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The Distinction Between Coronary and Myocardial Reperfusion After Thrombolytic Therapy by Clinical Markers of Reperfusion

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Objectives. **We sought to examine the hypothesis that rapid resolution of ST-segment elevation in acute myocardial infarction (AMI) patients with early peak creatine kinase (CK) after thrombolytic therapy differentiates among patients with early recanalization between those with and those without adequate tissue (myocardial) reperfusion.**

Background. **Early recanalization of the epicardial infarct-related artery (IRA) during AMI does not ensure adequate reperfusion on the myocardial level. While early peak CK after thrombolysis results from early and abrupt restoration of the coronary flow to the infarcted area, rapid ST-segment resolution, which is another clinical marker of successful reperfusion, reflects changes of the myocardial tissue itself.**

Methods. **We compared the clinical and the angiographic results of 162 AMI patients with early peak CK (≤12 h) after thrombolytic therapy with (group A) and without (group B) concomitant rapid resolution of ST-segment elevation.**

Results. **Patients in groups A and B had similar patency rates of the IRA on angiography (anterior infarction: 93% vs. 93%; inferior infarction: 89% vs. 77%). Nevertheless, group A versus B patients had lower peak CK (anterior infarction: 1,083 ± 585 IU/ml vs. 1,950 ± 1,216, $p < 0.01$; and inferior infarction: 940 ± 750 IU/ml vs. 1,350 ± 820, $p = 0.18$) and better left ventricular ejection fraction (anterior infarction: 49 ± 8, vs. 44 ± 8, $p < 0.01$; inferior infarction: 56 ± 12 vs. 51 ± 10, $p = 0.1$). In a 2-year follow-up, group A as compared with group B patients had a lower rate of congestive heart failure (1% vs. 13%, $p < 0.01$) and mortality (2% vs. 13%, $p < 0.01$).**

Conclusions. **Among patients in whom reperfusion appears to have taken place using an early peak CK as a marker, the coexistence of rapid resolution of ST-segment elevation further differentiates among patients with an opened culprit artery between the ones with and without adequate myocardial reperfusion.**

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Early reperfusion of the infarct-related artery (IRA) remains the most effective treatment for acute myocardial infarction (AMI). However, even early restoration of flow in the IRA does not assure adequate reperfusion of the myocardial tissue (1–4). Scintigraphic (1,2) and contrast echocardiographic (3,4) studies have shown that as many as 25% of the patients with angiographically successful thrombolysis lacked myocardial reperfusion, and failed thereafter to improve myocardial function (3,4).

After thrombolytic therapy, early and rapid resolution of ST-segment elevation (5–10) and early peaking of creatine kinase (CK) (8,11–14) are considered markers of successful reperfusion. However, while the early peak CK results from the abrupt washout of the previously occluded IRA and its related vasculature (3,15–17), the resolution of ST-segment elevation reflects the changes in the jeopardized myocardium itself (18). We hypothesized that absence of concordance between these two nonangiographic markers of reperfusion (early peak CK but without early resolution of ST-segment elevation) discloses a dissociation between reperfusion on the vascular (coronary) and tissue (myocardial) level. To examine this hypothesis we compared the outcome of patients with AMI who had early peak CK after thrombolytic therapy with and without concomitant early resolution of ST-segment elevation.

Methods

Study patients and study design. The study population consisted of 220 consecutive patients with AMI who were treated with recombinant tissue plasminogen activator within 4 h of the onset of symptoms. Acute myocardial infarction was diagnosed based on a history of typical chest pain lasting ≥30 min and ST-segment elevation of 1 mm or more in at least two contiguous leads.

Patients with complete left bundle branch block (CLBBB) on admission electrocardiogram (ECG) were excluded. In each patient CK level was determined on admission, every 3 h during the first 24 h, and once daily thereafter.

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Abbreviations and Acronyms

AMI = acute myocardial infarction
CK = creatine kinase
ECG = electrocardiography
IRA = infarct-related artery
LVEF = left ventricular ejection fraction
PTCA = percutaneous transluminal coronary angiography
TIMI = Thrombolysis In Myocardial Infarction (trial)

Early peak CK (within the first 12 h) was found in 168 patients. Fifty-one patients had late peak CK; and in one patient the peak CK could not be determined due to a technical problem. From the original cohort of 168 patients with early peak CK, 6 patients were excluded: 4 underwent rescue percutaneous transluminal coronary angiography (PTCA) within the first hours; in 1 patient complete left bundle branch block developed after inclusion; and in another patient, the ECG recording was not adequate for analysis of ST-segment changes. The aggregate ST-segment elevations (Σ ST$\uparrow$) in the three contiguous leads showing the highest initial ST-segment elevation were calculated in two ECGs: one immediately before the administration of thrombolytic therapy and the other 2 h later. Postthrombolysis early resolution of ST-segment elevation was defined as a decrease of at least 50% in the Σ ST$\uparrow$ between the two ECGs. The changes in Σ ST$\uparrow$ were evaluated independently and blindly by two investigators. The patients with early CK were divided into two groups based on the presence or the absence of early resolution of ST-segment elevation.

Radionuclide assessment of left ventricular function. Left ventricular ejection fraction (LVEF) was evaluated with rest multigated equilibrium blood pool scan performed in the 45° left anterior oblique projection. Global left ventricular function was assessed at discharge and 2, 6 and 12 months later.

Coronary angiography. Of the 162 patients, 125 consecutive patients underwent coronary angiography within 96 h. The perfusion status of the IRA was assessed using the Thrombolysis In Myocardial Infarction (TIMI) criteria for reperfusion, and the artery was considered patent when TIMI perfusion flow 2 or 3 was established. Thereafter, the number of coronary arteries with significant (≥50%) stenosis was determined.

Clinical follow-up. The patients were followed up during their hospitalization for any cardiac adverse event and for 2 years after their discharge through repeated visits to our outpatient clinic at intervals of 2, 6, 12 and 24 months. For the comparison of the clinical outcome, we specified in the present study a combined clinical end point of congestive heart failure and/or mortality which have a good clinical correlation with the extent of myocardial damage.

Statistical analysis. In the comparison of patients with ST-segment elevation resolution with those without, continuous variables are presented as mean ± SD and the differences are assessed by standard *t* test. Discrete variables are presented as numbers of patients or percentage, and differences are assessed by chi square or Fisher's exact test.

Table 1. Baseline Characteristics

	Early ST↑ Resolution			
	Anterior MI		Inferior MI	
	Present (n = 35)	Absent (n = 36)	Present (n = 73)	Absent (n = 18)
Age (yr)	57 ± 10	58 ± 9	56 ± 10	58 ± 9
Female/male	7/28	6/30	12/61	4/14
Previous myocardial infarction (% patients)	17	11	16	22
Time from symptoms to therapy (min)	133 ± 56	108 ± 38*	143 ± 50	123 ± 51
Time to peak creatine kinase (h)	7.0	7.0	7.0	7.3

*p = 0.03.

Results

Of the 162 patients with early peak CK who comprise the subject of the present study, 71 had anterior infarct and 91 had inferior infarct. While among the patients with anterior infarct, 35 (49%) had early resolution of ST-segment elevation; 73 (80%) with inferior infarct had early resolution. Thus, while among the patients with early ST-segment resolution, 32% had anterior AMI and 68% inferior AMI; among those without early ST-segment resolution, 67% had anterior AMI and 33% inferior AMI. Therefore, the results are being presented according to infarct site.

The baseline characteristics of the patients are shown in Table 1. Patients with and without rapid resolution of ST-segment elevation had similar baseline characteristics regardless of infarct site except for a trend toward earlier administration of thrombolytic therapy in patients without early resolution of ST-segment elevation, which reached statistical significance in patients with anterior infarction.

Indices of infarct size and left ventricular function. Early resolution of ST-segment elevation was associated with lower peak CK of 1,083 ± 888 versus 1,950 ± 1,216 ($p < 0.01$) for anterior and 940 ± 750 versus 1,350 ± 820 ($p = 0.18$) for inferior infarction. Patients with early ST-segment elevation resolution also had significantly better left ventricular function at discharge and throughout the follow-up period (Table 2).

Angiographic results. Fifty-seven of the 71 patients with anterior infarction were subsequently catheterized. The late patency rate was identical in patients with (28 of 30; 93%) and without (25 of 27; 93%) early resolution of the ST-segment elevation.

Among the 91 patients with inferior infarction, 68 were catheterized, and again the late patency rate of the IRA did not differ significantly between patients with (89%) and without (77%) early resolution of ST-segment elevations ($p = 0.34$). Multivessel coronary artery disease was demonstrated in 57% versus 37% ($p = 0.14$) of anterior infarct patients with

Table 2. Left Ventricular Function

	Early ST ↑ Resolution					
	Anterior MI			Inferior MI		
LVEF	Present	Absent	p Value	Present	Absent	p Value
Discharge	49 ± 9	44 ± 8	0.01	56 ± 12	51 ± 10	0.1
2 Months	50 ± 11	45 ± 9	0.04	60 ± 11	54 ± 9	0.04
6 Months	52 ± 10	49 ± 9	0.19	56 ± 11	52 ± 9	0.08
12 Months	53 ± 9	47 ± 10	0.01	59 ± 10	53 ± 11	0.03

MI = myocardial infarction.

and without early resolution of ST-segment elevation, respectively, and in 53% versus 64% in patients with inferior infarction with and without early ST-segment resolution.

Clinical course. There were no significant differences in the in-hospital clinical course between patients with and without rapid ST-segment resolution regardless of infarct site, except for a higher rate of reinfarction in patients with anterior infarct with as compared with those without rapid ST-segment resolution (17% vs. 0%, p = 0.01) (Table 3). However, at the end of the 2-year follow-up period, patients with early resolution of ST-segment elevation had lower incidence of chronic heart failure and mortality (Table 4) and significantly lower prevalence of the combined end point of heart failure and/or mortality whether they had anterior or inferior infarction: 3% versus 19% (p = 0.05) in patients with anterior and 3% versus 22% (p < 0.05) in patients with inferior infarct. The long-term incidence of adverse events did not differ significantly between patients with anterior and inferior infarct in patients with and those without early ST-segment elevation resolution. Thus, we present in Figure 1 the results of the comparison of patients with and without rapid ST-segment resolution in the whole study population (regardless of infarct site). Patients with rapid ST-segment resolution had significantly lower incidence of chronic heart failure (1% vs. 13%, p < 0.01) and mortality (2% vs. 13%, p < 0.01), although they had higher incidence of reinfarction (27% vs. 9%, p = 0.02).

Table 3. In-Hospital Clinical Outcome

	Early ST ↑ Resolution			
	Anterior MI		Inferior MI	
	Present (n = 35)	Absent (n =36)	Present (n = 73)	Absent (n = 18)
CHF	4 (11%)	2 (6%)	0 (0%)	1 (6%)
Reinfarction	6 (17%)	0 (0%)*	11 (15%)	4 (22%)
CABG	2 (6%)	1 (3%)	4 (5%)	1 (6%)
PTCA	18 (50%)	14 (39%)	29 (40%)	6 (33%)
Mortality	0 (0%)	2 (6%)	0 (0%)	1 (6%)

All results are presented as number of patients. *p = 0.01. CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Discussion

In the present study we found in a cohort of 162 patients with AMI and early peak CK after thrombolytic therapy concomitant rapid ST-segment elevation resolution only in 67% of the patients. Despite similar late (96 h) patency rate of the IRA on angiography, the patients with rapid resolution of ST-segment elevation as compared with those with early peak CK but without rapid ST-segment elevation resolution benefited more from thrombolysis judged from smaller enzymatic infarct size, more preserved LVEF, and eventually better long-term clinical outcome. These results suggest that in patients with early peak CK, ST-segment resolution may reflect myocardial reperfusion and salvage better than early peak CK alone.

Comparison with previous studies of nonangiographic signs of reperfusion. Although much has been written about the reliability of early ST-segment resolution and early peak CK to detect early reperfusion after thrombolytic therapy (5–14), little is known about the relationship between these two signs. Silber et al. (9) showed an improved LVEF and survival in patients with early resolution of ST-segment elevation and early peak CK after thrombolysis as compared with those with either one or none of these signs. It was also shown that each, that is, early ST-segment resolution and early peak CK, are independent predictors of infarct artery patency (8).

Our results are in strong agreement with those of van t' Hof et al. (18), who recently showed that rapid ST-segment elevation resolution after successful primary PTCA reflected myocardial reperfusion rather than the restoration of flow in the

Table 4. Long-Term (2-Year) Clinical Outcome

	Early ST ↑ Resolution			
	Anterior MI		Inferior MI	
	Present	Absent	Present	Absent
Chronic CHF	1 (3%)	5 (14%)	0 (4%)	2 (11%)†
Reinfarction	10 (28%)	1 (3%)‡	19 (26%)	4 (22%)
Revascularization (PTCA or CABG)	24 (69%)	19 (53%)	39 (53%)	9% (50%)
Mortality	0 (0%)	4 (11%)	2 (3%)	3 (17%)*
CHF and/or mortality	1 (3%)	7 (19%)*	2 (3%)	4 (22%)†

*p = 0.05; †p < 0.05; ‡p < 0.01. Abbreviations as in Table 3.

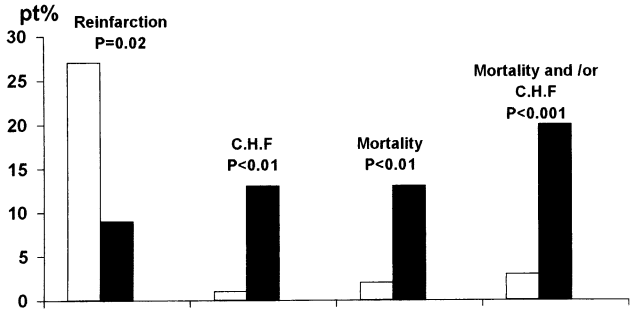

Figure 1. Comparison of long-term (2-year) clinical outcome of patients with and without rapid ST-segment resolution. **Open bars** = patients with rapid ST↑ resolution; **solid bars** = patients without rapid ST↑ resolution.

IRA and was a predictor of the extent of myocardial damage and of clinical outcome.

Possible mechanisms for the absence of ST-segment resolution in patients with early peak CK. Few mechanisms might be suggested for the absence of rapid resolution of ST-segment elevation despite early peak CK and for the diminished myocardial salvage in those patients:

(1) Previous studies showed that after thrombolytic therapy (1–4) or direct PTCA (18–23), coronary reflow in the ischemic myocardium might not have occurred despite early and adequate reopening of the IRA. The "no-reflow" phenomenon is due to microvascular dysfunction, which is caused by swelling of the endothelial cells, perivascular edema, intramural hemorrhage, capillary plugging by erythrocytes and leukocytes, and small vessels spasm (19,21,24–28). As a result of the inadequacy of the myocardial reperfusion, the no-reflow phenomenon is associated with poor myocardial functional recovery (3,4,29). The myocardium supplied by the reperfused IRA is not uniformly affected by the no-reflow phenomenon (3,4,25), and this phenomenon occurs to a variable extent in different patients (1,3,4). Thus, while the areas of the jeopardized myocardium with preserved microvasculature might account for the early peak CK after restoration of flow in the IRA, the extent of the jeopardized myocardium without effective reflow due to microvasculature damage would determine the eventual amount of myocardial salvage and whether concomitant rapid resolution of ST-segment elevation occurs and to what extent.

This theoretical explanation agrees with previous studies (19,21), which showed that the no-reflow phenomenon after direct PTCA for AMI is associated with persistent ST-segment elevation and myocardial damage despite the demonstration of patent IRA, and that reversal of the no-reflow is associated with resolution of the ST-segment elevation (21).

Kenner et al. (4) showed that the anterior, as opposed to the inferior, myocardial infarcts were more prone to the no-reflow phenomenon, supposedly due to the larger amount of ischemic muscle and therefore higher wall stress and regional oxygen demand and less collateral flow in the former infarcts. Thus, this may explain our finding of higher prevalence of early resolution of ST-segment elevation among patients with inferior as compared with those with anterior myocardial infarcts.

(2) During acute ischemia the ST-segment elevation on the surface ECG reflects the loss of resting membrane potential and shortening of the plateau phase of the action potential in the ischemic myocardium. Both changes are accounted for by an increase in the extracellular potassium concentration, and therefore, the washout of tissue potassium as a consequence of successful reperfusion results in rapid resolution of ST-segment elevation. Since the potassium ion is a smaller molecule than CK, in patients with CK washout, as evidenced by early peak CK, elevated extracellular potassium in areas that were washed out may not account for persistent ST-segment elevation. Previous experimental studies showed that peroxidation of myocytes membrane lipids by oxidative stress might lead to loss of resting membrane potential (30–32) and to aberration of the action potential duration (30,32,33), which are similar to the ones occurring as a result of ischemia.

Reperfusion of ischemic myocardium might be accompanied by accelerated generation of oxygen-derived free radicals and membrane lipids per oxidation (34,35). These radicals, which play a major role in the pathogenesis of "reperfusion injury," might also account for persistent ST-segment elevation despite rapid washout of the extracellular potassium along with the CK accounting for the continued myocardial tissue injury.

Study limitation. The patients in the present study were not catheterized immediately after the administration of thrombolytic therapy, and differentiation between TIMI grade II and III in the IRA was not made. Thus, one might claim that the differences between the patients with and without early resolution of ST-segment elevation lie in an earlier and/or higher grade of vascular reperfusion. However, previous studies that did differentiate between TIMI grade II and III showed that patients with TIMI grade II in early angiography did not have an abrupt increase in plasma CK and had an enzyme curve similar to the patients with TIMI 0 and I (36). Because all the patients in the present study had early peak CK differences in the epicardial coronary arteries, flow grade in the IRA itself could not explain the findings of the present study. Moreover, Kenner et al. (4) did not find any correlation between the TIMI grade flow in the epicardial artery and the occurrence of no-reflow as defined by contrast echocardiography. It should be remembered that in patients with prior infarct in the same site, persistent ST-segment elevation from the previous infarct might interfere with the interpretation of ST-segment changes.

Clinical implication. Although the immediate role of thrombolytic therapy for AMI is early recanalization and restoration of flow in the IRA, the eventual aim of all reperfusion strategies is the achievement of adequate reperfusion at the tissue level and thus myocardial salvage. However, that might not occur even with early restoration of TIMI grade III in the IRA (1–4). Therefore, early evaluation of the quality of myocardial reperfusion might have important prognostic value. In the present study among patients with an early peak CK, which is considered as a marker of reperfusion, we

observed that the presence or absence of rapid resolution of ST-segment elevation differentiates between patients with patent artery and improved myocardial perfusion (and better clinical outcome) and patients with patent artery but without successful myocardial reperfusion and worse prognosis and outcome.

References

1. Schofer J, Montz R, Mathey DG. Scintigraphic evidence of the "no reflow" phenomenon in human beings after coronary thrombolysis. J Am Coll Cardiol 1985;5:593–8.
2. Jeremy RW, Links JM, Becker LC. Progressive failure of coronary flow during reperfusion of myocardial infarction: documentation of the no reflow phenomenon with positron emission tomography. J Am Coll Cardiol 1990; 16:695–704.
3. Ito H, Tomooka T, Sakai N, et al. Lack of myocardial perfusion immediately after successful thrombolysis. A predictor of poor recovery of left ventricular function in anterior myocardial infarction. Circulation 1992;85:1699–705.
4. Kenner M, Zajac EJ, Kondos GT, et al. Ability of the no-reflow phenomenon during an acute myocardial infarction to predict left ventricular dysfunction at one-month follow-up. Am J Cardiol 1995;76:861–8.
5. Krucoff MW, Green CE, Satler LF, et al. Noninvasive detection of coronary artery patency using continuous ST-segment monitoring. Am J Cardiol 1986;57:916–22.
6. Barbash GI, Roth A, Hod H, et al. Rapid resolution of ST elevation and prediction of clinical outcome in patients undergoing thrombolysis with alteplase (recombinant tissue-type plasminogen activator): results of the Israeli Study of Early Intervention in Myocardial Infarction. Br Heart J 1990;64:241–7.
7. Bossaert L, Conraads V, Printens H. St-segment analysis: a useful marker for reperfusion after thrombolysis with APSAC? The Belgian EMS Study Group. Eur Heart J 1991;12:357–62.
8. Hohnloser SH, Zabel M, Kasper W, Meinertz T, Just H. Assessment of coronary artery patency after thrombolytic therapy: accurate prediction utilizing the combined analysis of three noninvasive markers. J Am Coll Cardiol 1991;18:44–9.
9. Silber H, Ovsyshcher I, Hausman MJ, Katz A, Gilutz H. The prognostic importance of two easily obtainable noninvasive markers after intravenous thrombolytic therapy in acute myocardial infarction. Isr J Med Sci 1993;29: 268–7.
10. Shah PK, Cercek B, Lew AS, Ganz W. Angiographic validation of bedside markers of reperfusion. J Am Coll Cardiol 1993;21:55–61.
11. Shell W, Mickle DK, Swan HJC. Effects of nonsurgical myocardial reperfusion on plasma creatine kinase kinetics in man. Am Heart J 1983;106:665–9.
12. Blanke H, von Hardenberg D, Cohen M, et al. Patterns of creatine kinase during acute myocardial infarction after nonsurgical reperfusion: comparison with conventional treatment and correlation with infarct size. J Am Coll Cardiol 1984;3:675–80.
13. Gore J, Roberts R, Ball ST, Montero A, Goldberg RJ, Dalem JE. Peak creatine kinase as a measure of effectiveness of thrombolytic therapy in acute myocardial infarction. Am J Cardiol 1987;59:1234–8.
14. Zabel M, Hohnloser SH, Koster W, Prinz M, Kasper W, Just H. Analysis of creatine kinase, CK-MB, myoglobulin, and troponin T time-activity curves for early assessment of coronary artery reperfusion after intravenous thrombolysis. Circulation 1993;87:1542–50.
15. van der Laarse A, van der Wall EE, van den Pol RC, et al. Rapid enzyme release from acutely infarcted myocardium after early thrombolytic therapy: washout or reperfusion damage? Am Heart J 1988;115:711–6.
16. de Zwaan Ch, Willems GM, Vermeer F, et al. Enzyme tests in the evaluation of thrombolysis in acute myocardial infarction. Br Heart J 1988;59:175–83.
17. Lewis B, Ganz W, Laramee P, et al. Usefulness of a rapid initial increase in plasma creatine kinase activity as a marker of reperfusion during thrombolytic therapy for acute myocardial infarction. Am J Cardiol 1988;62:20–4.
18. van t' Hof AWJ, Liem A, de Boer M-J, Zijlstra F. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Lancet 1997;350:615–9.
19. Kitazume H, Iwama T, Kubo I, Ageishi Y, Suzuki A. No-reflow phenomenon during percutaneous transluminal coronary angioplasty. Am Heart J 1988; 116:211–5.
20. Feld HF, Lichstein E, Schachter J, Shani J. Early and late angiographic findings of the "no-reflow" phenomenon following direct angioplasty as primary treatment for acute myocardial infarction. Am Heart J 1992;123: 782–4.
21. Piana RN, Paik GY, Moscucci M, et al. Incidence and treatment of 'no-reflow' after percutaneous coronary intervention. Circulation 1994;89: 2514–8.
22. Morishima I, Sone T, Mokuno S, et al. Clinical significance of no-reflow phenomenon observed on angiography after successful treatment of acute myocardial infarction with percutaneous transluminal coronary angioplasty. Am Heart J 1995;130:239–43.
23. Iwakura K, Ito H, Takiachi S, et al. Alternation in the coronary blood flow velocity pattern in patients with no reflow and reperfused acute myocardial infarction. Circulation 1996;94:1269–75.
24. Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary occlusion in the dog. J Clin Invest 1974;54:1496–508.
25. Kloner R, Rude R, Carlson N. Ultrastructural evidence of microvascular damage and myocardial cell injury after coronary artery occlusion: which comes first? Circulation 1980;62:945–52.
26. Kloner RA, Alker KJ. The effect of streptokinase on intramyocardial hemorrhage, infarct size, and the no reflow phenomenon during coronary reperfusion. Circulation 1984;70:513–21.
27. Engler R, Schmid G, Pavelec R. Leukocyte capillary plugging in myocardial ischemia and reperfusion in the dog. Am J Pathol 1983;111:98–111.
28. Ambrosio G, Becker L, Hutchins G. Reduction of experimental infarct size by recombinant human superoxide dismutase: insights into the pathophysiology of reperfusion injury. Circulation 1986;74:1424–33.
29. Komamura K, Kitakaze M, Nishida K, et al. Progressive decrease in coronary vein flow during reperfusion in acute myocardial infarction: clinical documentation of the no reflow phenomenon after successful thrombolysis. J Am Coll Cardiol 1994;24:370–7.
30. Nakaya H, Tohse N, Kanno M. Electrophysiological derangements induced by lipid peroxidation in cardiac tissue. Am J Physiol 1987;253(Heart Circ Physiol 22):H1089–97.
31. Pallandi RC, Perry MA, Campbell TJ. Proarrhythmic effects of an oxygen-derived free radical generating system on action potential recorded from guinea pig ventricular myocardium: a possible cause of reperfusion-induced arrhythmias. Circ Res 1987;61:50–4.
32. Matsuura H, Shattock M. Effects of oxidant stress on steady-state background currents in isolated ventricular myocytes. Am J Physiol 1991; 261(Heart Circ Physiol 30):H1358–65.
33. Barrington PL, Meier CF Jr, Weglicki WB. Abnormal electrical activity induced by free radical generating systems in isolated cardiocytes. J Mol Cell Cardiol 1988;20:1163–78.
34. Kloner RA. Does reperfusion injury exist in humans? J Am Coll Cardiol 1993;21:537–45.
35. Maxwell SRJ, Lip GYH. Reperfusion injury: a review of the pathophysiology, clinical manifestations and therapeutic options. Int J Cardiol 1997;58: 95–117.
36. Karagounis L, Sorensen SG, Menlove RL, Moreno F, Anderson JL. Does thrombolysis in myocardial infarction (TIMI) perfusion grade 2 represent a mostly patent artery or a mostly occluded artery? Enzymatic and electrocardiographic evidence from the Team-2 Study. J Am Coll Cardiol 1992;19:1–10.