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Clinical research

Time-to-treatment significantly affects the extent of ST-segment resolution and myocardial blush in patients with acute myocardial infarction treated by primary angioplasty

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KEYWORDS
Primary angioplasty;
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Aims The prognostic role of time-to-treatment in primary angioplasty is still a matter of debate. The aim of our study was to evaluate the relationship between time-to-treatment and myocardial perfusion in patients with ST-segment-elevation myocardial infarction (STEMI) treated by primary angioplasty.

Methods and results Our study population consisted of 1072 patients with STEMI treated by primary angioplasty from 1997 to 2001. Myocardial perfusion was evaluated by using ST-segment resolution and myocardial blush grade. Time-to-treatment was defined as the time from symptom-onset to the first balloon inflation. Time-to-treatment was significantly associated with the extent of ST-segment resolution, myocardial blush grade, enzymatic infarct size, and 1-year mortality. After adjustment for baseline confounding factors, time-to-treatment was still associated with impaired ST-segment resolution (adjusted OR [95% CI] = 1.01 [1.01–1.02], $p < 0.001$) and myocardial blush (adjusted OR [95% CI] = 1.01 [1.01–1.02], $p < 0.0001$).

Conclusions This study shows that in patients with STEMI treated by primary angioplasty prolonged ischaemic time is associated with impaired myocardial perfusion, larger infarct size, and higher 1-year mortality. Therefore, all efforts should be made to shorten ischaemic time as much as possible to achieve better myocardial perfusion and myocardial salvage in primary angioplasty for STEMI.

Introduction

Although a clear relationship between mortality and the delay from symptom onset to treatment has been demonstrated in patients with ST-segment-elevation myocardial infarction (STEMI) treated by thrombolysis,[1–3] the impact of the time delay on prognosis in patients

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undergoing primary angioplasty has yet to be clarified.[3–8] In the current study, we investigated the impact of time-to-treatment on myocardial perfusion after primary angioplasty for STEMI.

Methods

From April 1997 to October 2001, a total of 1548 patients with STEMI were treated with primary angioplasty. All patients admitted within the first 6 h, or from 6 to 24 h if they had persistent symptoms with evidence of ongoing ischaemia, were included in the current study. Our study was approved by the Institutional Review Board. Analyses were performed by an independent core laboratory (Diagram, Zwolle, the Netherlands) in which the technicians were unaware of all clinical data and outcome. Time-to-treatment was defined as the time from symptom onset to the first balloon inflation.

Myocardial blush grade (MBG) was assessed after primary angioplasty, as previously described:[9] Grade 0, no myocardial blush; Grade 1, minimal myocardial blush or contrast density; Grade 2, moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral noninfarct-related coronary artery; Grade 3, normal myocardial blush or contrast density, comparable to that obtained during angiography of a contralateral or ipsilateral noninfarct-related coronary artery. When myocardial blush persisted (staining), this phenomenon suggested leakage of contrast medium into the extravascular space and was graded 0.

ST-segment resolution was analysed by comparison of 12-lead electrocardiograms (ECGs) made at baseline and 3 h, as previously described.[10] ST-segment resolution was defined according to a threshold of 50%.

Enzymatic infarct size and predischarge ejection fraction were measured as previously described[9] and categorised according to the 50th percentile.

All patients were reviewed in the outpatient clinic. For patients who died during follow-up, hospital records and postmortem data were reviewed. No patient was lost to follow-up.

Statistical analysis

Statistical analysis was performed with the SPSS 10.0 statistical package. Continuous data were expressed as means and standard deviation and categorical data as percentages. The one-way analysis of variance and chi-square test were used for continuous and categorical variables, respectively (two-sided tests). A trend analysis was done as described by Schlesselman.[11] A p-value <0.05 was considered statistically significant.

Logistic regression analysis was performed to calculate the risk of impaired myocardial perfusion related to time-to-treatment adjusted for baseline confounding characteristics, which were identified on the basis of the results of univariate analysis. All variables were entered in block. The significance, odds ratios, and confidence intervals were calculated using Wald statistics. We assessed the linearity assumption by including new variables (the upper three quartiles vs. the lowest quartile of time-to-treatment) in the regression model and plotting the estimated logistic regression coefficients versus the quartile midpoints of time-to-treatment.

Results

ST-segment resolution analysis was available for 1072 patients, who represent our study population. Part of this population (73%) has been described previously.[8] The reasons for missing ST-segment resolution analysis were poor ECG quality (2.7%), intraventricular conduction delay (16.4%), and missing paired ECGs (80.8%).

Patient characteristics according to time-to-treatment are reported in Table 1. Patients with a longer ischaemic time were older, more often women or diabetics, had less often preprocedural recanalisation and procedural success.

As shown in Fig. 1, time-to-treatment was associated significantly with the extent of ST-segment resolution, myocardial blush grade, and enzymatic infarct size. The impact of time-to-treatment of myocardial perfusion was also confirmed in the analysis restricted to patients with

Table 1 Demographic, clinical and angiographic characteristics according to symptom-onset-to-balloon time

Ischaemic time (h)	<2	2–4	4–6	>6	p-value (trend)
Number of patients	114	555	227	176	
Age (>70 years)	15.7	22.0	25.1	28.0	0.011
Male gender (%)	80.4	80.1	77.3	65.5	<0.001
Diabetes (%)	8.9	8.0	10.7	19.0	<0.001
Previous MI (%)	12.5	9.9	11.6	6.3	0.18
Anterior MI or LBBB (%)	45.5	47.2	42.7	50.6	0.75
Killip class >1 (%)	10.7	6.1	4.9	8.0	0.58
Multivessel disease (%)	45.5	53.0	56.9	51.7	0.33
Pre TIMI 0-1 flow (%)	68.2	67.8	75.2	77.9	0.046
Post TIMI 3 flow (%)	94.6	92.4	87.6	84.5	<0.001
Angiographic success (%)	94.6	91.5	86.2	83.3	<0.001
Collaterals (%)	7.1	9.0	13.8	10.9	0.087
Stent (%)	56.3	58.4	60.0	55.2	0.69
Medical therapy at discharge					
Statins (%)	59.8	62.4	64.9	58.6	0.82
β-Blockers (%)	86.6	88.1	88.4	86.2	0.87
ACE inhibitors (%)	51.8	51.2	47.1	56.3	0.47

LBBB, left anterior bundle-branch block; MI, myocardial infarction and TIMI, thrombolysis in myocardial infarction.

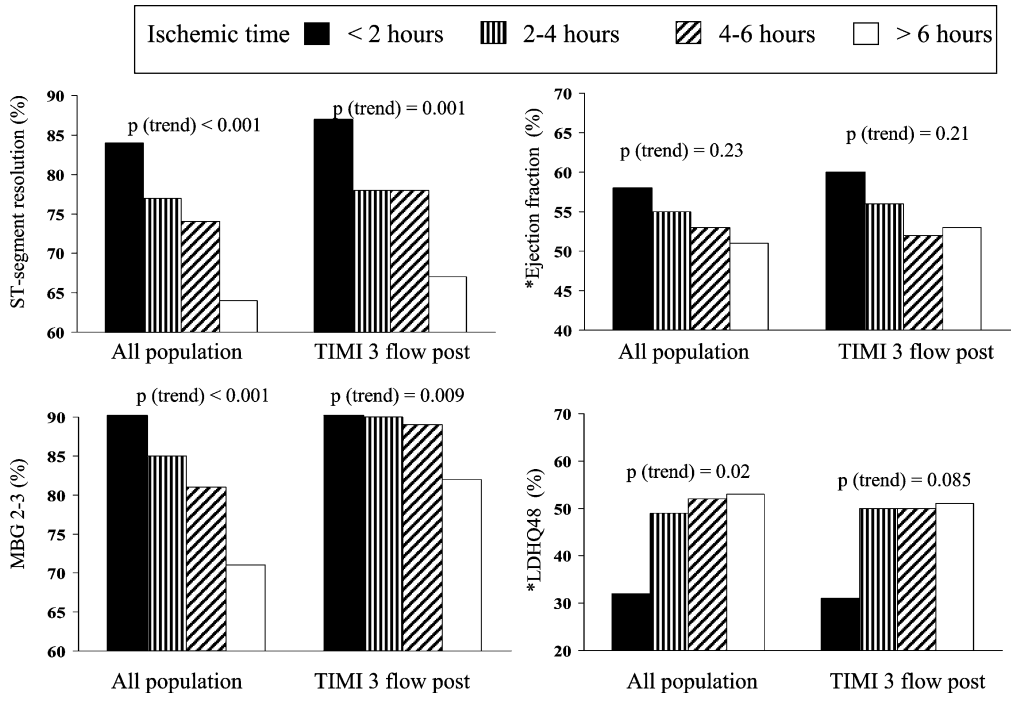

Fig. 1 Bar graphs show the relationship between time-to-treatment, ST-segment resolution, myocardial blush grade, predischarge ejection fraction, and enzymatic infarct size in the entire population and in patients with postprocedural TIMI 3 flow. *According to the 50th percentile.

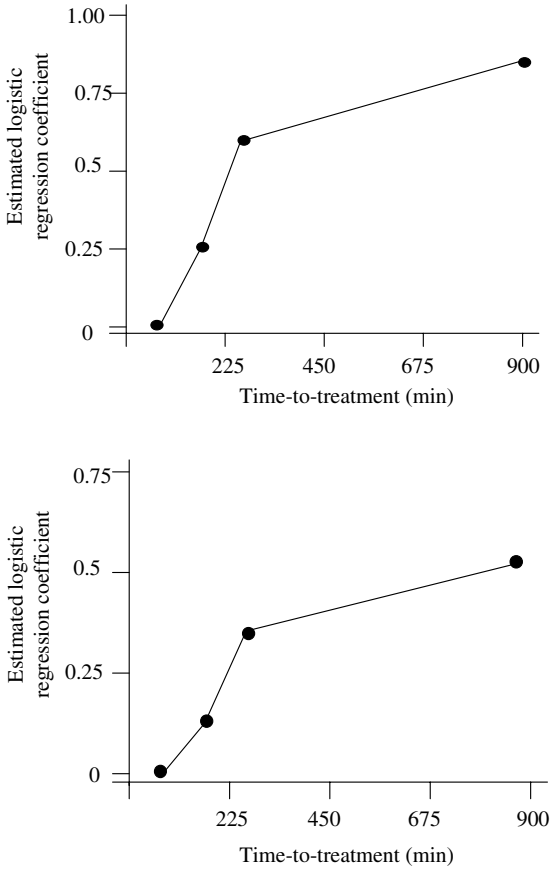

Fig. 2 The linearity assumption was visually analysed by plotting the estimated logistic regression coefficients of the highest three quartiles and the midpoint quartiles of time-to-treatment for both poor myocardial perfusion (upper graph) and ST-segment resolution (lower graph).

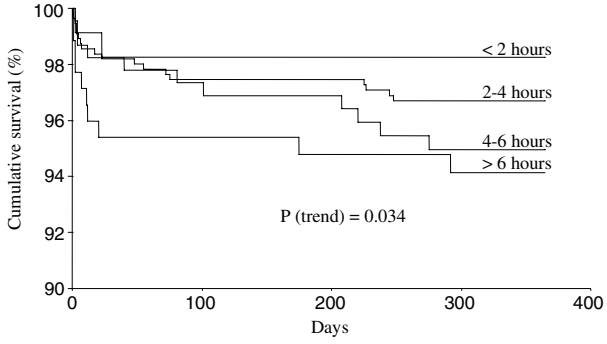

Fig. 3 Kaplan–Meier survival curves according to time-to-treatment.

postprocedural TIMI (Thrombolysis in Myocardial Infarction) grade 3 flow.

After adjustment for baseline confounding factors (age, diabetes, gender, and preprocedural TIMI flow), time-to-treatment (as a continuous variable) was still associated with impaired ST-segment resolution (adjusted OR [95% CI] = 1.001 [1.001–1.002], $p < 0.001$) and myocardial blush (adjusted OR [95% CI] = 1.001 [1.001–1.002], $p < 0.001$). The linearity assumption was confirmed by plotting the estimated logistic regression coefficients versus quartile midpoints of time-to-treatment (Fig. 2).

These data explained the significant impact of time-to-treatment on 1-year mortality (Fig. 3).

Discussion

The main finding of the present study is that among patients with STEMI undergoing mechanical reperfusion,

impaired myocardial perfusion and larger infarct size explain the higher mortality rate observed in patients with a more prolonged delay until treatment.

Time-to-treatment, myocardial perfusion, and mortality after primary angioplasty for STEMI

Although several studies have shown the relevant impact of time-to-treatment on myocardial perfusion,[12] myocardial salvage,[13] and mortality[1–3] in patients with STEMI treated by thrombolysis, the prognostic value of ischaemic time in patients with STEMI treated by primary angioplasty is still a matter of debate.[3–7] Brodie et al.[4] observed a better outcome among patients undergoing primary angioplasty within 2 h of symptom onset, whereas a relatively stable mortality rate was observed in those intervened from 2 to 12 h. These findings were confirmed by Cannon et al.[6] who, in a cohort of 27,080 patients undergoing primary angioplasty, found that only door-to-balloon time, but not time-to-treatment, was associated with mortality. Similar findings were reported by Zijlstra et al.[3] in a pooled analysis of several randomised trials comparing primary angioplasty and thrombolysis. They found a direct relationship between time-to-treatment and mortality only in patients treated by thrombolysis, but not by primary angioplasty. Confirming these observations, Schomig et al.[13] found a significant relationship between time-to-treatment and myocardial salvage only in patients treated by thrombolysis but not in those treated by primary angioplasty.

In our previous report,[8] we found time-to-treatment to be an independent predictor of mortality in patients with STEMI treated with angioplasty, particularly in those at high risk. These findings have been confirmed by Antoniucci et al.[7] in a population of 1332 patients undergoing primary angioplasty. Supporting the prognostic role of early restoration of antegrade flow in patients undergoing primary angioplasty, Stone and colleagues[14] found preprocedural TIMI 3 flow to be an independent predictor of mortality. In the current study, we found impaired myocardial perfusion and larger infarct size to be potential explanations for the higher mortality observed in patients with a prolonged delay before first balloon inflation. In fact, as demonstrated in animal models,[15–17] the duration of coronary occlusion is a main determinant of infarct size. Therefore, late reperfusion is expected to result in poor perfusion, less myocardial salvage and, thus, a higher mortality rate, in comparison with early reperfusion, even after optimal mechanical reperfusion. These results were also confirmed in the analysis restricted to patients with postprocedural TIMI 3 flow.

Several factors may explain the time-dependent mechanism of impaired myocardial perfusion despite optimal epicardial flow. Experimental studies have shown that long balloon inflations may induce morphological alterations (swelling of endothelial and cardiac cells with occlusion or compression of microcirculation) in the cardiac capillaries and arterioles.[12] Furthermore, recent studies have focused on the role of microembolisation of atherosclerotic debris, blood clots, and platelet plugs in the microcirculation.[15,16] A delay in reperfusion may be associated with an older, organised intracoronary thrombus in comparison with early reperfusion. This may result in a higher incidence of distal microembolisation and poor myocardial perfusion[10,18] despite optimal epicardial flow.

Further studies should investigate the additional role of pharmacological therapy[19–22] and mechanical devices[23] in patients with longer time delay to treatment in order to improve myocardial perfusion and reduce ischaemic reperfusion damage and infarct size, beyond epicardial reperfusion.

Limitations

A major limitation of the current study is that up to 30% of the total population was excluded due to missing or inadequate baseline and/or 3-h ECGs. Myocardial perfusion was evaluated using myocardial blush and ST-segment resolution. Despite the absence of uniformity between trials of the methods used,[11,22,24–26] they are still cheap, simple, and validated methods for evaluating myocardial reperfusion. In contrast to our previous report,[11] ST-segment resolution was analysed at 3 h, as has been our policy since 1997. In fact, analysis at 3 h would improve the sensitivity of identification of patients with complete resolution. Because the aim of the study was not prognostic risk stratification using different degrees of ST-segment resolution, we used an ST-segment resolution cutoff of 50% as a surrogate for effective reperfusion.[22] However, myocardial reperfusion is a dynamic process during which alternating episodes of ST-segment resolution may occur.[27] Thus, continuous ST-segment monitoring would have improved the evaluation of myocardial reperfusion.[27,28] Consistent with our first report on myocardial blush grade,[9] we defined optimal myocardial perfusion as myocardial blush grade 2 to 3.

Enzymatic infarct size and ejection fraction were not available in all patients. Since their benefits have only been recently proven,[22] the administration of glycoprotein IIb/IIIa inhibitors was used in less than 5% of our population. Furthermore, no distal protection devices were used in this series of patients.

Clinical implications

Although primary angioplasty has been demonstrated to be superior to thrombolytic therapy, several areas for improvement remain. The results of our study suggest that all efforts should be aimed at shortening total ischaemic time. This can be achieved by prehospital triage at home or in the ambulance for early identification of STEMI, direct transportation, and early pretreatment with pharmacological agents to obtain optimal reperfusion before primary angioplasty, particularly in high-risk

patients and when long-distance transportation to a tertiary centre with angioplasty facilities is required.

Conclusions

This study shows that in patients with STEMI treated by primary angioplasty, prolonged ischaemic time is associated with higher mortality, mainly due to impaired myocardial perfusion and larger infarct size. Therefore, all efforts should be made to shorten the delay to reperfusion in order to achieve better myocardial perfusion.

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