Journal of Cardiology (2011) 58, 137—142

View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

ScienceDirect

journal homepage: www.elsevier.com/locate/jjcc

Original article

Clinical study of the electrophysiological effects of ischemic post-conditioning in patients with acute myocardial infarctions

Kaoru Okishige (MD)*, Shigetaka Kanda (MD), Tsukasa Shimura (MD), Manabu Kurabayashi (MD), Daisuke Ueshima (MD), Naoyuki Miwa (MD), Koji Sugiyama (MD), Hideshi Aoyagi (MD), Koujirou Yoshimura (MD), Hidekiyo Yanagi (MD), Koji Azegami (MD)

Heart Center, Yokohama-City Bay Red Cross Hospital, Yokohama, Japan

Received 2 March 2011; received in revised form 25 May 2011; accepted 26 May 2011
Available online 8 July 2011

KEYWORDS
Ischemic post-conditioning;
Acute coronary syndrome;
QT dispersion;
Coronary angioplasty

Summary
Background: Ischemic ''pre''-conditioning has been shown to have antiarrhythmic effects. The aim of this study was to investigate whether ischemic ''post''-conditioning (post-CON) also has antiarrhythmic effects in ST-segment elevation myocardial infarction (STEMI) patients undergoing coronary angioplasty (PCI) as a clinical model of post-CON.
Methods and results: A total of 61 patients suffering from an acute myocardial infarction (AMI) were included. The QT dispersion (QTd) was measured before each balloon inflation (BI) and after deflation (BD) during PCI. The hemodynamic parameters and electrocardiogram were also assessed during PCI. All data were analyzed using a logistic regression analysis. A total of 36 of 61 STEMI patients could be analyzed according to the protocol. The QTd shortened significantly as the BI and BD were repeated ($p < 0.05$). Prior to the PCI, frequent premature ventricular contractions (PVCs) were observed in 5 patients, and the PVCs were remarkably suppressed or disappeared entirely as the BI and BD were repeated. Non-sustained ventricular tachycardia was observed prior to the PCI in 2 patients; this also disappeared as the BI and BD were repeated. Ventricular fibrillation (VF) occurred in 1 patient prior to PCI, necessitating D-C cardioversion. After repeating the BI and BD during PCI, VF no longer recurred.
Conclusions: In the majority of the AMI patients studied, post-CON exhibited significant antiarrhythmic effects as assessed by the change in the QTd. The ventricular dysarrhythmias were also suppressed during the PCI.
© 2011 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.

* Corresponding author at: Heart Center, Yokohama-City Bay Red Cross Hospital, 1-12-3 Shinyamashita, Naka-ward, Yokohama-City, Japan. Tel.: +81 045 628 6100; fax: +81 045 628 6100.
E-mail address: okishige@yo.rim.or.jp (K. Okishige).

0914-5087/$ — see front matter © 2011 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.jjcc.2011.05.002

Introduction

Ischemic preconditioning (pre-CON) was introduced as a potent endogenous form of cardioprotection against ischemic-reperfusion injury. Brief preceding periods of myocardial ischemia seem to delay the lethal myocardial cell injury observed during subsequent coronary occlusions [1,2]. This phenomenon of pre-CON may increase the ventricular fibrillation (VF) threshold and reduce the incidence of ischemic and reperfusion arrhythmias [3—6].

It has been observed that the heart seems to be able to effectively protect itself from reperfusion not only by preconditioning, but also by brief episodes of ischemia during the early reperfusion period following a pronounced ischemic event, which is called ischemic ''post-conditioning'' (post-CON) [7].

Post-CON can be provoked by reperfusion of the coronary arteries after a relatively longer occlusion. There is evidence to demonstrate that pre-CON may induce antiarrhythmic protection in humans [8—10]. However, whether the same antiarrhythmic effects can be expected for post-CON has not been clarified.

Hypothesis

A short series of repetitive cycles of brief reperfusion and re-occlusions of the coronary artery applied immediately at the onset of the reperfusion, termed ''post-CON,'' was cardioprotective due to the reduction in the infarct size, coronary artery endothelial dysfunction, and neutrophil accumulation in the area at risk [7]. Kin et al. experimentally investigated the cardioprotective effects of pre-CON by performing the following experiment using rat hearts [12]. They demonstrated this by occluding the coronary artery for 30 min, and then reperfusing it by loosening the ligature for 3 h. During that 3-h interval, immediately upon the onset of the reperfusion after the 30-min coronary occlusion, the reflow was initiated with 10 s of full coronary flow, followed by 10 s of re-occlusion, and repeated for a total of three to six cycles. We believed that those repeated coronary arterial occlusions and reperfusions were very similar to an ST-segment elevation myocardial infarction (STEMI). Therefore, a primary percutaneous coronary intervention (PCI) performed for STEMI patients could be regarded as a clinical model of post-CON. In addition, we considered that we might be able to assess the electrical effects of the post-CON by investigating several clinical parameters during the primary PCI in the STEMI cases.

Methods

The study design was accepted by the Ethics Committee of Yokohama-City Bay Red Cross Hospital. Informed consent was obtained from all patients.

Patients

This study consisted of 61 consecutive patients undergoing an emergency coronary angioplasty for acute coronary syndrome and fulfilling the following criteria after obtaining the informed consent from all the patients: (1) totally occluded single-vessel coronary lesion; (2) coronary lesion in a relatively proximal portion of the vessel; (3) documented acute myocardial ischemia; (4) no antiarrhythmic agents including beta-adrenergic blocking agents at the time of the procedure; and (5) no acute procedural complications. The clinical data from the study group are shown in Table 1.

Table 1 Patient characteristics.

Age (years)	58.4 ± 8.7
Men	27 (75%)
History of angina	4 (11%)
Beta-blockers	11 (30%)
Calcium antagonists	6 (17%)
Ejection fraction	49 ± 11%
Hypertension	58 ± 15%
Hyperlipidemia	39 ± 8%
Family history of hypertension Occluded coronary artery	42 ± 19%
LAD	20 (60%)
Cx	7 (19%)
RCA	9 (21%)

LAD, left anterior descending coronary artery; Cx, left circumflex artery; RCA, right coronary artery.

Study protocol

All the study patients had serious chest pain of sudden onset, and were transferred to our institute to undergo a needed medical assessment regarding their physical status. Blood chemistry examinations were performed revealing a significant rise in cardiac biomarker values suggestive of an acute massive necrosis of the myocardium.

All the study patients had a total coronary occlusion resulting in a STEMI when the coronary angiography was performed to assess the status of the coronary arteries.

PCI was performed according to the standard technique. Unfractionated heparin was given as an initial bolus of 60 IU/kg, and additional boluses were administered during the PCI procedure to achieve an activated clotting time of 250—300 s. The blood pressure was monitored through the sheath inserted into the radial artery. All patients who had not taken aspirin before the presentation of the STEMI received aspirin at a dose of 200 mg, followed by 100 mg/day by mouth indefinitely. The patients were loaded — if not previously taking clopidgrel — with 300 mg of clopidgrel before the PCI procedure, followed by 75 mg/day for at least 12 months. Serial samples for determination of the cardiac biomarkers such as creatine kinase and lactate dehydrogenase were routinely collected in all patients 6, 12, and 24 h after the procedure.

Electrocardiographic analysis

A 12-lead electrocardiogram (ECG) was recorded at a paper speed of 50 mm/s before and after each balloon inflation (BI) and deflation (BD) procedure at a timing when the ST segment elevation returned to the original level before the BI procedure in addition to just after the BD procedure.

The duration times of balloon inflation and deflation were approximately 10—30 and 5 s, respectively. All ECG tracings were analyzed for the measurement of the QT interval dispersion as a surrogate marker of the ventricular myocardial electrical inhomogeneity. The QT intervals in all the ECGs were measured routinely for 5 consecutive beats by two cardiologists. Those two investigators were blinded with respect to the patient to which the ECG under analysis belonged. The QT intervals were measured from the beginning of the Q wave to the return of the T wave to the isoelectric line in each lead, in which the end of the T wave could be discerned. In the presence of a U wave, the end of the T wave was defined as the intersection of the tangent to the repolarization slope with the isoelectric line. The QT dispersion (QTd) was defined as the difference between the maximal and minimal QT interval across the 12-lead ECG electrograms.

Statistical analysis

All values are expressed as the mean ± SD. Because all the measurements of the QTd were normally distributed, a logistic regression analysis was used for the analysis. A p-value <0.05 was considered significant.

Results

A total of 36 out of 61 patients were studied, 25 patients were excluded from the study because of the difficulty in precisely measuring the QT intervals in the 12-lead ECGs or transient ventricular back-up pacing. The QT intervals were measurable in an average of 10.9 leads. A proportion of the patients were taking beta-blockers and/or calcium-channel blockers, but no other antiarrhythmic drugs or other drugs known to influence the action potential duration.

During the primary PCI, the BI and BD cycles ranged from 2 to a maximum of 9. The average BI and BD cycles were 4 ± 1.1. In all the patients, the successful recanalization of the target coronary arteries was performed without any serious adverse effects such as a coronary dissection, acute recoiling, or sub-acute thrombosis.

Repeated measurements of the QTd from 50 randomly chosen 12-lead ECGs from the patients revealed a mean, non-significant intraobserver variability of the QTd of 8 ± 6 ms (range 4—32).

Hemodynamic status

The BI and BD were repeated for a maximum of 9 times in the PCI cases. During the PCI procedure, the systolic and diastolic blood pressures were relatively maintained well without any need of cardiac support agents. When VF spontaneously occurred during the procedure, the blood pressure dropped down seriously and was associated with a sudden loss of consciousness. However, it returned to the baseline level immediately after the electrical defibrillation.

The change in the QTd and arrhythmias during the PCI procedure

An example of the measurement of the QT interval and change in the QT dispersion are shown in Fig. 1. The change in the QTd significantly decreased as the BI and BD were repeated (Fig. 2). Prior to the PCI procedure, frequent premature ventricular contractions (PVCs) were observed in 5 patients, and those PVCs were suppressed by more than 70% or entirely disappeared as the BI and BD were repeated. Non-sustained ventricular tachycardia (VT) was observed prior to the PCI in 2 patients, however, that also disappeared as the BI and BD were repeated. VF occurred in one patient prior to the coronary arterial recanalization, and it necessitated external electrical defibrillation to regain sinus rhythm. After repetition of the BI and BD during the PCI procedure, the VF no longer recurred even though the coronary artery was totally occluded for approximately 30 s during the BI.

Discussion

Previously we were able to demonstrate that pre-CON had an antiarrhythmic effect as evaluated by the significant decrease in the QTd, which was investigated in cases that had undergone an elective PCI [6]. Hara et al. also reported a pharmacological study regarding the antiarrhythmic effects of intravenous nicorandil which is supposed to induce the ischemic pre-conditioning in STEMI patients [11].

Brief intermittent repetitive interruptions in the perfusion at the onset of reperfusion after a prolonged period of ischemia reduced the myocardial injury to an extent comparable to pre-CON [7]. In all the study patients, all the coronary lesions of interest were totally occluded, and primary PCI was successfully able to recanalize such coronary arteries.

This phenomenon has much similarity to the experimental model regarding the post-CON [12—14]. Therefore, we hypothesized that a primary PCI performed for a STEMI could be regarded as an appropriate clinical model of the post-CON.

The QT interval has been used to describe the time between the onset of the ventricular activation and electrical recovery after activation. The QTd is the range of the QT intervals across the 12-lead ECGs. Increased dispersion of the electrical recovery after the activation was experimentally demonstrated to be a key factor in the development of serious and fatal arrhythmias associated with ischemia [15]. In contrast, reduced dispersion was considered to suppress those types of arrhythmias [16,17]. In our study, the QTd became decreased as the BI and BD were repeated during the PCI procedure which resulted in the successful recanalization of the target coronary arteries. Accordingly, several kinds of malignant ventricular arrhythmias such as PVCs and nonsustained VT and VF were significantly suppressed in the present study. There may be a close relationship between the shortening of the QTd and the suppression of malignant ventricular dysrhythmias. However, the time course of these arrhythmias might be also associated with the consequences of the coronary reperfusion due to PCI.

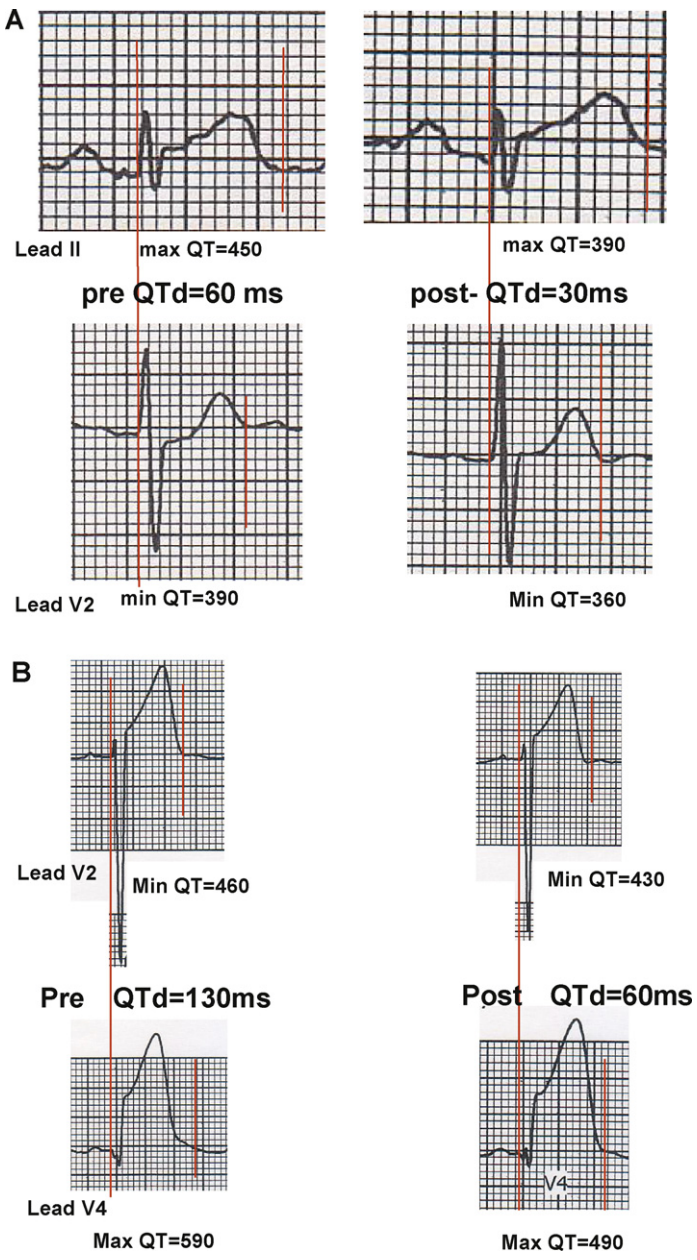

Figure 1 (A) This tracing shows an acute coronary syndrome of the left ventricular anterior wall. The longest QT interval was observed in lead V4 and the minimum QT interval in V2. After several balloon inflation (BI) and balloon deflation (BD) procedures, the maximum QT changed from 590 to 490 ms, and the minimum from 460 to 430 ms. Accordingly, the QT dispersion significantly decreased from 130 to 60 ms. (B) This tracing demonstrates an acute coronary syndrome of the left ventricular inferior portion. The maximum QT interval was observed in lead II and the minimum QT interval in lead V2. The maximum QT interval changed from 450 to 390 ms, and the minimum QT interval from 390 to 360 ms after several BI and BD procedures. Therefore, the QT dispersion exhibited a significant change from 60 to 30 ms. QTd, QT dispersion.

Halkos et al. experimentally investigated the interference between the pre- and post-CON when performing the repeated cycles of the coronary occlusions and reperfusions. They found that VF occurred less often in the treatment groups (providing coronary arterial intervention) compared to the control (no coronary intervention). Moreover, they also demonstrated that VT which occurred with the initiation of the reperfusion promptly resolved with the reocclusion during the post-CON period [14].

Therefore, our results in the present study could be regarded as showing the antiarrhythmic effects of post-CON. The suggested mechanisms of the post-CON effect on protecting the myocardium from ischemic injury were a reduction in the neutrophil accumulation, decrease in the endothelial dysfunction [7], attenuation of oxidative stress [12], reduction in apoptotic cell death, and attenuation of mitochondrial calcium accumulation [18]. Further study will be necessary to investigate which mechanism

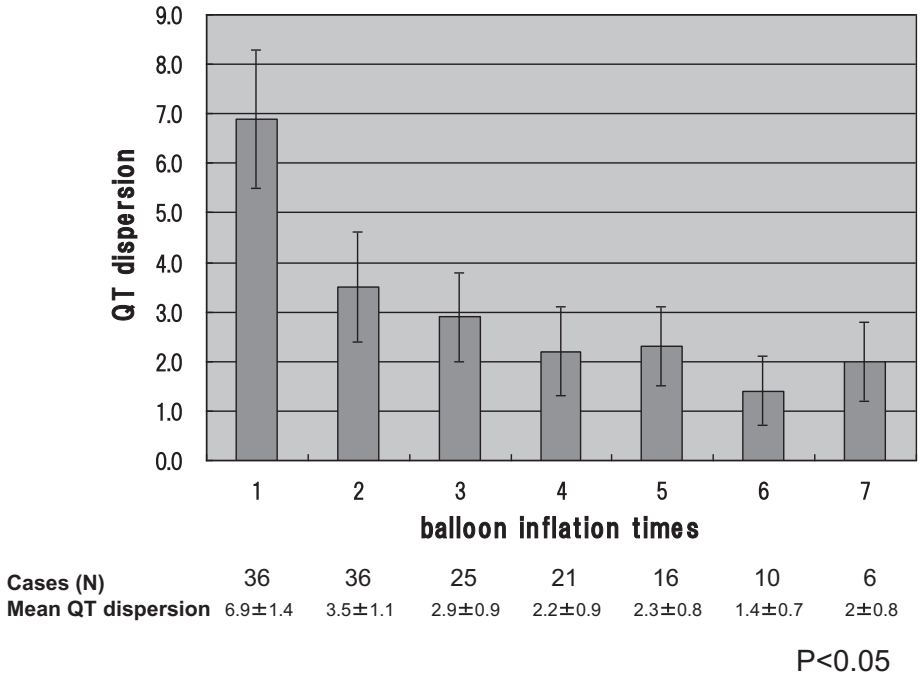

Figure 2 Effects of the balloon inflation and deflation during the primary percutaneous coronary intervention on the QT dispersion. The QT dispersion (*Y*-axis) for each balloon inflation and deflation (*X*-axis) is represented by the bars.

is responsible for the antiarrhythmic effects of the post-CON.

Yang et al. described that after the initial reperfusion of the infarct artery during the primary PCI in patients with an acute myocardial infarction, several brief, low-pressure balloon occlusions of the vessel could be performed before the procedure is completed with subsequent additional dilations to obtain a sufficient TIMI grade flow. This procedure of post-CON could be safely and readily adapted for clinical usage [19]. In the present study, we were successfully able to accomplish the PCI procedure with a sufficient TIMI grade flow in all cases, and significant antiarrhythmic effects could be expected in these kinds of successful recanalizations of the coronary arteries in STEMI cases.

Limitations

First, the present study lacks a control group, however, we were determined not to have a control group due to the ethical issue which might be provoked by the nonfulfilment of the appropriate treatment for patients with a STEMI. Therefore, this study can be regarded as a preliminary clinical study. Second, the portion of the occluded coronary arteries varied among the cases, therefore, the QT intervals and QTd measurements might have been influenced by the regional ischemia itself rather than the electrical effects provoked by the post-CON. Third, the TIMI grade after the first recanalization of the target coronary artery varied among the cases during the primary PCI and ranged grade II—III, and therefore, there might have been differences in regard to the strength of the antiarrhythmic effects provoked by the post-CON. Fourth, the time from the sudden occlusion of the coronary artery to the recanalization also varied among the cases (should be less than 1 h in all cases), therefore, there also might have been differences concerning the electrical effects associated with the post-CON. Fifth, the occluded portion of the coronary artery also varied, and therefore, we could not exclude the possibility that unmasked additive antiarrhythmic effects of the post-CON might have been induced if a more proximal coronary artery would have been occluded. Sixth, the pre- and post-CON were additive during prolonged ischemia [13], so the antiarrhythmic effects of the pre-CON in addition to post-CON might have contributed to the results in the present study. Seventh, relief of ischemia can reduce ischemia-induced arrhythmias during PCI. However, it might be possible that post-CON provoked by relief of ischemia principally might exert antiarrhythmic effects during PCI. Eighth, the re-occlusion of the coronary artery less than 1 min after the reperfusion is necessary to provoke ischemic post-conditioning [20]. Several cases might be involved in which the re-occlusion of the coronary artery was performed later than 1 min. However, we were unable to clarify this because of the lack of the detailed recording regarding the exact procedure of balloon inflation and deflation.

In summary, the post-CON performed within approximately less than 1 h of serious ischemia followed by reperfusions and occlusions of the coronary artery significantly reduced the QTd, and VT/VF associated with acute ischemia during the primary PCI.

References

[1] Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 1986;74:1124—36.

[2] Li GC, Vasquez JA, Gallagher KP, Lucchesi BR. Myocardial protection with reconditioning. Circulation 1990;82:609—19.

[3] Gulker H, Kramer B, Stephen K, Meesman W. Changes in ventricular fibrillation threshold during regional short-term coronary occlusion and release. Basic Res 1977;72:547—62.
[4] Hagar JM, Hale SL, Kloner RA. Effects of preconditioning ischemia on reperfusion arrhythmias after coronary artery occlusion and reperfusion in the rat. Circ Res 1991;68: 61—8.
[5] Vegh A, Komori S, Szekeres L, Parratt JR. Antiarrhythmic effects of preconditioning in anesthetized dogs and rats. Cardiovasc Res 1992;26:487—95.
[6] Okishige K, Yamashita K, Yoshinaga H, Satoh K, Satake S. Electrophysiologic effects of ischemic preconditioning on QT dispersion during coronary angioplasty. J Am Coll Cardiol 1996;28:70—3.
[7] Zhao ZO, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton R, Vinten-Johansen J. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. Am J Physiol Heart Circ Physiol 2003;285:H579—88.
[8] Airaksinen KE, Huikuri HV. Antiarrhythmic effect of repeated coronary occlusion during balloon angioplasty. J Am Coll Cardiol 1997;29:1033—8.
[9] Pasceri V, Lanza GA, Patti G. Preconditioning by transient myocardial ischemia confers protection against ischemia-induced ventricular arrhythmias in variant angina. Circulation 1996;94:1850—6.
[10] Pomerantz BJ, Joo K, Shames BD. Adenosine preconditioning reduces both pre and postischemic arrhythmias in human myocardium. J Surg Res 2000;90:191—6.
[11] Hara H, Horinaka S, Yabe A, Yagi H, Tsuboko Y, Yoshida K, Iemura T, Matsuoka H. Suppressive effect of nicorandil in ventricular arrhythmias after reperfusion therapy in patients with acute myocardial infarction. J Cardiol 2007;49:135—41.
[12] Kin H, Zhao ZQ, Sun HY, Wang NP, Corvera JS, Halkos ME, Kerendi F, Guyton RA, Johansen JV. Postconditioning attenuates myocardial ischemia-reperfusion injury by inhibiting events in the early minutes of reperfusion. Cardiovasc Res 2004;62:74—85.
[13] Galagudza M, Kurapeev D, Minasian S, Valen G, Vaage J. Ischemic postconditioning: brief ischemia during reperfusion converts persistent ventricular fibrillation into regular rhythm. Eur J Cardiothorac Surg 2004;25:1006—10.
[14] Halkos ME, Kerendi F, Corvera JS, Wang NP, Kin H, Payne CS, Sun HY, Guyton RA, Johansen JV, Zhao ZQ. Myocardial protection with postconditioning is not enhanced by ischemic preconditioning. Ann Thorac Surg 2004;78:961—9.
[15] Janse MJ, Wit AL. Electrophysiological mechanisms of ventricular arrhythmias resulting from myocardial ischemia and infarction. Physio Rev 1989;69:1049—69.
[16] Glancy JM, Garratt CJ, Woods KL, deBono DP. QT dispersion and mortality after myocardial infarction. Lancet 1995;354:945—8.
[17] Perkiomaki JS, Koistinen J, Yli-Mayry S, Huikuri HV. Dispersion of QT interval in patients with and without susceptibility to ventricular tachyarrhythmias after previous myocardial infarction. J Am Coll Cardiol 1995;26:174—9.
[18] Zhao ZQ, Sun HY, Wang NP, Kerendi F, Guyton RA, Johansen VJ. Hypoxic postconditioning reduces cardiomyocyte loss by inhibiting reactive oxygen species-triggering mitochondrial calcium overload. Circulation 2003;108:174.
[19] Yang XM, Proctor JB, Cui L, Krieg T, Downey JM, Cohen MV. Multiple, brief coronary occlusions during early reperfusion protect rabbit hearts by targeting cell signaling pathways. J Am Coll Cardiol 2004;44:1103—10.
[20] Staat P, Rioufol G, Piot C, Thien YC, Cung TT, L'Huillier I, Auperit JF, Bonnefoy E, Finet G, Andre-Fouet X, Ovize M. Postconditioning the human heart. Circulation 2005;112:2143—8.