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ORIGINAL PAPER

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Relationship between therapeutic time intervals and intermediate term left ventricular systolic function in patients treated with facilitated percutaneous coronary intervention for acute myocardial infarction

Summary *Background* The concept of initiating fibrinolytic therapy in patients who cannot undergo immediate percutaneous coronary intervention (PCI) in the setting of acute ST-segment-elevation myocardial infarction (STEMI) has been proposed as a strategy to improve outcomes. However, evidence supporting the use of this strategy is not conclusive, and the results of recent randomized controlled trials are apparently contradictory. Probably, the time points of administration of the adjunctive thrombolytics and antiplatelet agents and the time loss until coronary intervention have a major influence on the discrepancy of outcomes in different trials. Therefore, the relationship between therapeutic time intervals and outcome in patients treated with facilitated PCI has been analyzed. *Methods* In this single center retrospective study, 131 patients with STEMI were treated with a combined pharmaco-mechanical reperfusion strategy using half-dose r-tPA combined with a glycoprotein (GP) IIb/IIIa antagonist prior to PCI. Specific time points were recorded for each patient, including the time of symptom onset, the time of first medical contact, the start of intravenous thrombolysis, the time of administration of the GP IIb/IIIa antagonist and the start of coronary intervention. We then examined the relationship between the time delay from symptom onset to the initiation of various steps of treatment and the residual myocardial damage as expressed by the severity of both global and regional myocardial dysfunction calculated from a left ventriculography study performed 3 months later. *Results* The median time from symptom onset to the first medical contact, with 25th and 75th percentiles in parentheses, was 1.25 h (0.75, 3), from symptom onset to initiation of thrombolytic therapy 2.25 h (1.25, 3), to initiation of GP IIb/IIIa inhibitor therapy 3.5 h (2, 5.69), and to the start of coronary intervention 4.81 h (2.85, 7.91). The time between symptom onset and initiation of both thrombolytic therapy and coronary intervention was significantly related to the global ejection fraction and to the extent of regional hypokinesia at the 3-month follow-up ($p < 0.05$). The time to the initiation of GP IIb/IIIa inhibitors was only significantly related to the global ejection fraction ($p < 0.05$), while the time to the first medical contact did not show a similar relationship ($p > 0.05$). Furthermore, we observed a significant relationship between the infarct-related artery (IRA) patency at the initial angiogram and the residual regional myocardial damage at follow-up; normokinesia at follow-up was found in 61.3% of patients with an initially patent IRA and in 41.2% of patients with an initially occluded IRA, whereas severe hypokinesia was found in 13.8% and 37.3%, respectively ($p < 0.05$). *Conclusion* In patients with STEMI treated with a facili-

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tated PCI strategy using half dose r-tPA in combination with a glycoprotein IIb/IIIa receptor blocker, the 3-month global and regional residual myocardial dysfunction is significantly related to the time elapsed between the onset of symptoms and the start of both fibrinolytic therapy and coronary intervention.

Key words Facilitated PCI – acute myocardial infarction – thrombolysis

Introduction

Reperfusion of the infarct-related artery (IRA) needs to be early, complete, and sustained, to improve survival of patients presenting with ST-elevation myocardial infarction (STEMI). While both percutaneous coronary intervention (PCI) and thrombolytic therapy are used for reperfusion, the former is generally considered superior in terms of more complete revascularization and greater reductions in morbidity and mortality. In a quantitative review of 23 randomized trials in which primary PCI was compared with fibrinolytic therapy, primary PCI was superior in reducing the short-term rates of death, nonfatal reinfarction and stroke [4].

This is especially true when primary PCI is performed in a timely fashion in high-volume PCI facilities. The current ACC/AHA guidelines recommend a door-to-balloon time of <90 min for primary PCI [1]. This goal may be difficult to achieve, especially when patients initially present at a community hospital without a catheterization facility. The logistics of arranging transfer and assembling the catheterization team may be accompanied by long delays to reperfusion as reported in the National Registry of Myocardial Infarction NRMI-3/4 analysis [7].

So driven by the fact that time is a critical determinant of outcome in acute STEMI [9], the concept of facilitation with a thrombolytic agent has been proposed as a strategy to improve outcomes: i.e., thrombolysis to establish early patency followed by PCI to achieve complete and sustained reperfusion. The ASSENT-4 and CAPITAL AMI trials have recently addressed the outcome of such a strategy using full-dose thrombolytic therapy and came out with very different conclusions [2, 5]. The ongoing FINESSE trial assesses the value of combined thrombolysis and platelet inhibition with a GPIIb/IIIa inhibitor prior to PCI. Probably, the dose, regimen and time point of administration of the adjunctive thrombolytics and antiplatelet agents have a major influence on the discrepancy of outcomes in different trials.

In the present study, we attempted to analyze the impact of different time intervals on the outcome of patients presenting with acute STEMI and treated with facilitated percutaneous coronary intervention using half dose r-tPA in combination with a glycoprotein (GP) IIb/IIIa receptor blocker, bearing in mind that facilitating PCI by the use of thrombolytic agents expands the time interval to perform PCI only within limits.

Methods

Study population and design

In the period between April 2000 and October 2002, and within an established treatment regimen for patients with acute ST elevation myocardial infarction at the Cardiology Department of the Schleswig Holstein University Clinic, Campus Kiel, patients presenting at the city outskirts with a significant time delay until mechanical reperfusion were routinely treated with half-dose r-tPA during hospital transfer (pre-hospital fibrinolysis), followed by an upstream GP IIb/IIIa inhibitor therapy given upon hospital admission, and were then subjected to immediate cardiac catheterization. A follow-up angiography 3 months after presentation was part of this treatment regimen. During this time period, 227 patients with acute STEMI were treated within this program. Of these, 79 patients had no follow-up angiography, 10 patients died within the first 3 months after myocardial infarction, 3 patients received neither thrombolysis nor a GP antagonist, and in 4 patients the available data were incomplete. The remaining 131 patients formed the population of this retrospective analysis.

Procedures

Pharmaco-mechanical reperfusion

Patients diagnosed as having an acute ST-segment elevation myocardial infarction and considered eligible for reperfusion therapy were treated in a combined pharmaco-mechanical strategy in the absence of contraindications for thrombolysis. Initially, patients received 50 mg r-tPA given as a 15 mg intravenous bolus followed by a 35 mg intravenous infusion over 30 min. This was either combined with abciximab 0.25 mg/kg as a bolus injection followed by the infusion of 0.125 μg/kg/min over 12 h, or with tirofiban 0.4 μg/kg/min over 30 min followed by 0.1 μg/

kg/min as an intravenous infusion for 48 h. In addition, patients received 5000 IU unfractionated heparin and 500 mg acetylsalicylic acid as an intravenous bolus, and a 300 mg loading dose of clopidogrel directly before PCI (then 75 mg/day for 6 weeks). Following an informed consent, patients were then subjected to a diagnostic coronary angiogram through the femoral approach. PTCA and stenting were performed using standard techniques for the culprit lesion only, using bare metal stents in all included patients.

Calculation of therapeutic time intervals

Based on our local data archive, including ambulance, intensive care and cardiac catheterization laboratory files, specific time points were recorded for each patient. These included the time of symptom onset, the time of first medical contact, the start of intravenous thrombolysis, the time of administration of the GP IIb/IIIa antagonist and the start of coronary intervention. And based upon the time between symptom onset and the initiation of the different steps of therapy, four categories of time delay were defined (<2 h, 2–4 h, 4–6 h and >6 h).

Follow-up angiography and analysis of left ventricular function

At 3 months, a follow-up coronary angiography including a left ventriculography in RAO 30° and LAO 60° was performed in all included patients. Global left ventricular function was quantitatively calculated in RAO 30° projection, and patients were divided according to the left ventricular ejection fraction (EF) into three groups; patients with severe LV dysfunction were defined as having an EF of less than 40%, those with moderate dysfunction had an EF between 40 and 55%, and those with normal global LV function were defined as having an EF of more than 55%.

Regional wall motion was evaluated through manual tracing of the left ventricular endocardial borders in the RAO 30° projection using the centerline method [10, 13]. In brief, a normal, non-post-premature sinus beat was selected, and the endocardial contours at end-diastole and end-systole were traced. Motion was then measured along 100 cords drawn perpendicularly to a centerline constructed midway between the end-diastolic and end-systolic contours. The measured motion of the 100 cords was normalized for heart size by dividing by the length of end-diastolic perimeter. This resulted in a dimensionless shortening fraction. The wall motion was then plotted in units of standard deviations from the normal mean. A segment was considered hypokinetic when its shortening fraction was more than one standard deviation from the normal mean. The severity of hypokinesia of a given territory was estimated according to the sum of hypokinetic segments in this territory. The presence of more than 20 hypokinetic segments was defined as severe hypokinesia, between 1 and 20 as moderate hypokinesia, and the absence of hypokinetic segments naturally defined normokinesia.

Statistical analysis

All data analyses were performed with the Statistical Package for Social Sciences (SPSS for Windows 8.0, SPSS Inc.) software. As the obtained data were not normally distributed, medians and percentiles were computed as appropriate. Both the chi square test and the Fischer's exact test were used for the analysis of categorical variables. The relationship between therapeutic time intervals and regional left ventricular dysfunction is presented in mosaic plots. These are a special form of graphic presentation, in which columns are transversely divided to reflect the percentage of a specific variable, and column width is adjusted to reflect group size. The correlation between the number of hypokinetic cords and the global EF was calculated using Pearson's correlation coefficient. A p value <0.05 was considered significant.

Results

Baseline characteristics

The mean age of the study population was 57.2 ± 10.2 years, with the youngest patient being 33 years old and the oldest patient being 80 years old. Of the 131 analyzed patients 110 (84%) were males and 21 (16%) were females. The baseline demographic, clinical and angiographic characteristics are shown in Table 1.

Table 1 Baseline demographic, clinical and angiographic characteristics of the study population (n = 131)

Variable	Number (%)
Age in years (mean)	57.2 ± 10.2
Males	110 (84)
Diabetes mellitus	28 (21)
Hypertension	71 (54)
Hypercholesterolemia	85 (65)
Current smoking	75 (57)
Single vessel disease	65 (50)
Two vessel disease	46 (35)
Three vessel disease	20 (15)

Therapeutic time intervals

The median time from symptom onset to the first medical contact, with 25th and 75th percentiles in parentheses, was 1.25 h (0.75, 3). Of the 131 patients analyzed 97 patients (74%) received both thrombolytic therapy and a GP IIb/IIIa inhibitor. Because of existing contraindications to either medication, 19 patients (15%) were not given lytic therapy and 15 patients (11%) were not given a GP antagonist. Of the 116 patients given a GP antagonist, 90 (76%) were treated with abciximab and 26 (24%) were treated with tirofiban.

Prehospital thrombolysis was performed in a total of 90 patients, whereas in 22 patients thrombolysis was initiated immediately upon hospital admission. The median time from symptom onset to initiation of thrombolytic therapy was 2.25 h (1.25, 3). Between ambulance arrival and initiation of thrombolysis, a median time of 30 min has been estimated. The median time from symptom onset to initiation of GP IIb/IIIa inhibitor therapy was 3.5 h (2, 5.69).

The median time from symptom onset to the start of coronary intervention was 4.81 h (2.85, 7.91), while the median time from hospital arrival to the start of coronary intervention was 59 min (35, 88).

Angiographic outcome

Analysis of the follow-up ventriculograms revealed that 92 patients (70%) had a global EF > 55%, 31 patients (24%) had an EF between 40 and 55%, and only 8 patients (6%) had an EF of less than 40% at the 3-month follow-up. On the other hand, a highly variable residual regional myocardial dysfunction was estimated, with the number of calculated segments of hypokinesia ranging between 0 and 79 segments. At the time of follow-up ventriculography, 70 patients (53.4%) had no evidence of segmental hypokinesia, 31 patients (23.7%) had mild to moderate hypokinesia (1–20 hypokinetic segments), and 30 patients (22.9%) had severe hypokinesia (> 20 hypokinetic segments). Only one patient with moderate and four patients with severe hypokinesia had a past history of an old myocardial infarction. The remaining 56 patients with regional wall motion abnormalities had no history of infarction preceding the index event.

During follow-up angiography, 32 patients (24.4%) had evidence of angiographic binary restenosis in the treated vessel (> 50% diameter stenosis). A repeated percutaneous intervention was performed only in 18 patients.

Relationship between time delay and global left ventricular function

We analyzed the relationship between time delay and global ejection fraction at the 3-month angiographic follow-up (Table 2). Based upon the time between symptom onset and the initiation of the different steps of therapy, four categories of time delay were defined, and patients were classified according to the global EF into three groups as previously described. A significant relationship was observed between the EF at 3 months and the time from symptom onset and the initiation of both thrombolytic therapy and coronary intervention ($p = 0.003$ and 0.03, respectively). A significant relationship was also observed for the EF and the time to initiation of GP antagonists ($p = 0.034$). The time from symptom onset to first medical contact was not related to the global LV function ($p = 0.29$).

Relationship between time delay and residual myocardial damage

We further examined the relationship between time delay and residual myocardial damage as expressed by the severity of regional myocardial dysfunction at the 3-month angiographic follow-up study. Once

Table 2 Relationship between therapeutic time intervals and ejection fraction at 3 months

Time interval	EF > 55%	EF 40–55%	EF < 40%
Time to medical contact			
< 2 hours	62	20	3
2–4 hours	17	3	2
4–6 hours	6	3	2
> 6 hours	7	5	1
P value		0.29	
Time to thrombolysis			
< 2 hours	43	11	1
2–4 hours	23	5	3
4–6 hours	7	2	1
> 6 hours	8	7	1
P value		0.003	
Time to GP antagonist			
< 2 hours	30	4	0
2–4 hours	21	11	2
4–6 hours	12	9	4
> 6 hours	16	5	2
P value		0.034	
Time to intervention			
< 2 hours	14	0	0
2–4 hours	31	10	1
4–6 hours	21	11	1
> 6 hours	26	10	6
P value		0.03	

again, time intervals were grouped as previously mentioned, whereas regional myocardial dysfunction was evaluated according to the number of hypokinetic segments in the follow-up ventriculography as previously described.

Differences in the relationship between various time intervals and residual myocardial damage were clearly identified. While the time between symptom onset and the initiation of both thrombolytic therapy and coronary intervention was significantly related to the extent of residual myocardial damage ($p < 0.05$), the time to the first medical contact and to the initiation of GP IIb/IIIa inhibitors did not show a similar relationship ($p = 0.75$ and 0.52, respectively).

As the time delay between symptom onset and initiation of thrombolysis increased, the number of patients with severe hypokinesia at follow-up significantly increased, whereas the number of patients with no residual wall motion abnormality significantly decreased (Fig. 1). We also noticed that the percent of patients with no residual wall motion abnormality markedly fell in both groups treated >4 h after symptom onset (20% in the group treated after 4–6 h and 37.5% in those treated >6 h) when compared to those treated in the first 4 h (63.6% in the group treated <2 h and 58.1% in those treated after 2–4 h).

Similarly, in the group of patients where coronary intervention was performed in the first 2 h, 71.4% had no wall motion abnormalities at follow-up, 28.6% had modertae hypokinesia and none of them had severe hypokinesia at follow-up (Fig. 2). In contrast, patients for whom the coronary intervention started >6 h after symptom onset, 38.1% had no resting wall motion abnormalities, 26.2% had moderate and 35.7% had severe hypokinesia at follow-up (Fig. 2).

Correlation between regional and global left ventricular dysfunction

We further compared the regional LV function at follow-up as expressed by the absolute number of hypokinetic cords with global LV function expressed as the EF. A significant correlation between both parameters was evident, with a linear decline in the global EF with increasing nimber of hypokinetic cords (Fig. 3).

Relationship between IRA patency at angiography and residual myocardial damage

A significant relationship was also noticed between IRA patency at the initial angiogram and the residual myocardial damage at follow-up. In 80 patients (61.1%) the IRA was found to be patent at initial angiography, while in the remaining 51 patients

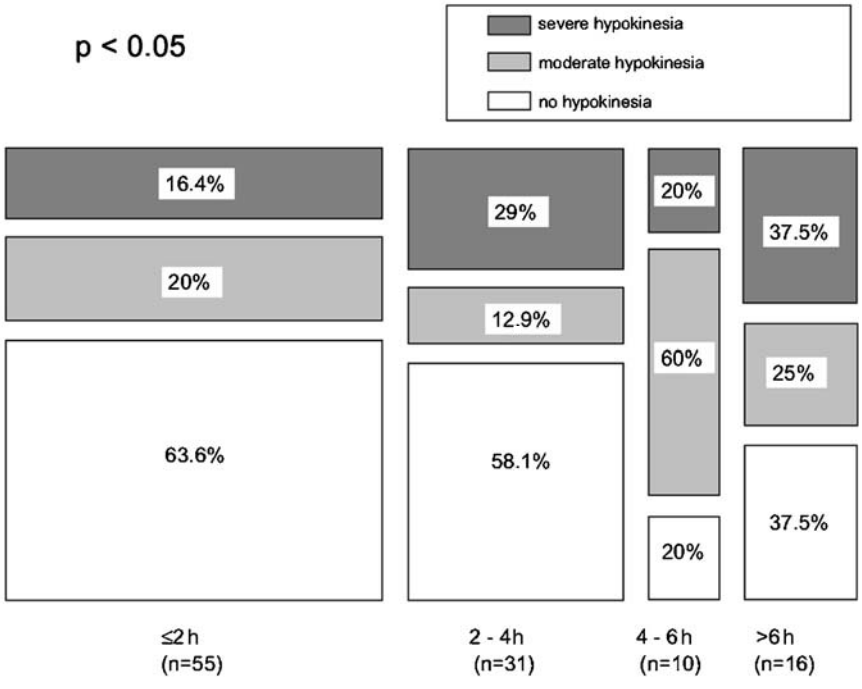

Fig. 1 Relationship between time from symptom onset to thrombolysis and 3-month regional left ventricular dysfunction

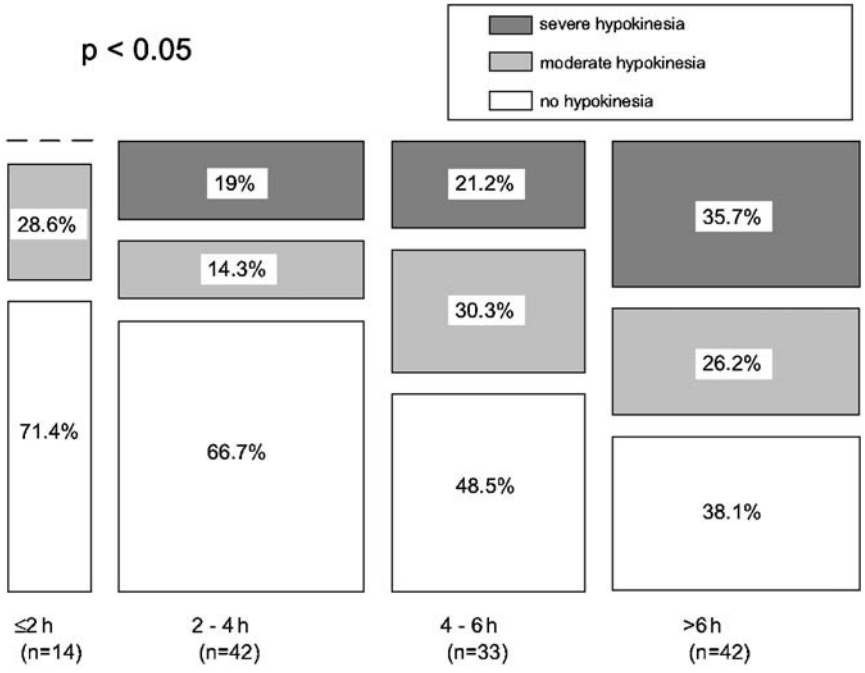

Fig. 2 Relationship between time from symptom onset to coronary intervention and 3-month regional left ventricular dysfunction

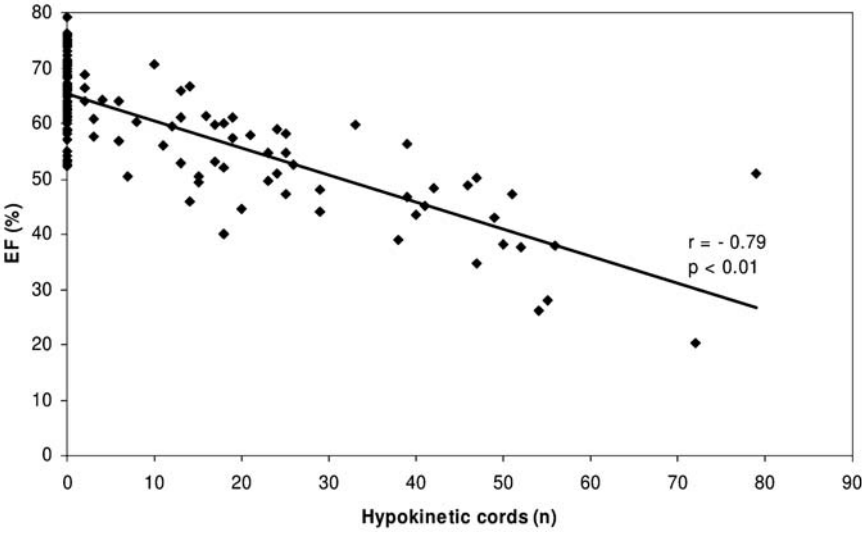

Fig. 3 Correlation between left ventricular ejection fraction (EF) and total number of hypokinetic cords at the 3-month follow-up angiography

(38.9%) the IRA was still occluded. Normokinesia at follow-up was found in 61.3% of patients with an initially patent IRA and in 41.2% of patients with an initially occluded IRA, moderate hypokinesia in 25% and 21.6% and severe hypokinesia in 13.8% and 37.3%, respectively ($p < 0.05$) (Fig. 4).

Discussion

The concept of initiating fibrinolytic therapy in patients who cannot undergo immediate PCI for a variety of reasons (lack of facility, lack of personnel, busy cath. lab, etc.) while waiting for intervention is appealing and seems to make sense. Previous studies, however, have failed to show a benefit when PCI is performed immediately after initiating thromboly-

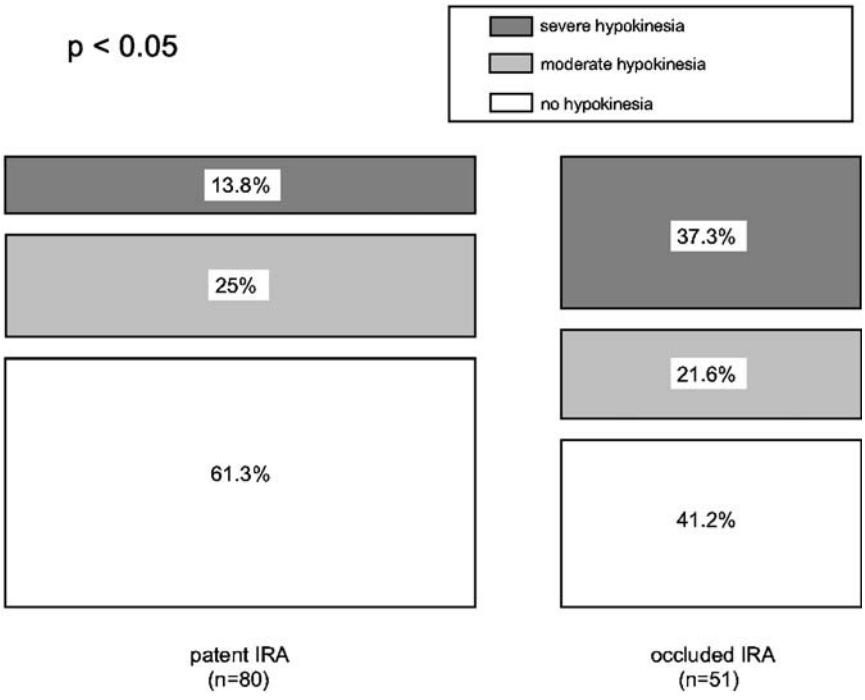

Fig. 4 Relationship between IRA patency at initial angiography and the 3-month regional left ventricular dysfunction (*IRA* infarct related artery)

sis [8, 12], but these studies may be outdated because they preceded significant advances in technology and technique of PCI. The concept of facilitating PCI with initial thrombolysis has therefore regained interest in the past few years and has been re-evaluated in a number of randomized controlled trials. While the ASSENT-4 trial, randomizing patients to either full-dose tenecteplase (TNK) plus PCI or to primary PCI, was prematurely terminated because of excessive ischemic events in the TNK-facilitated PCI group [2], the CAPITAL-AMI study showed that TNK-facilitated PCI significantly reduced ischemic events at both 30 days and 6 months compared to TNK alone [5]. In view of the apparently contradicting results of these two trials, the ongoing FINESSE trial, considering the use of half-dose lytic therapy in combination with GP IIb/IIIa antagonists as a preinterventional pharmacological combination, is expected to help define the optimal pharmacological regimen when facilitation is being considered.

In studies analyzing facilitated PCI, however, the time points of administration of the adjunctive thrombolytics and antiplatelet agents and the optimal time interval between initiating lytic therapy and starting PCI have never been adequately analyzed, although different timing intervals may have influenced the outcome of different studies. In the Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-term Follow-up (ADMIRAL) trial, patients pretreated with abciximab in the ambulance actually derived the most benefit, whereas patients treated upon hospital admission did not [6]. Similarly, in the ASSENT-4 trial, patients randomized after hospital admission and treated with facilitated PCI had the highest mortality, whereas the mortality rate was lowest in patients randomized before hospital admission where thrombolysis was initiated in the ambulance [2]. Furthermore, while minimizing the time interval from thrombolysis to intervention may raise some concern about higher procedure-related bleeding complications, delaying intervention may theoretically predispose patients to reocclusion of the IRA. Therefore, we thought that analyzing the time loss from symptom onset to the various steps of treatment may help in interpreting both safety and efficacy of facilitated PCI in previous and upcoming studies.

In our study population, consisting mainly of patients referred from rural areas without on-site PCI facilities, time from symptom onset to initiation of thrombolysis was significantly related to the extent of regional myocardial damage and global ejection fraction 3 months after myocardial infarction. Increasing the time delay between symptom onset and initiation of thrombolysis was associated with an increase in residual regional myocardial damage and a reduced EF, which has been previously shown to affect intermediate and long-term prognosis [3]. This was also true for increasing the time period between

symptom onset and coronary intervention, where patients with minimal time delay derived the most benefit. A possible explanation is that widening the time gap between thrombolysis and PCI may expose patients to reocclusion, especially when only half the usual dose of the thrombolytic drug has been given. In patients with STEMI, thrombolysis may dissolve much of the thrombus overlying the ulcerated plaque, but the disrupted endothelium and residual thrombus may reactivate the coagulation cascade leading to reocclusion. The use of potent antiplatelet inhibitors during the first few hours of STEMI has been previously shown to prevent this complication [11]; in our study the time from symptom onset until initiating the GP antagonists was significantly related to the global EF at 3 months, but not to the regional myocardial function, despite the positive correlation found between both parameters. An earlier intervention with the IRA still open seems to be more favorably linked with the patient's outcome. The timing of initiating thrombolytic therapy and starting coronary intervention following thrombolysis should therefore be carefully analyzed when facilitated PCI is being considered.

Study limitations

This retrospective study does not provide data about the relationship between therapeutic time intervals and procedure-related complications in patients treated with facilitated PCI. Performing PCI shortly after lytic therapy may increase the risk of bleeding, but this needs to be compared to the benefits obtained from such a hybrid procedure. In addition, the use of two different GP antagonists known to have different pharmacological behavior makes it difficult to draw firm conclusions about the role of GP antagonists in this context. Furthermore, because the performed follow-up angiography was at 3 months, providing data about long-term clinical outcome was not possible.

Conclusion

In patients with STEMI treated with a facilitated PCI strategy using half dose r-tPA in combination with a glycoprotein IIb/IIIa receptor blocker, the three-month global and regional residual myocardial dysfunction is significantly related to the time elapsed between the onset of symptoms and the start of both lytic therapy and coronary intervention.

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