Review Article

Preconditioning in Cardiac Anesthesia…… Where are we?

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Abstract

Preconditioning, a milestone concept in the cardiovascular sciences introduced 32 years back by Murry. This concept opened a new era in the field of organ protection. To start with extensive studies done on ischemic preconditioning for myocardial protection, ischemic preconditioning is an endogenous science of cellular kinetics. Several components in signal transduction cascade have been identified but still some mechanisms not yet revealed. Anesthetic preconditioning also contributed a lot for myocardial protection and concreted the concept of preconditioning. We, with an inquisitive brain meticulously persuing newer methods of cardioprotection. Remote ischemic preconditioning (RIPC) is a brilliant example of it. RIPC can be future of cardioprotection, clinical trials and studies proved the benefits but yet to conclude the superiority of RIPC over myocardial ischemic cardioprotection. This review is an attempt to reveal this extraordinary concept with its basic cellular kinetics, methods, and recent trends.

Keywords: *Anesthetic preconditioning, ischemic preconditioning, myocardial protection, remote ischemic preconditioning*

Introduction

"That which does not kill us makes us more stronger"

Greatest truth by Nietzsche in 1888.

This quote is perfect for the phenomenon of ischemic preconditioning and ischemic reperfusion injury to myocardium. Murry *et al*.[1] have given the concept of ischemic preconditioning to medicine in 1986.[1] Yellon *et al*. were the first to find a cardioprotective effect of IPC in humans.[2] Key researchers in this field like Warltier DC, Bolli R, Lee, Schultz ….and many more proved the benefits of this concept in clinical outcomes in cardiac surgery. Since, then, we are studying ischemic preconditioning meticulously. Ischemic heart disease (IHD) is among the major causes of morbidity and mortality worldwide. Unexpected deterioration in cardiac function in the postoperative period inspite of uneventful procedure can be related with ischemic reperfusion injuries to myocardium.

To avoid this complication, many nonpharmacological and pharmacological methods have been studied to protect myocardium. Ischemic preconditioning is universally accepted method to protect the myocardium. This review has been an attempt to update the science of preconditioning in cardiothoracic anesthesia and surgery.

Ischemic preconditioning and ischemic reperfusion injury is also a proven concept in other organs of body such as skeletal muscle, liver, kidney, brain, and spinal cord.[3-6] In this review, the preconditioning of myocardium has been studied extensively. Preconditioning in body and other organs is beyond the scope of this review.

Preconditioning is described in many clinical conditions such as angioplasty – repeated balloon inflation and brief occlusion in already stenosed coronary vessel, prepares the myocardium for reperfusion injury postangioplasty. Angina, though a painful symptom before acute coronary syndrome or myocardial infarction actually, reduces the infarct size.[7] Angina can be termed as body's own technique of preconditioning. Preconditioning can be natural, nonpharmacological, and anesthetic preconditioning.

Methods

We searched in International database, PubMed, COCHRANE database from 1986 to 2017. Keywords used to search–ischemic

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preconditioning, anesthetic precondition, myocardial protection, volatiles and opioids in precondition, and remote ischemic preconditioning (RIPC). We selected concluding 225 abstracts and 112 full articles for the study.

Gold Standard Concepts: Ischemic Preconditioning and Reperfusion Injury

Ischemic preconditioning of myocardium

It is defined as:

"An adaptive mechanism by which brief period of reversible ischemia increases the heart tolerance to a subsequent longer period of ischemia."

Ischemic preconditioning can be elicited by mechanical obstruction to coronary flow by occluding for certain time period. Unfortunately, we do not know the exact dose of ischemic preconditioning, dose can be correlated with the term called as CIT 50, i.e., critical time period which is duration of circulatory disruption compatible with 50% tissue survival. Other factors which can induce ischemic preconditioning are hypoxia,[8] stretch[9] heat-shock proteins,[10] and alpha1-receptor stimulation,[11] and exercise and pacing.

Ischemic preconditioning has been classified into two types:

1. Early preconditioning or classical myocardial ischemic preconditioning (MIPC):
   - Onset is immediate
   - Duration of early preconditioning is 2–3 h after the ischemic insult
   - It has robust infarct-sparing effect
   - The duration cannot increase by continuous infusion of any drug or giving repeated stimuli. Adenosine receptor desensitization is the reason for this
2. Late preconditioning or second window of protection:
   - Changes in gene expression lead to synthesis of stress proteins which protect cardiac cells
   - Duration of late preconditioning – from 12 to 24 h after ischemia up to 72 h
   - It has infarct-sparing effect, but in addition, it has anti-stunning effect.

Reperfusion injury

Timely reperfusion following acute coronary occlusion salvages the cardiomyocytes and reduces mortality. However, at the same time, this sudden reperfusion can have some lethal effects too. Clinically reperfusion injury presents with

1. Cardiomyocyte loss and impaired contractility and function
2. Increase in infarct size
3. Increase in arrhythmias
4. Increase in serum lactate levels.[12]

Transient ischemia <15 min is reversible without any cellular death.

Mechanism of reperfusion injury

Reperfusion injury in myocytes occurs in three ways:

1. Microvascular injury – Reperfusion-induced endothelial dysfunction causes vasoconstriction, aggregation of neutrophil, and platelets. No reflow phenomenon during ischaemia causes production of reactive oxygen species
2. Myocardial stunning – Reversible regional and global cardiomyocytes injury
3. Stone heart – Severe uncontrolled reperfusion injury causes disruptive necrosis and contracture band.[13]

Mediators of reperfusion injury

1. Endothelial enzymes – Endothelial dysfunction led to increased endothelin-1 and decreased NO production which causes vasoconstriction and prothrombotic occlusion
2. Oxygen free radicals – Superoxide anions, hydroxyl radical, and proxy nitrite are produced in radical oxygen scavenging pathway. Other enzymes released are xanthine oxidase, cytochrome oxidase, catecholamines, and cyclooxygenase (COX2). These enzymes also again reduce NO production and aggregate neutrophil and platelets
3. Altered calcium metabolism – Increased sarcolemmal calcium concentration by calcium influx is the main step of molecular myocardial injury. This calcium stimulates production of proteases such as Calapilin-1 and myofibrils get degraded
4. Altered myocardial metabolism – Sudden changeover from aerobic to anaerobic glycolysis increases lactate, pyruvate production and reduces high energy phosphates. Inhibition of mitochondrial pyruvate dehydrogenase activity increases pyruvate content. Reversible of metabolism to aerobic done by insulin and adenosine
5. Endogenous protective mechanism – ATP production, NO release, K-ATP channel, closure of mitochondrial permeability transitional pore (MPTP).

Pharmacological agents attenuating reperfusion injury

1. Antioxidants – Glutathione peroxidase, superoxide dismutase, and Vitamin E
2. Ionotropic stimulation – catecholamines
3. Endogenous cardioprotectants – Adenosine acts through A1 and A3 myocyte receptor. NO reverses endothelial dysfunction and improves coronary flow
4. Metabolic stimulation – by insulin and adenosine leads to rapid recovery of aerobic metabolism
5. Na-H_2-antiport inhibition–Acidosis stimulate Na–H_2 sarcolemmal antiport which removes intracellular H_2 for Na. Intracellular hypernatremia activates Na-Ca exchanger system extrudes Na for intracellular Ca.[14]

Future trends of reperfusion management

1. Guardian Trial with CARIOPRIDE which inhibit antiport system

2. Use of endothelin receptor antagonist, for example, Endothelin-1
3. Use of statin and tetrahydrobiopterin as anti-inflammatory agents
4. Erythropoietin – Epiomyocardial receptor causes antiapoptotic, remodeling, and stimulates endothelial progenitor cells
5. Use of interleukin-1 (IL-1) receptor antagonist-anakinra
6. Glucagon-like peptide analog for altered metabolism
7. Use of nitroprusside as NO donor
8. Cyclosporin A inhibitor of MPTP
9. C5a antibody – For example, pexelizumab
10. Elafin–potent endogeneous neutrophil elastase inhibitor also suppresses IL-8, tumor necrotic factor (TNF)
11. Stem cell therapy and angiogenic factor.

Table 1 summarizes the cellular changes in both phases – ischemia and reperfusion

Mechanism of ischemic preconditioning

Ischemic preconditioning is complex and multifaceted phenomenon. It includes many methods, but to study the concept of preconditioning, we should first understand the molecular biology of cardiomyocytes.

Cellular defense and proteomics of ischemic preconditioning

The cell is a machinery of many receptors, enzymes as mediators, and molecules as effectors with mitochondria as an engine. The cell has tremendous capacity and variable mechanisms to sustain in any untoward conditions. Ischemia is a stimulus to cardiac myocyte to start a battle against it in two phases: Early and Delayed or Late as described above. As soon as ischemia (stimulus) occurs, there is immediate release of endogenous trigger substances. Endogenous substances are adenosine, bradykinin, catecholamine, opioids, and acetylcholine.[15-18] Prostanoids, nitric oxide, reactive oxygen intermediates, and tumor necrosis factor-alpha also get released. These substances activate the kinase cascades.[19,20] Tyrosine kinase and mitogen-activated protein kinase are the main mediators. Two pathways are identified: The RISK pathway (Reperfusion-Induced Salvage Kinase)[21] and survivor activating factor enhancement (SAFE) pathway. The RISK pathway which was done by the phosphatidylinositol 3-Kinase (PI3-Kinase),[22] the protein kinase Akt,[23] and the extracellular signal-regulated kinase ½.[24] These kinases, in turn, activate glycogen synthetase kinase 3b, which oppose the opening of the mPTP.[25]

Table 1: Cellular changes in ischemia and reperfusion

Ischemia
1. Decrease in ATP reserve
2. Decrease adenosine nucleotide pool
3. Decrease in glycogen level
4. Increase in H+ ions
5. Increase in lactate levels
6. Na/K+ Pump
7. Ca + overload and cell damage
Reperfusion
1. Sudden increase in blood flow by 400%-600%
2. Hyperemia leads to cell swelling
3. Normalisation of PH
5. Decrease in lactate

ATP: Adenosine triphosphate

Advantages of avoiding opening of mitochondrial permeability transition pore are

1. Increased ATP production
2. Avoids cell membrane rupture secondary to mitochondrial swelling and Ca + overload.[26,27]

The SAFE pathway also has same mPTP actions through the TNFa and the signal transducer and activator of transcription-3;[28] in this way, the mPTP is the main effector of preconditioning. Sato *et al*. have described role of adenosine and protein kinase C (PKC) and the protein kinase G responsible for the activation of mitochondrial ATP-dependent potassium channels (Mk + ATP) which are also end effectors of ischemic preconditioning in the early phase.[29] Activation of K + ATP channels also stimulates release of ROS.[18]

Late preconditioning or delayed preconditioning or second window of protection

After activation of signaling pathway with early phase kinases, the main mediator of the late phase plays the role, and it is the nuclear factor kappa B (NFkB). Its main action is (A) transcription of genes which are responsible for proinflammatory effects of cytokines, chemokines, and leukocyte adhesion molecules.

(B) It translocates to the nucleus and transcripts to cardioprotective molecules such as antioxidants, inducible nitric oxide, and COX2.[30]

(C) NFkB has antiapoptotic effect by regulating many antiapoptotic molecules such as Bcl-2, survivin, inhibitor of apoptosis protein-1, and X-linked apoptosis protein-1.[31]

(D) It upregulates its inhibitor IkBa which reduces NFkB's inflammatory response to sustained ischemia.[32]

Ischemic preconditioning has been seen decreasing in elderly patients as aging causes atherosclerosis which hampers ischemic preconditioning and cardioprotection. Patients with chronic IHD with diabetes, hypertension, and arteriosclerosis have less preconditioning effect because of endothelial dysfunction.[33]

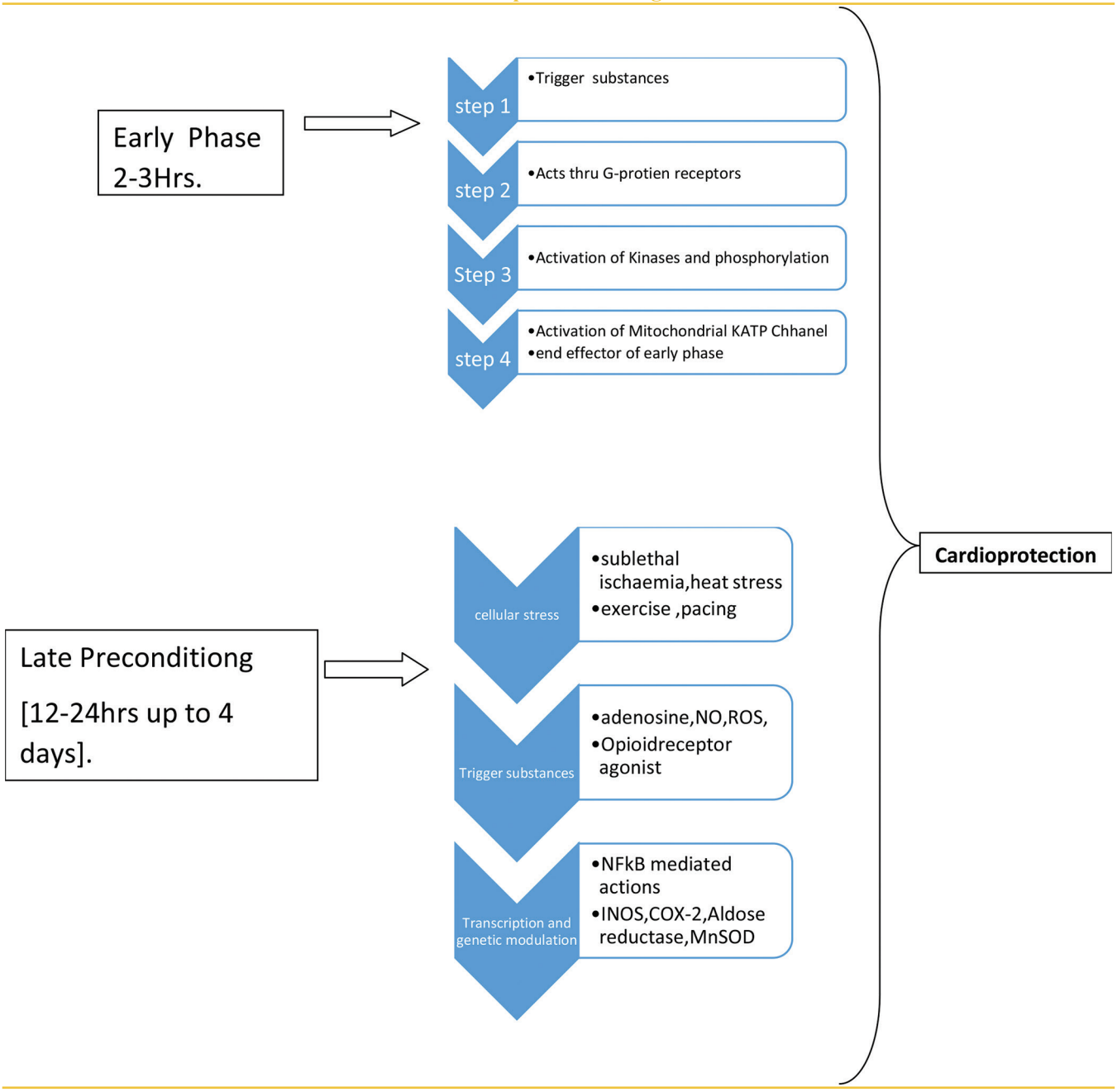
Table 2 –summerises the mechanism of ischaemic preconditioning.

Endogenous captain against ischemia

Adenosine

Adenosine plays an important role in ischemic preconditioning. It is a endogenous molecule which protects

Table 2: Ischemic preconditioning mechanism



the cell from ischemia, hypoxia as well as during reperfusion. Ischemia and hypoxia are potent stimulus for release of adenosine molecules. Adenosine acts through receptors such as A1, A3, and microvascular A3 receptors.[15,34-36] By acting through these adenosine receptors, it preserves cellular ATP molecules, inhibits neutrophil and mast cell activation, exerts antioxidant, and anti-free radicals, and inhibits " No Reflow" mechanism by antiplatelet activity.[37] Adenosine activates K + ATP channels and intracellular calcium as well as stimulate PKC. It stimulates premature degranulation of mast cells. Prolonged ischemia stimulates release of mast cell products which injures cell. Ischemic preconditioning prematurely degranulates mast cells and wash out their products and subsequent cellular injury.[38] Adenosine has a vasodilatory effect by inhibiting the action of vasoconstrictor substances such as thromboxane A2, platelet-activating factor, and endothelin-activating factors, so it improves collateral blood flow. It improves glycolytic influx and also increases heat-shock protein synthesis.[39] It accelerates the conversion of adenosine to ATP with the action of adenosine kinase and other nucleoside salvage pathway.[40] It inhibits ROS-mediated endothelial injury and limits the degree of microvascular injury. Extensive action of hyperpolarisation with K + adenosine and K + ATP channel coupled to

Adenosine receptor A1 AND A3 has efficacy in reducing the basal myocyte metabolic demand.[41] Intracellular hyperpolarisation because of adenosine decreases phosphorylation of slow Ca ++ channel through reduction in protein kinase A, the end point of all this reaction is reduction in cellular energy requirement. Whenever cellular ischemia occurs, cyclic AMP level increases because of increase in norepinephrine level. Adenosine has inhibitory action on norepinephrine which got two advantages, one decrease in cyclic AMP level and another increase regional blood flow in a ischemic vasculature.[42]

Acadesine

Acadesine is a synthetic prototype of Adenosine. It has all beneficial actions like adenosine. It has efficacious role against IRI. It gives protection to ischemic heart and maintain the ventricular contractility. The incidence of reperfusion arrhythmias also reduced with use of this agent for preconditioning.

Opioidergic preconditioning

Cardiac anesthesia has done excellent multifaceted development in the field of cardiothoracic surgery. The anesthetic drugs have potent role in support to preconditioning of heart from ischemic insult. The induction in cardiac patient is routinely opioid based. The reason is not only the hemodynamic stability but also the "opioidergic preconditioning."[43] How exactly it occurs?

Schultz *et al.* reported role of endogenous opioids in ischemic preconditioning in rat model for first time.

Opioids exert their cardioprotective effect through their receptors. Two types of opioids are available-endogenous, for example, endorphin, dynorphin, enkephalin, and exogenous such as morphine, fentanyl, remifentanil. Their action is associated with mu, delta, and kappa receptors. Most studies have demonstrated that cardiac myocytes have predominantly delta and kappa receptors than mu receptors. Cardiac myocytes can produce and release the endogenous opioid receptor peptides. Pre- and post-synaptic mechanism is involved in preconditioning. Opioid receptor agonist combines with G_i linked pathway and stimulating the protein kinases activity.[44] Clinically used opioids such as morphine, fentanyl, and remifentanil have potent cardioprotective effects though mitochondrial K ATP channel, morphine having more potent cardioprotection than fentanyl though the delta receptor action and reduces infarct size.[45] Morphine has anti-inflammatory action and has favorable effects in patient in myocardial infarction. Fentanyl also reduces infarct size as well as enhances cardiac contractile function.[46] Remifentanil, an ultrashort-acting opioid, has cardioprotective effect similar to fentanyl.[47]

Anesthetics preconditioning

Preconditioning effect exerted by volatile agents is termed as anesthetic preconditioning.

Meta-analysis by Symons JA, Myles PS and Yu CH, Beattie on effect of volatile anesthetics on coronary artery bypass surgeries and clinical outcome in 2006 given the permanent place to volatile anesthetics in cardiac anesthesia.

Volatile agents have taken a permanent place in the management of cardiac patient surgeries because of their preconditioning effect on the myocardium. They have direct cardioprotective effect by modulating action on K + ATP channels.[48]

Mechanism by which volatile anesthetics does Preconditioning can brief as follows:

1. Modulation of K + ATP channels
2. Interfering in neutrophil/Platelet–endothelin interaction./Immunological
3. Inhibit calcium overload in cytoplasm
4. Antioxidant effect
5. Gene transcription.

Isoflurane, sevoflurane, and desflurane have cardioprotective effects.[49] Isoflurane provides early and late preconditioning. Sevoflurane has greater preconditioning effects on previously nonpreconditioned heart.

Use of volatiles during cardiopulmonary bypass (CPB) period is also encouraged because of their pre- and post-conditioning effects.

Clinical evidences of volatile preconditioning are observed as:

1. Reduction in Troponin I levels
2. Reduction creatine kinase muscle/brain level
3. Reduction brain natriuretic peptide level
4. Reduction in free radical production
5. Improved cardiac indices
6. Minimal ionotropic requirement
7. Early extubation and less intensive care unit stay
8. Reduced incidences of MI.

Debate for superiority of volatile agents over propofol is the study of much interest. In large study of 10,335 patients, multicenter study by Carl-Johan Jakobsen *et al*., they concluded that both sevoflurane and propofol both possess different cardioprotective actions superior to each other. Sevoflurane has more cardioprotection in patients with noncoronary CABG surgeries without prior ischemia, while propofol has superiority over sevoflurane with severe ischemia.[50]

Other pharmacological agents in ischemic preconditioning

Nicorandil and pinacidil exert their cardioprotection by activation of K + ATP channel. Nicorandil has cardioprotective effect in diabetes mellitus patients. Diabetes mellitus and hyperglycemia impair the K + ATP channel and abolish the ischemic preconditioning effect.

Acetylcholine and carbachol action on coronary vasodilatory reserve. They reduce infarct size.

Ischemic preconditioning in cardiac surgery

Cardiac surgery constitutes coronary bypass grafting, valvular heart surgeries, aortic surgeries, congenital cardiac surgeries, cardiomyoplasty, ventricular assist device surgeries, cardiomyoplasty, and heart and lung transplant surgeries. Over a period, cardiac anesthesia has made excellent techniques and development of drugs which made remarkable improvement in outcome after surgical procedure. ERAS – early recovery from anesthesia and surgery – is also applicable in cardiothoracic procedures. The myocardial protection is the crux of postoperative recovery in cardiac patient. Preconditioning has applicable both on-pump and off-pump procedures.

Cardiopulmonary bypass and ischemic preconditioning
We follow many techniques of myocardial protection such as on-pump procedures with maintaining hypothermia, use of cardioplegia solution. Cardioplegic solution again has different types and methods of delivery which have impact on myocardial protection. CPB triggers preconditioning through alpha-adrenergic and adenosine-1 receptor stimulation and subsequent opening of K + channel.[51] CPB is responsible for inflammatory response, as described in mechanism of preconditioning these inflammatory products such as cytokines, ROS, and TNFa helps in cardioprotection on CPB.[52]

Off-pump coronary artery bypass grafting surgery
Ischemic preconditioning by giving brief period of occlusion in coronary flow can elicit cellular responses which give protection for prolonged ischemia which occurs during grafting. Aortic cross-clamping elicits preconditioning response.

Off-pump coronary bypass grafting is normothermic procedure with variability in ischemic episodes. ST elevation of 1–2 mm occurs during 40% OPCAB surgeries. The incidence of myocardial infarction during beating cardiac surgery is 1%–4.8%. Ischemic precondition causes decrease in lactate production in myocardial cells. Although some studies show no cardioprotection of ischemic preconditioning, many *n* = studies have concluded with benefits of cardioprotection.[53,54] Methods of occlusion vary 3 min and 5 min. It has proven that 15 min of ischemia can cause reversible injury to the heart.[55] Availability of various sizes of shunts can be helpful to prevent profound ischemia, but the positioning during beating heart surgery can lead to decrease coronary perfusion.

Ischemic preconditioning suppresses fatal arrhythmias. Decrease in release of myocardial enzymes and improves stroke volume.

Volatile anesthetics and opioids play an important role in preconditioning effects on myocardium in beating heart surgery.[56] Beneficial outcomes of preconditioning have been studied in the form of mortality, morbidity, incidences of MI, hospital stay, and cost.

Table 3 Summary of IPC.

Remote ischemic preconditioning

Multiple and short episodes of ischemic stimuli applied in distant organ or tissue renders cardioprotection against sustained or prolonged stimulus of ischemia.

Two types are as follows:

- Early RIPC – Effect similarly decreases after a few hours. It is more effective than delayed when it is applied for cardioprotection.[57-59] It is stronger and slows down the rate of ATP depletion
- Late RIPC – It starts after 12–24 h. It is more effective than early in preventing the kidney injury following cardiac surgery.[60]

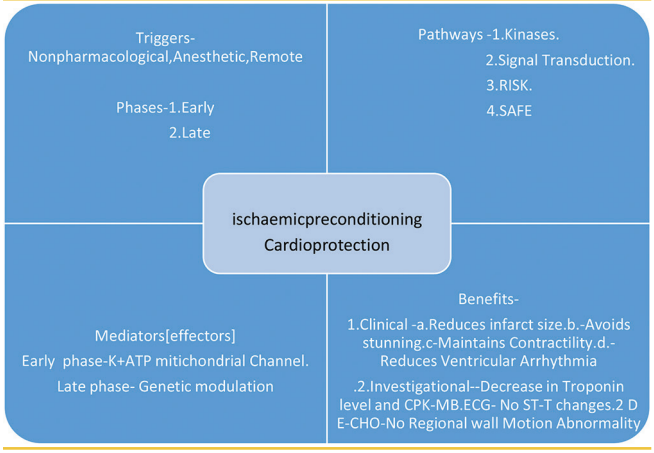
How to elicit remote ischemic preconditioning effect?

The concept of RIPC entails that initial ischemic insult gives protection from secondary ischemic insult.[61] Method of stimulating RIPC consists of 3 cycles of sphygmomanometer B. P. cuff inflation applied to upper or lower limbs for 5 min. Each and alternated rest time or deflation for 5 min. The blood pressure inflation is kept at 50 mmHg higher than systolic blood pressure.[62] After giving RIPC stimulus to one arm for 20 min, the endothelial dysfunction of contralateral arm gets reduced.[63] Chain of RIPC stimulus constitutes three components:

1. Signal generation from organ remote from the heart
2. Transmission of cardioprotective signal to the heart
3. Mechanism of cardiac responses.

RIPC represent promising, simple, effective, and noninvasive strategy to provide additional protection to the myocardium by giving ischemic insult to remote organ. It is practically safe method than MIPC. RIPC is supposed to protect myocardium primarily, but it protects other body organs such as kidney, liver, mesentery, brain, skeletal muscle, pancreas, and intestine.[64-66] Recent study shows favorable effects on target and another organ system too.[67,68] RIPC was first described by Przyntenk in 1993.

Table 3: Summary of ischemic preconditioning



He had classified the favorable outcomes as clinical, biochemical, and investigative.

- Clinical:
  1. Decrease size of infarct zone[69]
  2. Improve ventricular function
  3. Reduces arrhythmogenicity
  4. Decreases mortality and morbidity
  5. Multiorgan protection
  6. Reduces ionotropic support.
- Biochemical
  1. Reduces serum levels of CPK-MB, Troponin-I.
- Investigational
  1. Electrocardiography reduces ST elevation
  2. Two-dimensional Echo reduces regional wall motion abnormalities.

How remote ischemic preconditioning works?

Honest answer to this question---mechanism of action is still unknown!

Ischemic stimuli from remote organ act through neuronal signal and blood-borne humoral and systemic factors.[63,70]

Several following mechanisms are proposed.[71]

1. Systemic factor – Systemic protective responses are stimulated such as anti-inflammatory and antiapoptotic
2. Neural theory – RIPC generates endogenous substances such as adenosine, calcitonin gene-related peptide (C-GRP), and bradykinin which stimulate afferent neural pathway. Finally, these end up into heart and cardioprotection is achieved
3. Humoral hypothesis – Endogenous substances such as bradykinin, adenosine, angiotensin-1, C-GRP, and endocannabinoids release into bloodstream, reaches to the cellular membrane receptor of cardiomyocyte and stimulate various intracellular signaling pathways
4. Final common pathway involves induction of cascade of kinases and subsequent alteration of mitochondrial function
5. Bradykinin has dual role as proinflammatory and anti-inflammatory. It gets released as a humoral and systemic factor as a endogenous substance in the circulation. It is potent chemotactic for neutrophils and involved directly in RIPC.[72,73] It has inflammatory response by regulating the expression of adhesion molecule. It binds to B1 and B2 neutrophilic receptor. These receptors internalized within cell through formation of signalosomes.[74] Signalosomes get converted to phosphatidylinositol-3-kinase which again converted to protein kinase–G. Mitochondria are end effector which provides cytoprotection.[75]

Antiinflammatory action of bradykinin consists of

1. Decreases number of rolling, adherent, and emigrated neutrophils. 2. Acts on B2 receptor and inhibit microvascular dysfunction by NO production.

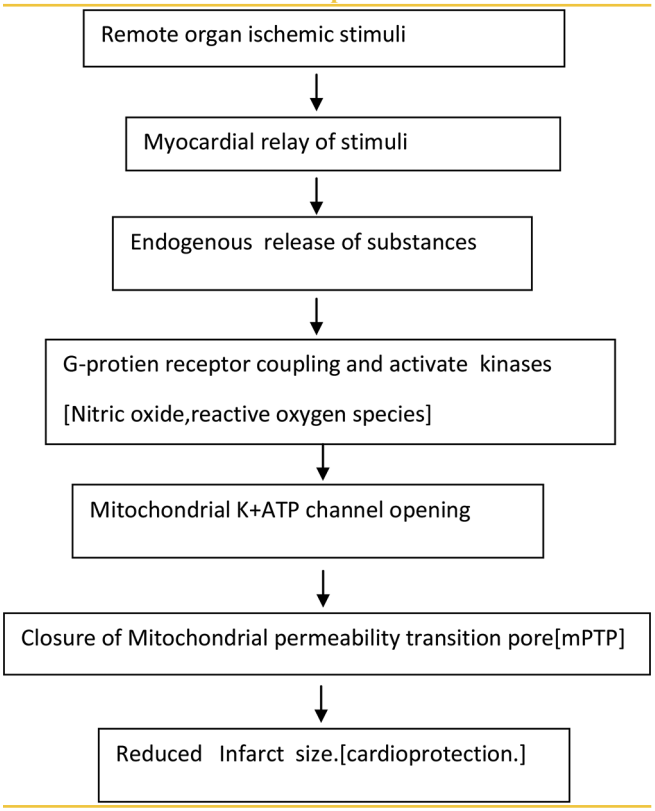
RIPC and cytosolic changes-Neutrophils have key role. RIPC modifies proinflammatory genetic expression.[76] It modify neutrophilic functional response.[77] RIPC causes down-regulation of the expression of kinin B1 and B2 receptor in neutrophil. Algorithm explains the steps of cytosolic reactions during RIPC [Table 4].

C-GRP is a neurotransmitter from capsaicin-sensitive sensory nerve endings. RIPC generate nitric oxide which stimulates nerve ending and release of C-GRP in the blood and delivered to heart.[78] RIPC also stimulate reperfusion injury salvage kinase (RISK) pathway and result in inhibition of Mptp, is a nonspecific high conductance channel of inner mitochondrial membrane.[79,80]

Clinical applications of remote ischemic preconditioning

1. RIPC have protective role on vascular endothelium
2. RIPC reduces platelet reactivity during cardiac invasive procedures. For example, Angioplasty
3. RIPC in kidney is having protective effect but some studies shown acute kidney injury in cardiac surgery by following mechanism-striated muscle damage by inflation and deflation results in release of injury specific iron lead to increase in plasma catalytic iron causes renal failure and second tourniquets cause rhabdomyolysis and acute kidney injury[81]
4. Ability to use limb ischemia as RIPC facilitated its translation from bench to bedside

Table 4: Remote ischemic precomdition-mechanism



5. Many randomized control trials have shown RIPC as an effective strategy for cardiac and noncardiac organs against IRI.

Future directives

We have achieved a lot in the field of cardioprotection and clinical outcomes of cardiac surgeries……but miles to go!

It is necessary to find a magic drug or method with accurate dose for assured outcomes. Role of whole-body preconditioning is coming now.

Sildenafil (phosphodiesterase Type-5 inhibitor) having action on K-ATP channel and also acts on mitochondrial Ca-activated K + channel, both are preconditioning favoring actions. Large trials needed to identify its role in preconditioning.[82]

Levosimendan is a new ionodilator with the action on Ca-sensitive contractile proteins and opening of ATP-dependent K + channels. It shows antiarrhythmic, anti-stunning, and. cardioprotective actions.[83]

Volatile anesthetics have pre- and post-precondition effects and improved long-term effects by protecting coronary endothelium. However, beneficial outcomes of volatiles on noncardiac procedures in cardiac patients at risk of MACE not yet demonstrated. Xenon is emerging study topic for cardioprotection.[84] Similarly, preconditioning with monophosphoryl lipid A also have shown improved survival of critically ischemic tissue and undertrials.[85] Multiorgan transplant and perfect methods of ischemic precondition yet to describe. RIPC can be future of cardioprotection, but clinical trials not yet proved the superiority of RIPC over MIPC.

Conclusion

Preconditioning, with all its types studied over 30 years or more, has certainly marked its importance in cardiac surgeries. However, still perfect method, accurate dose and assured outcome of preconditioning not found.

Ischemia and reperfusion injuries are puzzle to be solved because stunning and hibernation can lead to morbidity and mortality.

Anesthesic preconditioning with its glory influencing the cardiac surgery and anesthesia, but still we need better understanding of volatile agents mechanism for cardioprotection.

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Conflicts of interest

There are no conflicts of interest.

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