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Review - Derleme

Ischemic preconditioning and postconditioning in cardiovascular surgery

Kardiyovasküler cerrahide iskemik önkoşullanma ve sonradan koşullanma

İlker Şengül, Demet Şengül

Department of General Surgery (Assist Prof. İ. Şengül, MD) Giresun University School of Medicine ,TR-28100 Giresun, Department of Pathology (Specialist D. Şengül, MD) Prof. Dr. A. İlhan Özdemir State Hospital TR-28100 Giresun.

Abstract

Despite the technical improvements in the procedures of cardiovascular surgery; significant morbidity and mortality still continue in the patients undergoing cardiovascular surgery, especially in the high risk ones. Models of "conditioning" are suggested and evaluated as preserving the heart itself against ischemia - reperfusion injury which is an important cause of miyocardial injury created by the mentioned surgery and these models have been used in lots of experimental / clinical studies. In the mechanism of ischemic preconditioning; various systemic, chemical, physical stimuli, the substances affecting on the paired receptors of G - protein, proinflammatory substances, changes in the oxygen tension and various hypotheses were suggested such as protein kinase activation and activation of miyocardial potassium-ATP (KATP) channels. Lots of affirmative cardiovascular inteventions such as coronary artery bypass surgery, cardiac valve replacement, transplantation in vivo and vitro have been reported to benefit from the miyocardial preservation effect of ischemic preconditioning. Postconditioning have been widely used in various experimental / clinical studies such as acute miyocardial infarction, ventricular defibrillation, repair of tetralogy of Fallot and transplantation. Despite the fact that these "conditioning" phenomenons are promising, the demand for larger, multicenter, randomised, placebo - controlled experimental / clinical studies in this subject is increasing day by day.

Key words: Cardiovascular surgical procedure; conditioning; ischemic preconditioning; postconditioning; ischemia; reperfusion.

Özet

Kardiyovasküler cerrahi prosedürlerinde teknik ilerlemelere rağmen, hala kardiyovasküler cerrahiye giden - özellikle yüksek riskli – hastalarda, belirgin morbidite ve mortalite süregelmektedir. Anılan cerrahinin yarattığı miyokard hasarının ileri gelen nedeni olan iskemi – reperfüzyon hasarına karşı kalbin kendini koruması olarak bakılan "koşullanma" modelleri öne sürülmüş ve deneysel / klinik birçok çalışmada kullanılmıştır. İskemik önkoşullanmanın mekanizmasında; çok miktarda sistemik, kimyasal, fiziksel uyaran, G - proteinin çiftleşmiş reseptörleri üzerine etki eden maddeler, proinflamatuvar maddeler, oksijen tansiyonundaki değişimler ile birlikte protein kinaz aktivasyonu ve miyokardiyal potasyum - ATP (KATP) kanal aktivasyonu gibi daha birçok hipotez ileri sürülmüştür. İskemik önkoşullanmanın miyokard koruyuculuğu eylemi ile ilgili in vivo ve in vitro olmak üzere koroner arter "bypass" cerrahisi, kalp kapak replasmanı, transplantasyon gibi birçok olumlu kardiyovasküler cerrahi girişim raporlanmıştır. Sonradan koşullanma ise akut miyokard infarktüsü, ventriküler defibrilasyon, Fallot tetralojisi onarımı ve transplantasyon gibi alanlardaki deneysel / klinik birçok çalışmada geniş kullanım alanı bulmuştur. Bununla birlikte; bu "koşullanma" fenomenleri umut verici olsa da daha geniş, çok merkezli, randomize, placebo - kontrollü, deneysel ve klinik çalışmalara gereksinim gün geçtikçe artmaktadır.

Anahtar sözcükler: Kardiyovasküler cerrahi prosedür; koşullanma; iskemik önkoşullanma; sonradan koşullanma; iskemi; reperfüzyon.

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Dr. İlker Şengül Genel Cerrahi Anabilim Dalı Giresun Üniversitesi Tıp Fakültesi TR-28100 Giresun E-posta: dr.ilker52@mynet.com

Introduction

It has been observed that the patients undergoing cardiovascular surgery are still at great risk despite the various technical improvements and the results of cardiovascular (CV) surgical procedures beginning from the 1950s and 1960s. CV arrest is one of the critical parts of the CV surgery (CVS) and at the same time it means CV ischemia.

During the 1970s, in cardioplegic arrest; the heart was arrested by infusing a cold solution (4-8˚C) into coronary ciculation containing high concentrations of potassium which acts like an arrest forming agent. This method has been made a part of the CV repertoire since then.

Initially the solution was crystalloid based which later was replaced by blood based cardioplegia. Today the most commonly used form is the blood based one which has been proven in many studies to be superior to crystalline based ones.

Blood based CP can be applied as cold warm or hot but hot CP is the most popularly used.

Advanced regimens are still needed for myocardial protection of patients who are old, have accompanying diseases and who have significantly depressed CV function in order that they can undergo CVS. Ischemic preconditioning (IPC) and postconditioning (Postcon) a latest determined phenomenon can increase myocardial protection during cardiac surgery. The adaptive effect of them on myocardium was observed to be decreasing infarct area and functional improvement [1].

Ischemic preconditioning in cardiovascular surgery

Various systemic, chemical [2] and physical [3] stimuli have been suggested in the mechanism of IPC together with opioid and adenosine which act on the coupled receptors of G protein; proinflammatory substances such as lipopolysaccharides, TNF α and monophosphoryl lipid A and changes in oxygen tension in the form of anoxia, hypoxia and hyperoxia. A large variety of drugs and anesthetics used routinely in clinical practice form IPC effect. Various hypotheses have been also suggested such as protein kinase activation and myocardial potassium-ATP (K_{ATP}) channel activation [4–17].

There are some clinical studies in which IPC is used in open heart surgery. However the surgeons remained reluctant for classical IPC. They do not wish repeatedly clamping of aorta because of the risk of atheroembolism from calcifications in ascending aorta [18]. Additionally, IPC can itself become harmful by prolonging the surgical procedure for extra 15-30 minutes. Conflicting results were reported for the cardio protective effect of IPC when it was combined with hypothermia and/or CP [19, 20].The brittle side of this matter is that IPC can be in relation with estradiol and does not clarify the answer of the question “Can it be useful for the female population?” [21-24]. All considerations are valid for Postcon except prolonging the duration of the procedure [1].

It has been observed that the healthiness and youngness of animals in laboratory animal

studies concerning IPC and Postcon and the presence of accompanying diseases such as coronary heart disease, diabetes, heart failure and the age of the patient in clinical human studies can affect the results. The metabolic changes induced by hypercholesterolemia and atherosclerosis were investigated whether they can complicate IPC by causing chronic ischemic heart disease [16]. Szers et al [25] have not observed myocardial protection in rats fed on high cholesterol diet for 24 weeks, while Li et al [26] have demonstrated that IPC provides more protection in advanced age rats having overt atherosclerosis due to apolipoprotein E/LDL gene defect when compared with young rats with normal vascular structure.

Additionally Valen et al [27] have shown that rats with serious atherosclerosis experiencing in vivo spontaneous infarction were protected from ex vivo global ischemia. The adaptation way to this kind of ischemia was thought to be a phenomenon formed by natural ways and this condition is met in atherosclerosis types analogous to unstable angina. For this reason, atherosclerosis is not seen as a spontaneous factor that prevents IPC. Unstable coronary syndromes are progressed by systemic inflammatory events [28] or accompanied by these events and can mimic IPC like a clinical analogue. It has been shown in various studies that the outcome is better in patients with unstable angina [UA] than in patients experiencing acute myocardial infarction without angina; the mortality, the incidence of shock and serious congestive heart failure is also lower, the infarct areas are smaller in correlation with the decrease in creatinine phosphokinase activity and lesser Q wave activity were also observed in patients with unstable angina [29, 30]. In Tampere Finland; sensitive parameters for IPC concept were evaluated and "infarct area" was defined as "gold standard" [1].

The molecular changes observed in patients who have UA in CV tissue and undergo open cardiovascular surgery are the same as the changes in animals with experimentally induced IP [31]. Postoperative functional myocardial protection was observed in UA patients but an additional IP was reported not to bring any benefit [32]. It is very difficult to discriminate the reason for the adaptation to ischemia whether it is due to intermittent hypoxia and reoxygenation episodes or due to intravenous glycerin during treatment [33, 34]. Whatever the mechanism is patients who experience UA or myocardial infarction preoperatively, may not benefit from IPC or Postcon [1].

The initial studies about IPC in open heart surgery was performed by Yellon et al in 1993 by performing intermittent clamping for CV protection and showing protected CV ATP levels in patients undergoing coronary artery "bypass" surgery (CABS). Later this same group and one year after Szamagala et al [36] have shown decreased CV troponin T levels in this model [37].

It has been discussed that cardioplegic bypass during CABS cannot bring any benefit other than self-induced IPC [38] and Burns et al [39] have shown that IPC is induced by cardioplegic bypass via stimulating adrenergic and adenosin-1 receptors. Additionally like sevofluran which is known have an IPC effect, it activates kinase cascades which is related with the opening up of potassium channels [38]. Cardioplegic bypass can also induce general inflammatory response including cytokines like TNF α (tumor necrosis factor-alpha) and ROS (reactive oxygen species) production [40] and this can trigger the response of IP [41].

Illes and Swoyer [42] have found increased CV function and decreased inotropic support after IPC. Also in other studies IPC has been reported to be protective in patients undergoing valve surgery and coronary artery bypass graft surgery [43, 44].

IPC was shown to provide more cardiac protection when compared with the pharmacological preconditioning induced by adenosine A-1 receptors [45]. Finland Tampere cardiac surgery group has investigated prospectively ischemic preconditioning in a series of randomized patients undergoing coronary artery bypass surgery and found data yielding that IPC increases the functions of both two left and right ventricles in the

early postoperative period [46, 47]. It has been observed that the IPC response in the elderly patients (Age: >68) is not as clear as the response in younger (Age: <68) patients [48]. Wu et al reported that UA induced IPC during the last 48 hours before surgery increases the postoperative hemodynamic of patients [32]. IP was shown to significantly decrease postoperative ventricular tachycardia and ventricular fibrillation [49] and incidence of postoperative atrial fibrillation in patients with three vessel disease after CABS [50].The suppression of ventricular tachycardia during early reperfusion and 24 hours after surgery suggests that both the early and late effects of IPC are observed in patients undergoing IPC surgical protocol. In another study performed by Wu et al [51] cardioplegy induced apoptosis was not inhibited by IPC. Diaxozide induced myocardial protection during CABS suggests that ATP-dependent potassium channels are important in IPC during CVS [52].

Investigators from Finland have clamped aorta in its whole horizontal axis for 2 minutes before intermittent cold blood based cardioplegia and left to reperfusion for 3 minutes and repeated this for one time and showed a protection consistent with this regimen [44, 49]. Recently Venugopal et al. [53] have demonstrated in a randomized controlled study of IPC model in the arm. They reported that myocardial destruction was reduced in patients undergoing CABS by using the IPC model and that non-invasive cardio protective technique had a wide use of area clinically. However various anesthetics, different patient populations, the abundance of cardioplegic solutions become factors that make IPC complicated in CVS [1].

Postconditioning in cardiovascular surgery

In the recent years the phenomenon of Postcon defined as short term ischemic attacks observed after long term ischemia has been found to decrease infarct area as effective as IPC in a dog model [54] but has a lesser effect than IPC in a rat model [55]. Another aspect of ischemia-reperfusion injury is the reperfusion arrhythmia [56]. In a recent study, Zhang et al [57] have shown that Postcon of sevoflurane can convert persistent ventricular fibrillation to normal rhythm.

Postcon has initially been studied in the heart [54] followed by the liver [58] and recently in different organs such as the brain [59-61], kidney [62-64], the straighted muscle[65],skin flap [66] and in small intestines [67-71]. We investigated the effect of Postcon on intestinal ischemia reperfusion (I/R) injury (IRI) via inhibition of the events in the first few minutes in 5 group and 3 separate Postcon models (PC - 3, PC - 6 and delayed PC [DPC]) of rats. After applying 30 minutes of global ischemia to the superior mesenteric artery to each rat after laparatomy, 3 cycles (PC - 3) and 6 cycles (PC-6) lasting 10 minutes each and 3 cycles after one minute (DPC) were performed in the reperfusion period to maintain intermittent ischemia, after then we left them to global reperfusion for period of 120minutes. By using Postcon models, we demonstrated that infarct area (serum total creatine kinase [CK]), lipid peroxidation (tissue malonyl dialdehyde [MDA]) and the destruction in ileum morphology (Histopathological score) have decreased [67]. Postcon has been shown to decrease infarct area of a myocardial infarct model in dogs, rats, [72-74] and rabbits [75] and also decrease reperfusion arrhythmias of isolated rat heart [57]. After hypoxia-reoxygenation, alive cell count of neonatal rat cardiomyocytes were found to be increased by hypoxic PC [76].

The initial clinical studies about Postcon were conducted by Laskey [77] and Staat et al [78] in patients with acute myocardial infarction. In these studies it was reported that low pressure application induced in the angioplasty balloon for 4 times each lasting 1 minutes increases myocardial infarction, decreases myocardial infarction area both in the acute and during the 6 months period and increases the left ventricular ejection fraction during the 1 year period [77-79]. In 2007, Luo et al. [80] first conducted a randomized controlled study in which PC was investigated in surgery patients. This study included 24children

with Fallot tetrology and it was found that the PC group required significantly lesser inotrop during the first 24 hours and 50% lower levels of troponin I (p = 0,05) and 34% lower levels of CK-MB (p = 0,034) were detected. In 2008 the same group reported similar favorable results regarding the adult valve replacement surgery [81].Likewise in 2009; Li et al [82] suggested in their study including 99 patients who underwent Fallot tetrology repair that Postcon has beneficial effects on morbidity, ventilation time, hospitalization period in intensive care unit, troponin I and lactate release and inotrop requirement. Additionally the myocardial protective effect of Postcon in children who underwent cardioplegic arrest has first been demonstrated by the same group [83].

Cardiac transplantation surgeons can use Postcon. The preservation period of cardiac allograft can often exceed the protective effects of early IPC. For this reason Postcon can play an important role in allograft protection following storage and transplantation. Additionally, Postcon was shown to induce a high degree cardio protective effect in a long, cold (4 hours / 4 ˚C) ischemia protocol and also it was demonstrated that Postcon induces low oxygen production formed by a partial decrease in NADPH oxidase activity [84, 85].

Conclusion

There is still significant morbidity and mortality in patients undergoing CVS especially in high risk patient groups despite the recent developments in myocardial protective techniques and evolution of off-pump CABS. The major cause of myocardial injury during CVS is acute ischemia reperfusion injury (71) Conditioning which is regarded as self-protection of heart from this injury can be divided as IPC which means a cardioprotective intervention before myocardial ischemia and Postcon which is applied after ischemia. Until today various experimental studies have been carried out about this two phenomenon. Besides, although there are clinical, surgical and transplantation related articles, most of the ischemia is often not predictable. So the benefit of IPC is limited and Postcon seems to be more promising. For this reason, as the clinical application areas of Postcon are considered especially when the large patient group with myocardial infarction is taken account of Postcon becomes more attractive than IPC. Additionally, both in vivo and in vitro studies in the literature have demonstrated favorable results about IPC in various CV interventions such as CABS, cardiac valve replacement and transplantation and have found a large area of application.

In conclusion, we can say that although these conditioning phenomenons against IRI seems to be promising, there is still a need of large, randomized, placebo-controlled multicenter studies both experimental and clinical.

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