Analyse de la reperfusion spontanée à la phase aigue d'un infarctus du myocarde et son impact sur le pronostic à court terme

Analysis of spontaneous reperfusion in acute myocardial infarction and its effect on short-term prognosis

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Summary

Background: ST elevation myocardial infarction remains one of the most frequent emergencies, requiring an as early as possible reperfusion that may result, in some cases, from physiological fibrinolysis. Spontaneous recanalization (SR) of infarct related artery may give positive impact on myocardial functional recovery in cases of sufficient myocardial reperfusion.

Objective: We aimed to analyse the clinical characteristics of patients presenting with clinical markers of spontaneous reperfusion during acute myocardial infarction, and to evaluate its effect on hospital prognosis.

Methods: We enrolled 1382 patients who were admitted to hospital with STEMI. The patients were divided into SR group (spontaneous relief of chest pain less than 5 on a scale from 0 to 10, and ST segment elevation resolution of more than 50% from baseline) and non-SR group (the remaining population). The clinical and prognostic features of the patients were analyzed.

Results: The incidence of SR in our population was 11.2% of patients (n=155). SR patients were younger (57.6 ± 12 vs 61.1 ± 12 years; p=0,002) and had a higher prevalence of current smoking (77.9% vs 5.96%; p=0,003), less myocardial damage as indicated by lower peak creatine kinase (1158 vs 2022 UI/l; p < 0.001), and a shorter coronary care unit stay.

The intensive care unit stay was longer in the non SR group (4.89 ± 2.15 vs 4.89±3.73 days; p =0.006). In hospital mortality (3.2% vs 10%; p=0.013), congestive heart failure (8.4% vs 19.7%; p=0.001), atrial fibrillation (0.6% vs 7.3%; p=0.002) and acute pericarditis (0% vs 4%; p=0.011) were significantly lower for SR patients than for the other subgroups. By multivariate found smoking as the only independent predictor factor of SR (OR=1.82, 95% CI [1.2-2.7]; p=0.003).

Conclusion: Our data shows that SR decreased infarction size, improved heart function and reduced mortality. The subgroup of ST elevation myocardial infarction with spontaneous coronary artery reperfusion carries a more favorable prognosis.

Keywords

Myocardial infarction, Reperfusion, Prognosis, Mortality

Résumé

Introduction : L'infarctus du myocarde reste l'une des urgences les plus fréquentes, nécessitant une reperfusion la plus précoce possible pouvant résulter, dans certains cas, d'une fibrinolyse physiologique. Cette reperfusion spontanée peut avoir un impact positif sur la fonction myocardique en cas de reperfusion myocardique suffisante.

Objectif : Analyser les caractéristiques cliniques des patients présentant des marqueurs cliniques de reperfusion spontanée au cours d'un infarctus du myocarde, et évaluer son effet sur le pronostic hospitalier.

Méthodes : Nous avons recruté 1382 patients admis pour infarctus du myocarde. Les patients ont été divisés en groupe RS (Régression spontanée de la douleur thoracique à moins de 5 sur une échelle d'EVA de 0 à 10, et une résolution du sus-décalage du segment ST supérieure à 50 % par rapport à l'inclusion) et en groupe pas de RS (la population restante). Les caractéristiques cliniques et pronostiques des patients ont été analysées.

Résultats : L'incidence de la RS dans notre population était de 11,2 % des patients (n=155). Les patients RS étaient plus jeunes (57,6 ± 12 ans contre 61,1 ± 12 ans ; p = 0,002) et avaient une prévalence plus élevée de tabagisme actif (77,9 % contre 5,96 % ; p = 0,003), moins de lésions myocardiques comme indiqué par un pic de créatine kinase plus faible (1 158 vs 2022 UI/l ; p < 0,001), et un séjour plus court en unité de soins intensifs (p = 0,006). La mortalité hospitalière (3,2 % vs 10 % ; p=0,013), l'insuffisance cardiaque congestive (8,4 % vs 19,7 % ; p=0,001), la fibrillation auriculaire (0,6 % vs 7,3 % ; p=0,002) et la péricardite aiguë (0 % vs 4 % ; p = 0,011) étaient significativement plus faibles pour les patients RS que pour les autres sous-groupes.En analyse multivariée, le tabagisme était le seul facteur prédictif indépendant de RS (OR = 1,82, IC à 95 % [1,2-2,7] ; p = **0,003).**

Conclusion : Nos données montrent que la RS diminue la taille de l'infarctus, améliore la fonction myocardique et réduit la mortalité. La reperfusion spontanée est associée à un meilleur pronostic.

Mots-clés

Infarctus du myocarde, Reperfusion, Pronostic, Mortalité

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INTRODUCTION

Prompt reperfusion of the occluded artery has become the main goal in the care of acute myocardial infarction (AMI), and the extent of myocardial salvage during AMI depends on the quality of coronary flow restored by reperfusion therapy (1,2). Some patients with AMI undergo early spontaneous reperfusion (SR) before even receiving reperfusion therapy (intravenous thrombolysis or percutaneous transluminal coronary angioplasty [PTCA]).

DeWood et al. (3) demonstrated that 20% of patients diagnosed with AMI did not have occlusive thrombi at the time of acute coronary angiography, suggesting SR. This early SR is probably due to endogenous lysis of thrombi or relief of coronary spasm or both.

Recent studies showed that "spontaneous" reperfusion before primary PTCA is an independent determinant of procedural success, myocardial salvage, and improved outcome (4-6). However, data on characteristics, management, and outcome of patients with AMI presenting with clinical markers of SR and who are managed conservatively are limited.

In the present study, we aimed to analyse the clinical characteristics of patients presenting with clinical markers of SR during AMI, and to evaluate its effect on hospital prognosis compared with AMI patients who did not.

PATIENTS AND METHODS

Study design

We retrospectively analyzed a cohort of 1382 consecutive enrolled between January 1995 and September 2018.

Definitions

Diagnosis of AMI was based on the presence of any two of the following criteria:

• Typical chest pain lasting 30 minutes or longer

• Unequivocal new ECG changes (Q/QS or ST segment deviation or peaked, tall T waves or T wave inversion)

• An increase in creatine kinase (CK) to more than twice the upper normal limit of each hospital laboratory

SR was defined by clinical criteria (7-10) in patients with AMI who were fully eligible for thrombolysis or primary angioplasty but did not receive reperfusion because they developed, within six hours from symptom onset, markers of SR, defined as follows:

• Spontaneous, complete or partial (> 50%) resolution of ST segment elevation as diagnosed by serial (at least two) ECGs that were obtained before hospital admission or at the emergency department and the coronary care unit

• Significant relief of chest pain

• Early inversion of T waves in the infarct related ECG leads

• accelerated idioventricular rhythm.

The first two criteria were essential for the diagnosis of SR.

The criteria were selected following a review of the literature, with emphasis on criteria that could be measured quickly and at the bedside (11,12).

We routinely administer aspirin (250 mg intravenously) plus intravenous heparin (70 U/kg as a bolus and then an initial maintenance dose of approximately 15 U/kg/ hour) in the emergency room, and since 2004 a loading dose of clopidogrel (either 300 or 600 mg if aged < 75 years or 75 mg if aged > 75 years).

Management

No emergency PTCA was attempted at admission in patients with spontaneous patency of the infarct-related artery, who were managed conservatively with intravenous heparin, aspirin administration and clopidogrel since 2004. Patients received ß-blockers unless contraindicated, 250 mg of aspirin daily, 75 mg of clopidogrel, and low molecular weight heparin was maintained.

STATISTICAL ANALYSIS

Differences between categorical variables were analysed by the χ 2 test, means were compared using a Student t-test.

Variables included in the model were age, sex, history of AMI, smoking, hypertension, diabetes mellitus, dyslipidemia, anterior or lateral AMI, total hospital length of stay and complications.

Independant predictors were assessed using a univariate then a multivariate logistic regression (step by step descendant). Kaplan Meier survival curves are shown and compared using the Log Rank test.

A probability value of $p < 0.05$ was considered statistically. We calculated the odds ratio (OR) and 95% IC.

Analyses were performed with SPSS for Windows, version 26.0

RESULTS

Patient characteristics

Of the 1382 AMI patients, 155 patients (11.2%) presented our clinical criteria of SR. Thrombolytic treatment was administered to 425 (30.8%) patients, 332 (24%) patients were treated with primary PTCA and 51 (3.7%). Other 424 patients (30.6%) were managed only by medical therapy.

The study population was divided into 2 groups according to the presence (group I, n=155) or absence (group II, n=1227) of SR.

Table I describes the baseline characteristics of the patients with spontaneous patency. SR patients were younger than group II patients (57.6 ± 12 vs 61.1 ± 12 years; p=0.002), tended to be more often men (87.7% vs 81.5%, p=0.055), had a significantly lower prevalence of hypertension (23.2% vs 31.2%, p=0.041), a significantly higher prevalence of smoking (77.9% vs 65.9%; p=0.003), and a slightly lower prevalence of diabetes mellitus (30.3% vs 36.2%; p=0.14).

Table I. Baseline charateristics

	SR group (n=155)	No SR group (n=1227)	p Value
Age (yrs)			
Male sex (%)	87.7	81.5	0.055
Risk factors			
hypertension (%)	23.2	31.2	0.041
diabetes mellitus (%)	30.3	36.2	0.14
current smoking (%)	11.6	11	0.66
dyslipidemia (%)	77.9	65.9	0.003
time from pain to admission (min)	6.4 ± 5	8.38 ± 7	0.24
Heart failure on admission (kllip>1)	9.7	23.9	<0.001
Admission systolic blood preassure (mmhg)	111±42	115±39	0.32
Admission heart rate (bpm)	77±16	80±19	0.04
Anterior AMI (%)	45.5	51.7	0.001
Inferior AMI (%)	44.8	44.7	
Lateral AMI (%)	8.4	2.6	
Peak creatine kinase (IU/l)	1158±138	2022±198	<0.001

Spontaneous reperfusion has significantly increased over years (4.6% between 1995 and 2000, 13.5% between 2001 and 2005, and 19.5% between 2006 and 2011, p<0.001) (Figure1).

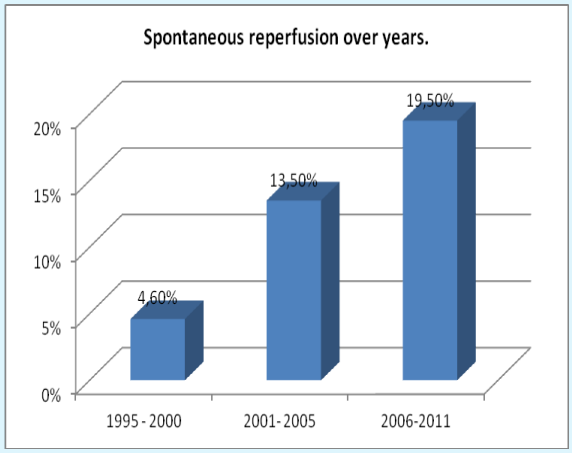

Figure 1. Evolution over years of spontaneous reperfusion

Multivariate analysis by logistic regression identified that smoking status was the only independent predictor factor of SR (OR=1.82, 95% CI [1.26 -2.78]; p=0.003).

SR patients were more likely to have a better initial haemodynamic status as reflected by the higher proportion of patients in Killip class I on admission and lower heart rate.

We observed a lesser extent of myocardial damage in SR patients, as indicated by a higher incidence of aborted AMI (CK < 250 IU) (17.6% vs 7.3%, p<0.001), a less frequent evolution of Q wave AMI (44.5% vs 65.1%, p<0.001), and a lower peak CK concentration (1158 vs 2202 IU; p<0.001).

The inhospital outcome of SR patients (Table 2) was excellent: there was five deaths (3.2%) related to cardiogenic shock. Two patients had sustained ventricular tachycardia and no one had a ventricular fibrillation, five (3.2%) had in hospital recurrent acute ischemia and five (3.2%) had high degree atrio-ventricular block. No pericarditis, ventricular rupture or acute mitral regurgitation were noticed among this group.

In hospital mortality (3.2% vs 10%; p=0.013), congestive heart failure (p=0.001), ventricular fibrillation (p=0.004), atrial fibrillation (p=0.002) and acute pericarditis (p=0.01) were significantly lower for SR patients than for the other subgroups.

The total hospital length of stay was longer in the non SR group with a non significant difference (p=0.26) whereas SR patients had a significantly shorter coronary care length of stay (p=0.004).

Survival at 30 days is significantly higher in the SR group (Log Rank (Mantel Cox) = 0.014), survival curves in the two groups are shown in figure 2.

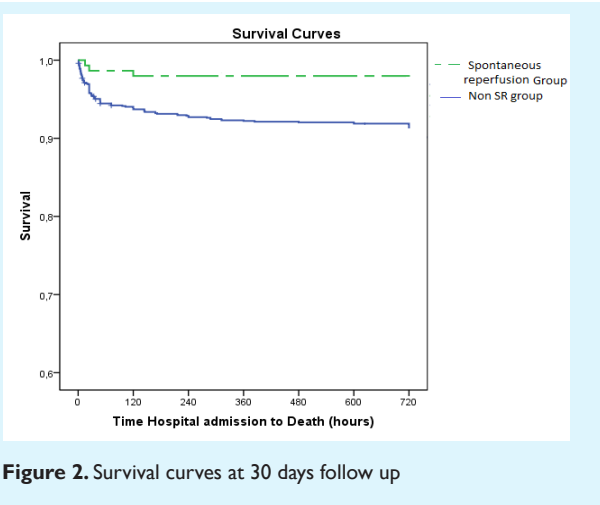

Figure 2. Survival curves at 30 days follow up

DISCUSSION

SR of the infarct-related artery has been described in a consistent minority of patients during myocardial infarction where acute coronary angiography has been performed. Patency of the infarct-related artery before thrombolytic therapy or direct coronary artery angioplasty in the absence of heparin or aspirin has ranged from 9% to 28%, and similar prevalence rates have been demonstrated at 90 minutes during heparin infusion (12-14).

Little data are available on the outcome and optimal treatment strategy of these patients. In particular, whether systematic direct PTCA should be applied to these patients or whether initial conservative management is safe has not yet been tested (10).

The major findings of our study are as follow: Firstly, patients with clinical markers of SR are more likely to develop less or no myocardial damage than reperfusion treated or non reperfused patients. Secondly, clinical SR is associated with improved survival compared with patients treated with thrombolysis or primary PTCA. Our combined observations support the data indicating the benefits of early reperfusion in AMI. This difference in outcome may be related to differences in the duration of infarct artery occlusion.

Thirdly, current smoking emerged as the only independent variable associated with the occurrence of SR.

Fourth, because the reocclusion rate was similar in patients with or without SR, this finding may constitute an incentive for early (3 to 24 hours) infarct-vessel angioplasty. However, the better global outcome of SR patients allows no immediate PTCA, in consistent with the fact that three randomized studies have shown no benefit of immediate PTCA when performed after successful thrombolysis.

An analysis of > 2500 patients published on 2001 which compared patients who achieved TIMI grade 3 flow "spontaneously" on the angiography before primary PTCA (16% of the population) with those who had TIMI 0 to 2 flow (6). Those with spontaneous TIMI grade 3 flow had improved left ventricular function, a lower rate of congestive heart failure, and lower mortality. In addition, the authors observed that procedural success was higher in patients with baseline TIMI 3 flow.

Recent clinical reports suggest that preinfarct angina is associated with SR (5) or more rapid thrombolysis (15). In experimental studies, brief "preconditioning" ischemia, in addition to its ability to render myocytes resistant to infarction, may also have favourable effects on arterial patency. Release of adenosine from ischemic/reperfused myocardium and resultant adenosine receptor stimulation may contribute to enhanced coronary patency (16-17).

Patients with initial TIMI-3 flow had lower in-hospital rates of new-onset heart failure and hypotension, all surrogates of improved myocardial function (6). The presence of TIMI-3 flow at baseline was associated with better initial left ventricular function.

This observation suggests that early pre-PTCA reperfusion has salutary benefits independent of promoting ultimate restoration of TIMI-3 flow.

The modest and early peak value of creatine kinase, and the fact that there was no silent reocclusion are findings consistent with the hypothesis that early SR is likely to have resulted in substantial myocardial salvage and therefore in improved prognosis.

Smoking is associated with significantly increased rates of AMI and death from coronary artery disease (18-20). Paradoxically, despite the increased prevalence of acute coronary syndromes (ACS) in active smokers, prior studies have found that the mortality rate of smokers after AMI may actually

be lower than in non-smokers, especially after fibrinolytic therapy (21). This phenomenon, termed the smoker's paradox, has been partly explained by fewer coexisting high-risk features in patients with AMI who are current smokers and by the fact that smokers are younger than non smokers (22).

Smoking is associated with a hypercoagulable state, aggregation, particularly higher fibrinogen and thrombin generation. As a result, the pathogenesis of vascular occlusions may be more thrombogenic than atherogenic in smokers (12). This may predispose smokers to thrombotic vessel occlusion at an earlier stage of atheromatous disease with are more susceptible to thrombolysis. Alternatively, smokers may have a more complete fibrinolytic response to thrombolysis, leading to improved vessel recanalization for the same degree of stenosis compared with non smokers, thereby contributing to the more benign long-term prognosis in these patients.

In summary, our data confirm the finding of previous studies, compared with previous reports, with an increasing incidence of SR reaching 19.4% over the last 6 years.

We chose to investigate myocardial reperfusion because it strongly predicts short-term mortality and can be estimated non invasively by ST segment measurement. The persistent ST elevation is associated with suboptimal infarct related vessel recanalization and high short term mortality.

Clinical implications

This study has several clinical implications. The apparent smoker's paradox, that is, enhanced survival in smoker's undergoing SR for AMI, should not be interpreted as a serendipitous benefit of cigarette smoking. The deleterious cardiovascular effects of cigarette smoking are manifested as the appearance of AMI in patients more than a decade earlier than might otherwise have occurred, with a similar risk-adjusted prognosis. Intensive efforts to encourage smoking cessation as a primary and secondary preventive measure must continue, including physician to patient interdiction as well as societal initiatives, if the prevalence of CAD and mortality from acute coronary syndromes are to be reduced.

LIMITATIONS

Our study has several important limitations. Firstly, it is an observational study. Secondly, our analysis was done retrospectively and the available data depend on the quality of the information recorded by the research nurses and physicians. To overcome this limitation and to confirm the diagnosis of SR, we reviewed medical records of all patients with SR. We are aware of the weakness that we did not review the records of non-reperfused patients.

CONCLUSION

Patients with early spontaneous patency of the infarct related artery have an excellent in-hospital prognosis and rend to have a smaller infarction than patients in whom patency was achieved through reperfusion therapy. Initial conservative treatment appears safe but similar rates of recurrent ischemia incite to early invasive angiography. Current smokers admitted with ACS have a more SR

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