The Impact of Preinfarction Angina on Electrocardiographic Ischemia Grades in Patients with Acute Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention

Turgay Celik, M.D.,* U. Cagdas Yuksel, M.D.,† Atila Iyiso, M.D.,* Selim Kilic, M.D.,‡ Ejder Kardesoglu, M.D.,§ Baris Bugan, M.D.,* and Ersoy Isik, M.D.*

From the *Gulhane Military Medical Academy, School of Medicine, Department of Cardiology, Etlik, Ankara, Turkey; †Sarikamis Army District Hospital, Department of Cardiology, Sarikamis, Turkey; ‡Gulhane Military Medical Academy, School of Medicine, Department of Epidemiology, Etlik, Ankara, Turkey; and §Gulhane Military Medical Academy, Haydarpasa Training Hospital, Department of Cardiology, Etlik, Ankara, Turkey

Objective: Grade 3 ischemia (G3I) is defined as ST elevation with distortion of the terminal portion of the QRS (emergence of the J point >50% of the R wave in leads with qR configuration, or disappearance of the S wave in leads with an Rs configuration). Patients with G3I on the presenting electrocardiogram (ECG) had worse prognosis than the patients with lesser (grade 2-G2I) ischemia. The aim of this study is to examine the effects of preinfarct angina (PIA) on electrocardiographic ischemia grades.

Methods: One hundred forty-eight consecutive patients with ST-segment myocardial infarction (STEMI) were included in this study. All patients underwent primary percutaneous coronary intervention. The admission ECGs were analyzed retrospectively for electrocardiographic ischemia grades and compared with the presence of PIA.

Results: Study population consisted of 110 patients with G2I (88 men, mean age = 63 ± 6 years) and 38 patients with G3I (32 men, mean age = 61 ± 8 years). Baseline characteristics of the groups were the same except for patients with G3I had significantly longer pain to balloon time and higher admission creatine kinase MB isoenzyme (CK-MB) levels. Tissue myocardial perfusion grade (TMPG) was better in patients with G2I. While 18 patients (47%) with G3I had PIA, 81 patients (70%) with G2I had PIA ($P = 0.005$). Although pain to balloon time and admission CK-MB were independent predictors of worse electrocardiographic ischemia grade (OR 1.69, 95% CI 1.09–2.62; $P = 0.01$; OR 1.01, 1.00–1.02, $P = 0.04$), PIA and left ventricular ejection time (LVEF) were independent predictors of better electrocardiographic ischemia grade (OR 0.4, 95% CI 0.17–0.90; $P = 0.02$, OR 0.92, 95% CI 0.85–0.99; $P = 0.03$, respectively) in multivariate logistic regression analysis.

Conclusion: PIA is one of the most important clinical predictors of better ischemia grades especially when combined with the pain to balloon time, LVEF, and admission CK-MB levels in patients with STEMI. This study provided another evidence for the protective effects of PIA.

Ann Noninvasive Electrocardiol 2008;13(3):278–286

preinfarction angina; ST-segment myocardial infarction; ischemia grade; ECG

Primary percutaneous coronary intervention (pPCI) is considered to be the most effective method of reestablishing coronary blood flow in patients with acute ST-elevation myocardial infarction (STEMI).^{1,2} Although normal epicardial flow can be restored in >85% of cases, prognosis is heavily dependent upon restoration of adequate

perfusion at the level of the microcirculation.³ Despite prompt restoration of brisk epicardial blood flow with primary PCI, a significant proportion of patients with acute myocardial infarction (AMI) have impairment of microvascular integrity and myocardial perfusion.⁴ Grade 3 ischemia (G3I) is defined as ST elevation with distortion of the

Address for reprints: Turgay Celik, M.D., Assistant Professor, Gata Kardiyoloji A.D., 06018 Etlik, Ankara, Turkey. Fax: +90(312)3044250; E-mail: benturgay@yahoo.com

©2008, Copyright the Authors
Journal compilation ©2008, Blackwell Publishing, Inc.

terminal portion of the QRS (emergence of the J point >50% of the R wave in leads with qR configuration, or disappearance of the S wave in leads with an Rs configuration).⁵ Previous studies showed that patients with STEMI who have terminal QRS distortion in two or more adjacent leads (G3I) on the admission electrocardiogram (ECG) have worse prognosis⁵ and less benefit from pPCI.^{6,7} Grade 3 ischemia on the presenting ECG is a strong predictor of failure of microvascular reperfusion and of the need for rescue PCI following thrombolytic therapy.⁸ Whether grade 3 ischemia at presentation reflects a larger myocardial area at risk, or more severe ischemia due to lack of protective mechanisms such as residual blood supply or metabolic protective mechanisms, remains unclear.

Presence of the metabolic protective mechanisms (i.e., "ischemic preconditioning") is one of the important determinants of final infarct size in patients with AMI.⁹ Final infarct size is closely related with prognosis after AMI.^{9,10} The reduction in infarct size associated with preinfarction angina (PIA) has been confirmed in previous studies.^{11,12} The aim of this clinical study is to investigate the impact of PIA on electrocardiographic ischemia grade that is known to be an important predictor of prognosis in patients with AMI treated with pPCI.

METHODS

Study Population

One hundred forty-eight consecutive patients (120 men, mean age = 62 ± 7 years) with STEMI referred to the cardiac catheterization laboratory for pPCI between March 1999 and June 2007 were included in this study. Of those, 42 patients (28%) had acute anterior myocardial infarction. Exclusion criteria were: (1) left bundle branch block, (2) left ventricular hypertrophy, (3) paced or ventricular rhythm, (4) negative T waves in >2 adjacent leads with maximal ST elevation, (5) incomplete or uninterpretable ECG data, and (6) isolated posterior MI (ST depression in V_1 - V_3 without ST elevation in the limb leads or V_4 - V_6).

Data Collection

Multiple demographic and clinical characteristics available on admission were recorded from the patients' medical records. We conducted a retrospective analysis of the catheterization laboratory

quality assurance database and reviewed hospital records, cardiac catheterization reports, interventional reports, and ECGs. PIA was defined as new onset of angina or worsening of previously existing angina within 48 hours prior to admission. Besides electrocardiographic analyses, preprocedural parameters namely admission heart rate, Killip class, preprocedural medications, and pain to balloon time were also analyzed.

Electrocardiographic Analysis

On admission, ECGs (Hewlett Packard M 1700 A, Houston, TX, USA) were immediately obtained in the coronary care unit. The admission ECG was analyzed by an investigator blinded to the patients' subsequent clinical, electrocardiographic, and angiographic outcomes. The following parameters were recorded:

1. ST-segment elevation: The magnitude of ST-segment elevation at the J point in each lead (except aVR) was measured manually to the nearest 0.05 mV using a magnifying glass.
2. Grade of ischemia: Patients were divided into two groups according to their ischemia grade on the admission ECG, as defined by Birnbaum and coworkers.^{13,14} G3I) was defined as (1) absence of an S wave below the TP-PR isoelectric line in >2 leads that usually have a terminal S configuration (leads V_1 - V_3), or (2) ST J-point amplitude >50% of the R-wave amplitude measured from the TP-PR baseline in >2 all other infarct-related leads (Fig. 1). Patients meeting the ST-elevation criteria but not the G3I criteria (J point elevation >1.0 mm but <50% of the R-wave amplitude) were classified as having grade 2 ischemia (G2I) (Fig. 2).
3. ST-segment resolution (STR): ECGs were obtained immediately upon the patient's return to the coronary care unit after primary PCI, within 15 to 30 minutes from completion of the procedure. Seventy percent or greater reduction in ST elevation in the single lead with maximum ST elevation on the baseline ECG is accepted as complete ST-segment resolution.

Angiographic Analysis

Coronary angiography (Siemens HICOR T.O.P Image System, Forchheim, Germany) was performed in multiple orthogonal projections using

Figure 1. Admission electrocardiograms of a patient with inferior STEMI showing grade 3 ischemia. The J point is above 50% of the R-wave amplitude in leads II, III, and aVF.

Judkins' technique. Coronary angiographic data were quantitatively analyzed.

Angiograms were examined by two experienced angiographers who were blinded to all clinical and electrocardiographic data of the study patients.

Angiographically successful primary PCI was defined as residual stenosis <30% with thrombolysis in myocardial infarction (TIMI) 3 flow. A clinically successful primary PCI was defined as angiographic success with resolution of presenting

Figure 2. Admission electrocardiograms of a patient with inferior STEMI showing grade 2 ischemia. The J point is below 50% of the R-wave amplitude in leads II, III, and aVF.

symptoms, without major adverse outcome (death, emergent coronary artery bypass graft (CABG), stroke). Greater than 70% diameter stenosis in 1, 2, or 3 coronary arteries was defined as one-, two-, or three-vessel disease, respectively. Flow in the infarct-related artery was graded according to the TIMI scale¹⁵ and grouped for the purpose of this analysis as TIMI flow = 3 or TIMI flow <3. TIMI myocardial perfusion grade (TMPG) was graded densitometrically based on visual assessment of relative contrast opacification of the myocardial territory subtended by the infarct vessel in relation to epicardial density.^{16,17} Adverse procedural result was defined as the presence of dissection, coronary emboli, no-reflow, a significant (>50%) residual stenosis, or residual thrombus. No-reflow was defined by the presence of TIMI flow <3 at the end of the procedure in the absence of a flow-limiting stenosis.

Adjunctive Therapy

Upon admission, all the patients received aspirin 300 mg a day, heparin, clopidogrel with a starting dose of 300 mg, and maintenance dose of 75 mg and nitroglycerine. Primary PCI was performed as quickly as possible (average door to first balloon time 55 ± 16 minutes). The use of other medications, including GpIIb/IIIa receptor antagonists was at the discretion of the attending operator.

Echocardiographic Analysis

Admission transthoracic echocardiography was performed by using EASOTE 2.5 Mhz probe (ESAOTE, Genova, Italy) at the left lateral decubitus position before primary PCI. All echocardiographic examinations were performed by an experienced echocardiographer who was blinded to all clinical, electrocardiographic, and angiographic data. Left ventricular ejection fraction (LVEF) was calculated by the modified Simpson method as described before.¹⁸

Statistical Analysis

Results are expressed as the mean $\pm$ SD and percentages. The differences between groups were tested for significance by chi-square, Fisher's exact test, independent samples *t*-test. The relationship between PIA and TMPG was analyzed with Phi-coefficient test. Differences were considered significant at $P < 0.05$. We investigated the effects

of different variables on G3I by calculating odds ratios in univariate analysis for all the variables. Variables for which the unadjusted *P* value was < 0.20 in logistic regression analysis were identified as potential risk markers and included in the full model. We reduced the model by using backward elimination and we eliminated potential risk markers by using likelihood ratio tests. Statistical analyses were performed by using SPSS 11.5 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline Clinical, Demographic, and Biochemical Variables

A total of 148 patients (120 male, mean age = 62 ± 6 years) were included in this study. Study population consisted of 110 patients with G2I (88 men, mean age = 63 ± 6 years) and 38 patients with G3I (32 men, mean age = 61 ± 8 years) (Table 1). There were no statistically significant differences between the groups regarding the male-to-female ratio, infarction location, and the presence of other risk factors including age, diabetes mellitus, hypertension, hypercholesterolemia, history of previous MI, smoking, and family history of premature coronary artery disease. Admission heart rate and Killip class was also comparable between the two groups. There was no difference in the use of medications including aspirin, nitrates, beta adrenergic blockers, angiotensin-converting enzyme inhibitor (ACE-I), and statins. However, history of PIA is strongly associated with G2I. On the other hand, admission CK-MB levels were found to be higher in patients with G3I than in patients with G2I (177.7 ± 47.3 U/L vs 148.3 ± 42.5 U/L, $P = 0.02$, Table 1). Besides, the patients with G3I had a significantly longer pain to balloon time than that of the patients with G2I as shown in Table 1.

Angiographic Variables

Baseline angiographic characteristics of the study patients are listed in Table 2. All the patients had total or subtotal occlusion of infarct-related artery with TIMI 0 or 1 flow before coronary intervention. Tissue myocardial perfusion in patients with G2I was better than in patients with G3I grade (90% vs 23%, $P = 0.01$, Table 2). Besides, there was a moderate positive correlation between the presence of PIA and good tissue myocardial perfusion ($r = 0.41$,

Table 1. Baseline Demographic, Clinical, and Biochemical Characteristics of the Study Patients

	Grade-3 Ischemia (n = 38)	Grade-2 Ischemia (n = 110)	P Value
Age (years)	61 ± 8	63 ± 6	0.15
Sex (M), n (%)	32 (84)	88 (80)	0.63
Hypercholesterolemia, n (%)	14 (36)	52 (47)	0.34
Diabetes, n (%)	14 (37)	36 (33)	0.69
Family history, n (%)	3 (8)	15 (13)	0.56
Hypertension, n (%)	19 (50)	52 (47)	0.85
Smoking, n (%)	13 (34)	36 (33)	0.95
Preinfarction angina, n (%)	18 (47)	81 (73)	0.005
Previous MI, n (%)	7 (18)	14 (13)	0.42
Admission HR (bpm)	80 ± 15	82 ± 16	0.42
Killip Class			
Class I, n (%)	27 (71)	88 (70)	0.26
Class II-III, n (%)	11 (29)	22 (20)	
Preprocedural medications			
Aspirin, n (%)	29 (76)	78 (71)	0.67
Nitrat, n (%)	11 (29)	22 (20)	0.52
BAB, n (%)	14 (37)	32 (29)	0.41
ACE-I, n (%)	17 (45)	40 (36)	0.44
Statin, n (%)	20 (46)	43 (38)	0.40
Pain to balloon time (hour)	5.5 ± 0.8	4.9 ± 1.0	0.002
Admission CKMB (U/L)	177.7 ± 47.3	148.3 ± 42.5	0.02
Glucose (mg/dL)	122.7 ± 28.7	117.6 ± 30.6	0.38
Total cholesterol (mg/dL)	181.7 ± 26.1	184.2 ± 24.1	0.59
Triglyceride (mg/dL)	151.9 ± 46.2	141.0 ± 46.7	0.21
LDL cholesterol (mg/dL)	106.4 ± 31.4	109.1 ± 27.9	0.62
HDL cholesterol (mg/dL)	44.3 ± 9.7	43.8 ± 8.1	0.74

MI = myocardial infarction; HR = heart rate; BAB = beta adrenergic blocker; ACE-I = angiotensin-converting enzyme inhibitor; CKMB = creatine kinase-MB isoenzyme; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

$P < 0.001$). Patients presenting with G3I were similar to the patients with G2I in terms of the extent of the coronary artery disease, tirofiban use, lesion length, reference, and final luminal diameter stenoses (Table 2).

Echocardiographic Variables

Admission echocardiography was performed on all study participants. Mean LVEF was lower in the patients with G3I compared to that of the

Table 2. Angiographic, Electrocardiographic, and Echocardiographic Characteristics of the Patients

	Grade-3 Ischemia (n = 38)	Grade-2 Ischemia (n = 110)	P Value
3-vessel disease, n (%)	10 (26)	24 (22)	0.65
Tirofiban use, n (%)	15 (39)	33 (30)	0.31
Reference diameter (mm)	3.10 ± 0.2	3.11 ± 0.1	0.77
Lesion length (mm)	16.2 ± 2.5	16.7 ± 2.8	0.36
ST-segment resolution (%)	63.0 ± 10.1	71.8 ± 10.9	<0.001
TMPC, n (%)			
Grade 0–1, n (%)	10 (26)	10 (9)	0.001
Grade 2–3, n (%)	28 (23)	100 (90)	
LVEF (%)	51.5 ± 4.3	54.0 ± 5.5	0.01

TMPC = tissue myocardial perfusion grade; LVEF = left ventricular ejection fraction.

Table 3. Effects of Various Variables on the Prediction of Grade-3 Ischemia in Univariate and Multivariate Logistic Regression Analyses

	Unadjusted OR	95% CI	P Value	Adjusted OR*	95% CI	P Value
Age (years)	1.03	0.95–1.03	0.15	1.02	0.93–1.03	0.41
PIA, n (%)	0.32	0.15–0.69	0.004	0.4	0.17–0.90	0.02
Pain to balloon time (hours)	1.93	1.25–2.95	0.003	1.69	1.09–2.62	0.01
LVEF (%)	0.91	0.85–0.98	0.01	0.92	0.85–0.99	0.03
Admission CKMB (U/L)	1.01	1.00–1.02	0.04	1.01	1.00–1.02	0.04
TMPG, n (%)	0.28	0.10–0.74	0.01	0.82	0.24–2.74	0.75
DM, n (%)	0.83	0.38–1.80	0.64			

PIA = preinfarction angina; LVEF = left ventricular ejection fraction; CKMB = creatine kinase MB isoenzyme; TMPG = tissue myocardial perfusion grade; DM = diabetes mellitus.

*Adjusted for age, admission CKMB, left ventricular ejection fraction, pain to balloon time, TMPG, and preinfarction angina.

patients with G2I (51.5 ± 4.3 vs 54.0 ± 5.5 , $P = 0.01$, Table 2).

ST-Segment Resolution

Complete ST-segment resolution is defined as 70% or greater reduction in ST elevation in the single lead with maximum ST elevation on the baseline ECG. ST-segment resolution was found to be lower in patients with G3I than in patients with G2I ($63.0 \pm 10.1\%$ vs $71.8 \pm 10.9\%$; $P < 0.001$, Table 2).

Logistic Regression Analysis

Effects of variables on G3I were analyzed by using univariate and multivariate logistic regression analyses. Data for two groups were combined and all the variables were analyzed in univariate analysis as the predictor of worse ischemia grade. As shown in Table 3, univariate analysis identified that age ($P = 0.15$), pain to balloon time ($P = 0.003$), LVEF ($P = 0.01$), TMPG ($P = 0.01$), PIA ($P = 0.004$), and admission CK-MB levels ($P = 0.04$) have significant relation with G3I in our study population. When multivariate analyses were done by using those variables in backward logistic regression analysis, statistical significance of age and TMPG disappeared (Table 3). Although there was no significant relation between diabetes mellitus and G3I in univariate analysis, we included diabetes mellitus in multivariate analysis. Again, we detected no significant association between diabetes mellitus and G3I (Table 3). PIA, pain to balloon time, LVEF, and admission CK-MB levels continued to have statistically significant independent association with G3I in the model. Adjusted odds ratios were calculated as 0.4 for PIA ($P = 0.02$; $CI = 0.17$ –

0.90), 1.69 for pain to balloon time ($P = 0.01$, $CI = 1.09$ – 2.62), 0.92 for LVEF ($P = 0.03$; $CI = 0.85$ – 0.99), and 1.01 for CK-MB ($P = 0.04$, $CI = 1.00$ – 1.02) as shown in Table 3.

DISCUSSION

The primary finding of this study is that PIA is one of the strongest independent predictors of better ischemia grades, namely G2I, in patients with STEMI. In addition, we showed that lower ischemia grade (G2I) is associated with much more ST-segment resolution and better admission left ventricular systolic functions, which are both markers of better prognosis compared to those of the patients with G3I as shown in previous studies.^{19–21}

Shortly after occlusion of an epicardial coronary artery, serial ECG changes are detected by the leads facing the ischemic zone. First, the T waves become tall, symmetrical, and peaked (grade 1 ischemia); second, there is ST elevation without distortion of the terminal portion of the QRS (grade 2 ischemia); and third, changes in the terminal portion of the QRS complex may appear (grade 3 ischemia).^{22–24} During regional myocardial ischemia, the activation wave in the local Purkinje fibers is conducted more slowly.²⁵ 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 ECG.^{26,27} The Purkinje system is less sensitive to ischemia than are the contracting myocytes.^{7,28} 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.^{25,29} Birnbaum et al. showed that patients with distortion of the terminal part of the QRS complex (grade 3 ischemia) on the presenting

ECG had higher rates of reinfarction and mortality, larger infarcts, and less myocardial salvage by reperfusion therapy, although their area at risk was comparable to that of patients with lesser (grade 2) ischemia.^{13,30} The mechanism underlying these correlations remained unclear. In our study, it was found that G3I on the presenting ECG was associated with the failure of ST resolution and poor tissue myocardial perfusion grades. This observation suggests that grade 3 ischemia is a manifestation of severe ischemia that involves the microcirculation. Buber and coworkers assessed the predictive value of grade 3 ischemia on the admission ECG for early ST resolution.⁸ For failure of ST resolution at 1 hour, grade 3 ischemia on the admission ECG had a sensitivity of 46%, a specificity of 85%, a positive predictive value of 95%, and a negative predictive value of 22%. Whether mechanical reperfusion can achieve superior results in these patients remains to be unclarified. However, Birnbaum et al.³¹ showed that in the GUSTO IIB trial, the outcome of patients with G3I on the admission ECG was not better with primary angioplasty than those of the patients undergoing thrombolytic treatment. One can conclude that the clinical outcomes of patients with G3I undergoing primary PCI can be improved with widespread use of stents and GP IIb/IIIa inhibitors in the current daily routine. Similarly, it was shown that the combination of glycoprotein IIb/IIIa receptor antagonists with thrombolytic agents attained much greater ST resolution than that of thrombolysis alone.³² Further studies are needed to assess whether this strategy is beneficial in patients who are identified on admission as being at high risk for failure of myocardial reperfusion. On the other hand, conflicting results were also reported. Sejersten et al. pointed out the importance of timing in grade 3 ischemia patients.³³ They found that the ischemia grade on the presenting ECG in patients with STEMI is a strong and independent predictor of mortality irrespective of the reperfusion modality. In addition, there was a trend toward a larger absolute mortality reduction with primary PCI in grade 3 ischemia patients treated within 3 hours of onset of symptoms. Interestingly, the magnitude of ST-segment elevation did not remain an independent predictor of mortality when the ischemia grade included in the logistic regression analysis. Overall, reinfarction was independent of ischemia grade and the duration of symptoms but was significantly lower in patients treated with primary PCI than with thrombolytic therapy. If treated with

thrombolytic therapy, patients with G3I presenting late (>3 hours) tended to have more reinfarctions. Thus, ischemia grade and timing may provide decision support for the choice of reperfusion strategy for patients with STEMI.

In this study our main objective was to evaluate the effect of the presence of metabolic protective mechanisms (i.e., "ischemic preconditioning") on ischemia grades in patients with STEMI. It was shown that, brief episodes of ischemia not only in animals, but also in humans protected the heart from a more sustained and severe ischemic insult, such as an AMI. Several studies suggested that the PIA, which is a consequence of brief ischemic episodes, paradoxically may have protective effects.^{11,12,34–36} PIA was found to reduce in-hospital death and congestive heart failure/shock and was associated with a smaller myocardial infarct size as measured by CK-MB release. In the thrombolysis in myocardial infarction (TIMI)-4 study, 416 patients with AMI were enrolled; of these, 218 patients had PIA before AMI and 198 did not.¹¹ Despite a preponderance of multivessel disease and diabetes, and a longer time to thrombolysis, the patients with PIA had lower mortality, severe congestive heart failure, or shock rates compared to those of the patients with G2I. Infarct size was also smaller in patients with preinfarction ischemia caused by angina, a finding that parallels the results of animal studies of preconditioning. Analysis of patients in the TIMI-9B study confirmed that patients with PIA, compared with patients without, had smaller infarct size and fewer adverse cardiac events.¹² In the TIMI-9 study, it appeared that for the benefit to be manifest, the PIA had to occur temporally close to the AMI.¹² The brief episodes of transient ischemia (angina) that occurred temporally close to the infarct could have rendered the heart resistant to the subsequent severe and prolonged ischemia associated with the coronary artery occlusion of AMI.

Ischemic preconditioning is a phenomenon that has been observed in virtually every species that has been tested.³⁷ Brief periods of ischemia render the heart resistant to a longer duration of ischemia through a complex series of mechanisms involving complex second messenger pathways that appear to involve such components as adenosine, adenosine receptors, the epsilon isoform of protein kinase C, the ATP-dependent potassium channels, as well as others, including a paradoxical protective role of oxygen radicals.³⁸ In the current study,

history of PIA has a strong association with grade 2 ischemia. In our study group, although 81 patients (70%) with grade 2 ischemia had PIA, only 18 patients (47%) with grade 3 ischemia had a history of PIA ($P = 0.005$). More importantly, multivariate logistic regression analysis showed that PIA was a strong predictor of better electrocardiographic ischemia grades (OR 0.4, 95% CI 0.17–0.90; $P = 0.02$). This finding is consistent with the previous studies revealing the protective effects of PIA. On the other hand, one might speculate that PIA may stimulate collateral coronary flow and have nothing to do with ischemic preconditioning, especially since the interval between PIA and STEMI was not absolutely known as in our study population. Lee and coworkers have thoroughly examined the determinants and prognostic implications of terminal QRS complex distortion in 153 consecutive patients treated with pPCI for AMI.³⁹ In that clinical study, the authors revealed that the pressure-derived fractional collateral flow is a major determinant of terminal QRS complex distortion during AMI, suggesting that collateral flow appears to play a crucial role in preventing terminal QRS complex distortion.

In conclusion, PIA is one of the most important clinical predictors of better ischemia grades in patients with STEMI especially when combined with the pain to balloon time, LVEF, and admission CK-MB levels. Although this study provided another evidence for the protective effects of PIA, further large-scale prospective randomized clinical trials are needed to elucidate the underlying mechanisms and clinical importance of these findings.

STUDY LIMITATIONS

The major limitation of this study is the small sample size. Besides, our study is a retrospective study that has inherently many drawbacks. Although we propose that the PIA is a reflection of ischemic preconditioning that is reasonable, there is no direct proof and there are other explanations PIA is associated with collaterals that have been shown to be associated with lower grades of ischemia. However, this study is only a preliminary study aiming to give inspiration for the future large-scale prospective randomized studies.

REFERENCES

1. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). *J Am Coll Cardiol* 2004;44:E1–E211.
2. Andersen HR, Nielsen TT, Rasmussen K, et al. DANAMI-2 Investigators. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* 2003;349:733–742.
3. Assessment of the Safety and Efficacy of a New Treatment Strategy with percutaneous Coronary Intervention (ASSENT-4 PCI) Investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): Randomized trial. *Lancet* 2006;367:569–578.
4. Ito H, Okamura A, Iwakura K, et al. Myocardial perfusion patterns related to thrombolysis in myocardial infarction perfusion grades after coronary angioplasty in patients with acute anterior wall myocardial infarction. *Circulation* 1996;93:1993–1999.
5. Birnbaum Y, Kloner R, Sclarovsky S, et al. Distortion of the terminal portion of the QRS on the admission electrocardiogram in acute myocardial infarction and correlation with infarct size and long term prognosis (Thrombolysis In Myocardial Infarction 4 trial). *Am J Cardiol* 1996; 78:396.
6. Lee CW, Hong MK, Yang HS, et al. Determinants and prognostic implications of terminal QRS complex distortion in patients treated with primary angioplasty for acute myocardial infarction. *Am J Cardiol* 2001;88:210.
7. Billgren T, Maynard C, Christian TF, et al. Grade 3 ischemia on the admission electrocardiogram predicts rapid progression of necrosis over time and less myocardial salvage by primary angioplasty. *J Electrocardiol* 2005;38:187–194.
8. Buber J, Gilutz H, Birnbaum Y, et al. Grade 3 ischemia on admission and absence of prior beta-blockade predict failure of ST resolution following thrombolysis for anterior myocardial infarction. *Int J Cardiol* 2005;104:131–137.
9. Ottani F, Galvani M, Ferrini D, et al. Prodromal angina limits infarct size. A role for ischemic preconditioning. *Circulation* 1995;91:291.
10. Sheehan FH, Mathey DG, Schofer J, et al. Effect of interventions in salvaging left ventricular function in acute myocardial infarction: A study of intracoronary streptokinase. *Am J Cardiol* 1983;52:431.
11. Kloner RA, Shook T, Przyklenk K, et al. Previous angina alters inhospital outcome in TIMI 4. A clinical correlate to preconditioning? *Circulation* 1995;91:37–45.
12. Kloner RA, Shook T, Antman EM, et al. Prospective temporal analysis of the onset of preinfarction angina versus outcome: An ancillary study in TIMI-9B. *Circulation* 1998;97:1042–1045.
13. Birnbaum Y, Mahaffey KW, Criger DA, et al. Grade III ischemia on presentation with acute myocardial infarction predicts rapid progression of necrosis and less myocardial salvage with thrombolysis. *Cardiology* 2002;97:166–174.
14. Birnbaum Y, Maynard C, Wolfe S, et al. Terminal QRS distortion on admission is better than ST segment measurements in predicting final infarct size and assessing the potential effect of thrombolytic therapy in anterior wall acute myocardial infarction. *Am J Cardiol* 1999;84:530–534.
15. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. *N Engl J Med* 1985;312:932–936.
16. Gibson CM, Cannon CP, Murphy SA, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation* 2000;101:125–130.

1. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation

17. Gibson CM, Murphy SA, Rizzo MJ, et al. Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. Thrombolysis In Myocardial Infarction (TIMI) Study Group. *Circulation* 1999;99:1945-1950.
18. Otterstad JE, Froeland G, St John Sutton M, et al. Accuracy and reproducibility of biplane two-dimensional echocardiographic measurements of left ventricular dimensions and function. *Eur Heart J* 1997;18:507-513.
19. Matetzky S, Novikov M, Gruberg L, et al. The significance of persistent ST elevation versus early resolution of ST segment elevation after primary PTCA. *J Am Coll Cardiol* 1999;34:1932-1938.
20. de Lemos JA. ST-Segment resolution as a marker of epicardial and myocardial reperfusion after thrombolysis: Insights from the TIMI 14 and in TIME-II trials. *J Electrocardiol* 2000;33(Suppl.):67-72.
21. Saran RK, Been M, Furniss SS, et al. Reduction in ST segment elevation after thrombolysis predicts either coronary reperfusion or preservation of left ventricular function. *Br Heart J* 1990;64:113-117.
22. Atar S, Barbagelata A, Birnbaum Y. Electrocardiographic diagnosis of ST-elevation myocardial infarction. *Cardiol Clin* 2006;24:343-365.
23. Sclarovsky S, Mager A, Kusnec J, et al. Electrocardiographic classification of acute myocardial ischemia. *Isr J Med Sci* 1990;26:525-531.
24. Birnbaum Y, Wagner GS. The initial electrocardiographic pattern in acute myocardial infarction: Correlation with infarct size. *J Electrocardiol* 1999;32(Suppl.):122-128.
25. Holland R, Brooks H. The QRS complex during myocardial ischemia: An experimental analysis in the porcine heart. *J Clin Invest* 1976;57:541.
26. Barnhill J, Tendera M, Cade H, et al. Depolarization changes early in the course of myocardial infarction: Significance of changes in the terminal portion of the QRS complex. *J Am Coll Cardiol* 1989;14:143.
27. Wagner N, Sevilla D, Krucoff M, et al. Transient alterations of the QRS complex and ST segment during percutaneous transluminal balloon angioplasty of the left anterior descending coronary artery. *Am J Cardiol* 1988;62:1038.
28. DeHaan R. Differentiation of the atrioventricular conducting system of the heart. *Circulation* 1961;24:458.
29. Feldman T, Chua K, Childres R. R wave of the surface and intracoronary electrogram during acute coronary artery occlusion. *Am J Cardiol* 1986;58:885.
30. Birnbaum Y, Herz I, Sclarovsky S, et al. Prognostic significance of the admission electrocardiogram in acute myocardial infarction. *J Am Coll Cardiol* 1996;27:1128-1132.
31. Birnbaum Y, Goodman S, Barr A, et al. Comparison of primary coronary angioplasty versus thrombolysis in patients with ST-segment elevation acute myocardial infarction and grade II and grade III myocardial ischemia on the enrollment electrocardiogram. *Am J Cardiol* 2001;88:842-847.
32. de Lemos JA, Antman EM, Gibson CM, et al. Abciximab improves both epicardial flow and myocardial reperfusion in ST-elevation myocardial infarction: Observations from the TIMI 14 Trial. *Circulation* 2000;101:239-243.
33. Sejersten M, Birnbaum Y, Ripa RS, et al. DANAMI-2 Investigators. Influences of electrocardiographic ischaemia grades and symptom duration on outcomes in patients with acute myocardial infarction treated with thrombolysis versus primary percutaneous coronary intervention: Results from the DANAMI-2 trial. *Heart* 2006;92:1577-1582.
34. Anzai T, Yoshikawa T, Asakura Y, et al. Effect on short-term prognosis and left ventricular function of angina pectoris prior to first Q-wave anterior wall acute myocardial infarction. *Am J Cardiol* 1994;74:755-759.
35. Nakagawa Y, Ito H, Kitakaze M, et al. Effect of angina pectoris on myocardial protection in patients with reperfused anterior wall myocardial infarction: Retrospective clinical evidence of "preconditioning." *J Am Coll Cardiol* 1995;25:1076-1083.
36. Ottani F, Galvani M, Ferrini D, et al. Prodromal angina limits infarct size. A role for ischemic preconditioning. *Circulation* 1995;91:291-297.
37. Kloner RA, Bolli R, Marban E, et al. Medical and cellular implications of stunning, hibernation, and preconditioning. An NHLBI workshop. *Circulation* 1998;97:1848-1867.
38. Kloner RA, Jennings RB. Consequences of brief ischemia: Stunning, preconditioning, and their clinical implications: part 1. *Circulation* 2001;104:2981-2989.
39. Lee CW, Hong MK, Yang HS, et al. Determinants and prognostic implications of terminal QRS complex distortion in patients treated with primary angioplasty for acute myocardial infarction. *Am J Cardiol* 2001;88:210-213.