Effect of Preinfarction Angina Pectoris on Myocardial Blush Grade After Reperfusion in First Anterior Wall Acute Myocardial Infarction

Akira Tamura, MD; Kazuhiro Shinozaki, MD; Toru Watanabe, MD;
Toru Nakaishi, MD; Kimiaki Nagase, MD; Jun-ichi Kadota, MD

Background The aim of the present study was to clarify the effect of preinfarction angina pectoris (PIA) on myocardial blush grade (MBG), a simple marker of myocardial tissue-level reperfusion, in acute myocardial infarction (AMI).

Methods and Results One hundred forty-two patients with first anterior wall AMI who were admitted within 6h after onset of symptoms were examined. PIA was defined as typical chest pain within 48h before onset of symptoms. MBG was evaluated by coronary angiography after reperfusion. Patients with MBG 2 or 3 (n=103) had a higher frequency of PIA and a lower frequency of diabetes mellitus than those with MBG 0 or 1 (n=39) (57% vs 28%, $p=0.004$, and 23% vs 44%, $p=0.03$, respectively). The former had a lower peak creatine kinase level and a greater left ventricular ejection fraction at predischARGE than the latter ($3,652\pm2,440$ vs $5,507\pm3,058$ IU/L, $p=0.0002$, and $57\pm12\%$ vs $45\pm11\%$, $p<0.0001$, respectively). Multivariate logistic regression analysis showed that PIA ($p=0.004$) and diabetes mellitus ($p=0.03$) were independently associated with MBG 2 or 3 after reperfusion.

Conclusions PIA has beneficial effects on myocardial tissue-level reperfusion evaluated by MBG in first anterior wall AMI. (Circ J 2006; 70: 698–702)

Key Words: Acute myocardial infarction; Myocardial blush grade; Preinfarction angina pectoris

The presence of preinfarction angina pectoris (PIA) has been shown to have beneficial effects on left ventricular (LV) function and prognosis after acute myocardial infarction (AMI).^{1–7} Recently, myocardial blush grade (MBG) has been shown to be a simple and useful marker of myocardial tissue-level reperfusion in AMI.^{8–11} Because the effect of PIA on MBG has not yet been investigated, we conducted the present study.

Methods

Study Patients

We examined 142 consecutive patients (115 men, 27 women, mean age 61 ± 11 years) with first anterior wall AMI who were admitted within 6h after onset of symptoms and who met the following criteria: (1) typical chest pain lasting ≥ 20 min; (2) ST-segment elevation ≥ 0.2 mV in ≥ 2 adjacent precordial leads on the admission electrocardiogram; (3) an increase in the serum creatine kinase (CK) level more than twice the normal value; (4) no other heart or lung disease; (5) emergency coronary angiography and coronary angiography and left ventriculography performed at predischARGE; and (6) adequate assessment of MBG after reperfusion. Informed consent for revascularization therapy and follow-up catheterization was given by all patients.

(Received May 12, 2005; revised manuscript received March 16, 2006; accepted March 28, 2006)

Second Department of Internal Medicine, Faculty of Medicine, Oita University, Oita, Japan

Mailing address: Akira Tamura, MD, Second Department of Internal Medicine, Oita University, Hasama, Oita 879-5593, Japan. E-mail: akira@med.oita-u.ac.jp

PIA was defined as typical chest pain within 48h before onset of AMI. Diabetes mellitus (DM) was considered present if this diagnosis and treatment, including diet, drugs, or insulin, had been given to the patient or if an abnormal oral glucose tolerance test or hemoglobinA1c $\geq 6.5\%$ was found after admission.

Cardiac Catheterization

Emergency coronary arteriography was performed using the Judkins or Amplatz technique. Multiple projections were recorded to ensure optimal visualization of the coronary vessels. The coronary flow in the infarct-related artery was graded according to the classification used in the Thrombolysis In Myocardial Infarction (TIMI) trial.¹² Proximal left anterior descending coronary artery (LAD) occlusion was defined as an occlusion of the artery proximal to its first septal branch. The grade of collateral filling in the LAD was determined according to the criteria of Rentrop et al.¹³ A collateral circulation with a grade of 2 or 3 was defined as “good”. After angiographic confirmation of total or subtotal occlusion of the LAD, primary coronary angioplasty was performed. If an optimal result (residual stenosis $<50\%$ without severe dissection) could not be obtained by balloon coronary angioplasty, coronary stenting was performed (n=59). Successful reperfusion was defined as the establishment of TIMI grade 3 flow in the infarct-related artery on the final coronary arteriogram. MBG was evaluated as follows⁸ on the final left coronary angiogram in the lateral view after reperfusion: 0=no myocardial blush or contrast density; 1=minimal myocardial blush or contrast density; 2=moderate myocardial blush or contrast density, but less than that obtained during angiography of the con-

Table 1 Clinical and Angiographic Characteristics of the Study Patients

	MBG		p value
	2 or 3 (n=103)	0 or 1 (n=39)	
Age (years)	61±11	61±10	NS
Men	83 (81%)	32 (82%)	NS
Time to admission (min)	135±74	144±70	NS
PIA	59 (57%)	11 (28%)	0.004
Hypertension	56 (54%)	25 (64%)	NS
Diabetes mellitus	24 (23%)	17 (44%)	0.03
Smoking	69 (67%)	28 (72%)	NS
Emergency coronary angiography			
TIMI flow 3	7 (7%)	1 (3%)	NS
Good collaterals	39 (38%)	9 (23%)	NS
Multivessel disease	35 (34%)	16 (41%)	NS
Proximal LAD occlusion	66 (64%)	24 (62%)	NS
Reperfusion therapy			
Balloon angioplasty	96 (93%)	36 (92%)	NS
Stenting	42 (41%)	17 (44%)	NS
TIMI flow 3 on the final coronary angiogram	101 (98%)	28 (72%)	<0.0001
Peak CK level (IU/L)	3,652±2,440	5,507±3,058	0.0002
TIMI flow 3 at predischARGE	98 (95%)	36 (92%)	NS
LVEF at predischARGE (%)	57±12	45±11	<0.0001
Calcium antagonist	31 (30%)	13 (33%)	NS
β-blocker	18 (17%)	6 (15%)	NS
ACEI or ARB	70 (68%)	28 (72%)	NS

Data are mean±SD or number (%).

MBG, myocardial blush grade; PIA, preinfarction angina pectoris; TIMI, Thrombolysis In Myocardial Infarction; LAD, left anterior descending artery; CK, creatine kinase; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor antagonist.

Table 2 Associations of PIA With Clinical and Angiographic Characteristics

	PIA (+) (n=70)	PIA (−) (n=72)	p value
Age (years)	61±12	61±10	NS
Men	54 (77%)	61 (85%)	NS
Time to admission (min)	134±70	141±76	NS
Hypertension	42 (60%)	39 (54%)	NS
Diabetes mellitus	21 (30%)	20 (28%)	NS
Smoking	45 (64%)	52 (72%)	NS
Emergency coronary angiography			
TIMI flow 3	4 (6%)	4 (6%)	NS
Good collaterals	29 (41%)	19 (26%)	NS
Multivessel disease	24 (34%)	27 (38%)	NS
Proximal LAD occlusion	45 (64%)	45 (63%)	NS
Reperfusion therapy			
Balloon angioplasty	64 (91%)	68 (94%)	NS
Stenting	31 (44%)	28 (39%)	NS
TIMI flow 3 on the final coronary angiogram	66 (94%)	63 (88%)	NS
MBG	2.0±0.6	1.7±0.8	0.02
Peak CK (IU/L)	3,280±2,107	5,020±3,017	0.0001
TIMI flow 3 at predischARGE	68 (97%)	66 (92%)	NS
LVEF at predischARGE (%)	59±11	49±13	<0.0001
Calcium antagonist	23 (33%)	21 (29%)	NS
β-blocker	16 (23%)	8 (11%)	NS
ACEI or ARB	50 (71%)	48 (67%)	NS

Data are mean±SD or number (%).

See Table 1 for abbreviations.

tralateral or ipsilateral non-infarct-related coronary artery; and 3=normal myocardial blush or contrast density, comparable to that obtained during angiography of a contralateral or ipsilateral noninfarct-related coronary artery. When myocardial blush persisted, this finding was graded as 0. MBG 2 or 3 was defined as good myocardial tissue-level perfusion. Reproducibility of the MBG was evaluated by 2 observers viewing 20 samples of the coronary angiograms. Intra- and interobserver agreement was 95% and 90%, respectively. Coronary arteriography and left ventriculog-

raphy were repeated at predischARGE. Left ventriculograms performed in the 30 degree right anterior oblique projection were analyzed for LV ejection fraction (LVEF) by an experienced cardiologist who was unaware of the patients' data. LV end-diastolic and end-systolic volumes were calculated by the area-length method.¹⁴

Measurements of Serum CK Levels

Venous blood samples for determination of the peak CK level were obtained every 3 h during the first 24 h and once

Table 3 Logistic Regression Analysis to Determine Factors Related to MBG 2 or 3

Variables	Univariate analysis		Multivariate analysis	
	Chi-square	p value	Chi-square	p value
Age (years)	0.02	0.88		
Men	1.31	0.25		
Time to admission (min)	0.45	0.5		
PIA	7.62	0.006	8.19	0.004
Hypertension	1.81	0.18	1.29	0.26
Diabetes mellitus	5.5	0.02	5.02	0.03
Smoking	0.07	0.8		
Initial TIMI flow grade	1.08	0.3		
Proximal LAD occlusion	0.004	0.95		
Good collaterals	1.94	0.16	0.55	0.46
Multivessel disease	0.61	0.44		
Use of stent	0.09	0.76		

See Table 1 for abbreviations.

daily from the second day until reaching a normal value.

Statistical Analysis

Data are expressed as mean±SD. Continuous variables were analyzed by the unpaired t-test or Mann-Whitney U-test. Univariate and multivariate logistic regression analysis was performed to determine independent factors of MBG 2 or 3 after reperfusion. The variables used for univariate analysis were age, gender, coronary risk factors, PIA, time elapsed from the onset of symptoms to admission, initial TIMI flow grade, good collateral circulation to the LAD, multivessel disease, proximal LAD occlusion, and use of coronary stent. Multivariate logistic regression analysis was performed using variables that showed $p < 0.2$ in univariate regression analysis. A p -value < 0.05 was considered statistically significant.

Results

Table 1 shows the clinical and angiographic characteristics of the study patients. Distal protection devices were not used in any of them. Patients with MBG 2 or 3 ($n=103$) had a higher frequency of PIA and a lower frequency of DM than those with MBG 0 or 1 ($n=39$) (57% vs 28%, $p=0.004$, and 23% vs 44%, $p=0.03$, respectively). The former had a higher incidence of TIMI flow 3 after reperfusion, a lower peak CK level, and a greater LVEF at predischARGE than the latter (98% vs 72%, $p<0.0001$; $3,652\pm2,440$ vs $5,507\pm3,058$ IU/L, $p=0.0002$, and $57\pm12\%$ vs $45\pm11\%$, $p<0.0001$, respectively). Patients with PIA ($n=70$) had a greater MBG, a lower peak CK level, and a greater LVEF at predischARGE than those without it ($n=72$) (2.0 ± 0.6 vs 1.7 ± 0.8 , $p=0.02$, $3,280\pm2,107$ vs $5,020\pm3,017$ IU/L, $p=0.0001$, 59 ± 11 vs $49\pm13\%$, $p<0.0001$, respectively) (Table 2).

Table 3 shows the results of univariate and multivariate logistic regression analysis performed to determine independent factors of MBG 2 or 3 after reperfusion. Variables with a value of $p < 0.2$ on univariate regression analysis (PIA, DM, hypertension, and good collateral circulation) were used for the multivariate logistic regression analysis, which showed that PIA ($p=0.004$) and DM ($p=0.03$) were independently associated with MBG 2 or 3 after reperfusion.

Discussion

The present study results indicate that PIA and DM are

associated with MBG 2 or 3 after reperfusion in first anterior wall AMI. As MBG is a simple and useful marker of myocardial tissue-level reperfusion in AMI^{8–11} the results indicate that PIA has protective effects against myocardial tissue-level damage in AMI. The beneficial effects of PIA can be attributed to a reduction in infarct size through myocardial ischemic preconditioning^{1,2,15} PIA could also protect from coronary microvascular damage after reperfusion through microvascular ischemic preconditioning¹⁶ Ischemia/reperfusion generates reactive oxygen species (ROS)¹⁷ which induce impaired endothelium-dependent relaxation and platelet aggregation in arterioles, resulting in vasospasm and thrombosis^{18,19} Capillary endothelial cell swelling, leukocyte-capillary plugging, and leukocyte-dependent edema after reperfusion lead to capillary no-reflow^{20–24} In postcapillary venules, ROS promotes the production of chemotactic mediators and the expression of adhesion molecules on the surface of leukocytes and endothelial cells, contributing to endothelial barrier disruption and leukocyte adhesion.^{25,26} These changes after reperfusion lead to microvascular damage. Experimental studies have shown that ischemic preconditioning induces the development of protected phenotypes in endothelial cells lining arterioles, capillaries, and venules.^{18,27–32} As a consequence of ischemic preconditioning, vasospasm and thrombosis are less likely to develop in arterioles, capillary perfusion deficits are reduced, and the inflammatory responses in the postcapillary venules are prevented. Thus, ischemic preconditioning could contribute to high MBG at risk area in AMI patients with PIA.

Previous studies have demonstrated that DM is associated with an adverse outcome after AMI^{33,34} Angeja et al³⁵ reported that despite an equal rate of TIMI 3 flow after thrombolytic therapy and adjunctive/rescue percutaneous coronary intervention (PCI), diabetic patients had a lower incidence of complete ST-segment resolution after revascularization therapy than nondiabetic patients, suggesting that impaired microvascular flow is greater in the former than in the latter. Our evaluation by MBG provided additional information that the presence of DM affects myocardial tissue-level perfusion in patients with AMI. This unfavorable effect of DM on myocardial tissue-level perfusion may contribute at least in part to the poorer outcomes observed in diabetic patients with AMI.^{33,34} The exact mechanisms for impaired myocardial tissue-level perfusion after reperfusion in diabetic patients with AMI are unclear, but several have been proposed. First, preexisting impaired endothelium-

dependent vasodilation;^{36–38} preexisting impaired autoregulatory response of microvessels to increased myocardial demands^{39,40} and preexisting structural changes in the coronary microvasculature⁴¹ could be involved in the poor MBG after reperfusion in patients with DM. Second, hyperglycemia itself could enhance microvascular damage after reperfusion by the generation of ROS via multiple pathways.⁴²

Study Limitations

First, our study sample was relatively small. Second, we examined only selected patients with anterior wall AMI. Therefore, our results might not be applicable to all patients with anterior wall AMI or those with other types of AMI. Third, because we did not record the electrocardiogram at 60 min after reperfusion in all the patients, we could not evaluate the relationship between PIA with ST-segment resolution, another marker of myocardial tissue-level reperfusion in AMI.^{43–46} Takahashi et al⁴⁷ recently reported that PIA is associated with a greater degree of resolution of ST-segment elevation in patients with TIMI 3 flow after primary PCI. The relationship between PIA and resolution of ST-segment elevation or MBG remains to be further investigated. Fourth, PCI-induced distal embolism could have affected MBG after reperfusion. However, it is unlikely that the incidence of this type of embolism differed between patients with and without PIA. In addition, the use of distal protection devices also could affect MBG after reperfusion in AMI patients at high risk of clinically relevant embolization.⁴⁸ None of the present patients had these devices.

Conclusions

This study indicates that PIA is associated with MBG 2 or 3 after reperfusion in patients with first anterior wall AMI, suggesting that PIA has beneficial effects on myocardial tissue-level reperfusion.

References

- Ottani F, Galvani M, Ferrini D, Sorbello F, Limonetti P, Pantoli D, et al. Prodromal angina limits infarct size: A role for ischemic preconditioning. *Circulation* 1995; **91**: 291–297.
- Nakagawa Y, Ito H, Kitakaze M, Kusuoka H, Hori M, Kuzuya T, 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.
- Anzai T, Yoshikawa T, Asakura Y, Abe S, Akaishi M, Mitamura H, et al. Preinfarction angina as a major predictor of left ventricular function and long-term prognosis after a first Q-wave myocardial infarction. *J Am Coll Cardiol* 1995; **26**: 319–327.
- Andreotti F, Pasceri V, Hackett DR, Davies GJ, Haider AW, Maseri A. Preinfarction angina as a predictor of more rapid coronary thrombolysis in patients with acute myocardial infarction. *N Engl J Med* 1996; **334**: 7–12.
- Nagao K, Satou K, Arima K, Watanabe I, Yamashita M, Kanmatsuse K. Relationship between preinfarction angina and time interval to reperfusion with thrombolytic therapy in acute myocardial infarction. *Jpn Circ J* 1997; **61**: 843–849.
- Ishihara M, Sato H, Tateishi H, Kawagoe T, Shimatani Y, Kurisu S, et al. Implications of prodromal angina pectoris in anterior wall acute myocardial infarction: Acute angiographic findings and long-term prognosis. *J Am Coll Cardiol* 1997; **30**: 970–975.
- Solomon SD, Anavekar NS, Greaves S, Rouleau JL, Hennekens C, Pfeffer MA, for the HEART investigators. Angina pectoris prior to myocardial infarction protects against subsequent left ventricular remodeling. *J Am Coll Cardiol* 2004; **43**: 1511–1514.
- Van't Hof AWJ, Liem A, Suryapranata H, Hoorntje JCA, de Boer MJ, Zijlstra F, on behalf of the Zwolle Myocardial Infarction Study Group. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: Myocardial blush grade. *Circulation* 1998; **97**: 2302–2306.
- Gibson CM, Cannon CP, Murphy SA, Ryan KA, Mesley R, Marble SJ, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation* 2000; **101**: 125–130.
- Henriques JPS, Zijlstra F, van't Hof AWJ, de Boer MJ, Dambrink JHE, Gosselink M, et al. Angiographic assessment of reperfusion in acute myocardial infarction by myocardial blush grade. *Circulation* 2003; **107**: 2115–2119.
- Hoffmann R, Haager P, Arning J, Christott P, Radke P, Blindt R, et al. Usefulness of myocardial blush grade early and late after primary coronary angioplasty for acute myocardial infarction in predicting left ventricular function. *Am J Cardiol* 2003; **92**: 1015–1019.
- The TIMI Study Group. The Thrombolysis In Myocardial Infarction (TIMI) trial. *N Engl J Med* 1985; **312**: 932–936.
- Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol* 1985; **5**: 587–592.
- Kennedy JW, Trenholme SE, Kasser IS. Left ventricular volume and mass from single-plane cineangiograms: A comparison of antero-posterior and right anterior oblique methods. *Am Heart J* 1970; **80**: 343–352.
- Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: A delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; **74**: 1124–1136.
- Dayton C, Yamaguchi T, Warren A, Korthuis RJ. Ischemic preconditioning prevents postischemic arteriolar, capillary, and post capillary venular dysfunction: Signaling pathways mediating the adaptive metamorphosis to a protected phenotype in preconditioned endothelium. *Microcirculation* 2002; **9**: 73–89.
- Bolli R, Jeroudi MO, Patel BS, DuBose CM, Lai EK, Roberts R, et al. Direct evidence that oxygen-derived free radicals contribute to postischemic myocardial dysfunction in the intact dog. *Proc Natl Acad Sci USA* 1989; **86**: 4695–4699.
- DeFily DV, Chillian WM. Preconditioning protects coronary arteriolar endothelium from ischemia-reperfusion injury. *Am J Physiol* 1993; **265**: H700–H706.
- Davenpeck KL, Gauthier TW, Lefer AM. Inhibition of endothelial-derived nitric oxide promotes P-selection expression and actions in the rat microcirculation. *Gastroenterology* 1994; **107**: 1050–1058.
- Engler RL, Schmid-Schonbein GW, Pavelec RS. Leukocyte capillary plugging in myocardial ischemia and reperfusion in the dog. *Am J Pathol* 1983; **111**: 98–111.
- Mazzoni M, Intaglietta M, Crogue Jr EJ, Arfors KE. Amiloride-sensitive Na⁺ pathways in capillary endothelial cell swelling during hemorrhagic shock. *J Appl Physiol* 1992; **73**: 1467–1473.
- Jerome SN, Akimitsu T, Korthuis RJ. Leukocyte adhesion, edema, and the development of postischemic capillary no-reflow. *Am J Physiol* 1994; **267**: H1329–H1336.
- Grisham MB, Granger DN, Lefer DJ. Modulation of leukocyte-endothelial interactions by reactive metabolites of oxygen and nitrogen: Relevant to ischemic heart disease. *Free Radic Biol Med* 1998; **25**: 404–433.
- Watanabe N, Akasaka T, Toyota E, Fujimoto K, Kajita T, Shigeto F, et al. Three-dimensional microstructural abnormality of the coronary capillary network after myocardial reperfusion: Comparison between ‘reflow’ and ‘no-reflow’. *Circ J* 2004; **68**: 868–872.
- Taylor A, Granger DN. Role of adhesion molecules in vascular regulation and damage. *Curr Hypertens Rep* 2000; **2**: 78–83.
- Korthuis RJ, Gute DC, Cepinskas G, Kvietys PR. Cellular mechanisms of acute vs delayed preconditioning. *Pathophysiology* 1998; **5**: 35–48.
- Richard V, Kaeffer N, Tron C, Thuillez C. Ischemic preconditioning protects against coronary endothelial dysfunction induced by ischemia and reperfusion. *Circulation* 1994; **89**: 1254–1261.
- Jerome SN, Akimitsu T, Gute DC, Korthuis RJ. Ischemic preconditioning attenuates capillary no-reflow induced by prolonged ischemia and reperfusion. *Am J Physiol* 1995; **268**: H2063–H2067.
- Bouchard JF, Lamontagne D. Mechanisms of protection afforded by preconditioning to endothelial function against ischemic injury. *Am J Physiol* 1996; **271**: H1801–H1806.
- Rubino A, Yellon DM. Ischaemic preconditioning of the vasculature: An overlooked phenomenon for protecting the heart? *Trends Pharmacol Sci* 2000; **21**: 225–230.
- Beauchamp P, Richard V, Tamion F, Lallemand F, Lebreton JP, Vaudry H, et al. Protective effects of preconditioning in cultured rat endothelial cells: Effects on neutrophil adhesion and expression of

- ICAM-1 after anoxia and reoxygenation. *Circulation* 1999; **100**: 541–546.
32. Laude K, Thuillez C, Richard V. Coronary endothelial dysfunction after ischemia and reperfusion: A new therapeutic target? *Braz J Med Biol Res* 2001; **34**: 1–7.
 33. Jacoby RM, Nesto RW. Acute myocardial infarction in the diabetic patients: Pathophysiology, clinical course and prognosis. *J Am Coll Cardiol* 1992; **20**: 736–744.
 34. Ishihara M, Sato H, Kawagoe T, Shimatani Y, Kurisu S, Nishioka K, et al. Impact of diabetes mellitus on long-term survival after acute myocardial infarction in patients with single vessel disease. *Heart* 2001; **86**: 133–138.
 35. Angeja BG, de Lemos J, Murphy SA, Marble SJ, Antman EM, Cannon CP, et al. Impact of diabetes mellitus on epicardial and microvascular flow after fibrinolytic therapy. *Am Heart J* 2002; **144**: 649–656.
 36. Cohen RA. Dysfunction of vascular endothelium in diabetes mellitus. *Circulation* 1993; **87**(Suppl 5): 67–76.
 37. Tesfamariam B. Free radicals in diabetic endothelial cell dysfunction. *Free Radic Biol Med* 1994; **16**: 383–391.
 38. Nitenberg A, Valensi P, Sachs R, Dali M, Aptekar E, Attali JR. Impairment of coronary vascular reserve and ACh-induced coronary vasodilation in diabetic patients with angiographically normal coronary arteries and normal left ventricular systolic function. *Diabetes* 1993; **42**: 1017–1025.
 39. Bucala R, Tracey KJ, Cerami A. Advanced glycosylation products quench nitric oxide and mediate defective endothelium-dependent vasodilation in experimental diabetes. *J Clin Invest* 1991; **87**: 432–438.
 40. Nasher PJ Jr, Brown RE, Oskarsson H, Winniford MD, Rossen JD. Maximal coronary flow reserve and metabolic coronary vasodilation in patients with diabetes mellitus. *Circulation* 1995; **91**: 635–640.
 41. Zarich SW, Nesto RW. Diabetic cardiomyopathy. *Am Heart J* 1989; **118**: 1000–1012.
 42. Gerich JE. Clinical significance, pathogenesis, and management of postprandial hyperglycemia. *Arch Intern Med* 2003; **163**: 1306–1316.
 43. Van't Hof AWJ, Liem A, de Boer M, Zijlstra F, for the Zwolle Myocardial Infarction Study Group. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. *Lancet* 1997; **350**: 615–619.
 44. Matetzky S, Freimark D, Chouraqui P, Novikov I, Agranat O, Rabinowitz B, et al. The distinction between coronary and myocardial reperfusion after thrombolytic therapy by clinical markers of reperfusion. *J Am Coll Cardiol* 1998; **32**: 1326–1330.
 45. Matetzky S, Novikov M, Gruberg L, Freimark D, Feinberg M, Elian D, 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.
 46. Johanson P, Jernberg T, Gunnarsson G, Lindahl B, Wallentin L, Dellborg M. Prognostic value of ST-segment resolution: When and what to measure. *Eur Heart J* 2003; **24**: 337–345.
 47. Takahashi T, Anzai T, Yoshikawa T, Maekawa Y, Asakura Y, Satoh T, et al. Effect of preinfarction angina pectoris on ST-segment resolution after primary coronary angioplasty for acute myocardial infarction. *Am J Cardiol* 2002; **90**: 465–469.
 48. Limbruno U, de Caterina R. EMERALD, AIMI, and PROMISE: Is there still a potential for embolic protection in primary PCI? *Eur Heart J* 2006; 1–7.