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Predictors of infarct-related artery patency following combined lytic therapy in patients with ST-segment elevation myocardial infarction treated with immediate percutaneous coronary intervention

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Abstract

Background and aim: Patency of infarct-related artery (IRA) before percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) is associated with better outcomes. Little is known of the clinical or angiographic predictors of IRA recanalisation after administration of combined fibrinolytic therapy before PCI.

Methods: A total of 225 STEMI patients, admitted to remote hospitals with anticipated transfer time to cathlab > 90 min were enrolled. All patients received a half dose of alteplase and a full dose of abciximab at the remote hospital and were immediately transferred for angiography. In angiographic analysis, the culprit lesion (CL) was defined as the minimal lumen diameter (MLD) point in IRA (CLMLD) (in group with occluded IRA, measurement was done after the first pass of the guidewire).

Results: Occluded IRA (TIMI 0+1) was found in 14.2% of patients (n = 32) and patent IRA (TIMI 2+3) in 85.8% (n = 193) at baseline angiography. Baseline and angiographic characteristics were similar in both groups, except for a higher rate of smoking in the TIMI 2+3 group (73.1% *vs* 50%; p = 0.009) and longer distance from CLMLD point to the nearest proximal side branch in the TIMI 0+1 group (21.2 ± 10.3 mm *vs* 13.8 ± 11.2 mm; p = 0.002). In multivariate analysis, smoking and distance from CLMLD to the nearest proximal side branch were independent predictors of IRA patency at baseline.

Conclusions: Angiographic (anatomical) IRA parameter as distance from CLMLD point to nearest proximal side branch may influence the efficacy of combined fibrinolytic therapy before PCI despite the similar clinical characteristics and time delay to angiography. Smoking has a paradoxical beneficial effect on combined thrombolytic therapy effectiveness.

Key words: ST-elevation myocardial infarction, thrombolysis, reperfusion, angiography, infarct-related artery

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INTRODUCTION

Flow restoration in the infarct-related artery (IRA) after reperfusion therapy is an important predictor of outcome in patients with ST-elevation myocardial infarction (STEMI). It has been shown that spontaneous or pharmacologically driven early recanalisation of IRA before primary percutaneous coronary intervention (PCI) allows a reduction in infarct size and is correlated with a better clinical outcome [1–3]. The clinical

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and angiographic parameters/factors influencing the success of lytic therapy, especially when administered with glycoprotein (GP) IIb/IIIa inhibitor, remain undefined.

The aim of our study was to assess clinical and angiographic parameters associated with early IRA recanalisation after therapy with half dose alteplase and full dose abciximab before PCI for STEMI.

METHODS

Study population

A total of 225 patients entered the study. Details concerning study design and clinical results have been published previously [3]. The study was approved by the Institutional Review Board. All patients provided informed consent and the study conformed to applicable institutional and national guidelines for research on human subjects, as well as to the Declaration of Helsinki. Briefly, patients presenting with STEMI to community hospitals without on-site catheterisation laboratories were enrolled if: (1) they presented with non-shock acute MI (onset of chest pain < 12 h earlier and ST elevation > 1 mm in two contiguous electrocardiographic leads); (2) they had no contraindications to thrombolytic therapy and were < 75 years of age; and (3) anticipated transfer time to the interventional centre was > 90 min. After phone contact with the primary PCI centre, consecutive patients were enrolled and started on a combination thrombolytic treatment in a community hospital prior to transfer to the primary PCI centre. They received heparin 40 U/kg (maximum 3000 U), alteplase 15 mg and abciximab 0.25 mg/kg (intravenous bolus), followed by intravenous infusion of alteplase (35 mg for 60 min) and abciximab (0.125 μg/kg/min over 12 h). Abciximab infusion was continued throughout transfer, intervention and recovery. All patients received aspirin (100–350 mg) upon first presentation. A loading dose of 300 mg of clopidogrel was administered in all patients in catheterisation laboratories before angiography.

Angiography analysis

Angiographic parameters were analysed in an independent Core Angiographic Laboratory (Krakow Cardiovascular Research Institute, Poland) using the NewQuant32 software (Sanders Data Systems, Palo Alto, CA, USA) by analysts blinded to clinical and treatment data. Patency of the IRA was determined by Thrombolysis in Myocardial Infarction (TIMI) classification [4]. Culprit lesion (CL) was defined as minimal lumen diameter (MLD) region in the target lesion of IRA (CLMLD). In patients with occluded IRA, measurements were done after artery opening (after guidewire crossing). In quantitative angiography, reference diameters, lesion length, distance from artery ostium to CLMLD and distance from CLMLD to first proximal side branch with diameter of ≥ 1.5 mm were analysed. Distance from CLMLD to first proximal side branch parameter was introduced based on the concept that a large side branch close to the occlusion site may limit thrombus formation by flow redistribution from occluded vessel lumen to side branch lumen. The longer the distance from occlusion site to the site branch, potentially the larger the thrombus that may by formed. Coronary artery segments were assessed in standardised projections to avoid foreshortening [5].

Statistical analysis

Results are expressed as means ± SD or percent of patients. Difference between continuous and dichotomous variables were assessed by the Mann-Whitney U-test, Fisher's exact test and χ^2 test as appropriate. Multivariable analysis was performed to identify predictors of early IRA patency. Receiver-operating characteristic (ROC) curve analysis was performed to calculate sensitivity and specificity of CLMLD to first proximal branch distance in predicting IRA TIMI grade 0+1 flow in baseline angiography. A p value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 225 consecutive patients were enrolled into the study. Two study groups were stratified based on flow in IRA at baseline angiography. This showed early recanalisation (combined preprocedural TIMI grade 2+3 flow) in 193 (85.8%) patients, and occluded IRA (TIMI grade 0+1 flow) in the other 32 patients. Baseline characteristics were similar in the two groups, except for smoking (Table 1).

In angiographic analysis, both groups were similar in terms of IRA localisation, reference diameter, lesion length and distance from artery ostium to CLMLD. The distance from CLMLD to first proximal branch was significantly longer in the TIMI 0+1 group (Table 2).

In multivariate analysis, smoking was an independent negative predictor, and distance from CLMLD to first proximal branch was an independent positive predictor of occluded IRA at baseline angiography (Table 3).

In ROC curve analysis, the optimal cut-off point for distance from CLMLD to first proximal branch was > 11.05 mm with a 92% sensitivity and a 50% specificity (AUC = 0.72) for predicting TIMI grade 0+1 flow at baseline angiography.

DISCUSSION

The main finding of our study is that some anatomical IRA parameters, such as distance from CLMLD point to nearest proximal side branch, may influence the efficacy of combined fibrinolytic therapy. We also observed a paradoxical beneficial effect of smoking on lytic therapy effectiveness.

Primary PCI is the preferred reperfusion therapy when it is performed promptly, and in well organised primary PCI-centres [6–8]. When time to primary PCI is longer than 90–120 min, initial lytic therapy is recommended, but not as the last step of treatment, rather as a bridge to invasive diagnostics and treatment if required [3, 9]. However, this initial

Table 1. Characteristics of study population

	TIMI 0+1 (n = 32)	TIMI 2+3 (n = 193)	P
Age [years]	59.6 ± 8.6	56.6 ± 9.5	0.10
Male [%]	78.1	76.2	0.80
History of angina [%]	50	44	0.43
Previous MI [%]	21.9	13	0.14
Diabetes mellitus [%]	9.4	10.9	0.81
Arterial hypertension [%]	53.1	51.8	0.80
Hypercholesterolaemia [%]	75	73.1	0.45
Smoking [%]	50	73.1	0.009
History of PCI [%]	0	0.5	0.68
History of CABG [%]	0	0.5	0.68
Killip class 3+4 on admission [%]	15.6	13	0.70
SBP on admission [mm Hg]	132 ± 20	130 ± 23	0.79
DBP on admission [mm Hg]	80 ± 11	80 ± 15	0.83
Heart rate on admission	83 ± 11	78 ± 15	0.13
IRA:			0.72
LAD [%]	28.1	43.5	
Cx [%]	18.8	11.4	
RCA [%]	53.1	45.1	
Stent implantation [%]	53.1	45.1	0.40
Multi-vessel disease [%]	46.9	50.3	0.72
Time from symptoms onset to lysis [min]	247 ± 145	212 ± 135	0.19
Time from lysis to angiography [min]	137 ± 39	132 ± 40	0.52

CABG — coronary artery bypass graft; Cx — circumflex artery; DBP — diastolic blood pressure; MI — myocardial infarction; IRA — infarct-related artery; LAD — left anterior descending artery; PCI — percutaneous coronary intervention; RCA — right coronary artery; SBP — systolic blood pressure

Table 2. Angiographic analysis

	TIMI 0+1 (n = 32)	TIMI 2+3 (n = 193)	P
Proximal reference diameter [mm]	3.2 ± 0.7	3.27 ± 0.6	0.59
Distal reference diameter [mm]	2.8 ± 0.6	2.7 ± 0.5	0.51
Mean reference diameter [mm]	3.0 ± 0.6	3.0 ± 0.5	0.93
Lesion length [mm]	18.3 ± 6.8	16.1 ± 4.4	0.099
Ostium to CLMLD distance [mm]	41.4 ± 28	32.8 ± 20	0.18
CLMLD to first proximal branch distance [mm]	21.2 ± 10.3	13.8 ± 11.2	< 0.001

CLMLD — minimal lumen diameter point in culprit lesion

Table 3. Multivariate predictors of TIMI grade 0+1 flow in baseline angiography after combined lytic therapy

Variable	OR	P	95% CI
Age	0.46	0.20	0.14–1.51
Sex	1.03	0.25	0.98–1.09
Smoking	0.30	0.022	0.11–0.84
CLMLD to first proximal branch distance (per 1 mm)	1.07	0.002	1.02–1.11

CLMLD — minimal lumen diameter point in culprit lesion; OR — odds ratio; CI — confidence interval

pharmacological reperfusion is not effective in IRA opening in some patients. Failed thrombolysis may be related to several factors and this problem has not been well explored. That is why we have analysed clinical and angiographic factors in that cohort of patients pretreated with combined therapy following immediate angiography.

Spontaneous IRA patency before primary PCI is an important predictor of outcome [1, 2]. The role of pharmacologically driven patency has been discussed based on early facilitated PCI studies, with the consensus being that it does not necessarily translate into additional clinical benefit [10].

However, a growing number of studies and analyses have shown the role of GP IIb/IIIa inhibitors driven patency and its important impact on outcome, especially in high-risk patients [11, 12]. Moreover, analysis of the FINESSE study showed one-year mortality benefit in high-risk patients transferred to the cathlab with early STEMI presentation which was not seen in general FINESSE population in short-term observation [13, 14].

The paradoxical beneficial effect of smoking with regard to early IRA patency in patients receiving lytic therapy has been previously reported. In the TEAM-2 study, current smokers were more likely to achieve TIMI 3 flow after lytics administration than non-smokers [15]. The smoking paradox has also been described in the GUSTO I study analysis [16]. The pathophysiological background of this paradox is not clearly defined, but it may be related to a larger thrombus burden than the plaque burden proportion in the occluded artery [17]. We did not observe any other clinical characteristics influencing combined therapy success in patency restoration. In the analysis of the GUSTO I cohort, other factors such as body weight and IRA localisation were correlated to IRA TIMI 3 flow [16]. Similarly to our study, time from symptoms onset to lysis was not a significant predictor of outcome in the GUSTO I trial, but such a relationship has been described in other studies [16, 18].

In angiographic analysis, no factors significantly influencing IRA patency except the distance from CLMLD to first proximal side branch were identified. We have added this parameter into analysis based on the concept that it may influence the process of thrombus formation proximally from the initial vessel occlusion. A relatively large side branch may limit thrombus formation by flow redistribution from occluded vessel lumen to side branch lumen. The longer the distance from the occlusion site to the branch, the bigger the thrombus that may be formed, and thus thrombolytic therapy may be less successful.

To the best of our knowledge, this parameter has been analysed for the first time in our study. Other angiographic morphological features indicating high burden thrombus formation have previously been described, including vessel size, minimal lumen diameter, IRA cut-off pattern of occlusion, accumulated thrombus proximal to the occlusion, and culprit location [19, 20]. Some of these 'anatomical' factors were important predictors of coronary blood flow assessed with TIMI and corrected TIMI frame count scales in patients after thrombolysis [20].

The problem of the individual response to pharmacological reperfusion therapy is complex and comprises many factors. Besides the clinical or anatomical factors described above, others, like lytic type, biochemical haemostasis and fibrinolysis parameters or thrombus composition (causing resistance of thrombus to dissolution), may be important [21, 22].

Thrombolysis directly before PCI in STEMI patients promotes IRA patency before the intervention, and shortens the time from pain onset to reperfusion [23]. However, lack of aggressive antiplatelet therapy may lead to an increased prothrombotic state after thrombolysis, one potential reason for the failure (increased mortality) of the facilitated PCI arm in the ASSENT-4 PCI study [24]. In many clinical trials, PCI following full-dose thrombolysis has been associated with lower angiographic efficacy and a higher risk of complications [24, 25]. To overcome this limitation in the present study, a reduced dose of lytic was administered, with a full dose of the potent antiplatelet drug abciximab.

Limitations of the study

The main study limitation is the relatively small number of patients. We used angiography for coronary artery characterisation, but none of the modern visualisation techniques such as intravascular ultrasound or virtual histology. However, angiographic analysis was performed in an independent core lab which provides high quality analysis.

CONCLUSIONS

Angiographic (anatomical) IRA parameter as the distance from CLMLD point to the nearest proximal side branch may influence the efficacy of combined thrombolytic therapy before PCI despite the similar clinical characteristics and time delay to angiography. Smoking has a paradoxically beneficial effect on combined thrombolytic therapy effectiveness.

Conflict of interest: *none declared*

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Czynniki predykcyjne drożności tętnicy dozawałowej po zastosowaniu skojarzonej terapii litycznej u chorych z zawałem serca z uniesieniem odcinka ST leczonych przezskórną interwencją wieńcową

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Streszczenie

Wstęp i cel: Wczesne przywrócenie przepływu w tętnicy dozawałowej (IRA) wiąże się z korzystnym rokowaniem pacjentów z zawałem serca z uniesieniem odcinka ST (STEMI). Kliniczne i angiograficzne czynniki wpływające na skuteczność leczenia litycznego, a zwłaszcza zastosowania terapii skojarzonej z użyciem zredukowanej dawki lityku i pełnej dawki dożylnego blokera receptora IIb/IIIa, nie zostały dokładnie zbadane.

Metody: Do badania włączono 225 pacjentów ze STEMI z przewidywanym czasem transportu do pracowni hemodynamiki przekraczającym 90 minut. Pacjenci otrzymywali zredukowaną dawkę lityku i pełną dawkę dożylnego blokera receptora IIb/IIIa, a następnie byli transportowani do ośrodka kardiologii interwencyjnej. Za zmianę odpowiedzialną za incydent (CL) przyjęto miejsce minimalnego światła naczynia (MLD) w zakresie IRA (CLMLD). W grupie z zamkniętą IRA pomiaru dokonywano po udrożnieniu IRA (po pierwszym przejściu prowadnikiem).

Wyniki: U 193 spośród 225 pacjentów (85.8%) stwierdzono drożną IRA w wyjściowej angiografii (TIMI 2+3). Nie zaobserwowano istotnych różnic w charakterystyce klinicznej między grupą z TIMI 0+1 a grupą z TIMI 2+3, z wyjątkiem częstości palenia tytoniu, która była istotnie wyższa w grupie z drożną IRA (73,1% *v.* 50%; p = 0,009) oraz w ocenie angiograficznej wyższej wartości odległość od CLMLD do pierwszej proksymalnie odchodzącej bocznicy w grupie TIMI 0+1 (21,2 ± 10,3 mm *v.* 13,8 ± 11,2 mm; p = 0,002). W analizie wieloczynnikowej palenie tytoniu było niezależnym czynnikiem wpływającym pozytywnie, natomiast odległość od CLMLD do pierwszej proksymalnie położonej bocznicy niezależnym czynnikiem wpływającym negatywnie na drożność IRA.

Wnioski: Angiograficzne (anatomiczne) parametry IRA, takie jak odległość od CLMLD do pierwszej proksymalnie położonej bocznicy mogą wpływać na skuteczność skojarzonej terapii fibrynolitycznej mimo podobnej charakterystyki klinicznej i czasu do angiografii. Palenie tytoniu ma paradoksalny pozytywny wpływ na skuteczność skojarzonej terapii fibrynolitycznej.

Słowa kluczowe: zawał z uniesieniem odcinka ST, tromboliza, reperfuzja, angiografia, tętnica dozawałowa

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