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Patency of the infarct-related artery and time-dependant infarct transmurality on cardiovascular magnetic resonance in patients with ST-segment elevation myocardial infarction treated by primary percutaneous intervention

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SOUHRN

Kontext: Výsledek léčby infarktu myokardu s elevacemi úseku ST (STEMI) je ovlivněn průchodností infarktové tepny (IRA) zjištěné na angiogramu při příjmu pacienta. Rozhodli jsme se proto zhodnotit vztah mezi průchodnou IRA a transmuralitou infarktu v závislosti na čase.
Materiál a metody: Do studie bylo zařazeno 62 pacientů po prvním STEMI (věk 61 ± 9 let, 76 % mužů), u nichž byla provedena primární perkutánní koronární intervence (PCI). Všichni nemocní byli vyšetřeni magnetickou rezonancí (MR) kardiovaskulárního systému v subakutní fázi s cílem stanovit transmuralitu infarktu. Infarkt byl hodnocen jako transmurální při transmuralitě > 75 %. Průchodnost IRA byla definována jako průtok TIMI 2 nebo 3 na počátečním angiogramu.
Výsledky: Průchodná IRA při příjmu byla zjištěna u 23 pacientů (37 %) a souvisela s menší transmuralitou infarktu než při uzávěru IRA (46,9 ± 27,3 % vs. 82, 4 ± 21,3 %; $p < 0{,}0001$). Pacienti byli rozděleni do tří skupin podle doby do provedení PCI (≤ 2 h, > 2–6 h a > 6–12 h). Transmuralita infarktu se zvyšovala s prodlužující se dobou do PCI u pacientů s uzávěrem IRA na vstupním angiogramu ($p = 0{,}0006$), ne však u pacientů s původně průchodnou IRA ($p = 0{,}07$). Podobně se i výskyt transmurálních infarktů zvyšoval s prodlužující se dobou do PCI u pacientů s uzávěrem IRA ($p = 0{,}01$), ne však u pacientů s původně průchodnou IRA ($p = 0{,}12$).
Závěry: Vyšetření kardiovaskulárního systému s použitím MR prokázalo vztah mezi počáteční průchodností IRA při STEMI a transmuralitou infarktu s přibývajícím časem. Šest až dvanáct hodin od nástupu symptomů byl transmurální infarkt zjištěn u všech pacientů s uzávěrem IRA při příjmu a pouze u třetiny pacientů s původně průchodnou IRA.

ABSTRACT

Background: Outcome in ST-segment elevation myocardial infarction (STEMI) is affected by patency of the infarct-related artery (IRA) on the initial angiogram. Therefore we decided to assess the relation between patent IRA and time-dependent infarct transmurality.

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Materials and methods: The study included 62 patients with first STEMI (age 61 ± 9 years, 76% male) undergoing primary percutaneous coronary intervention (PCI). All patients underwent cardiovascular magnetic resonance (CMR) in the sub-acute phase to assess infarct transmurality. Infarction was considered as transmural if mean infarct transmurality exceeded > 75%. IRA patency was defined as TIMI flow 2 or 3 on the initial angiogram.
Results: Patent IRA at baseline was found in 23 patients (37%) and was related to lower infarct transmurality in comparison to IRA occlusion (46.9 ± 27.3% vs. 82.4 ± 21.3%, $p < 0.0001$). Patients were divided into three groups according to time-to-PCI (≤ 2 h, > 2–6 h, > 6–12 h). Infarct transmurality increased with increasing time-to-PCI in patients with occluded IRA on the initial angiogram ($p = 0.0006$), but not in patients with intially patent IRA ($p = 0.07$). Similarly, the frequency of transmural infarctions increased with longer time-to-PCI in patients with occluded IRA ($p = 0.01$), but not in patients with initially patent IRA ($p = 0.12$).
Conclusions: Cardiovascular magnetic resonance demonstrated the relation between initial IRA patency in STEMI and time-dependant infarct transmurality. After 6 to 12 h from the onset of symptoms transmural infarctions were found in all patients with initially occluded IRA and only in about a third of patients with initially patent IRA.

Keywords:
Acute myocardial infarction
Delayed enhancement
Infarct-related artery
Late gadolinium enhancement
Patency
Percutaneous coronary intervention
Transmurality

Introduction

The prognosis in ST-segment elevation myocardial infarction (STEMI) is affected by initial patency of the infarct-related artery (IRA) [1–3]. Patients who arrive in the cath-lab with patent IRA are more likely to have successful primary percutaneous coronary intervention (PCI), lower infarct size and better survival in comparison to those with initially occluded IRA [1–3].

Infarct transmurality and size in STEMI depend on the time-to-reperfusion as demonstrated consequently by previous studies with the use of cardiovascular magnetic resonance (CMR) [4–8]. Although this is true for all STEMI patients and for patients who present with occluded IRA there are no sufficient data analyzing the same concept in patients with initially patent IRA [8].

Therefore we decided to assess the relation between patency of the IRA on the initial angiogram and time-dependant infarct transmurality.

Materials and methods

Study population

The study group included 62 patients with first STEMI (age 61 ± 9 years, 76% male) treated with primary PCI. All patients received loading doses of 300 mg of aspirin and 600 mg of clopidogrel in the pre-hospital phase (in the referring hospital or in the ambulance) and unfractionated heparin (in the pre-hospital phase or in the ambulance). None of the patients received thrombolytics. Maintenance doses of aspirin and clopidogrel were 75 mg daily. CMR examination was performed in the sub-acute phase of AMI (days 3–5) in all patients.

STEMI was defined as (1) presence of continuous chest pain for at least 30 min, (2) ST-segment elevation in 2 or more contiguous ECG leads (≥ 1 mm for the arm leads and ≥ 2 mm for precordial leads), (3) presence of coronary artery occlusion or significant coronary artery stenosis on the initial coronary angiogram in the territory corresponding with ECG changes. Each case of STEMI had to be eventually confirmed with the presence of elevated troponin I (TnI). The STEMI onset time was obtained from the referral charts and was verified by the patient. Time-to-PCIwas defined as time between the onset of STEMI and balloon expansion (recorded from the procedure timing chart). Patency of the IRA was based on the TIMI flow and defined as TIMI flow 2 or 3 [9].

All patients with contraindications to CMR in the sub-acute phase of STEMI were excluded. These included: critical clinical condition, acute or chronic renal failure defined as estimated glomerular filtration rate < 50 ml/min (value suggested by the local ethics committee as a contraindication to gadolinium-based contrast agents), severe form of claustrophobia and the presence of temporary or permanent pacemakers or some other metallic foreign objects in the body.

Informed consent was obtained from each participating patient. The study was approved by the local ethics committee.

Cardiovascular magnetic resonance

CMR studies were performed with the use of 1.5 Tesla scanner (Magnetom Avanto, Siemens, Erlangen, Germany). Scout images and electrocardiographic gated breath-hold steady state free precession (SSFP) cine images in 2- and 4-chamber views were registered to set up final short-axis imaging planes. Short-axis SSFP cine images were obtained from the mitral valve insertion point to the apex with 8 mm thick slices and 2 mm gap between subsequent slices to encompass the entire left ventricle (LV). The same short-axis and long-axis slice positions were used to obtain dark-blood T2-weighted short-tau inversion-recovery (STIR) fast-spin echo sequences. Finally, a 0.1 mmol/kg of body weight of gadolinium contrast (gadobutrol – Gadovist, Bayer Schering Pharma AG, Berlin, Germany) was administered via the antecubital vein and flushed with 30 ml of isotonic saline. Delayed enhancement (DE) images were performed with a breath-hold segmented inversion recovery sequence 10 min after contrast injection and acquired in the same orientation as the cine images. The inversion time was adjusted to completely null normal myocardium.

Image analysis

Cine images were analyzed with the use of a dedicated software (MASS 6.2.1, Medis, Leiden, the Netherlands). Initially, short-axis images were previewed from the base to the apex in a cinematic mode, then endocardial and epicardial contours for end-diastole and end-systole were

manually traced. Delineated contours were used for the quantification of end-diastolic and end-systolic volumes normalized to body surface area (LVEDVI, LVESVI) and ejection fraction (LVEF).

Intramyocardial hemorrhage was defined as a hypointense zone within the area at risk defined as myocardial tissue with signal intensity of 2 standard deviations (SD) above mean signal obtained in the remote myocardium on STIR images [10]. Infarct size was defined as area above 50% of the maximal signal intensity within DE (full-width at half maximum – FWHM) and expressed in grams (absolute infarct size) and as a percentage of LV mass (relative infarct size) [11]. Mean infarct transmurality was calculated as a sum of infarct transmurality in each segment divided by the number of segments with subendocardial DE and presented as percent. Infarction was labeled as transmural if mean infarct transmurality exceeded > 75%. Microvascular obstruction (MVO) was defined as dark areas of absent contrast surrounded by DE [12].

All images were analyzed by a single cardiologist with 6 years of training in CMR (ŁAM) and supervised by a senior expert with 10 years of experience in CMR (JM).

Statistical analysis

All results for categorical variables were expressed as number and percentage and for continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the normality of distribution assessed with the use of a Kolmogorov-Smirnov test. Chi-square test or Fisher's exact test were used for comparison of categorical variables, when appropriate. Student's t-test or Mann-Whitney test for unpaired samples was applied to compare continuous variables depending on the normality of distribution. For comparisons between 3 groups of continuous variables without normal distribution Kruskal-Wallis test was computed. All tests were two-sided with the significance level of $p < 0.05$. Statistical analyses were performed with MedCalc statistical software 10.0.2.0 (MedCalc, Mariakerke, Belgium).

Results

Successful PCI (defined as lack of residual stenosis and TIMI flow 3) was observed in 59 patients (95%) of pa-

Table 1 – Characteristics of patients with and without infarct-related artery (IRA) patency on the initial angiogram.

Parameter	Occluded IRA n = 39 (63%)	Patent IRA n = 23 (37%)	*p*
Age – yrs. (SD)	61.1 (11.2)	61.6 (9.4)	0.86
Male sex – no. (%)	29 (74)	18 (78)	1.00
Hypertension – no. (%)	22 (56)	13 (57)	0.80
Hyperlipidemia – no. (%)	19 (49)	13 (57)	0.74
Diabetes mellitus – no. (%)	6 (15)	3 (13)	1.00
Current cigarette smoking – no. (%)	17 (44)	10 (43)	0.80
Time-to-PCI ≤ 2 h > 2–6 h > 6–12 h	 5 (13) 21 (54) 13 (33)	 6 (26) 10 (43) 7 (31)	0.41
Infarct related artery – no. (%) LAD RCA Cx	 22 (56) 14 (36) 3 (8)	 13 (57) 9 (39) 1 (4)	0.28
Lesion location in IRA – no. (%) Proximal Mid Distal	 26 (67) 10 (25) 3 (8)	 9 (39) 13 (57) 1 (4)	0.05
Peak TnI – ng/ml (IQR)	81.0 (55.8–106.9)	11.1 (3.9–21.9)	< 0.0001
LVEDVI – ml/m^2 (SD)	95.0 (21.6)	83.9 (15.2)	0.035
LVEF – % (SD)	48.7 (9.2)	57.2 (8.3)	0.0006
Absolute infarct size – g (SD)	33.8 (16.3)	16.9 (11.5)	< 0.0001
Relative infarct size – % (SD)	22.8 (8.2)	11.3 (6.3)	< 0.0001
Mean infarct transmurality – % (SD)	82.4 (21.3)	46.9 (27.3)	< 0.0001
Transmural infarction – no. (%)	29 (74)	3 (13)	< 0.0001
MVO – no. (%)	31 (79)	8 (35)	0.0001
Intramyocardial hemorrhage – no. (%)	22 (56)	3 (13)	0.001

Cx – circumflex artery; IRA – infarct related artery; LAD – left anterior descending artery; LVEDVI – left ventricular end-diastolic volume index; LVEF – left ventricular ejection fraction; MVO – microvascular obstruction; PCI – percutaneous coronary intervention; peak TnI – peak concentration of troponin I; RCA – right coronary artery.

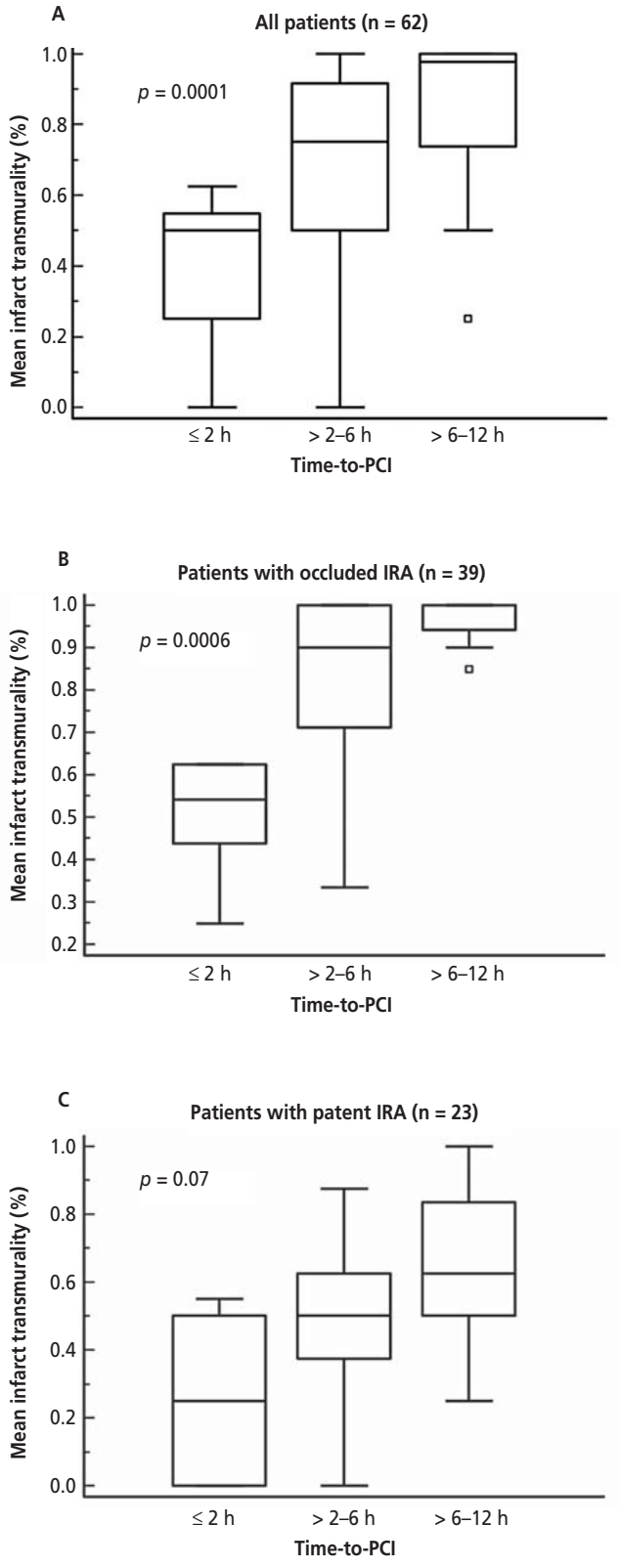

Fig. 1 – Mean infarct transmurality (%) according to time-to-PCI (≤ 2 h, > 2–6 h, > 6–12 h) in all patients (A) and in patients with occluded (B) and patent (C) infarct-related artery (IRA). Central box represents the interquartile range (IQR). The middle line represents the median. The horizontal line extends from the minimum to the maximum value, excluding "outside"and "far out" values which are displayed as separate points.

tients. Three patients (5%) had TIMI flow 2 at the end of the procedure. All of those 3 patients presented with initial TIMI flow 0.

Patients with and without initial IRA patency

Patent IRA at baseline was found in 23 patients (37%). There were no differences in baseline characteristics between patients with and without IRA patency except a trend towards more frequent presence of proximal lesions in patients with the occluded IRA (67% vs. 39%, $p = 0.05$) (Table 1). Initial IRA patency was related to smaller infarct size measured as peak TnI and with means of the CMR (all $p < 0.0001$). Other measures of larger infarct size such as the presence of intramyocardial hemorrhage or MVO were also less frequently found in patients with initial IRA patency (13% vs. 56%, $p = 0.001$ and 35% vs. 79%, $p = 0.0001$, respectively).

IRA patency at baseline was related to lower mean infarct transmurality in comparison to IRA occlusion (46.9 ± 27.3% vs. 82.4 ± 21.3%, $p < 0.0001$). As a consequence patients with patent IRA on the initial angiogram were less likely to have a transmural infarction (13% vs. 74%, $p = 0.0001$), they had a higher LVEF (57.2 ± 8.3% vs. 48.7 ± 9.2%, $p = 0.0006$) and lower LVEDVI (95.0 ± 21.6 ml/m² vs. 83.9 ± 15.2 ml/m², $p = 0.035$).

Seven of the 23 patients with initially patent IRA had TIMI flow 2. Additional analysis showed that patients with initial TIMI flow 2 had similar absolute infarct size (13.3 IQR 3.5–48.0 g vs. 15.3 IQR 8.1–21.1 g, $p = 0.55$), relative infarct size (10.0% IQR 3.8–25.9% vs. 9.5% IQR 6.1–16.2%, $p = 0.54$) and median infarct transmurality (62.5% IQR 0–90.6% vs. 45.8% IQR 25.0–62.2%, $p = 0.13$) in comparison to those with initial TIMI flow 3.

Time-to-PCI and infarct transmurality

Patients were divided into three groups according to time-to-PCI (≤ 2 h, > 2–6 h, > 6–12 h). Mean infarct transmurality increased with increasing time-to-PCI in all patients and in patients with occluded IRA on the initial angiogram ($p = 0.0001$ and $p = 0.0006$) (Fig. 1A and B). On the contrary, in patients with initially patent IRA there was only a trend toward increase in means infarct transmurality with time (Fig. 1C).

Similarly, the frequency of transmural infarctions increased with longer time-to-PCI, but only in the whole group (0% for ≤ 2 h, 55% for > 2–6 h, 75% for > 6–12 h, $p = 0.0001$) and in patients with occluded IRA (0% for ≤ 2 h, 76% for > 2–6 h, 100% for > 6–12 h, $p = 0.01$), but not in patients with initially patent IRA (0% for ≤ 2 h, 10% for > 2–6 h, 29% for > 6–12 h, $p = 0.12$).

Discussion

Myocardial salvage by reduction of time-to-reperfusion is a key concept of the STEMI management according to the rule that "time is muscle" [13]. This has been confirmed in modern studies with non-invasive methods of infarct size assessment as SPECT and CMR [3–8]. Recent analysis demonstrated that to achieve significant myocardial salvage reperfusion must occur within the first 3 h from the onset of symptoms [4]. Most of the studies analyze patients with STEMI as a homogenous group, despite the evidence

that those who arrive in the cath-lab with patent IRA have different prognosis [1–3]. Patency of the IRA (TIMI 2/3) is related to better post-procedural perfusion, smaller infarct size, higher LVEF, less frequent progression to heart failure and lower mortality [1–3]. The smaller infarct size leading to less extensive remodeling in patients with patent IRA (TIMI flow 2/3) in comparison to those with the occluded artery (TIMI flow 0/1) was also confirmed in our study.

We have demonstrated that the group of STEMI patients is not homogenous. The narrow time frame to infarct transmurality is observed mainly in patients with initially occluded IRA (TIMI flow 0/1) in whom only reperfusion in the first 2 h from the onset of symptoms prevents development of transmural necrosis. At the same time in patients with initially patent IRA there is only a trend towards increase in transmurality of myocardial infarction in time. This trend also demonstrates that IRA may undergo reocclusion and reopening in time and therefore supports the role of immediate primary PCI and antiplatelet treatment in this group as in the whole population of STEMI patients. Our results are similar to the findings of Ortiz-Pérez et al. who demonstrated that infarct transmurality increased in time in patients with poor residual flow, but not in patients with preserved residual flow [8].

Our study has some limitations. First of all it included a relatively small group of patients, however due to the costs of CMR most other studies in that area were not performed on much larger patient cohorts [5–8]. Inclusion of a larger group of patients could have demonstrated that the time-dependent increase of infarct transmurality is also significant in patients with initially patent IRA. Nevertheless this process seems slower than in patients who present with occluded IRA. Secondly, the infarct size analysis was performed only in the sub-acute phase of STEMI and not after the end of the infarct healing process. It was shown that the infarct zone undergoes decrease during that time, which may be partially related to resolution of tissue inflammation including myocardial edema [14,15]. Therefore the final infarct size may be lower, but only by about 10–20 percent.

Conclusions

Cardiovascular magnetic resonance demonstrated the relation between initial IRA patency in STEMI and time-dependant infarct transmurality. After 6 to 12 h from the onset of symptoms transmural infarctions were found in all patients with initially occluded IRA and only in about a third of patients with initially patent IRA.

Conflict of interest
None of the authors reported any conflict of interest concerning the submitted paper.

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Ethical statement
The document was done according to ethical standards.

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