Factors influencing probability of reperfusion with intracoronary ostial infusion of thrombolytic agent in patients with acute myocardial infarction

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ABSTRACT A multivariate logistic regression equation was used to evaluate variables related to successful intracoronary thrombolytic therapy. One hundred seventeen patients with a totally occluded infarct-related artery were randomly given ostial infusions of urokinase or streptokinase in a blinded study. The opening rate was 57%. The agent used and time from onset of symptoms to beginning of treatment did not significantly influence opening rate (p > .25). The site of occlusion was a strong predictor of opening rate (p = .0004). The anterior descending coronary artery was successfully opened more frequently than the left circumflex or right coronary artery (p = .012). Presence of collaterals adversely affected the recanalization rate in all groups (p = .0004). These variables had an additive effect on the probability of opening. Patients with proximal anterior descending occlusion and no collaterals had a 90% recanalization rate, while those with distal occlusions in vessels other than the anterior descending and with collaterals had only a 24% chance for reperfusion. Thus location of occlusion and presence or absence of collaterals may strongly influence opening rates.


INTRACORONARY thrombolysis is a frequent therapeutic approach for patients in the early phase of acute myocardial infarction. Protocols vary widely among institutions. Important variables include dose and rate of infusion, type of thrombolytic agent, and use of subselective technique. Patient characteristics may also be expected to influence opening rates. Reported reperfusion rates range from 54% to 95%.1–11 In our previous series of 80 patients the opening rate was 60%.12

The objective of this study was to evaluate the influence on myocardial thrombolysis of the following variables: (1) the artery involved, (2) location of the thrombus, (3) presence or absence of collateral flow to the obstructed artery, and (4) time from onset of symptoms to beginning of the infusion. Previous analysis demonstrated that the thrombolytic agent used did not influence opening rates.12

Methods

The study group comprised 117 consecutive patients (99 men and 18 women), ages 36 to 80 years (57 ± 10, mean ± SD) who met the entry criteria. All patients had (1) onset of chest pain less than 12 hr before the beginning of infusion, (2) ST segment changes suggesting acute myocardial injury, (3) angiographically documented complete occlusion of the infarct related artery, and (4) no specific contraindications to thrombolytic therapy.

After informed consent was obtained, patients with complete occlusions were given intracoronary urokinase (Abbokinase) or streptokinase (Streptase) at doses of 6000 or 2000 U/min, respectively, in a previously described randomized double-blind fashion.12 Time elapsed from the onset of chest pain to beginning of the infusion varied between 30 min and 590 min (281 ± 102, mean ± SD). The infusion was carried out with a standard Judkins catheter placed in the ostium of the right or left coronary artery according to the site of the occlusion. The effect of therapy was assessed angiographically every 15 min and infusion time was limited to 120 min.

The occlusion was considered proximal if located before the first diagonal branch in left anterior descending artery (LAD), the first obtuse marginal branch in the left circumflex artery (LCX), and the acute marginal branch in the right coronary artery (RCA). Other obstructions were defined as distal. Collaterals were regarded as present if the infarct-related artery distal to occlusion was opacified after injection of the contrast material in the contralateral coronary vessel. No attempt was made to quantify collateralization. The result of thrombolytic therapy was assessed at the end of infusion. Only those patients displaying patency of the previously closed coronary artery at comple-
tion of the infusion were considered to have had successful openings.

Statistical analysis. Stepwise multivariate logistic regres-
sion was used to analyze the relationship between variables that
characterized the occlusion and probability of reperfusion.\textsuperscript{13}
The rationale for this analysis is twofold. First, this multivariate
analysis assesses the independent impact of each variable on
rates of thrombolysis, controlling for the effects of other vari-
bles. Second, it provides a predictive equation with which prob-
ability of reperfusion for a subgroup of patients with a specific
type of occlusion can be estimated. The concordance of predict-
ed probabilities with actual reperfusion rates is a measure of the
variability in opening rates explained by the characteristics of
the occlusions in the multivariate analysis.

The initial model began with an equation that contained five
variables: thrombolytic agent, time, location, involved artery,
and presence or absence of collaterals and interaction among
these variables. The significance of each variable was tested
with a likelihood ratio test.\textsuperscript{13} Variables were not eliminated from the
model in a stepwise fashion until all that remained were signifi-
cant at the $p = .2$ level. The combined significance of the final
variables in the equation (excluding the constant term) was
tested with a likelihood ratio test.

In the stratified analysis of the effect of collateralization, the
significance of the direction of within-subgroup differences was
tested with probabilities from the binomial distribution.

Results

In 66 of 117 patients (57%) thrombolytic therapy
achieved a successful recanalization of the previously
occluded vessel.

Selection of variables associated with reperfusion. No
significant interactions between the variables character-
zizing the occlusions were found ($p > .25$). The
thrombolytic agent used was not significantly associat-
ed with reperfusion (59% opening for streptokinase vs
52% for urokinase; $p > .025$) nor was time from onset
of pain to start of the thrombolytic therapy (268 ± 99
min, mean ± SD, for patients with opening vs 294 ±
98 min for those with no opening; $p > .25$). Moreover,
there was no significant distinction between the RCA
and LCX (46% openings for RCA, 36% for LCX; $p >
.25$). Hence, the final variables selected as signifi-
cantly predictive of reperfusion were site of occlusion
(proximal vs distal), artery (LAD vs RCA or LCX),
and absence or presence of collaterals.

Site of occlusion. The strongest predictor of reperfu-
sion was site of occlusion ($p = .0004$). Arteries with
proximal occlusions recanalized 74% of the time (45/
61) vs 38% (21/56) for distal occlusions (figure 1).

Artery occluded. The artery occluded was a strong
predictor of successful reperfusion ($p = .012$). The
LAD was recanalized in 74% of the patients (35/47) as
opposed to 44% (31/70) for the RCA or LCX (figure
2).

Collaterals. Presence of collaterals decreased the rate
of opening ($p = .17$) (figure 3). Although the signifi-
cance given by the multivariate logistic regression
analysis was borderline, the reperfusion rates were
consistently lower for patients with collaterals in each of
eight patient groups defined by location, artery, and
collateralization ($p = .004$) (figure 4). This result indi-
cates a small, yet definite effect of collaterals.

Combined effect. Taken together, these three vari-
ables had a strong cumulative effect on reperfusion rates
($p = .0002$) (figure 4). The highest rates were for
proximal occlusion of the LAD without collaterals
(90%). For distal occlusions of the RCA or LCX with
collaterals to the distal portion of the thrombosed ves-
sel, the reperfusion rate was 24%.

Predictive equation. The multivariate logistic equa-
tion predicted well the reperfusion rates in subgroups

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure1.png}
\caption{Opening rates: proximal vs distal occlusion.}
\end{figure}
for this series of patients, the observed occlusion characteristics predict well the outcome of thrombolytic therapy. However, we did not test the predictive power of the equation in a separate series of patients.

The higher probability of proximal thrombolysis may be related to local availability of the thrombolytic agent and/or plasminogen. With a distal occlusion, penetration of the thrombolytic solution to the clot may be decreased by a "cul-de-sac" phenomenon, producing an area of stagnant blood proximal to the thrombus and/or runoff through patent branches originating proximal to the obstruction. The importance of delivering thrombolytic agent in proximity to the thrombus has been previously emphasized.

The variation in opening rates of occluded arteries is poorly understood. Weinstein, summarizing the experience of this series of patients (p = .0002) (figure 4). For this series of patients the equation was:

$$ p = \frac{\exp(Z)}{1 + \exp(Z)} $$

where $Z = -1.287 + 1.182X_A + 1.514X_L + 0.651X_C$, with $X_A = 1$ for LAD, $X_A = 0$ for RCA or LCX, $X_L = 1$ for proximal, $X_L = 0$ for distal location, $X_C = 1$ for no collaterals, and $X_C = 0$ for present collaterals. For example, the predicted rate in the most successful subgroup was 89% (observed 90%), and 22% in the least successful subgroup (observed 24%) (table 1).

**Discussion**

Close concordance of the observed reperfusion rates with those predicted by the logistic model shows that
experience of several centers, noted opening rates for the LAD, LCX, and RCA of 79%, 80%, and 78%. Merx et al.\(^\text{15}\) and Cowley and Gold\(^\text{6}\) found recanalization rates for the LAD and RCA to be similar, but higher than for the LCX. However, these studies included patients with incomplete occlusions, and in some, sub-selective coronary infusion was used. Our results were similar to the recent findings of Berte et al.\(^\text{16}\) and Giambartolomei et al.\(^\text{17}\).

We can offer only hypotheses as to the reasons for these differences. With ostialy perfused LCX occlusions there is always a considerable runoff of the thrombolytic agent through the LAD. The left Judkins catheter may selectively direct flow to the LAD. The RCA would appear to have the least runoff of thrombolytic solution proximal to the occlusion. As noted by Ganz et al.,\(^\text{2}\) a column of stagnant blood proximal to the thrombus is common in the RCA. Both the RCA and LCX may have less motion than the LAD because of their location in the atrioventricular groove.

Although collateral flow may prolong myocardial viability and improve the functional result of reperfusion,\(^\text{18-22}\) the tendency of collaterals to decrease the likelihood of recanalization has not been previously described.

Absence of collateral flow should allow a greater pressure gradient across the thrombus. Angiographically apparent perfusion in or around the thrombus resulting in enhanced permeation of the thrombolytic agent is a possible result. An alternative explanation may be that the mechanism of occlusion is influenced by collateral flow, resulting in a more prolonged process with a relatively smaller zone of thrombus in the occluded artery.

In multivariate analysis with time treated as a continuous value, time was not a predictor of opening. This corroborates the observation of Lee et al.\(^\text{23, 24}\) that although older thrombi may require higher doses and more time to dissolve, opening rates are similar.

### TABLE 1

<table>
<thead>
<tr>
<th>Location</th>
<th>Artery</th>
<th>Collaterals</th>
<th>n</th>
<th>Observed</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal</td>
<td>LAD</td>
<td>No</td>
<td>19</td>
<td>.895</td>
<td>.887</td>
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<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>9</td>
<td>.778</td>
<td>.804</td>
</tr>
<tr>
<td></td>
<td>LCX or RCA</td>
<td>No</td>
<td>17</td>
<td>.706</td>
<td>.706</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>16</td>
<td>.563</td>
<td>.557</td>
</tr>
<tr>
<td>Distal</td>
<td>LAD</td>
<td>No</td>
<td>12</td>
<td>.667</td>
<td>.633</td>
</tr>
<tr>
<td></td>
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<td>Yes</td>
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<td>.474</td>
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<tr>
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<td>LCX or RCA</td>
<td>No</td>
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<td>.417</td>
<td>.346</td>
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<td></td>
<td></td>
<td>Yes</td>
<td>21</td>
<td>.238</td>
<td>.216</td>
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</tbody>
</table>
Our analysis suggests stratification of candidates for thrombolytic therapy according to reperfusion probability. This probability is high (86%) for proximal LAD occlusions. When the thrombus is present in the proximal portion of the RCA or LCX or in the distal segment of LAD, probability of successful opening is intermediate (64%, 60%, and 58%) but still in a range presented in the literature. 1-11 Distal occlusions of the LCX and RCA are associated with a low probability of reperfusion. Presence of collateral flow consistently diminishes the likelihood of opening in all subgroups.

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References
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M P Tendera, W B Campbell, S N Tennant and W A Ray

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