Int J Clin Exp Med 2016;9(7):14604-14611
www.ijcem.com /ISSN:1940-5901/IJCEM0023656

Original Article

Primary versus delayed percutaneous coronary intervention in terms of autonomic nervous function, inflammtory responses and cardiac function

Qing-Bo Cao, Zeng-Lei Han, Xue-Yu Sun, Bo Zhou, Xiu-Wei Wang

Department of Cardiology, Qingdao Eighth People's Hospital, Qingdao 266100, Shandong, P. R. China

Received January 9, 2016; Accepted May 5, 2016; Epub July 15, 2016; Published July 30, 2016

Abstract: Percutaneous coronary intervention is an effective treatment in acute myocardial infarction (AMI) patients, as it can rapidly improve the blood supply of ischemic coronary artery. Studies have shown that different PCI approaches have different effect in AMI patients. The aim of this study was to explore the effect of primary or delayed PCI therapy on autonomic nervous function, inflammtory responses and cardiac function of AMI patients. 150 patients diagnosed as AMI were divided into three groups based on the different treatment they received: the primary PCI group (n=60), the delayed PCI group (n=50) and the control group (n=40). All patients were tested on their serum hs-CRP, sCD40L and NT-proBNP level, LVEF and LVEDD value, and autonomic nervous function parameters at certain time points after treatment. Our results showed that when compared with the control group, the two PCI groups showed significant improvement regarding patients' hs-CRP, sCD40L and NT-proBNP level and LVEF, LVEDD value, and autonomic nervous function parameters. Moreover, the difference between was also significant. In conclusion, both primary and delayed PCI are effective in restoring coranary blood flow, alleviating post-AMI inflammatory responses and improving left ventricular function and autonomic nervous function. And primary PCI is even superior to delayed PCI in terms of the above aspects.

Keywords: Acute myocardial infarction, percutaneous coronary intervention, left ventricular remodeling, autonomic nervous, heart rate turbulence

Introduction

As a serious life-threatening disease, the incidence of acute myocardial infarction (AMI) is increasing worldwide, especially in the developing countries [1]. Luckily, advances made in the area of medical therapy and reperfusion therapies such as fibrinolytic therapy and percutaneous coronary intervention have resulted in a significant decrease in the mortality rates [2]. In all the viable therapies, restoring the blood flow to an infarct-related artery (IRA) within the first 12 hours from onset of symptoms is currently considered the most important to the treatment of ST-elevation myocardial infarction (STEMI) [3]. Several studies have shown a clear superiority of primary PCI to other therapies, with higher initial reperfusion rates, improved event-free survival, and lower incidence of intracranial bleeds [4]. However, only a small proportion of AMI patients can have access to timely and effective PCI due to patient or treatment delay, and this proportion of patients is even lower in developing countries including China [5]. What' more, the recent open-artery hypothesis proposes that recanalization of a totally occluded IRA, even late in the course of an acute MI, has a favorable effect on LV remodeling and long-term outcomes [6]. In fact, some clinical studies have demonstrated that myocardium can be salvaged beyond the first 12-hour time limit [7, 8] even days to weeks after acute MI [9, 10]. Moreover, a previous study by Di Pasquale P et al claimed that when compared with those in the immediate PCI group, patients who recieved delayed facilitated PCI had similar results in EF and CK release, plus a significant reduction in thrombotic residues in IRA, and a favourable, although not significant, trend in ischemic events, restenosis and bleedings [11]. In summary, the continuing controversy about the potimal time-window for

PCI has motivated us in searching for the better approach between primary and delayed PCI in patients with AMI.

In addressing this problem, we set the criteria for primary PCI as less than 12 h from the onset of ischemic symptoms (or more then 12 h but with continued chest pain and (or) ST-segment elevation). Meanwhile, delayed PCI was defined as administering PCI treatment 1-2 weeks after the onset of AMI symptoms (without previous intravenous thrombolysis or thrombolytic unsuccessful). In addition, cases treated with only the base-line drug therapy was set as control.

In the present study, we managed to answer the raised question by analyzing the pathophysiology of post-AMI conditions. Since post-AMI inflammatory responses and left ventricular remodeling have been considered as important pathophysiological processes by previous research [12, 13], we selected a bunch of representative detection indexes from these aspects such as hs-CRP, NTproBNP, LEVF etc. and tried to determine the optimal intervention strategy for patients with AMI using these information.

In this study, we also focused on the autonomic nervous function of AMI patients. Because according to previous studies, autonomic nervous system dysfunction is closely related to malignant arrhythmias and sudden death during early acute myocardial infarction [14]. Heart rate turbulence (HRT) and heart rate variability (HRV) are two groups of parameters to effectively evaluate the cardiac autonomic function [15, 16]. However, few studies have touched upon the effect of PCI therapy and blood restoration on the improvement of autonomic nervous function. So in the present study, we emphasized on comparing primary and delayed PCI from the aspect of autonomic nervous function, together with some other conventional evaluation indexes including hs-CRP, NTproBNP, LEVF etc.

Materials and methods

Study subjects and grouping

The study included 150 inpatients consecutively admitted to the Qingdao Eighth People's Hospital as first-time AMI from October 2010 to October 2013. Patients were aged from 38 to 89 (65.3 ± 14.6) years old, with a female to male ratio of 32/43. Approved by the local medical ethics committee, this study was performed in accordance with the guidelines of the Declaration of Helsinki, and informed consent was obtained from all participants. All patient information, including demographic data, cardiovascular risk factors and history, clinical data, and cardiovascular medications, were collected using a standard case-report form.

The diagnostic criteria for patients with ST-segment elevation and non-ST-segment elevation AMI was in line with The Third Universal Definition of Myocardial Infarction published in October 2012 by the global Myocardial Infarction Task Force [17]: it requires cardiac myocyte necrosis with an increase and/or a decrease in a patient's plasma of cardiac troponin (cTn) with at least one cTn measurement greater than the 99th percentile of the upper normal reference limit during: ① symptoms of myocardialischemia; ② new significant electrocardiogram (ECG) ST-segment/T-wave changes or left bundle branch block; ③ the development of pathological ECG Q waves; ④ new loss of viable myocardium or regional wall motion abnormality identified by an imaging procedure; or ⑤ identification of intracoronary thrombus by angiography or autopsy. In addition, patients had to show sinus rhythm, with more than twice ventricular premature complex (VPC) during their 24-hour-Holter monitoring which was carried out two weeks after treatment. Patients were excluded if they had idiopathic cardiomyopathy, congenital heart disease, atrial fibrillation, advanced sinoatrial or atrioventricular block, valvular heart disease, rheumatic or autoimmune disease, malignant tumors, severe liver or kidney dysfunction, or other uncontrollable systemic diseases like severe infections; if they had long term use of anti arrhythmia drugs, or if they had installed temporary or permanent pacemakers.

Patients were divided into the following groups according to the treatment they received: ① primary PCI group (60 cases) was composed of patients with chest pain duration ≤12 h, or duration >12 h but continued chest pain or ST-segment continued; ② delayed PCI group (50 cases) included patients with ischemic chest pain or evidence of myocardial ischemia and with decreased left ventricular systolic function but without intravenous thrombolysis

(or with unsuccessful thrombolytic) who received PCI treatment after AMI for 1~2 weeks (basic standard); and ③ 40 cases who received drug therapy only were included in the control group. There were no significant differences (P>0.05) among the three groups in terms of patients' age, gender, weight, blood pressure, blood glucose, blood lipid, MI type and other general conditions.

All the cases were given aspirin, clopidogrel, low molecular heparin, nitrates, β-blockers, ACEI/ARB and other conventional treatment as basic treatment. According to line of Judkins method, patients in the primary PCI group were given a coronary angiography to determine the infarct-related artery (IRA), followed by a PTCA or coronary stenting by the standard method. Coronary flow was assessed according to Thrombolysis in Myocardial Infarction (TIMI) grading score [18]. And interventional success was defined as residual stenosis <20%, and TIMI grade 2 flow after procedure, without major complications including cardiac death, myocardial infarction and target vessel revascularization. On the other hand, patients in the delayed PCI group were given a coronary angiography and condecutive surgery at least one week after the onset of myocardial infarction. The surgery method and success criteria used were the same as those in the primary PCI group. Meanwhile, patients in the control group received only the basic drug treatment as mentioned above.

Detection of serum hs-CRP, sCD40L and NT-proBNP

Patients' blood samples were drawn before treatment, as well as 24 hours, seven days and four weeks after treatment, into test tubes containing heparin as anticoagulant. The whole blood samples were centrifuged and the corresponding blood plasma samples were stored at -20°C until analysis.

Upon analysis, hs-CRP was detected by ELISA and they were purchased from the Canadian BioCheck. Tests were run strictly according to the kit instructions. sCD40L was also detected by ELISA, using testing kits from Bender Medsystems Inc., Austria. Patients' blood NT-proBNP was determined by electrochemiluminescence with the Roche Elecsys 2010 immunoassay system from Canadian BioCheck company.

Performing of cardiac ultrasound

Echocardiographic analysis of cardiac structure and function was performed one week and three months after treatment, by experienced physicians who were blinded to patients' information. Left ventricular end-diastolic diameter (LVEDD) was measured via the 2-dimensional guided M-mode and normalized according to body surface area. Left ventricular ejection fraction (LVEF) was measured according to the biplane Simpson method [19]. All measurements were averaged over 3 cardiac cycles. The indexes of LV end-diastolic diameter, LV end-systolic diameter, were normalized according to body surface area. Two observers blinded to the clinical and ECG data, evaluated the echocardiographic images. In the case of any discrepancies, the images were again reviewed, and a decision was taken by consensus. The mean of 3 measurements was used and the interobserver coefficients of variation were 4%.

Collection of HRT and HRV parameters by monitoring electrocardiogram

All the cases were tested with 24 h Holter using dynamic electrocardiogram from PI Corporation, America, 2 weeks after treatment. This monitoring electrocardiogram can analyze HRT and HRV parameters automatedly by measuring RR interval (RRI), and thus reflect patients' autonomic nervous function in a timely manner.

HRT analysis was performed according to the previously published method [20] on sequences of sinus RR intervals related to VPCs showing the following features: ① single non-interference VPC, ② in the 10 beats preceding the index VPC, and ③ sinus rhythm in the 20 beats following the index VPC. HRT was assessed using 2 standard parameters [21]: ① the turbulence onset (TO), which is a measure of the early sinus acceleration after a VPC; and ② the turbulence slope (TS), which is a measure of the late sinus deceleration after a VPC. TO<0 represents normal condition, while TO>0 is the positive sign for abnormal conditions. The neutral value of TS is 2.5 ms/RRI. So TS>2.5 ms/RRI indicates the presence of deceleration phenomenon after sinus rhythm acceleration,

Table 1. Demographic clinical characteristics of patients in each group (n, %)

Group	M/F	Age (years, $\bar{x}$ ± s)	Hypertension	Diabetes	Hyperlipidemia	Smoking history
Control (n=40)	23/17	58.9 ± 7.8	33 (82.5)	12 (27.5)	31 (77.5)	26 (65.0)
Primary PCI (n=60)	34/26	59.0 ± 8.2	50 (83.3)	17 (28.3)	47 (78.3)	40 (66.7)
Delayed PCI (n=50)	29/21	59.0 ± 7.9	41 (82.0)	13 (26.0)	39 (78.0)	32 (64.0)

Table 2. Comparison of serum NT-proBNP, hs-CRP among three groups ($\bar{x}$ ± s)

Group	24 h after treatment			7 d after treatment			4 w after treatment		
	hs-CRP (mg/L)	sCD40L (ng/L)	NT-proBNP (ng/L)	hs-CRP (mg/L)	sCD40L (ng/L)	NT-proBNP (ng/L)	hs-CRP (mg/L)	sCD40L (ng/L)	NT-proBNP (ng/L)
Control (n=40)	$\bar{x}$ 14. 36	22.1	2850. 62	10.42	16.87	2586.32	6.13	9.76	1862.53
	s 1. 38	2.42	1095. 04	1.25	2.12	1158.13	1.02	0.79	1120.18
Primary PCI (n=60)	$\bar{x}$ 7. 22	15.32	1922. 10	4.64	9.53	1275.62	2.68	4.58	769.62
	s 0. 96*,#	2.35*,#	1082. 63*,#	0.83*,#	2.07*,#	958.13*,#	0.83*,#	0.91*,#	482.35*,#
Delayed PCI (n=50)	$\bar{x}$ 14. 28	19.5	2845. 30	9.83	13.01	2163.84	4.52	7.02	1073.02
	s 1. 45	2.52*	1102. 52	1.19*	1.98*	1107.20*	0.95	1.21*	892.65*

Note: compared with the control group, *P<0.01; between the two treatment groups, #P<0.01.

while TS≤2.5 ms/RRI indicates the absence of sinus rhythm deceleration.

HRV parameters include 24 h average standard deviation of RR interval (SDNN) and the standard deviation of the mean RR interval per five minutes (SDANN) [20]. Mean RR interval, the SD of all RR intervals, the SD of the means of RR intervals of all 5-minute sequences were obtained for time-domain analysis. After data collection, Holter tapes were carefully analyzed by expert cardiologists using the Holter device system.

Statistical analysis

Continuous variables are presented as $\bar{x}$ ± SD or median and interquartile range, as appropriate. Categorical variables are presented as frequencies and percentages. Kolmogorov-Smirnov analysis was performed to assess the normality of data distribution. Independent-samples t test and Mann-Whitney U test, or 1-way analysis of variance and Kruskal-Wallis H test, were used to compare the differences between continuous variables. The Pearson χ^2 test or Fisher exact test were used to compare the differences between categorical variables. All statistical tests were 2-tailed, and a *P* value<0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows, version 18.0.

Results

Demographic and clinical characteristics of study population

Demographic and clinical characteristics of patients included in the study were summarized in **Table 1**. There were 86 males (57.3%) and 64 females (42.7%, male/female ratio 43/32) whose ages ranged from 38 to 89 years, with a median age of 61 years old. No significant difference was observed (P>0.05) among the three groups in terms of patients' age, gender, smoking history, or incidence of hypertension, diabetes and hyperlipidemia.

Comparison of serum hs-CRP, sCD40L and NT-proBNP among the three groups

There was no significant difference among the groups regarding patients' evaluation indexes (hs-CRP, sCD40L and NT-proBNP) before treatment, indicating similar baseline conditions (data not shown). Besides, it can be seen from **Table 2** that at all three time points after different treatment (24 h, one week and four weeks), the amount of serum NT-proBNP, sCD40L and hs-CRP in the two PCI groups were significantly lower than that in the control group (P<0.01). Meanwhile, the difference between the two PCI groups was also significant (P<0.01).

Table 3. Comparison of LVEF and LVEDD among three groups ($\bar{x} \pm s$)

Group	1 w after treatment		3 m after treatment	
	LVEF (%)	LVEDD (mm)	LVEF (%)	LVEDD (mm)
Control (n=40)	45.40 ± 9.62	53.72 ± 6.41	48.08 ± 10.31	52.36 ± 6.28
Primary PCI (n=60)	52.40 ± 11.38*	49.76 ± 4.29*	56.23 ± 9.97*,#	49.02 ± 4.15*,#
Delayed PCI (n=50)	50.78 ± 10.24	51.48 ± 5.52	53.08 ± 10.05*	50.96 ± 5.63*

Note: compared with the control group, *P<0.01; between the two treatment groups, #P<0.05.

Table 4. The comparison of TO, TS, SDNN, SDANN among three groups ($\bar{x} \pm s$)

GROUP	TO (%)	TS (ms/RRI)	SDNN (ms)	SDANN (ms)
Control (n=40)	0.37 ± 1.62	5.72 ± 4.38	91.6 ± 24.3	82.9 ± 21.4
Primary PCI (n=60)	-2.84 ± 2.25*,#	12.19 ± 3.76*,#	128.3 ± 22.7*,#	119.6 ± 23.2*,#
Delayed PCI (n=50)	-1.26 ± 2.12*	8.32 ± 3.94*	101.7 ± 23.6*	98.4 ± 22.7*

Note: compared with the control group, *P<0.01; between the two treatment groups, #P<0.05.

Comparison of post-treatment LVEF and LVEDD among the three groups

As can be seen from **Table 3**, when observed one week after treatment, LVEF in the primary PCI group was significantly higher than that in the control group (P<0.01), while LVEDD in the primary PCI group was significantly lowerd (P<0.01). On the other hand, LVEF and LVEDD in the delayed PCI group did not show significant improvement comparing with the control group (both P>0.05). However, when measured again three months after treatment, LVEF in both PCI groups (primary and delayed) were significantly higher when compared with the control group, and LVEDD in both PCI groups were significantly lower, with all four *P* values less then 0.01. Also, during this second cardiac ultrasound (three months after treatment), cardiac function of patients in the primary PCI group was significantly improved (with significantly higher LVEF level and significantly lower LVEDD value, both P<0.01) comparing with that in the delayed PCI group.

Comparison of HRT and HRV parameters (TO, TS, SDNN, SDANN) among the three groups

Compared with the drug treatment group (control group), TS, SDNN and SDANN in the two PCI groups two weeks after treatment were all significantly higher, while the level of TO was significantly lower (P<0.01). Additionally, significant differences of all these four parameters were observed between the two PCI groups (P<0.05) (**Table 4**).

Discussions

Early rapid reperfusion is extremely important in the treatment of acute myocardial infarction. It is critical to the salvage of the ischemic myocardial cells, and it helps to improve heart function and reduce mortality. Primary PCI, when performed in a timely manner at a high patient volume center has been proved to be superior to fbrinolytic therapy [2]. It has also been proposed that delays in door-to-balloon times (DTB) are associated with increased mortality in patients with AMI [22]. However, primary PCI is not universally available [23]. Also previous research has indicated that primary PCI is associated with increased rates of bleeding complications at access sites [24]. On the other hand, there are increasing evidences proving that late-PCI strategy can also prevent LV remodeling and improve clinical outcomes in STEMI patients [5] in a even safer manner considering its lower rates of bleeding complications [11]. This has thrown the choice of optimal therapeutic time-window of PCI once again into controvercy.

Despite all these controversial results in the research field of AMI, we thought it would be appropriate to address this question from the phathophysiological aspect of this disease.

First of all, it has been reported by previous studies that increased levels of inflammatory factors in patients with AMI undergoing PCI may affect myocardial perfusion [25]. Among all the inflammatory factors associated with

AMI, high CRP levels in patients treated with primary PCI have been shown by a few studies as the predictor of a worse short-term prognosis [26, 27]. Moreover, our previous study has also indicated that sCD40L may have participated in the development of acute coronary syndrome (ACS) and that by administering different doses of atorvastatin during the perioperative period of PCI, the post-operation hsCRP and sCD40L level could be significantly lowerd [28]. In the present study, we chose hs-CRP and sCD40L as the representitives for AMI-related inflammatory factors and evaluated their expression level in patients treated with primary PCI, delayed PCI and basic drugs only. Our results showed that the amount of serum sCD40L and hs-CRP in the two PCI groups were significantly lower than that in the control group, and the difference between the two PCI groups was also significant. Our results which was consistent with previous studies [29], indicated that PCI, especially when performed in a timely manner, could alleviate post-AMI inflammotory responses and may thus influence patient prognosis favorably.

Second of all, some studies have also suggested a strong relationship between LV function and mortality outcomes following PCI, with worsening LV function independently predicting 30-day and longer-term mortality outcomes across all indications for PCI [30]. In this study, we used three classic indicators of cardiac function (LVEF, LVEDD and NT-proBNP) in the comparison of post-treatment conditions among the three groups. We found that cardiac function of patients in both primary and delayed PCI groups got significantly improved comparing with patients treated by drug therapy only (with significantly higher LVEF level and significantly lower LVEDD value and serum NT-proBNP, as shown in the results part), and improvement in the primary PCI group was even more obvious than that in the delayed PCI group. This result was also in line with previous research [13].

Last but not least, we managed to compare the treatment effect of different therapeutic strategies in terms of patients' autonomic nervous function. Because in previous research it has been found that sudden cardiac death (SCD) of AMI remained to be in high incidence even after timely restoration of blood flow, and that autonomic nervous dysfunction was a possible trigger of malignant ventricular arrhythmias [14], yet few studies have tried to compare the effect which primary or delayed PCI procedure may have on autonomic nervous function of patients with AMI. Heart rate turbulence and heart rate variability may reflect the performance of cardiac autonomic nerve function, and they may be high-risk predictors of sudden cardiac death [31-33]. Successful revascularization may improve the TS value in a short time after AMI, and HRV index may be quickly recovered [34, 35]. The results of the present study showed that the value of TS, SDNN, SDANN in the two PCI groups were significantly higher than that in the control group, while TO was significantly lower. And there was significant difference of these parameters between the two PCI groups. Our results proposed that PCI could improve cardiac autonomic function and may thus reduce the incidence of malignant arrhythmias in the long run, and that primary PCI in a timely manner was even better than delayed PCI. Actually, in the present study, it could be found that delayed PCI could also facilitate the recovery of abnormal levels of HRT and HRV to different extents. The recovery of cardiac autonomic nerve function may be associated with the following reason that successful revascularization of the coronary artery can save hibernating and stunned myocardium, thus alleviate myocardial ischemia disorder and limit the development of infarct size, causing improvement of cardiac remodeling and left ventricular function, and thus reduce the incidence of malignant ventricular arrhythmia and improve the prognosis of patients with AMI [36].

In conclusion, the results of this study suggests that the AMI patients should be treated early with primary PCI, and that patients treated with delayed PCI would also benefit from this procedure. However, the patients in this study were successfully reperfused, with TIMI-2 flow and our data may not apply to patients with TIMI 1 or 3 flow. And due to the lack of coronary angiographic characteristics for the nonrevascularization group (control group), we could not report the details of the coronary artery lesions of these patients. So future studies regarding the comparison of primary and delayed PCI in terms of the autonomic nervous system function and other pathophisiological aspects are suggested.

Acknowledgements

The Scientific and Technological Project of Qingdao City (Grant 2011-KZJ-17).

Disclosure of conflict of interest

None.

Address correspondence to: Zeng-Lei Han, Department of Cardiology, Qingdao Eighth People's Hospital, No. 84, Fengshan Road, Licang District, Qingdao, Shandong Province, P. R. China. Tel: +86-15963289264; Fax: +86-15963289264; E-mail: hanzenglei_l@163.com

References

[1] Yusuf S, Reddy S, Ounpuu S and Anand S. Global burden of cardiovascular diseases: Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. Circulation 2001; 104: 2855-2864.

[2] Reddy K, Khaliq A and Henning RJ. Recent advances in the diagnosis and treatment of acute myocardial infarction. World J Cardiol 2015; 7:243-276

[3] Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van't Hof A, Widimsky P and Zahger D. Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012; 33: 2569-2619.

[4] Di Pasquale P, Cannizzaro S, Parrinello G, Giambanco F, Vitale G, Fasullo S, Scalzo S, Ganci F, La Manna N, Sarullo F, La Rocca G and Paterna S. Is delayed facilitated percutaneous coronary intervention better than immediate in reperfused myocardial infarction? Six months follow up findings. J Thromb Thrombolysis 2006; 21: 147-157.

[5] Fan Y, Bai X, Chen Y, Shen G, Lu Q, Wan Z, Zhou D, Shen Y and Ma A. Late Percutaneous Coronary Intervention Prevents Left Ventricular Remodeling and Improves Clinical Outcomes in Patients With ST-Elevation Myocardial Infarction. Clin Cardiol 2015; 38: 82-91.

[6] Abbate A, Biondi-Zoccai GG, Baldi A, Trani C, Biasucci LM and Vetrovec GW. The 'openartery hypothesis': new clinical and pathophysiologic insights. Cardiology 2003; 100: 196-206.

[7] Schömig A, Mehilli J, Antoniucci D, Ndrepepa G, Markwardt C, Di Pede F, Nekolla SG, Schlotterbeck K, Schühlen H, Pache J, Seyfarth M, Martinoff S, Benzer W, Schmitt C, Dirschinger J, Schwaiger M and Kastrati A. Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptom onset: a randomized controlled trial. JAMA 2005; 293: 2865-2872.

[8] Parodi G, Ndrepepa G, Kastrati A, Conti A, Mehilli J, Sciagrà R, Schwaiger M, Antoniucci D and Schømig A. Beyond 12 Hours Reperfusion Alternative Evaluation (BRAVE-2) Trial Investigators. Ability of mechanical reperfusion to salvage myocardium in patients with acute myocardial infarction presenting beyond 12 hours after onset of symptoms. Am Heart J 2006; 152: 1133-1139.

[9] Schwaiger M, Brunken R, Grover-McKay M, Krivokapich J, Child J, Tillisch JH, Phelps ME and Schelbert HR. Regional myocardial metabolism in patients with acute myocardial infarction assessed by positron emission tomography. J Am Coll Cardiol 1986; 8: 800-808.

[10] Brunken R, Tillisch J, Schwaiger M, Child JS, Marshall R, Mandelkern M, Phelps ME and Schelbert HR. Regional perfusion, glucose metabolism, and wall motion in patients with chronic electrocardiographic Q wave infarctions: evidence for persistence of viable tissue in some infarct regions by positron emission tomography. Circulation 1986; 73: 951-963.

[11] Di Pasquale P, Cannizzaro S, Fasullo S, Ganci F, Marenghini G, Scalzo S, Giambanco F, Vitale G, Polizzi G and Paterna S. Immediate versus delayed facilitated percutaneous coronary intervention: a pilot study. J Cardiovasc Pharmacol 2005: 46: 83-88.

[12] Roy D, Quiles J, Avanzas P, Arroyo-Espliguero R, Sinha M and Kaski JC. A comparative study of markers of inflammation for the assessment of cardiovascular risk in patients presenting to the emergency department with acute chest pain suggestive of acute coronary syndrome. Int J Cardiol 2006; 109: 317-321.

[13] Uslu H, Cakmak N, Erkan ME, Hacımahmutoğlu S, Yılmaz S, Ozkan S, Sayar N. Left ventricular remodeling assessment in patients with anterior acute myocardial infarction treated with successful primary percutaneous coronary intervention: an observational study. Anadolu Kardiyol Derg 2013; 13: 675-681.

[14] Huikuri HV, Exner DV, Kavanagh KM, Aggarwal SG, Mitchell LB, Messier MD, Becker D, Sheldon RS and Bloch Thomsen PE. Attenuated recovery of heart rate turbulence early after myocardial infarction identifies patients at high risk for fatal or near fatal arrhythmic events. Heart Rhythm 2010; 7: 229-235.

[15] Avsar A, Acarturk G, Melek M, Kilit C, Celik A and Onrat E. Cardiac Autonomic Function Evaluated by the Heart Rate Turbulence Method

Was Not Changed in Obese Patients without Co-Morbidities. J Korean Med Sci 2007; 22: 629-632.
[16] Abrootan S, Yazdankhah S, Payami B and Alasti M. Changes in Heart Rate Variability Parameters after Elective Percutaneous Coronary Intervention. J Tehran Heart Cent 2015; 10: 80-84.
[17] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR and White HD. Third universal definition of myocardial infarction. Nat Rev Cardiol 2012; 9: 620-633.
[18] TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. N Engl J Med 1985; 312: 932-936.
[19] Carluccio E, Biagioli P, Alunni G, Murrone A, Leonelli V, Pantano P, Vincenti G, Giombolini C, Ragni T, Reboldi G, Gentile F andAmbrosio G. Effect of revascularizing viable myocardium on left ventricular diastolic function in patients with ischaemic cardiomyopathy. Eur Heart J 2009; 30: 1501-1509.
[20] Sestito A, Valsecchi S, Infusino F, Sgueglia GA, Bellocci F, Zecchi P, Crea F and Lanza GA. Differences in heart rate turbulence between patients with coronary artery disease and patients with ventricular arrhythmias but structurally normal hearts. Am J Cardiol 2004; 93: 1114-1118.
[21] Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L, Camm AJ, Bigger JT Jr and Schomig A. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet 1999; 353: 1390-1399.
[22] Bates ER and Nallamothu BK. Commentary: the role of percutaneous coronary intervention in ST-segment-elevation myocardial infarction. Circulation 2008; 118: 567-573.
[23] Antman EM. Time is muscle: translation into practice. J Am Coll Cardiol 2008; 52: 1216-1221.
[24] Keeley EC, Boura JA and Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003; 361: 13-20.
[25] Jiao Q, Ke Q, Li W, Jin M, Luo Y, Zhang L, Yang D and Zhang X. Effect of inflammatory factor-induced cyclo-oxygenase expression on the development of reperfusion-related no-reflow phenomenon in acute myocardial infarction. Clin Exp Pharmacol Physiol 2015; 42: 162-170.
[26] Tomoda H and Aoki N. Prognostic value of c-reactive protein levels within six hours after the onset of acute myocardial infarction. Am Heart J 2000; 140: 324-328.
[27] Yip HK, Hang CL, Fang CY, Hsieh YK, Yang CH, Hung WC and Wu CJ. Level of high-sensitivity c-reactive protein is predictive of 30-day outcomes in patients with acute myocardial infarction undergoing primary coronary intervention. Chest 2005; 127: 803-808.
[28] Cao QB, Wang XW, Han ZL, Sun XY and Han T. The impact of intensive statins therapy on hs-CRP and sCD40L in AMI patients during perioperative period of emergency PCI. Chinese Journal of Clinical Research 2011; 12: 97-100.
[29] Hedström E, Aström-Olsson K, Ohlin AK, Ohlin H, Arheden H. Initial results of inflammatory response, matrix remodeling, and reactive oxygen species following PCI in acute ischemic myocardial injury in man. J Invasive Cardiol 2011; 23: 371-376.
[30] Mamas MA, Anderson SG, O'Kane PD, Keavney B, Nolan J, Oldroyd KG, Perera D, Redwood S, Zaman A, Ludman PF and de Belder MA. Impact of left ventricular function in relation to procedural outcomes following percutaneous coronary intervention: insights from the British Cardiovascular Intervention Society. Eur Heart J 2014; 35: 3004-3012a.
[31] Bauer A, Barthel P, Schneider R, Ulm K, Müller A, Joeinig A, Stich R, Kiviniemi A, Hnatkova K, Huikuri H, Schömig A, Malik M and Schmidt G. Improved Stratification of autonomic regulation for risk prediction in post-infarction patients with preserved left ventricular function (ISAR-Risk). Eur Heart J 2009; 30: 576-583.
[32] Wang HY. The new standard heart rate turbulence technologies, new applications,new evaluation. Journal of Clinical Anesthesiology 2007; 16: 333.
[33] Arya A, Haghjoo M, Sadr-Ameli MA. Risk stratification for arrhythmic death after myocardial infarction:Current perspective and future direction. Int J Cardiol 2006; 108: 155-164.
[34] Barthel P, Schneider RD and Bauer A. Risk Stratification After Acute Myocardial Infarction by Heart Rate Turbulence. Circulation 2003; 108: 1221-1226.
[35] Lind P, Hintze U, Møller M and Mickley H. Thrombolytic therapy preserves vagal activity early after acute myocardial infarction. Scand Cardiovasc J 2001; 35: 92-95.
[36] Fabbiocchi F, Bartorelli AL, Montorsi P, Cozzi S, Trabattoni D, Calligaris G and Loaldi A. Elective coronary stent implantation in cardiogenic shock complicating acute myocardial infarction: in hospital and six-month clinical and angiographic results. Catheter Cardiovase Interv 2000; 50: 384-389.