVi (80.6±1.7 versus 59.4±2.0, P=.0001).

Other Variables

To examine other possible confounding variables related to ventricular volume and function after infarction, the multiple regression analysis was extended to include other factors with backward selection used to eliminate nonsignificant factors from the model. All of the following added variables were eventually dropped from the model (P>.10 for all): sex, blood pressure at presentation, history of hypertension, diabetes, and tobacco use. Age was of borderline significance (P=.06) only for EDVi. Additionally, the initial value of ESVi, EDVi, and EF did not significantly predict the slope of the respective variable independent of vessel patency, thrombolysis, and infarct location.

Discussion

The long-term prognosis of patients with acute myocardial infarction is directly related to left ventricular size and function.8 After acute myocardial infarction, there are complex changes in ventricular architecture9 in both infarct and noninfarct zones. A critical change is that of infarct expansion,9 in which disruption of normal myofibrils leads to thinning and dilation of the necrotic zone.1 Infarct expansion can be detected by two-dimensional echocardiography as an alteration of left ventricular geometry due to elongation of the noncontractile region.10 Expansion occurs almost exclusively in patients with large transmural infarcts and may be associated with heart failure, aneurysm formation, or myocardial rupture.11 Experimental13,14 and clinical studies1 have shown that left ventricular remodeling affects both infarcted and normal ventricular segments.

Echocardiographic Quantitation of Ventricular Remodeling

Picard et al15 have used two-dimensional echocardiography to assess changes of left ventricular size in acute myocardial infarction on admission and 3 months later. They have found that the increase of left ventricular volume was the consequence of three different processes: infarct expansion, global ventricular dilation,
and infarct extension. Most importantly, their study demonstrated that infarct expansion can be detected within 24 hours from the onset of infarction.

The current study showed that left ventricular end-systolic volume was the most sensitive index of changes in ventricular geometry, demonstrating differences between thrombolytic subgroups as early as day 1, in accordance with the prior observation that end-systolic volume is the major determinant of survival after myocardial infarction. Although most thrombolytic trials have used ejection fraction to assess left ventricular function after the intervention, it seems clear that serial assessment of left ventricular volume provides better insight into left ventricular systolic function after myocardial infarction.

Prior Studies of Ventricular Function After Thrombolytic Therapy

Jeremy et al have shown that patency of the infarct-related artery had a significant impact on left ventricular size 1 month after infarction in patients treated with conventional therapy; the same group demonstrated that left ventricular dilation may continue over 6 months. The effect of thrombolytic therapy on left ventricular dilation was also evaluated in the GISSI study, which showed that end-diastolic and end-systolic volumes at discharge and 6 months later were lower in patients treated with thrombolytic therapy. Lavie et al have found in patients receiving thrombolysis that successful reperfusion was associated with lower left ventricular volume 6 weeks after infarction. Recently, Leung and Lau have assessed the influence of the degree of residual stenosis of the infarct-related artery after thrombolysis on left ventricular dilation determined 1 week, 6 months, and 1 year after infarction. They found no differences in end-diastolic volume between patients with minimal lesion diameter of 0 mm (completely occluded), <1.5 mm, and ≥1.5 mm at the initial measurement, but subsequently progressive increase of end-

### Table 5. Separate Impact of Thrombolysis and Vessel Patency

<table>
<thead>
<tr>
<th>Day</th>
<th>EDVI, mL/m²</th>
<th>ESVI, mL/m²</th>
<th>Ejection Fraction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T-P-</td>
<td>T-P+</td>
<td>T-P-</td>
</tr>
<tr>
<td>1</td>
<td>64.8</td>
<td>70.3</td>
<td>61.6</td>
</tr>
<tr>
<td>2</td>
<td>69.8</td>
<td>71.8</td>
<td>63.6</td>
</tr>
<tr>
<td>3</td>
<td>71.8</td>
<td>71.9</td>
<td>65.4</td>
</tr>
<tr>
<td>7</td>
<td>73.3</td>
<td>74.5</td>
<td>68</td>
</tr>
<tr>
<td>21</td>
<td>78.9</td>
<td>78.5</td>
<td>69.3</td>
</tr>
<tr>
<td>42</td>
<td>82.5</td>
<td>80</td>
<td>70.9</td>
</tr>
</tbody>
</table>

EDVI indicates left ventricular end-diastolic volume index; ESVI, left ventricular end-systolic volume index; T, thrombolytic therapy; P, patent infarct-related artery; +, present; and −, absent.
diastolic and end-systolic volumes occurred in the first two groups. Finally, Sheehan et al13 have reported that thrombolytic therapy improved left ventricular function in the first days after infarction, leading to further improvement after 5 weeks.

Importantly, none of the prior studies have examined in depth the interplay between thrombolytic therapy and late vessel patency in determining ventricular dilation. For example, White et al10 showed clearly that thrombolytic therapy favorably impacts late ventricular volume and function, but that analysis did not include ventricle patency in the statistical model even though only 75% of the streptokinase patients had patent vessels, whereas fully 54% of the placebo patients had at least TIMI 2 flow at catheterization. Conversely, Lavie et al15 showed the salutary effect of vessel patency after thrombolysis, but all patients in that study were thrombolysed, so assessment of the impact of spontaneous reperfusion was not possible. More fundamentally, the current study is the largest one with frequent enough assessments of ventricular volume to realistically differentiate between initial size and subsequent dilation.

Results of the Current Study

Our data confirm the above findings and also extend them in several important ways. First of all, we have shown the clear benefit of thrombolysis in limiting ventricular enlargement after myocardial infarction, demonstrating significantly smaller volume and higher ejection fraction as early as day 1, with even greater divergence subsequently.

Second, we showed that thrombolysis and late patency of the infarct-related artery have independent and complementary roles in preserving ventricular size and function. For example, Fig 4 suggests that thrombolysis has a beneficial effect on left ventricular size even in patients with an occluded infarct-related artery (T+P- patients). This may reflect some patients who had early reperfusion, with its salutary effect on ventricular volume; subsequent reocclusion may have been associated with improved collateral flow into the infarct zone, limiting the size of the infarct. The converse group in Fig 4—those with late vessel patency but no thrombolytic therapy (T-P+) — show less beneficial effect, suggesting that these patients achieved vessel patency relatively late, resulting in less myocardial salvage (P=.027 comparing T+P- with T-P+ patients for EDVi at all time points). Still, these patients appeared to have better preserved ventricular function than those with neither thrombolysis nor reperfusion, supporting the experimental finding that even “late” achievement of patency may reduce infarct expansion and ventricular dilation.20,21

Finally, our data demonstrate an interesting discordance between the timing of benefit of thrombolysis and vessel patency. Throughout several types of statistical analyses, we showed that thrombolysis has its primary impact on initial ventricular volumes, whereas vessel patency relates primarily to subsequent dilation. This is shown most clearly in the two-stage linear regression model (Table 6), where thrombolysis—not patency—has a significant impact on the data intercept (corresponding to day 1), whereas patency has the overwhelming effect on the slope of the data (subsequent change).

Impact of Infarct Location

Important differences were seen in this study between patients with inferior versus anterior infarctions. Overall, we observed ventricular enlargement primarily in patients with anterior infarctions, consistent with the prior clinical15 and experimental22 observations that inferior infarcts are usually small and rarely associated with ventricular dilation. It is thus not surprising that the major benefit we observed from both thrombolysis and vessel patency was in patients with anterior infarctions. In particular, the small number of patients (n=4) with anterior infarctions who failed to reperfuse after thrombolysis showed a particularly striking degree of dilation, with ESVi rising from 43.2 mL/m² on day 1 to 66.4 mL/m² at 6 weeks.

Limitations

The major limitation of the study is that the patients were not randomized to receive thrombolytic therapy but rather were assigned on the basis of their time to presentation to the hospital and the wishes of their attending cardiologist. Given the wealth of prior studies demonstrating the clinical efficacy of thrombolytic therapy in acute myocardial infarction, it would have been unethical to randomize these patients to placebo. Table 1 demonstrates that the two treatment groups were quite similar demographically. Furthermore, the multivariate regression demonstrates that conclusions hold even after adjusting for multiple clinical variables.

Because of death and patient refusal, data were not available at every time point on every patient. If anything, this may have biased the remainder of the data to less dilation, since the patients who died tended to have large infarcts. However, 97 patients underwent quantitative echocardiography at all six time points, and the multivariate ANOVA was based only on patients with all data available. The two-step regression analysis was
designed to use the available data on all patients. Overall, these slightly different patient groups seemed to make little difference to the statistical conclusions reached.

Because time from onset of chest pain to presentation was a factor in determining whether a patient received thrombolysis, it may be that the day 1 echoes of the T− patients showed larger ventricles in part because they were performed farther into the course of the infarct than the T+ patients. However, stepwise regression analysis of the day 1 data showed no significant contribution of echo ascertainment time in predicting EDVi, ESVi, and EF (P = .463, .754, and .728, respectively), with time to echo accounting on average for only 6% of the variance accounted for by the thrombolytic status. Furthermore, even assuming a worst-case delay of 24 hours, comparing T− patients on day 1 with T+ patients on day 2 showed significant impact of thrombolysis on ESVi (37.7 ± 2.2 versus 32.5 ± 1.2 mL/m², P = .013) and EF (42.6 ± 1.7% versus 48.2 ± 1.2%, P = .003). Thus, it seems appropriate to ascribe most of the early difference in ventricular volume to factors other than the time of the initial echo.

Conclusions

We have shown in serial echocardiographic studies that both thrombolytic therapy and patency of the infarct-related artery significantly preserve ventricular volume and function in patients suffering a first myocardial infarction, with differences noted as early as the day of the infarction. Thrombolytic therapy and vessel patency appear to have independent and complementary effects; thrombolysis primarily impacts early ventricular size and function, whereas patenty is mainly predictive of subsequent changes. That thrombolysis favorably impacts ventricular size even in the absence of late vessel patency is likely due to myocardial salvage from transient reperfusion in a few patients. Although salutary benefits were most striking in patients with anterior infarcts, we conclude that thrombolysis and vessel patency, in an additive manner, prevent infarct expansion and subsequent left ventricular remodeling.

Acknowledgments

The authors would like to thank Eric J. Topol, MD; Harvey D. White, MB; Michael H. Picard, MD; and Thomas H. Marwick, MD, for reviewing the manuscript.

References


Independent impact of thrombolytic therapy and vessel patency on left ventricular
dilation after myocardial infarction. Serial echocardiographic follow-up.
A D Popovic, A N Neskovic, R Babic, V Obradovic, L Bozinovic, J Marinkovic, J C Lee, M
Tan and J D Thomas

_Circulation_. 1994;90:800-807
doi: 10.1161/01.CIR.90.2.800

_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/90/2/800

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/