CARDIOVASCULAR MEDICINE

Improved prognosis of patients presenting with clinical markers of spontaneous reperfusion during acute myocardial infarction

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Objective: To describe the clinical features, management, and prognosis of patients presenting with clinical markers of spontaneous reperfusion (SR) during acute myocardial infarction (AMI).
Design: Cohort study.
Setting: National registry of 26 coronary care units.
Patients: 2382 consecutive patients with AMI.
Main outcome measures: Patient characteristics, management, and mortality.
Results: The incidence of SR was 4% of patients (n = 98) compared with thrombolytic treatment (n = 1163, 49%), primary angioplasty (n = 102, 4%), and non-reperfusion (n = 1019, 43%). SR patients were more likely to develop less or no myocardial damage as indicated by a higher percentage of non-Q wave AMI (58% *v* 32%, 47%, and 44%, respectively, p < 0.0001), aborted AMI (25% *v* 9%, 8%, and 12%, p < 0.001), and lower peak creatine kinase (503 *v* 1384, 1519, and 751 IU, p < 0.0001). SR patients, however, were more likely to develop recurrent ischaemic events (35% *v* 17%, 12%, and 16%, respectively; p < 0.001) and subsequently were more likely to be referred to coronary angiography (67%), angioplasty (41%), or bypass surgery (16%, p < 0.001). Mortality at 30 days (1% *v* 8%, 7%, and 13%, respectively, p < 0.0001) and one year (6% *v* 11%, 12%, and 19%, p < 0.0001) was significantly lower for SR patients than for the other subgroups. By multivariate analysis, SR remained a strong determinant of 30 day survival (odds ratio (OR) 0.16, 95% confidence interval (CI) 0.01 to 0.74). At one year, the association between SR and survival decreased (OR 0.49, 95% CI 0.18 to 1.13).
Conclusions: Clinical markers of SR are associated with greater myocardial salvage and favourable prognosis. The vulnerability of SR patients to recurrent ischaemic events suggests that they need close surveillance and may benefit from early intervention.

The significance and implications of clinical markers of spontaneous reperfusion (SR) in acute myocardial infarction (AMI) have not yet been investigated in detail. The incidence of SR during acute AMI, reported by angiographic studies, varies widely (7–57%).[1–6] Recent studies showed that "spontaneous" reperfusion before primary percutaneous transluminal coronary angioplasty (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 treated conservatively are limited.

We therefore decided to evaluate patients who presented with clinical markers of SR during AMI as compared with AMI patients who did not. Better characterisation and additional knowledge of SR may promote early recognition and risk stratification, avoid unnecessary procedures and complications, and improve outcome.

PATIENTS AND METHODS

Patients admitted to all 26 coronary care units in Israel were prospectively enrolled in a national survey, conducted in January through February and May through July 1996.[7] Briefly, patient demographic data, medical history, hospital management, hospital complications, and 30 day and 12 month follow up were prospectively recorded on a predefined survey form. The reasons for excluding patients from thrombolytic treatment, including SR, were recorded. Medical records of all patients with SR were retrospectively reviewed by two investigators to validate the diagnosis of SR. All surviving patients were seen or contacted by telephone at 30 days. One year mortality data were obtained from records of the Ministry of Interior.

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 and a concomitant increase in CK MB isoenzyme.

For the purpose of our study, SR was defined by clinical criteria[8–11] in patients with AMI who were fully eligible for thrombolysis but did not receive reperfusion because they developed, within six hours from symptom onset, markers of SR, defined as follows:

Abbreviations: ACE, angiotensin converting enzyme; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CK, creatine kinase; PAMI, primary angioplasty in myocardial infarction; PTCA, percutaneous coronary angioplasty; SR, spontaneous reperfusion; TIMI, thrombolysis in myocardial infarction

Table 1 Baseline characteristics

	Spontaneous reperfusion (n=98)	Thrombolysis (n=1163)	Primary PTCA (n=102)	No reperfusion (n=1019)	p Value
Age (years) (mean (SD))	63 (12)	61 (12)	60 (12)	65 (13)	<0.0001
Women	29 (30%)	263 (23%)	19 (19%)	297 (29%)	0.001
Medical history					
Myocardial infarction	18 (18%)	186 (16%)	31 (30%)	300 (29%)	<0.0001
Diabetes mellitus	21 (21%)	272 (23%)	28 (27%)	272 (27%)	0.25
Current smoking	48 (49%)	341 (43%)	49 (48%)	273 (27%)	<0.0001
Hypertension	44 (45%)	405 (35%)	34 (33%)	493 (48%)	<0.0001
Dyslipidaemia	36 (37%)	336 (29%)	30 (29%)	289 (28%)	0.38
Prior angina	38(39%)	436 (37%)	39 (38%)	411 (40%)	0.60
Angina 48 h before admission	15 (15%)	110 (9 %)	10 (10%)	89 (9%)	0.21
Previous medications					
β Blockers	16 (16%)	155 (13%)	21 (21%)	164 (16%)	0.10
Nitrates	12 (12%)	263 (23%)	19 (19%)	233 (23%)	0.08
Calcium channel blockers	19 (19%)	215 (19%)	20 (20%)	217 (21%)	0.44
Aspirin	27 (28%)	283 (24%)	39 (38%)	277 (27%)	0.01
ACE inhibitors	16 (16%)	117 (10%)	10 (10%)	175 (17%)	0.0001
Time (minutes) from symptom onset to emergency room admission (median (25th to 75th centiles))	136 (73–266)	103 (60–175)	108 (61–188)	220 (105–516)	<0.0001
Anterior AMI	48 (50%)	526 (47%)	65 (64%)	426 (45%)	0.001
Q wave AMI	33 (37%)	694 (65%)	50 (53%)	497 (51%)	0.001
Non-Q wave AMI	56 (57%)	373 (32%)	44 (47%)	422 (44%)	0.001
Aborted AMI* (CK <250 IU)	23 (25%)	73 (6%)	7 (8%)	113 (12%)	0.001
CK (IU) (median (25th to 75th centiles)	503 (254–818)	1384 (685–2599)	1519 (774–3297)	751 (420–1341)	<0.0001
Heart failure on admission (Killip >1)	7 (7%)	187 (16%)	37 (36%)	282 (28%)	0.001
Admission heart rate (beats/min) (mean (SD))	75 (14)	78 (18)	86 (22)	81 (20)	<0.0001
Admission systolic blood pressure (mm Hg) (mean (SD))	138 (27)	136 (24)	128 (29)	135 (27)	0.02

*Missing data on creatine kinase (CK) in 4, 26, 10, and 53 patients in each group, respectively. ACE, angiotensin converting enzyme; AMI, acute myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

- 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.

Aborted AMI[12] was defined as AMI that, because of SR, thrombolysis, or primary PTCA, resulted in peak CK < 250 IU and absence of the Q wave in the discharge ECG.

Statistical analysis

Statistical analysis was performed using SAS software (version 6, SAS Institute, Cary, North Carolina, USA). Continuous variables are expressed as mean (1 SD), or as medians with 25th and 75th centiles where appropriate. Differences between SR and other subgroups were calculated by analysis of variance or the Kruskal-Wallis test (non-parametric analysis of variance) where appropriate. Differences between SR and thrombolysis treated patients were calculated by the *t* test or Wilcoxon test, where appropriate. Differences between categorical variables were analysed by the χ^2 test. A probability value of $p < 0.05$ was considered significant. All p values are two tailed.

We performed logistic regression analyses to assess the independent association of various variables with mortality using the SAS LOGISTIC procedure. Variables included in the model were age, sex, history of AMI, congestive heart failure, smoking, angina 48 hours before admission, hypertension, diabetes mellitus, anterior AMI, time from symptom onset to admission (< 2 hours), in-hospital use of nitrates or angiotensin converting enzyme (ACE) inhibitors, and PTCA or coronary artery bypass grafting (CABG) in hospital.

To determine whether there is an association between certain clinical variables or medications and the occurrence of SR, we performed stepwise logistic regression analysis on SR and thrombolysis treated patients. The first model included age, sex, past myocardial infarction, premyocardial infarction angina, smoking, hypertension, anterior myocardial infarction, Q wave myocardial infarction, congestive heart failure, and diabetes mellitus. The second model included the above mentioned variables, with the addition of prior (seven days) use of ACE inhibitors, nitrates, aspirin, insulin, and calcium channel blockers.

RESULTS

Of the 2382 AMI patients, 98 patients (4%) met our clinical criteria of SR. Thrombolytic treatment was administered to 1163 (49%) patients and 102 (4%) patients were treated with primary PTCA. Other patients (n = 1019, 43%) were not treated with acute reperfusion.

Baseline characteristics

Table 1 compares the clinical characteristics of the patient subgroups. SR patients were slightly older than thrombolysis or primary PTCA treated patients, had a higher prevalence of hypertension, and were more likely to experience angina in the 48 hours before infarction (table 1). SR patients arrived at the hospital later than patients treated with reperfusion but earlier than non-reperfused patients. For thrombolysis treated patients, the door to needle time (median (25th to 75th centiles)) was 71 (49–106) minutes. Major reasons for exclusion from thrombolysis were late arrival (n = 342, 34%), lack of ECG criteria (n = 303, 30%), and contraindications to thrombolysis (n = 210, 21%). SR patients were more likely to have a better haemodynamic status as reflected by the higher proportion of patients in Killip class 1 on admission and lower heart rate. Patients selected for primary PTCA were at high risk as reflected by the higher percentage of anterior myocardial infarction and heart failure on admission.

Previous medical treatment during the seven days before infarction differed between SR and reperfusion treated patients with regard to two drugs—SR patients were more likely to have been taking ACE inhibitors but less likely to

Table 2 In-hospital complications, treatment, and procedures

	Spontaneous reperfusion (n=98)	Thrombolysis (n=1163)	Primary PTCA (n=102)	No reperfusion (n=1017)	p Value
Recurrent ischaemia	34 (35%)	196 (17%)	12 (12%)	161 (16%)	<0.001
Heart failure	12 (12%)	151 (13%)	21 (21%)	197 (19%)	<0.001
Cardiogenic shock	1 (1%)	33 (3%)	14 (14%)	69 (7%)	<0.0001
VT or VF	10 (10%)	174 (15%)	31 (30%)	112 (11%)	<0.0001
Recurrent AMI	3 (3%)	37 (3%)	2 (2%)	18 (2%)	0.2
In-hospital treatment					
Aspirin	90 (92%)	1100 (95%)	99 (97%)	869 (85%)	<0.0001
β Blockers	58 (59%)	703 (60%)	44 (43%)	512 (50%)	<0.0001
ACE inhibitors	42 (43%)	602 (52%)	62 (61%)	492 (48%)	0.02
Heparin	89 (91%)	970 (83%)	90 (88%)	814 (80%)	0.006
In-hospital procedures					
Coronary angiography	51 (52%)	434 (37%)	102 (100%)	305 (30%)	<0.0001
PTCA	32 (33%)	244 (21%)	102 (100%)	140 (14%)	<0.0001
CABG	11 (11%)	61 (5%)	3 (3%)	55 (5%)	0.05
Procedures within 30 days					
Coronary angiography	66 (67%)	585 (50%)	102 (100%)	441 (43%)	<0.0001
PTCA	40 (41%)	303 (26%)	102 (100%)	180 (18%)	<0.0001
CABG	16 (16%)	105 (9%)	6 (6%)	106 (10%)	0.05

ACE, angiotensin converting enzyme; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 3 Mortality after myocardial infarction

Mortality	Spontaneous reperfusion (n=98)	Thrombolysis (n=1163)	Primary PTCA (n=102)	No reperfusion (n=1019)	p Value
7 days	0 (0%)	66 (6%)	4 (4%)	83 (8%)	0.003
30 days	1 (1%)	91 (8%)	7 (7%)	132 (13%)	<0.0001
1 year	6 (6%)	130 (11%)	12 (12%)	191 (19%)	<0.0001
30 day OR* (95% CI)	0.16 (0.01 to 0.74)	0.94 (0.67 to 1.32)	1.12 (0.41 to 2.68)	1.0	
1 year OR* (95% CI)	0.49 (0.18 to 1.13)	0.94 (0.71 to 1.26)	1.12 (0.52 to 2.30)	1.0	

*Adjusted for age, sex, history of AMI, congestive heart failure, smoking, angina 48 hours before admission, hypertension, diabetes mellitus, anterior AMI, time from symptom onset to admission (<2 hours), in hospital use of nitrates or ACE inhibitors, and PTCA or CABG in hospital.
CI, confidence interval; OR, odds ratio.

receive nitrates. There was no difference in the frequency of previous use of aspirin, calcium channel blockers, or β blockers (table 1).

We observed a lesser extent of myocardial damage in SR patients (table 1), as indicated by a higher incidence of aborted AMI (CK < 250 IU), a less frequent evolution of Q wave AMI, and a lower peak CK concentration (table 1).

In-hospital course

Compared with other AMI patients, patients with SR were more likely to develop recurrent ischaemia during hospitalisation. Compared with thrombolysis treated patients, there was no difference in the incidence of other complications such as heart failure or shock (table 2).

Compared with thrombolysis treated and non-reperfused patients, SR patients were more likely to undergo coronary angiography, PTCA, or CABG during hospitalisation or within 30 days (table 2).

Mortality

Mortality of patients with SR was lower than that of reperfusion treated and non-reperfused patients at seven days, at one month, and at one year (table 3, fig 1).

After covariate adjustment (table 3), with the non-reperfused group as the reference group, SR was independently associated with improved survival at 30 days (odds ratio (OR) 0.16, 95% confidence interval (CI) 0.01 to 0.74). At one year the association between SR and survival decreased (OR 0.49, 95% CI 0.18 to 1.13).

Variables associated with the occurrence of SR

In attempting to identify variables associated with the evolution of SR we focused on a subgroup of patients eligible for thrombolysis as a reference group. Patients who were referred for primary PTCA constituted a selected, high risk group and non-reperfused patients arrived in a significant delay. Compared with thrombolysis treated patients, among SR patients several clinical variables and medication use were more frequent (table 1). Age, preinfarction angina, hypertension,

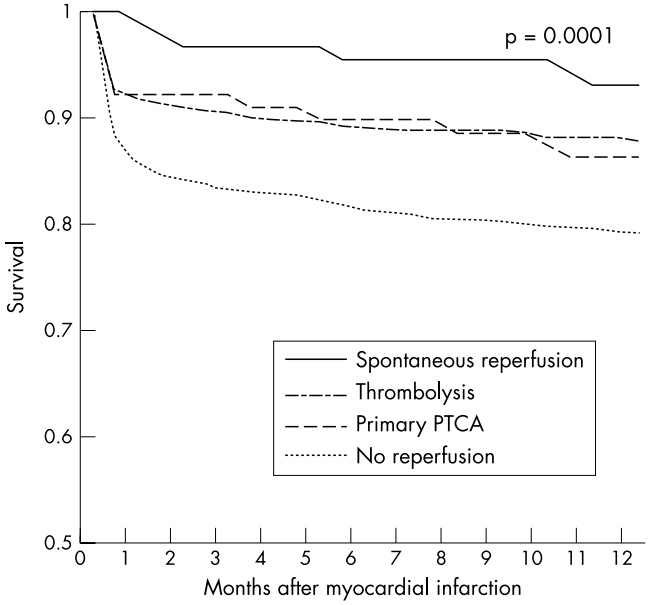

Figure 1 Kaplan-Meier survival curve. Cumulative survival after acute myocardial infarction in patients according to reperfusion treatment ($p_{log\ rank\ test} = 0.0001$).

Table 4 Variables associated with the evolution of spontaneous reperfusion

	Odds ratio	95% CI
A. Logistic model without previous medications		
Age (for 1 year increment)	1.02	1.00 to 1.04
Preinfarction angina (<48 h)	1.80	0.95 to 3.22
Hypertension	1.50	0.94 to 2.38
Q wave myocardial infarction	0.32	0.20 to 0.51
Heart failure on admission (Killip class >1)	0.33	0.12 to 0.73
B. Logistic model with previous medications		
Age (for 1 year increment)	1.02	1.00 to 1.04
Preinfarction angina (<48 h)	1.76	0.92 to 3.19
Hypertension	1.53	0.89 to 2.58
Q wave myocardial infarction	0.34	0.21 to 0.53
Heart failure on admission (Killip class >1)	0.31	0.11 to 0.69
Previous medications		
Aspirin	1.50	0.84 to 2.61
ACE inhibitors	1.60	0.76 to 3.17
Nitrates	0.31	0.13 to 0.64

non-Q wave myocardial infarction, and Killip class 1 on admission emerged as independent variables associated with the occurrence of SR (table 4). After the use of previous medications was added into the model, previous treatment with nitrates was shown to have an inverse association with SR (table 4). The interaction between SR and time to admission (> 2 hours) was examined and found not to be significant.

DISCUSSION

The major findings of our study are as follows. 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, these patients are predisposed to recurrent ischaemic events and consequently are more likely to be referred for cardiac catheterisation, PTCA, or CABG. Thirdly, 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.

Comparison with previous studies

Most of the recent reports on the occurrence of SR have been based on data from AMI patients who were referred for primary PTCA.[4–6] This information showed that patients with SR tended to have all the surrogates of improved myocardial salvage[3]: less cardiac enzyme release, a higher left ventricular ejection fraction, fewer complications, and a better outcome than patients in whom reperfusion was required to achieve TIMI (thrombolysis in myocardial infarction) grade 3 patency. Furthermore, SR in AMI was associated with faster coronary flow after primary angioplasty.[5]

A recent analysis[6] of > 2500 patients in the four PAMI (primary angioplasty in myocardial infarction) trials 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.

Our and other studies[1 13] found a higher rate of recurrent ischaemic events among SR patients. A possible explanation is that greater myocardial salvage, without complete revascularisation, renders more viable myocardium vulnerable to subsequent ischaemia and infarction.[14 15] The higher incidence of reischaemia among SR patients may explain the higher use of coronary angiography, PTCA, and CABG in this subgroup.

Determinants of SR

We identified preinfarction angina and hypertension as clinical variables associated with the occurrence of SR. Q wave AMI and heart failure on admission had inverse associations with SR. Recent clinical reports suggest that preinfarct angina is associated with SR[5] or more rapid thrombolysis.[16] In experimental studies, brief "preconditioning" ischaemia, in addition to its ability to render myocytes resistant to infarction, may also have favourable effects on arterial patency.[17 18] Release of adenosine from ischaemic/reperfused myocardium and resultant adenosine receptor stimulation may contribute to enhanced coronary patency.[17]

We observed a borderline association between previous ACE inhibitor or aspirin treatment and the occurrence of SR. This is likely to be mediated by the beneficial effects of treatment on vascular reactivity and the coagulation system.[19 20] ACE inhibitors reduce recurrent ischaemic events[21 22] and restore sympathovagal imbalance. ACE inhibitors may also improve endothelial function and counteract reduced fibrinolysis by suppression of plasminogen activator inhibitor 1 expression.[19]

The provocative and new observation of an inverse association between previous nitrate treatment and SR is surprising. The mechanisms for this can only be speculated on; recent evidence suggests that continuous treatment with nitrates may worsen endothelial function in the coronary arteries of patients with coronary artery disease, including increased superoxide anion or endothelin production and sensitivity to vasoconstrictors.[23 24] This mechanism appears to have an important role in the development of nitrate tolerance.[23 24] Recent analysis has suggested that continuous treatment with nitrates may worsen the prognosis of patients with ischaemic heart disease.[25 26] In our study, however, it is possible that nitrates simply were a surrogate for more severe cardiac disease.

Limitations

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.

Compared with previous reports, the 4% incidence of SR is relatively low.[1–6] Possible explanations are, firstly, that our clinical criteria[8 9] are less sensitive than coronary angiography in identifying coronary artery patency. Secondly, the patency of the infarct related artery may increase with time.[2 27] We studied patients with SR < 6 hours while several studies included patients up to 24 hours after symptom onset. Thirdly,

other studies included selected candidates for primary PTCA[1 4–6] who were treated with aspirin, heparin, and ticlopidine, which may promote the evolution of SR. Finally, our ECG criteria may reflect myocardial reperfusion and are less sensitive in detecting coronary reperfusion.[11 28 29] On the other hand, using bedside criteria for myocardial reperfusion is more convenient and has strong prognostic implications.[11 28 29]

The longer time from symptom onset to emergency room admission in SR patients may introduce a form of selection bias in that these patients have already survived longer than reperfusion treated patients. However, the interaction between SR and time to admission (> 2 hours) was examined and found not to be significant.

Conclusions and implications

Our study has shown that bedside clinical markers of SR are associated with smaller infarcts and more favourable outcome than in AMI patients treated with thrombolysis or primary PTCA. SR patients, however, are prone to recurrent ischaemic events. The implication of our study is that SR patients need close surveillance and early risk stratification. They may be protected by strategies to prevent reischaemia such as use of aspirin, heparin, β receptor blockers, ACE inhibitors, statins, and clopidogrel. These patients may benefit from early coronary angiography and coronary artery revascularisation. The best time for coronary intervention, immediate versus delayed, needs further investigation.

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The first two authors contributed equally. This study was done as part of the MD thesis requirements at the Faculty of Health Sciences, Ben-Gurion University.

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