

Grade 3 ischemia on the admission electrocardiogram predicts rapid progression of necrosis over time and less myocardial salvage by primary angioplasty

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Abstract

Background: Among patients with ST-elevation acute myocardial infarction, those with terminal QRS distortion (grade 3 ischemia) have higher mortality and larger infarct size (IS) than patients without QRS distortion (grade 2 ischemia).

Methods: We assessed the relation of baseline electrocardiographic ischemia grades to area at risk (AR) and myocardial salvage [$100 (AR - IS)/AR$] in 79 patients who underwent primary angioplasty for first ST-elevation acute myocardial infarction and had technetium Tc 99m sestamibi single-photon emission computed tomography before angioplasty (AR) and at predischARGE (IS). Patients were classified as having grade 2 ischemia (ST elevation without terminal QRS distortion in any of the leads, $n = 48$), grade 2.5 ischemia (ST elevation with terminal QRS distortion in 1 lead, $n = 16$), or grade 3 ischemia (ST elevation with terminal QRS distortion in >2 adjacent leads, $n = 15$).

Results: Time to treatment was comparable among groups. AR was comparable among groups ($38\% \pm 20\%$, $33\% \pm 23\%$, and $34\% \pm 23\%$, respectively; $P = .70$). There were no differences among groups in residual myocardial perfusion (severity index 0.28 ± 0.12 , 0.29 ± 0.16 , and 0.30 ± 0.15 in grades 2, 2.5, and 3 ischemia, respectively; $P = .97$). In contrast, there was a trend toward lower myocardial salvage ($45\% \pm 32\%$) in the grade 3 group than in the grade 2 ($65\% \pm 33\%$) and grade 2.5 ($65\% \pm 40\%$) groups ($P = .16$). Salvage was dependent on time only in the grade 3 group. Spearman rank correlation coefficients between time to treatment and percentage salvage were 0.003 ($P = .99$), -0.24 ($P = .38$), and -0.63 ($P = .022$) for grades 2, 2.5, and 3, respectively.

Conclusions: Patients with grade 3 ischemia have rapid progression of necrosis over time and less myocardial salvage. This admission pattern is a predictor of myocardial salvage by primary angioplasty.

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Keywords:

Acute myocardial infarction; Electrocardiography; Infarct size; Area at risk

1. Introduction

Prognosis after acute myocardial infarction (MI) is related to final infarct size (IS) [1–3]. Final IS is determined by the size of the initial ischemic myocardium at risk [4–8], the duration of coronary artery occlusion [4,6,9], and the rate of progression of the wave front of

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necrosis [5], or the “severity” of ischemia. The latter depends on at least 2 factors: (1) the presence of residual blood supply to the infarct zone, either by antegrade flow in the infarct-related artery (subtotal occlusion or intermittent reperfusion) or by collateral circulation [4,6–9]; and (2) metabolic factors such as the oxygen requirement of the myocardium [4] and presence of metabolic protective mechanisms (ie, “ischemic preconditioning”) [10–13]. The ability to estimate immediately upon admission the expected rate of progression of necrosis may enable physicians to identify patients in whom reperfusion would not be expected to salvage myocardium and conversely those who might benefit from reperfusion even if the time elapsed from symptom onset is prolonged.

The extent of myocardial involvement (ischemic area at risk [AR]) can be estimated by searching for symptoms and signs of heart failure and using echocardiography, radionuclide techniques, ventriculography, or magnetic resonance imaging. However, imaging methods increase delays in treatment and can neither measure the “severity” of ischemia nor differentiate between viable myocardium and already

infarcted myocardium during the evolving phase of infarction. Although single-photon emission computed tomography (SPECT) with technetium Tc 99m sestamibi can quantify the AR and its residual flow and the final IS [6–9,14–18], this method likewise is relatively expensive, time consuming, and technically demanding; and yet does not give answers in real time when decisions concerning reperfusion therapy or transfer to other centers for primary transcutaneous coronary interventions (PCI) are being made.

Previous studies showed that patients with ST-elevation acute myocardial infarction who have terminal QRS distortion in 2 or more adjacent leads (grade 3 ischemia) on the admission electrocardiogram (Figs. 1–3) have worse prognoses [19–21], larger IS [20,22,23], and less benefit from thrombolysis [22,23]. We have also shown that even with primary angioplasty, patients with grade 3 ischemia have higher mortality than patients with grade 2 ischemia (ST elevation without terminal QRS distortion) [24]. Whether grade 3 ischemia at presentation reflects a larger myocardial AR, or more “severe” ischemia due to lack of the above mentioned protective mechanisms, remains unclear.

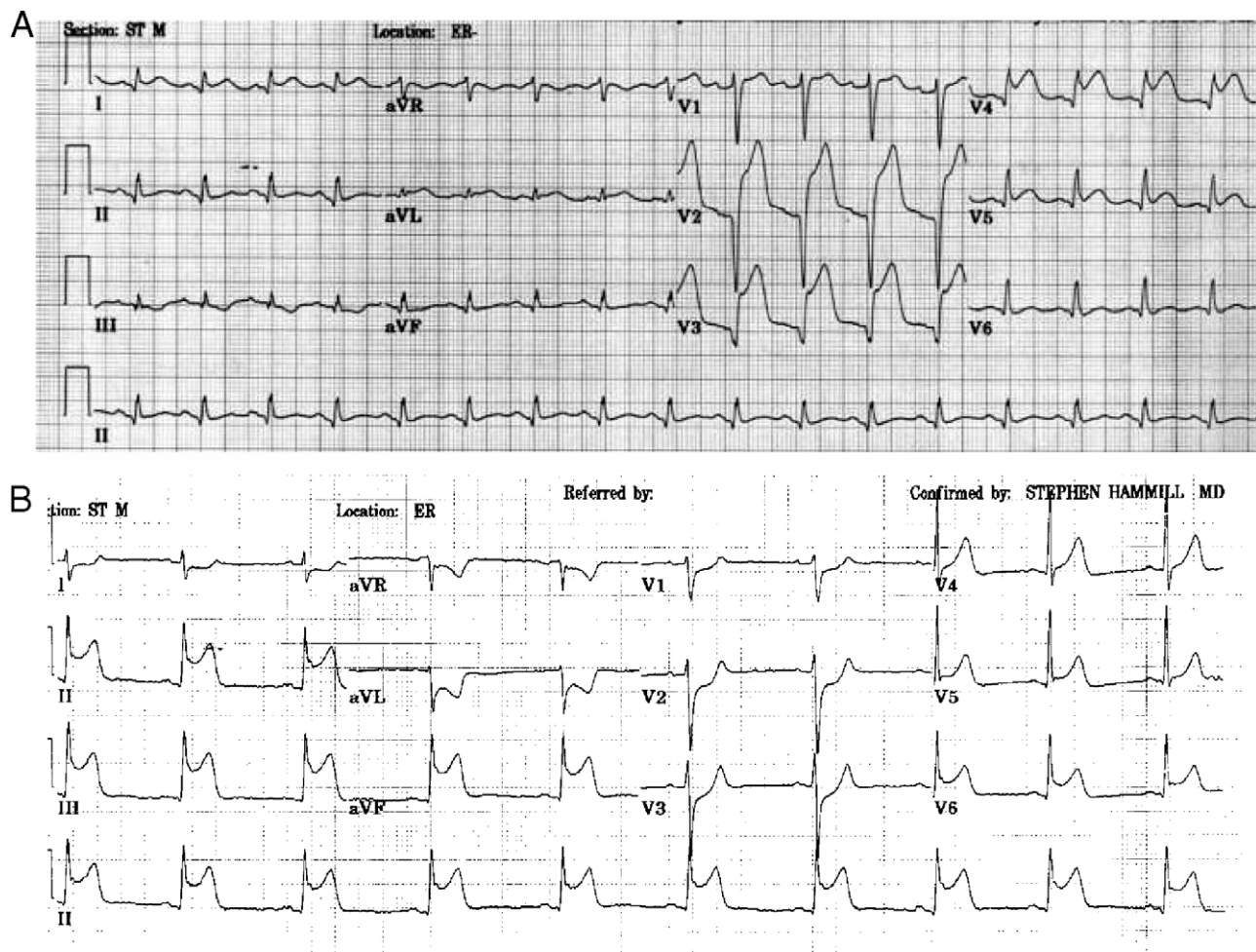


Fig. 1. Admission electrocardiograms of patients with anterior acute MI (A) and inferior acute MI (B) with grade 2 ischemia. A, There is ST-segment elevation in leads V₁ to V₅. However, S waves are preserved in V₁–V₃ and the J point/R wave ratio is <0.5 in V₄ and V₅. B, There is ST-segment elevation in leads II, III, and aVF and V₅ to V₆. The J point/R wave ratio is <0.5 in all.

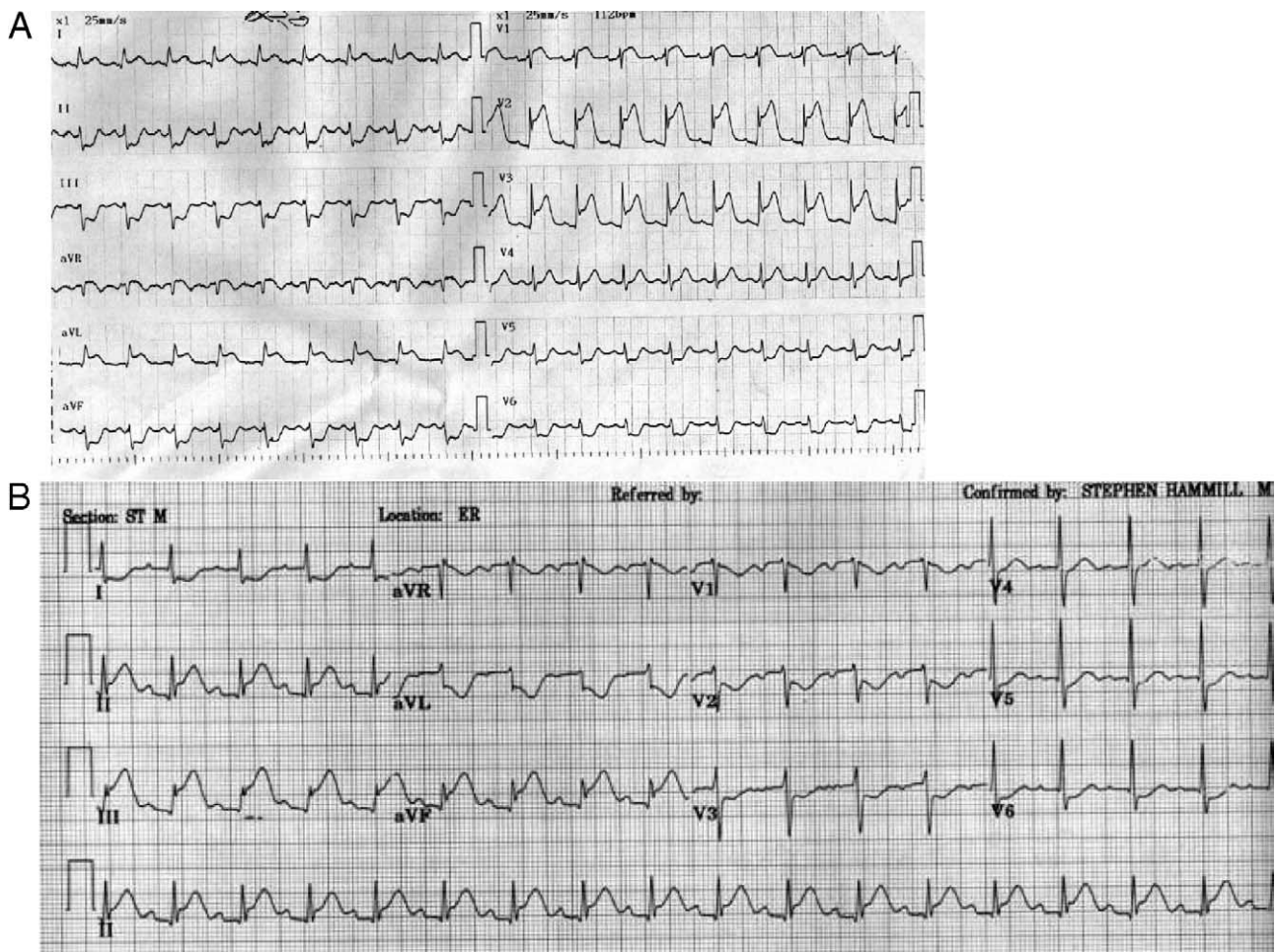


Fig. 2. Admission electrocardiograms of a patient with anterior acute MI (A) and inferior acute MI (B) with grade 3 ischemia. A, There is ST-segment elevation in leads aVL and V₁ to V₃. There are no S waves in leads V₂ and V₃. B, There is ST-segment elevation in leads II, III, and aVF. The J point/R wave ratio is ≥ 0.5 .

We retrospectively assessed a cohort of patients with first acute myocardial infarction who received primary angioplasty and underwent SPECT with technetium Tc 99m sestamibi imaging both before angioplasty and at predischarge to determine (1) whether patients with grade 3 ischemia have larger initial AR, (2) whether grade 3 ischemia on the admission electrocardiogram is associated with larger final IS, (3) whether grade 3 ischemia is a sign of lack of residual myocardial perfusion (lack of collaterals or antegrade flow), and to determine the relations between time of ischemia and myocardial salvage in patients with and without terminal QRS distortion on their admission electrocardiogram.

2. Methods

2.1. Patients

We retrospectively studied 79 patients who presented to the Mayo Clinic with first ST-elevation acute MI, treated with primary angioplasty and studied with SPECT technetium Tc 99m sestamibi before angioplasty and at predischarge.

We included only patients with admission ST-segment elevation and positive T waves in the leads with maximal ST-segment elevation [19,20,23,24]. Patients with intraventricular conduction delays, ventricular rhythms, ventricular paced rhythms, negative T waves in the 2 or more adjacent leads with maximal ST-segment elevation, or incomplete or uninterpretable admission electrocardiograms were excluded [19,20,23,24].

2.2. Electrocardiographic evaluation

The enrollment 12-lead electrocardiogram was assessed by 1 investigator (Y.B.) who was unaware of clinical and scintigraphic data. The location of MI (anterior vs other) and the grade of ischemia were noted. Patients were divided into 3 groups: grade 2 ischemia, ST elevation without terminal QRS distortion (Fig. 1); grade 2.5 ischemia, ST elevation with terminal QRS distortion in only 1 lead; and grade 3 ischemia, ST elevation with terminal QRS distortion in 2 or more spatially adjacent leads (Fig. 2). Distortion of the terminal portion of the QRS was defined as (1) disappearance of the S wave in leads V₁ to V₃, where typically there is an rS configuration (Fig. 2A); or (2) emergence of the J point at

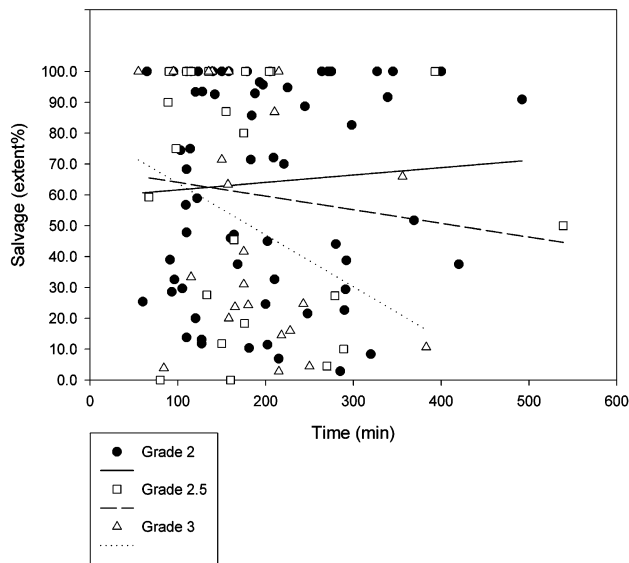


Fig. 3. The extent of myocardial salvage is indicated from 0% to 100%, by comparison of the initial and final scintigraphic studies according to the times from onset of symptoms until primary angioplasty in minutes. The symbols used to identify electrocardiographic grades 2, 2.5, and 3 of ischemia and the resulting regression lines are indicated in the box.

50% or greater of the R wave amplitude in the other leads (Fig. 2B) [19,20,24,25]. The number of leads with 0.1-mV or greater ST-segment elevation and the sum ST-segment elevation above the isoelectric line was measured at a central electrocardiographic core laboratory (Duke Clinical Research Institute) by personnel unaware of the clinical and scintigraphic data.

2.3. Radionuclide imaging

All imaging data were analyzed by the nuclear core laboratory (Mayo Clinic Foundation), which was unaware of clinical data, treatment assignment, and electrocardiographic data. The methods for tomographic imaging have been previously described [6,8,15,17,18,26–28]. Briefly, tomographic images were obtained within 6 hours after injection of 20 to 30 mCi technetium Tc 99m sestamibi before primary angioplasty and before discharge at days 5 to 7. Short-axis slices of the left ventricle were obtained every 6 mm and normalized to the peak counts in the heart. Circumferential count profiles were generated for representative 5 slices from base to apex by identifying the peak counts every 6° around the left ventricle. The ventricle was assumed to consist of a hollow cylinder in all slices except the apex, which was assumed to be a hollow cone [6]. The relative volume of each geometrical cylinder and cone was estimated using the radius of the representative slice and standard geometric formulas. The extent of the defect was determined by the number of radians (60 per slice) in the 5 count profiles less than 60% of maximal counts in the slice weighted by the radius of the slice and/or apical location and was expressed as a percentage of the left ventricular myocardial volume [6,29]. The extent of the defect on the pretreatment images

represents the ischemia AR, and the extent of the defect on the predischARGE images represents final IS. The salvage index $[(AR - IS)/AR \times 100]$ was calculated.

Residual myocardial perfusion (collateral flow or residual antegrade flow) was estimated by 2 methods: (1) the “severity index,” the ratio of the cumulative area of the curve less than 60% maximal counts over the potential cumulative area for the extent of the defect for all 5 short-axis slices, and (2) area, the cumulative area of the 5 slices with less than 60% maximal counts [6,15].

2.4. Statistical analysis

Continuous variables are summarized as means $\pm$ SD and categorical data as frequencies and percentages. For continuous variables, differences among groups were analyzed by nonparametric analysis of variance (Kruskal-Wallis). The χ^2 test was applied to compare differences between discrete variables. Spearman rank correlation was used to assess the relations between time from onset of symptoms to angioplasty and myocardial salvage in each grade of ischemia group.

3. Results

3.1. Patients

Seventy-nine patients were included in the study. There were 48 patients in the grade 2 ischemia group, 16 in the grade 2.5 ischemia group, and 15 in the grade 3 ischemia group.

Age, sex, and infarct location did not differ significantly by ischemia grade (Table 1). Time from onset of symptoms to treatment tended to be longer in the grade 2 group and shorter for grade 3, but the differences did not reach statistical significance.

3.2. SPECT results

The extent of the pretreatment defect size (AR) was comparable among the 3 groups (Table 2). There was no difference in residual myocardial perfusion (the severity index and the area) among the groups.

There were no significant differences in predischARGE perfusion defect size (final IS) among the groups.

Table 1
Baseline clinical variables by ischemia grade

Variable	Ischemia grade			P
	2.0	2.5	3.0	
n	48	16	15	
Sex (% men)	73%	81%	67%	.65
Age (mean $\pm$ SD)	59 $\pm$ 10	58 $\pm$ 12	64 $\pm$ 8	.20
Time from onset to therapy (h)	4.6 $\pm$ 3.7	3.6 $\pm$ 2.0	3.1 $\pm$ 1.5	.19
Infarct location				.17
Anterior (n = 40)	58%	44%	33%	
Inferior (n = 36)	35%	56%	67%	
Posterior (n = 3)	6%	0%	0%	

Table 2
Radionuclide data

Measure	Ischemia grade			<i>P</i> *
	2.0	2.5	3.0	
Pretreatment extent (AR)	37.6 ± 20.1 (n = 47)	32.9 ± 23.2 (n = 16)	34.2 ± 23.4 (n = 13)	.70
Collaterals				
Severity index	0.28 ± 0.12 (n = 41)	0.29 ± 0.16 (n = 15)	0.30 ± 0.15 (n = 13)	.97
Area	0.12 ± 0.09 (n = 40)	0.13 ± 0.12 (n = 15)	0.13 ± 0.11 (n = 12)	.93
Predischarge extent (IS)	16.0 ± 18.4 (n = 47)	10.7 ± 16.3 (n = 16)	23.4 ± 21.4 (n = 13)	.19
Percent salvage	0.65 ± 0.33 (n = 47)	0.65 ± 0.40 (n = 16)	0.45 ± 0.32 (n = 13)	.16

* One way analysis of variance.

However, myocardial salvage, as a percentage of the AR, tended to be smaller for the grade 3 ischemia group than in the other 2 groups.

Spearman rank correlation coefficient between time to treatment and salvage showed that myocardial salvage was not dependent on time to treatment in the grades 2 and 2.5 ischemia groups. However, salvage was significantly dependent on the time elapsed from onset of symptoms to therapy in the grade 3 ischemia group (Table 3). These relationships between time to treatment and salvage are illustrated in Fig. 3.

Multivariate regression analysis showed that the severity index, ischemia grade, female gender, and time to treatment were independent predictors of myocardial salvage (Table 4).

4. Discussion

The main findings of the present study are that patients with grade 3 ischemia on the admission electrocardiogram tend to have less myocardial salvage than patients with grade 2 ischemia, despite the fact that the ischemic time tended to be shorter in the grade 3 group. Ischemia time does not seem to affect myocardial salvage in patients presenting with grade 2 ischemia or the intermediate group, grade 2.5. In contrast, myocardial necrosis progresses rapidly over time, and myocardial salvage decreases as time from onset of symptoms to reperfusion increases in patients with grade 3 ischemia. Thus, grade 3 ischemia is a sign of more “severe” ischemia; however, grade 3 ischemia is not a manifestation of a larger initial ischemic AR, a sign of more advanced stage of infarction (time from onset of symptoms to therapy tended to be shorter in the grade 3 group), or a sign of paucity of residual myocardial perfusion.

4.1. Ischemia grades and IS

During regional myocardial ischemia, the activation wave in the local Purkinje fibers is conducted more slowly [30,31]. The delayed conduction reduces the degree of

cancellation, resulting in an increase in R-wave and decrease in the S-wave amplitudes on the surface electrocardiogram [30–35]. The Purkinje system is less sensitive to ischemia than are the contracting myocytes [36,37]. Hence, for an alteration in the terminal portion of the QRS to occur, there must be severe prolonged ischemia that would affect the Purkinje fibers [30,38].

This study confirms the findings from the Acute Myocardial Infarction Study of ADenosine that ischemic AR is comparable between patients with grades 2 and 3 ischemia [39]. We found that the time from onset of symptoms to therapy was not statistically significantly different among the groups (Table 1). All previous studies showed that the time from onset of symptoms to therapy was comparable among groups, suggesting that grade 3 ischemia is not an electrocardiographic manifestation of a more advanced stage of infarction [19–22,24,39]. In addition, grade 3 ischemia is not a sign that myocardial necrosis has already occurred, because terminal QRS distortion is frequently seen during episodes of Prinzmetal angina that may resolve without detectable myocardial necrosis [40].

Previously, it has been shown that there is no difference between grades 3 and 2 patients in the rate of recanalization of the epicardial coronary arteries by either thrombolytic therapy [20,25] or primary angioplasty [21,24]. Thus, lower rates of reperfusion cannot explain the different salvage patterns among the groups. However, despite similar rates of recanalization of the epicardial coronary arteries, “no-reflow” phenomenon is more prevalent among patients with grade 3 ischemia, suggesting more extensive damage to the myocardial tissue and microvasculature by the time reperfusion occurs in patients with grade 3 ischemia [21,41].

The present study shows that, while in patients with grade 3 ischemia necrosis progresses rapidly over time, time from symptom onset does not affect myocardial salvage in

Table 3
Correlation (Spearman rank correlation coefficient) between time to treatment and salvage measures

Ischemia grade	2.0 (n = 46)	2.5 (n = 16)	3.0 (n = 13)
Salvage (%)	0.003 (<i>P</i> = .99)	−0.24 (<i>P</i> = .38)	−0.63 (<i>P</i> = .022)

Table 4
Regression results with extent (%) as dependent variable (n = 68)

Variable	Regression coefficient	SE	<i>P</i>
Severity index	−1.367	0.272	<.0001
Ischemia grade	−0.210	0.091	.025
Women	0.129	0.081	.12
Time to treatment (h)	−0.019	0.011	.09

patients with grade 2 ischemia. The relationship between time and myocardial necrosis in patients with grade 2.5 ischemia was intermediate between that of grades 2 and 3 ischemia. Thus, it seems that patients without grade 3 ischemia on admission are somehow protected. Lee et al [21], assessing collateral circulation by the pressure-derived fractional collateral flow (PDFCF), reported that group with grade 3 ischemia ($n = 41$) had lower PDFCF index than the grade 2 ischemia group ($n = 112$) (16.1 ± 9.1 vs 20.7 ± 10.5 ; $P < .05$). Less patients with grade 3 ischemia had adequate collateral circulation (PDFCF >24) (19.5% vs 37.5%; $P < .05$). They concluded that terminal QRS distortion is a sign of lack of collateral circulation [21]. We assessed residual myocardial perfusion by technetium Tc 99m sestamibi imaging and found no difference in residual perfusion of the AR among the 3 groups, suggesting that collateral circulation or antegrade residual flow does not explain the difference in the rate of progression of necrosis over time among the 3 groups.

Ishihara et al [42] suggested that prodromal angina may alter the relation between time to reperfusion and outcomes after myocardial infarction by inducing ischemic preconditioning. Tamura et al [22] concluded that grade 3 ischemia is a sign of lack of protection by ischemic preconditioning. In their study, 52% of the patients with grade 2 ischemia ($n = 83$) versus only 26% in patients with grade 3 ($n = 23$) ischemia had preinfarction angina ($P < .01$) [22]. However, in the Global Utilization of Streptokinase and TPA (alteplase) for Occluded Coronary Arteries (GUSTO-I) Israeli population [19], the GUSTO-I angiographic substudy [25], the Thrombolysis In Myocardial Infarction 4 trial [20], and the Acute Myocardial Infarction Study of ADenosine study [39], as well as the study by Lee et al [21], there was no difference in preinfarction angina between patients with grades 2 and 3 ischemia, suggesting that lack of ischemic preconditioning may not be the underlying mechanism for grade 3 ischemia.

4.2. Effect of time from symptom onset to reperfusion therapy

In experimental models, the total time from coronary artery occlusion to reperfusion is 1 of the major determinants of how much myocardial AR undergoes irreversible necrosis [5,43]. In 54 patients with acute myocardial infarction undergoing successful primary angioplasty, the elapsed time from symptom onset to reperfusion correlated with myocardial salvage (assessed by pretreatment and predischARGE SPECT) [44]. In the 5 patients reperfused less than 2 hours after symptom onset, 80% of the jeopardized myocardium was salvaged. However, myocardial salvage beyond 2 hours was much more variable [44]. When patients undergoing thrombolysis were investigated, the time from symptom onset to the start of thrombolytic therapy did not correlate significantly with final IS [6,8]. When thrombolytic therapy was given after 2 hours of symptoms, myocardial salvage varied highly and depended on residual myocardial perfusion

[9]. We also showed that myocardial salvage is dependent on residual myocardial perfusion. However, we found a new independent predictor of myocardial salvage: distortion of the terminal portion of the QRS. Although the underlying mechanisms of this electrocardiographic sign are yet unclear, this simple electrocardiographic sign differentiates between patients with rapid progression of necrosis over time and patients in whom the rate of progression of necrosis is much slower. In the Israeli population within the GUSTO-I study, inhospital mortality among patients with acute myocardial infarction and grade 2 ischemia on the enrollment electrocardiogram was 4.2% and 3.6% in those treated 2 hours or less and more than 2 hours after symptom onset, respectively. In contrast, among patients with grade 3 ischemia at enrollment, mortality increased from 4.8% for those treated less than 2 hours to 5.6% for those treated more than 2 hours after symptom onset [19]. The difference in mortality between the grades 2 and 3 patients treated more than 2 hours after symptom onset was statistically significant ($P = .0005$). Due to slower rate of progression of necrosis in patients with grade 2 ischemia, significant myocardial salvage is expected even if reperfusion takes place late. This may have important implications concerning reperfusion therapy. Recent studies have shown that transfer of ST-elevation acute myocardial infarction patients for primary angioplasty from hospital without on-site catheterization facility is better than administration of intravenous thrombolytic therapy [45,46]. It is plausible that especially the patients with grade 2 ischemia benefit from this strategy, despite possible delay in achieving reperfusion, because in these patients, necrosis does not progress rapidly over time. It might be that more aggressive approach is needed for patients with grade 3 ischemia for achieving reperfusion as early as possible because of their steep decline in myocardial salvage over time.

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