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Preconditioning in humans

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Abstract Brief ischemia to the myocardium initiates a cascade of biochemical events in cardiac myocytes that protects the heart muscle during subsequent ischemic insults. This phenomenon is called ischemic preconditioning. If an acute myocardial infarction is preceded by preinfarction angina, it results in smaller infarction size, fewer cardiac arrhythmias, and better-left ventricular function. During coronary intervention, brief balloon inflation protects the heart during subsequent inflations. Patients vary in the degree of preconditioning and those patients who have the ability to demonstrate a significant preconditioning effect will have lesser incidence of subsequent cardiac events. Preconditioning protects the myocardium during coronary artery bypass surgery, particularly in the off-pump procedure, yet the thoracic surgery community has not universally adopted this technique.

Keywords Coronary artery bypass surgery · Ischemic preconditioning · Percutaneous transluminal coronary angioplasty · Preinfarction angina

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Introduction

Whereas it was initially believed that repeated episodes of angina may result in a worsened cardiac insult, there is evidence that brief episodes of transient ischemia may actually have a protective effect. Lange et al. first demonstrated that the rate of ATP depletion is less upon repeated ischemic episodes compared to those associated with a single ischemic episode [1]. In their landmark study, Murry et al. described the benefit of brief episodes of transient ischemia on the myocardium and termed this phenomenon 'ischemic preconditioning' [2]. In a canine model of coronary ischemia these investigators performed four 5-min coronary occlusions separated by 5 min of reperfusion prior to a 40-min occlusion and reperfusion. Myocardial infarct size was measured and compared to a second group of animals which underwent 40 min of occlusion followed by reperfusion to serve as a control to the treated group. A 25% reduction in infarct size was observed in the group of animals subjected to repeated brief occlusions prior to the 40-min occlusion, and the phenomenon of ischemic preconditioning was first recognized. Various implications of ischemic preconditioning in humans will be explored herein in order to increase clinician awareness of this important phenomenon.

Preconditioning and acute myocardial infarction

Since brief episodes of ischemia prior to a prolonged coronary occlusion resulted in smaller infarct size in animals, would angina prior to myocardial infarction result in a similar benefit in humans? This issue was addressed in a subanalysis of the TIMI-4 study. Out of 416 study patients, the 218 who experienced angina preceding the infarction

demonstrated a smaller infarction size and more clinically favorable outcome. Patients with preinfarction angina were less likely to experience severe congestive heart failure or shock (1%) versus patients without preinfarction angina (7%, $P = 0.006$) [3]. Their findings were confirmed prospectively in the TIMI-9B study, which further noted a lower 30-day cardiac event rate and a trend towards lower creatine kinase levels when onset of angina occurred within 24 h of the myocardial infarction event [4]. Multiple other studies further confirmed that preinfarction angina is protective in the setting of acute Q wave or ST segment elevation myocardial infarction, resulting in decreased infarct size, and better clinical outcome [5]. It is likely that similar benefits may be achieved during non-Q wave myocardial infarction as well [6].

While preinfarction angina offers a prognostic value in humans, it has no therapeutic value in high-risk patients or in patients with known coronary artery disease. The value of exercise and preconditioning mimetic drugs as preconditioning stimuli will be reviewed, as well as other drugs that may neutralize or limit the benefit of preconditioning.

Exercise and preconditioning

Zdrenghea et al. sought to mimic the beneficial effect of angina-induced preconditioning utilizing an exercise regimen [7]. Patients with known coronary artery disease underwent two sequential exercise stress tests 1 h apart. The study tested the hypothesis that the first exercise exposure would provide a protective effect that would manifest during the second test. Patients demonstrated less ischemia as measured by the degree of ST-segment depression at peak exercise during the second stress test compared to the first. In another study by Rinaldi et al., the window of preconditioning with exercise was even shorter with benefit shown at 30 min yet no longer observed at 60 min [8]. Other studies confirmed the benefit of exercise and suggested that the mechanism is likely secondary to preconditioning rather than to collateral recruitment [9].

Tomai et al. conducted an important study on exercise and preconditioning [10]. Fifteen consecutive patients with chronic stable angina and angiographically validated coronary artery disease underwent three treadmill exercise tests–two on day one of the study and a third test 24 h later. The second stress test showed a clear benefit manifested by decreased cardiac ischemia, yet this benefit was lost during a third stress test performed 1 day later. This observation suggested that exercise mainly triggers the early phase of preconditioning. However, animal data [11] and some human studies [9] showed that exercise may induce delayed preconditioning as well. These data underscore the importance of regular exercise programs to our patients.

The elderly seem to have an attenuated benefit of preconditioning. Regular exercise in this vulnerable group of patients appears to preserve the benefits of preconditioning [12]. Thus, supervised regular daily exercise should be a principal component in the management of patients with coronary artery disease, particularly the elderly.

Preconditioning mimetic drugs

Drug-induced effects reminiscent of preconditioning have been reported for some pharmacologic agents. Some of the preconditioning mimetic drugs most widely studied in various ischemic models include adenosine, nicorandil, and nitroglycerin. Heidland et al. administered intracoronary adenosine or placebo to 30 patients during percutaneous coronary angioplasty of the left anterior descending coronary artery prior to balloon inflation. Patients who received intracoronary adenosine tolerated longer balloon inflations and had less objective evidence of ischemia compared to controls [13]. Similar protective effects were noted when adenosine was added to the cardioplegic solution during coronary artery bypass surgery. Compared with controls, outcomes of treated patients included a better ejection fraction, less incidence of myocardial infarction, and a more favorable postoperative course [14, 15]. Can adenosine offer a cardioprotective effect during acute myocardial infarction? During the Acute Myocardial Infarction Study of Adenosine (AMISTAD-II) study, 2118 patients with evolving acute anterior myocardial infarction were randomized to treatment with 50 μg/kg/min adenosine, 70 μg/kg/min adenosine, or placebo. The drug was given within 15 min of thrombolytic therapy or prior to primary intervention. The high-dose adenosine group had smaller infarction size, the hallmark evidence of cardioprotection, ascertained by technetium 99m Sestamibi tomography [16]. A recent substudy of AMISTAD-II showed that patients who had reperfusion therapy within 3.2 h of symptoms benefited most from adenosine. In these patients adenosine reduced 1 month mortality (5.2% vs. 9.2%, $P = 0.014$), 6 month mortality (7.3% vs. 11.2%, $P = 0.033$), and the primary 6 month composite endpoint of death and heart failure (12.0% vs. 17.2%, $P = 0.022$) [17]. Since the drug was administered during the acute infarction, the term ‘conditioning’ is more appropriate. It is also quite possible that the mechanism of the beneficial effect is not entirely based on a conditioning effect, but was also related to reduced incidence of coronary no-reflow and/or other known beneficial effects of the drug.

Nicorandil, a K-ATP channel activator, is an emerging drug that is now approved for treatment of angina in several countries, but not yet available in the United States. Administration of nicorandil to patients experiencing acute myocardial infarction undergoing acute intervention

resulted in improvement in left ventricular function, more favorable ventricular remodeling, and decreased incidence of cardiac events in one study [18]. These benefits were thought to be mediated in part through the vasodilatory properties of the drug, its favorable effect on coronary microcirculation, and further through its cardiac conditioning effect. Matsuo et al. studied 44 patients with angina who underwent percutaneous when transluminal coronary angioplasty of the proximal left anterior descending coronary artery. Patients were randomly assigned to an intravenous injection of nicorandil or saline 5 min before balloon inflation. The treatment group had significantly less ischemia per electrocardiogram documentation. There was no difference in either group relative to cardiac perfusion during balloon occlusion as measured by technetium-99m-tetrofosmin single photon emission computed tomography. The study suggested that at least a significant part of the beneficial effect of nicorandil was due to a conditioning effect and not solely to an increase in coronary blood flow [19]. Unfortunately, a larger multi-center trial (called the J-WIND study) recently reported that nicorandil did not reduce myocardial infarction size [20]. When it was administered chronically to patients who had had a myocardial infarction, it did reduce recurrent ischemia [21].

Intravenous nitroglycerin is yet another drug that appears to have preconditioning properties. Over the last few decades, many studies investigated nitrates in acute coronary syndromes and acute ST segment elevation myocardial infarction with mixed outcomes. Despite these equivocal results, most clinicians continued to use nitroglycerin for patient treatment, suggesting a perceived or real clinical benefit. Studies in the 1980s suggested that intracoronary injection of nitroglycerin ameliorated ischemia during balloon angioplasty with benefits thought to be related to venous dilation with less preload and/or dilation of coronary collaterals. In fact, intravenous nitroglycerin does induce cardiac preconditioning as demonstrated in the study by Leesar et al. These investigators randomized 66 patients to receive either intravenous nitroglycerin or saline for 4 h a day prior to coronary angioplasty. On the following day, angioplasty in the group of patients who received nitroglycerin resulted in significantly less ischemia during balloon inflation compared to controls [22]. This benefit persisted long after the vasodilatory effects of nitroglycerin had subsided, strongly suggesting a preconditioning effect for the drug.

Clinical situations unfavorable to preconditioning

Two situations appear to lack the normal tissue adaptive process to ischemia, namely older age and diabetes. Abete et al. studied 503 patients who presented with acute myocardial infarction [23]. Patients who were older than 65 years of age did not show any clinical benefit from preinfarction angina. Only patients younger than 65 years with preinfarction angina had a lower incidence of cardiogenic shock, congestive heart failure, and in-hospital death. Preconditioning in the elderly was only preserved in patients who maintained a high level of exercise [24], further promoting that patients of all ages should be involved in some supervised daily exercise routine. Attenuation of the preconditioning effect was also noted in the presence of diabetes mellitus. Ishihara et al. studied 611 patients with a first anterior wall myocardial infarction. Patients with diabetes and with preinfarction angina had smaller infarction size as judged by the peak creatine kinase enzyme release. However, among the 121 patients with non-insulin dependent diabetes mellitus, no clinical benefit from prodromal angina was observed [25]. The lack of ischemic preconditioning effect does not seem to be limited to non-insulin diabetes mellitus but extends to all patients with hyperglycemia [26]. Notably, use of sulfonylurea hypoglycemic agents may interfere with ischemic preconditioning, and their use is associated with incidence of increased cardiovascular events [27–29]. It remains controversial whether the incidence of increased cardiovascular events is intrinsic to the diabetic drugs or is associated with the suboptimal blood sugar control. More controlled prospective studies are needed to definitively characterize the factors contributing to the observed increase in event rates in diabetic patients.

Preconditioning and left ventricular function

Since preconditioning results in smaller infarction size, it preserves left ventricular function with less incidence of congestive heart failure. In the TIMI-4 study, preinfarction angina patients had smaller infarction size and the combined incidence of significant congestive heart failure or shock were 1% versus 7% in the control group ($P = 0.006$) [3].

Ischemic preconditioning and arrhythmias

As already stated, ischemic preconditioning results in smaller infarction size and less compromise to cardiac function. Would the incidence of cardiac arrhythmias decrease concomitantly? Two controlled studies were conducted to test the hypothesis that ischemic preconditioning may decrease the incidence of ventricular arrhythmias. Wu et al. randomized 86 patients undergoing coronary artery bypass surgery to either an ischemic preconditioning protocol or control group [30]. Ischemic preconditioning was accomplished by aortic cross clamping for 2 min followed by 3 min of reperfusion prior to surgery. Patients in the preconditioning group demonstrated less ventricular

tachycardia at perfusion and in the first 24 h following surgery. Utilizing the model of human angioplasty, atrial and ventricular ectopic beats were less frequent in the aftermath of ischemic preconditioning [31]. Gheeraert et al. examined 136 patients who had experienced an out-of-hospital cardiac arrest in the course of acute myocardial infarction. Patients who had preinfarction angina were more likely to survive the cardiac arrest [32]. Collectively, these data demonstrate that ischemic preconditioning resulted in a lower incidence of cardiac arrhythmias in various clinical settings.

Preconditioning during percutaneous coronary intervention

In the late 1970s, Andreas Gruntzig introduced percutaneous coronary angioplasty. A major limitation to sustained balloon inflation, in order to optimize balloon outcome, was the development of significant regional ischemia and consequent severe chest pain, hypotension, and cardiac arrhythmias. To avoid these complications, an alternative protocol was instituted consisting of multiple balloon inflations with each inflation lasting for only 60–90 s. Notably, ischemic changes observed during the first inflation were usually attenuated with subsequent inflations and initially this was attributable to collateral recruitment that occurs with the first inflation. Argaud et al. studied 36 patients who underwent balloon coronary angioplasty. The degree of myocardial ischemia was measured using intracoronary electrocardiogram, and the size of the area at risk and the degree of the collateral perfusion were measured using photon emission computed tomography. The degree of ischemia during the second balloon inflation was less than the first, yet there was no difference in the degree of the collateral perfusion [33]. This landmark study proved that preconditioning occurred during coronary balloon angioplasty. With the introduction of the modern stents, coronary occlusion now rarely exceeds 30 s, and in general, preconditioning the myocardium in this clinical setting will not have clinical value. The only exception would be in the context of a high-risk complex balloon procedure. The preconditioning effect afforded by transient balloon occlusions and reperfusions of the coronary artery could protect the distal myocardium during subsequent balloon occlusion. In their study of 382 patients during coronary balloon angioplasty, Laskey and Beach made two important observations. First, patients differ in their degree of preconditioning, with some patients experiencing attenuated preconditioning, particularly those who are elderly and/or diabetic. Second, in-hospital ischemic events were more likely to occur in those patients who had attenuated ischemic preconditioning [34].

Could preconditioning mimetic drugs be beneficial in the clinical setting for use during coronary intervention? We believe it is unlikely since the majority of procedures are done with one brief inflation during stent development. A notable exception may be during acute coronary syndromes where the drug nicorandil may have some potential as a preconditioning mimetic drug [35], as well as a known treatment for no-reflow phenomenon [36].

Preconditioning and coronary artery bypass surgery

On-pump bypass surgery

Preconditioning mimetics were investigated during on-pump bypass surgery. However, the data did not always show a consistent benefit. Mentzer et al. showed that patients who received adenosine required less frequent use of postoperative dopamine or nitroglycerin [14]. However, Belhomme et al. failed to show a benefit [37]. Nicorandil also did not consistently prove to be useful when used during coronary bypass surgery [38, 39]. None of these conditioning mimetic drugs are now being utilized routinely in conjunction with on-pump coronary bypass surgery. A plethora of studies reported on the benefit of some volatile anesthetics [18]. However, the availability of such drugs currently in various hospitals depends on their safety profile and cost. The only reliable technique to achieve preconditioning is to perform an aortic cross clamp, followed by 1 or 2 min of reperfusion prior to the start of surgery. While in clinical studies that technique was of benefit in achieving a higher cardiac index, [40] its current use is not widespread. Cross clamping always carries a risk of causing embolic stroke during the surgery, and is unlikely to be popular, particularly in elderly patients with significant aortic atherosclerosis. Thus, currently there is no clinically useful preconditioning tool that is routinely utilized during on-pump bypass surgery.

Off-pump bypass surgery

In off-pump bypass surgery, arterial bypasses are done by individually clamping the artery, making the distal anastomosis, and then releasing the clamp. The process of clamping the coronary artery for 1 or 2 min and then releasing the clamp to allow a 2–3 min reperfusion followed by re clamping, duplicates the known model of preconditioning. Wu et al. randomized a group of patients undergoing off-pump coronary artery bypass surgery to a preconditioning ischemic protocol or control group. The preconditioning protocol was produced by a temporary occlusion of the coronary artery followed by reperfusion and a second coronary occlusion to perform the distal

anastomosis. Patients in the preconditioning protocol had less ventricular and supraventricular arrhythmias compared with controls. Patients also had a lower heart rate compared to controls [41]. While this cardioprotective technique carries great potential, it has not been adopted by most thoracic surgeons [41].

Conclusion

Brief ischemia prior to a longer duration of ischemia results in a biochemical cascade that renders the heart resistant to ischemia. Angina prior to acute myocardial infarction results in a smaller infarct, better left ventricular function, and reduced incidence of ventricular arrhythmias. Ischemic preconditioning is attenuated in diabetics and in the elderly, yet it can be enhanced by regular daily exercise. Since preinfarction angina can only be of prognostic significance, most research work focuses on potential benefits of preconditioning mimetic drugs to minimize the adverse outcomes related to ischemia.

The value of ischemic preconditioning is limited in patients with coronary intervention since the majority of these patients require only a single, very brief balloon inflation. Preconditioning mimetic drugs may be useful only in high-risk patients and those with acute coronary syndromes. Among patients undergoing coronary artery bypass surgery, many techniques to precondition the heart were studied. Surgeon surveys suggest that most of these techniques are not routinely utilized. Temporary occlusion of coronary arteries prior to performing distal anastomosis appears to be the only single technique that is simple to perform, and proven to be of some value during off-pump bypass.

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References

1. Lange R, Ingwall JS, Hale SL, Alker KJ, Kloner RA (1984) Effects of recurrent ischemia on myocardial high energy phosphate content in canine hearts. Basic Res Cardiol 79:469–478
2. Murry CE, Jennings RB, Reimer KA (1986) Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 74:1124–1136
3. Kloner RA, Shook T, Przyklenk K, Davis VG, Junio L, Matthews RV, Burstein S, Gibson M, Poole WK, Cannon CP et al (1995) Previous angina alters in-hospital outcome in TIMI 4. A clinical correlate to preconditioning? Circulation 91:37–45
4. Kloner RA, Shook T, Antman EM, Cannon CP, Przyklenk K, Yoo K, McCabe CH, Braunwald E (1998) Prospective temporal analysis of the onset of preinfarction angina versus outcome: an ancillary study in TIMI-9B. Circulation 97:1042–1045
5. Rezkalla SH, Kloner RA (2004) Ischemic preconditioning and preinfarction angina in the clinical arena. Nat Clin Pract Cardiovasc Med 1:96–102
6. Kushwaha SS, Ambrose JA (2000) Does ischemic preconditioning limit infarct size in non-Q-wave myocardial infarction? Coron Artery Dis 11:191–194
7. Zdrenghea D, Ilea M, Predescu D, Potang E (1998) Ischemic preconditioning during successive exercise testing. Rom J Intern Med 36:161–165
8. Rinaldi CA, Linka AZ, Masani ND, Avery PG, Jones E, Saunders H, Hall RJ (1998) Randomized, double-blind crossover study to investigate the effects of amlodipine and isosorbide mononitrate on the time course and severity of exercise-induced myocardial stunning. Circulation 98:749–756
9. Lambiase PD, Edwards RJ, Cusack MR, Bucknall CA, Redwood SR, Marber MS (2003) Exercise-induced ischemia initiates the second window of protection in humans independent of collateral recruitment. J Am Coll Cardiol 41:1174–1182
10. Tomai F, Perino M, Ghini AS, Crea F, Gaspardone A, Versaci F, Chiariello L, Gioffre PA (1999) Exercise-induced myocardial ischemia triggers the early phase of preconditioning but not the late phase. Am J Cardiol 83:586–588, A7–8
11. Yamashita N, Hoshida S, Otsu K, Asahi M, Kuzuya T, Hori M (1999) Exercise provides direct biphasic cardioprotection via manganese superoxide dismutase activation. J Exp Med 189:1699–1706
12. Abete P, Ferrara N, Cacciatore F, Sagnelli E, Manzi M, Carnovale V, Calabrese C, de Santis D, Testa G, Longobardi G, Napoli C, Rengo F (2001) High level of physical activity preserves the cardioprotective effect of preinfarction angina in elderly patients. J Am Coll Cardiol 38:1357–1365
13. Heidland UE, Heintzen MP, Schwartzkopff B, Strauer BE (2000) Preconditioning during percutaneous transluminal coronary angioplasty by endogenous and exogenous adenosine. Am Heart J 140:813–820
14. Mentzer RM Jr, Rahko PS, Molina-Viamonte V, Canver CC, Chopra PS, Love RB, Cook TD, Hegge JO, Lasley RD (1997) Safety, tolerance, and efficacy of adenosine as an additive to blood cardioplegia in humans during coronary artery bypass surgery. Am J Cardiol 79:38–43
15. Mentzer RM Jr, Birjiniuk V, Khuri S, Lowe JE, Rahko PS, Weisel RD, Wellons HA, Barker ML, Lasley RD (1999) Adenosine myocardial protection: preliminary results of a phase II clinical trial. Ann Surg 229:643–649
16. Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW; AMISTAD-II Investigators (2005) A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). J Am Coll Cardiol 45:1775–1780
17. Kloner RA, Forman MB, Gibbons RJ, Ross AM, Alexander RW, Stone GW (2006) Impact of time to therapy and reperfusion modality on the efficacy of adenosine in acute myocardial infarction: the AMISTAD-2 trial. Eur Heart J 27:2400–2405
18. Kloner RA, Rezkalla SH (2006) Preconditioning, postconditioning and their application to clinical cardiology. Cardiovasc Res 70:297–307
19. Matsuo H, Watanabe S, Segawa T, Yasuda S, Hirose T, Iwama M, Tanaka S, Yamaki T, Matsuno Y, Tomita M, Minatoguchi S, Fujiwara H (2003) Evidence of pharmacologic preconditioning during PTCA by intravenous pretreatment with ATP-sensitive K^+ channel opener nicorandil. Eur Heart J 24:1296–1303
20. Minamino T, Jiyoong K, Asakura M, Shintani Y, Asanuma H, Kitakaze M; The J-WIND Investigators (2004) Rationale and design of a large-scale trial using nicorandil as an adjunct to percutaneous coronary intervention for ST-segment elevation acute myocardial infarction: Japan-Working groups of acute

myocardial infarction for the reduction of Necrotic Damage by a K-ATP channel opener (J-WIND-KATP). Circ J 68:101–106
21. Kitakaze M. (2006) Large-scale trial using atrial natriuretic peptide or nicorandil as an adjunct to percutaneous coronary intervention for ST-segment elevation acute myocardial infarction. Late breaking clinical trials II. Presented at the American Heart Association, Chicago, IL, November 2006
22. Leesar MA, Stoddard MF, Dawn B, Jasti VG, Masden R, Bolli R (2001) Delayed preconditioning-mimetic action of nitroglycerin in patients undergoing coronary angioplasty. Circulation 103:2935–2941
23. Abete P, Ferrara N, Cacciatore F, Madrid A, Bianco S, Calabrese C, Napoli C, Scognamiglio P, Bollella O, Cioppa A, Longobardi G, Rengo F (1997) Angina-induced protection against myocardial infarction in adult and elderly patients: a loss of preconditioning mechanism in the aging heart? J Am Coll Cardiol 30:947–954
24. Abete P, Ferrara N, Cacciatore F, Sagnelli E, Manzi M, Carnovale V, Calabrese C, de Santis D, Testa G, Longobardi G, Napoli C, Rengo F (2001) High level of physical activity preserves the cardioprotective effect of preinfarction angina in elderly patients. J Am Coll Cardiol 38:1357–1365
25. Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Kurisu S, Nishioka K, Kouno Y, Umemura T, Nakamura S, Sato H (2001) Diabetes mellitus prevents ischemic preconditioning in patients with a first acute anterior wall myocardial infarction. J Am Coll Cardiol 38:1007–1011
26. Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Kurisu S, Nishioka K, Umemura T, Nakamura S, Yoshida M (2003) Effect of acute hyperglycemia on the ischemic preconditioning effect of prodromal angina pectoris in patients with a first anterior wall acute myocardial infarction. Am J Cardiol 92:288–291
27. Cleveland JC Jr, Meldrum DR, Cain BS, Banerjee A, Harken AH (1997) Oral sulfonylurea hypoglycemic agents prevent ischemic preconditioning in human myocardium. Two paradoxes revisited. Circulation 96:29–32
28. Engler RL, Yellon DM (1996) Sulfonylurea KATP blockade in type II diabetes and preconditioning in cardiovascular disease. Time for reconsideration. Circulation 94:2297–2301
29. Meier JJ, Gallwitz B, Schmidt WE, Mugge A, Nauck MA (2004) Is impairment of ischaemic preconditioning by sulfonylurea drugs clinically important? Heart 90:9–12
30. Wu ZK, Iivainen T, Pehkonen E, Laurikka J, Tarkka MR (2002) Ischemic preconditioning suppresses ventricular tachyarrhythmias after myocardial revascularization. Circulation 106:3091–3096
31. Airaksinen KE, Huikuri HV (1997) Antiarrhythmic effect of repeated coronary occlusion during balloon angioplasty. J Am Coll Cardiol 29:1035–1038
32. Gheeraert PJ, Henriques JP, De Buyzere ML, De Pauw M, Taeymans Y, Zijlstra F (2001) Preinfarction angina protects against out-of-hospital ventricular fibrillation in patients with acute occlusion of the left coronary artery. J Am Coll Cardiol 38:1369–1374
33. Argaud L, Rioufol G, Lievre M, Bontemps L, Legalery P, Stumpf M, Finet G, Itti R, Andre-Fouet X, Ovize M (2004) Preconditioning during coronary angioplasty: no influence of collateral perfusion or the size of the area at risk. Eur Heart J 25:2019–2025
34. Laskey WK, Beach D (2003) Frequency and clinical significance of ischemic preconditioning during percutaneous coronary intervention. J Am Coll Cardiol 42:998–1003
35. Matsuo H, Watanabe S, Segawa T, Yasuda S, Hirose T, Iwama M, Tanaka S, Yamaki T, Matsuno Y, Tomita M, Minatoguchi S, Fujiwara H (2003) Evidence of pharmacologic preconditioning during PTCA by intravenous pretreatment with ATP-sensitive K^+ channel opener nicorandil. Eur Heart J 24:1296–1303
36. Rezkalla SH, Kloner RA (2002) No-reflow phenomenon. Circulation 105:656–662
37. Belhomme D, Peynet J, Florens E, Tibourtine O, Kitakaze M, Menasche P (2000) Is adenosine preconditioning truly cardioprotective in coronary artery bypass surgery? Ann Thorac Surg 70:590–594
38. Kawamura T, Kadosaki M, Nara N, Wei J, Endo S, Inada K (2005) Nicorandil attenuates NF-kappaB activation, adhesion molecule expression, and cytokine production in patients with coronary artery bypass surgery. Shock 24:103–108
39. Blanc P, Aouifi A, Bouvier H, Joseph P, Chiari P, Ovize M, Girard C, Jegaden O, Khder Y, Lehot JJ (2001) Safety of oral nicorandil before coronary artery bypass graft surgery. Br J Anaesth 87:848–854
40. Wu ZK, Tarkka MR, Pehkonen E, Kaukinen L, Honkonen EL, Kaukinen S (2000) Ischaemic preconditioning has a beneficial effect on left ventricular haemodynamic function after a coronary artery biopass grafting operation. Scand Cardiovasc J 34:247–53
41. Karthik S, Grayson AD, Oo AY, Fabri BM (2004) A survey of current myocardial protection practices during coronary artery bypass grafting. Ann R Coll Surg Engl 86:413–415