Recent innovations in myocardial protection strategies during cardiac surgeries

Pierre Zarif Tawadros

Assistant Professor of Anesthesia and Surgical Intensive Care, Cairo University, Egypt

Correspondence to Pierre Zarif Tawadros, MD, 16 Ahmed Eldarderi, Heliopolice, Cairo, 11341, Egypt. Tel: 01223647115; e-mail: pierre_zarif@hotmail.com

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Better understanding of the pathophysiology of myocardial injury has led to the development of multiple modifications and new strategies for myocardial protection. New drugs and techniques are always being investigated to add to the already proven techniques applied for myocardial protection.

Keyword:
conditioning and cardioplegia, ischemia-reperfusion injury, myocardial protection

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Learning objectives

The following were the objectives of the study:

(1) To understand the pathophysiology of myocardial injury.
(2) To report myocardial protection strategies.
(3) To report the mechanisms of myocardial conditioning against ischemia-reperfusion injury.
(4) To report the types of cardioplegia.

Pathophysiology of myocardial injury

Myocardial injury during cardiac surgery may result from the ischemia itself, the deleterious effects of cardiopulmonary bypass, and from restoration of blood flow during reperfusion.

Effects of ischemia

Short periods of ischemia lead to reversible changes in the myocytes which if prolonged will lead to necrosis and cell death. Changes include depletion of high-energy phosphate, intracellular acidosis, calcium overload inside the cells, cellular swelling, and loss of membrane integrity, with leaking of enzymes and metabolites [1].

Spectrums of ischemia are as follows:

(1) Reversible:
   (a) Stunning: it is defined as postischemic myocardial impairment after restoration of coronary blood flow. Proposed mechanisms are intracellular calcium overload and oxygen free radicals. It can be overcome by inotropes. Examples include unstable angina and after removal of aortic cross clamp.
   (b) Hibernation: it was first described by Rahimatoola (1989) and defined as a state of persistent impairment of myocardial function due to reduced coronary blood flow. It is reversed partially or completely if oxygen supply/demand balance is restored. It can be diagnosed by dobutamine stress echocardiography, positron emission tomography, and cardiac magnetic resonance. Recent theories consider hibernation is a repeated attack of ischemia, possibly silent, causing repeated stunning [2].
(2) Irreversible: it includes apoptosis and cell death.

Effects of cardiopulmonary bypass

They include hemodilution, hemolysis, stress response with release of catecholamines, altered glucose metabolism, activation of complement and neutrophils, and fibrinolysis.

Reperfusion injury

It is defined as paradoxical myocardial injury after restoration of perfusion to the myocardium. Clinically, it may manifest by variable degree of dysfunction and/or arrhythmias. Causes include intracellular calcium overload, oxygen free radicals, neutrophil activation, and endovascular damage. Severity and duration depends on the extent of ischemia and the reperfusate composition [3].

Mediators of reperfusion injury include the following:

(1) Endothelial dysfunction: it leads to increased endothelin-1 and decreased nitric oxide 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. These enzymes also again reduce nitric oxide 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 and pyruvate production and reduces high-energy phosphates. Inhibition of mitochondrial pyruvate dehydrogenase activity increases pyruvate content. Reversibility of metabolism to aerobic is done by insulin and adenosine.

Endogenous protective mechanism include ATP production, nitric oxide release, K-ATP channel, and closure of mitochondrial permeability transitional pore (MPTP) [4].

Aim

The aim of cardioprotective strategies is as follows:

(1) Prepare the heart to ischemia (preconditioning).
(2) Minimize metabolic requirements during arrest (hypothermia and cardioplegia).
(3) Provide favorable metabolic environment during arrest.
(4) Ameliorate the reperfusion injury.

Now, it is established that optimal cardioprotection may require a combination of additive or synergistic multitarget therapies to cover the multifactorial myocardial injury and to overcome the comorbidities that may affect the protection provided by a single protection tool [5].

Preconditioning

'That which does not kill us makes us stronger' (Nietzsche, 1888).

It is an adaptive mechanism in which exposure to a physical or pharmacological stimulus may ameliorate the injury from subsequent ischemia [1].

The extent of myocardial protection may be recently measured by what is called critical time period (50) which is the duration of circulatory disruption compatible with 50% tissue survival [4].

Ischemic preconditioning

Repeated balloon inflation and deflation during angioplasty was proven to prepare the heart to reperfusion after angioplasty. Moreover, recurrent angina attacks were associated with reduced infarct size [6].

Ischemic preconditioning may occur in two phases

Early preconditioning: it starts within 15 min and last for several hours. It protects against myocardial infarction but not stunning. Adenosine activates protein kinase C leading to activation of mitochondrial ATP-sensitive potassium channels (K_{ATP}). 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. Sulfonylureas drugs may inhibit preconditioning by blocking K_{ATP} channels [7].

Late preconditioning: this involves gene transcription and synthesis of stress proteins, so it starts from 12 to 24 h after ischemia. It protects against both infarction and stunning [4].

Pharmacologic preconditioning

Anesthetic preconditioning

Volatile anesthetics: they have direct effect by modulating action on K_{ATP} channels, interfering with neutrophils and platelets activation, gene transcription, and decrease calcium overload. As low as 0.25 minimum alveolar concentration may be protective but maximum protection is achieved at 1.5–2 minimum alveolar concentration. Halothane, isoflurane, sevoflurane, and desflurane have cardioprotective effects [8].

Opioids: opioid receptor agonist combines with G_i linked pathway and stimulates the protein kinases activity. Morphine, fentanyl, and remifentanil have potent cardioprotective effects though mitochondrial K_{ATP} channel. Morphine has more potent cardioprotection than fentanyl through the delta receptor action and reduces infarct size [9]. Remifentanil, an ultrashort-acting opioid, has cardioprotective effect similar to fentanyl [10].

Acadesine: it is a synthetic protype of adenosine and has all protective activity of adenosine.

Nicorandil and pinacidil: they are calcium channel blockers with cardioprotective activity through activation of K_{ATP}. Nicorandil has special cardioprotective action in diabetic patients.

Propofol: it ameliorates lipid peroxidation and has cardioprotective effect.

Other pharmacological agents: xenon, norepinephrine, α-2 agonists, acetylcholine and carbachol have protective action [4].

Remote ischemic preconditioning

Remote ischemic preconditioning (RIPC) involves inducing multiple and short episodes of ischemia distant to the myocardium to obtain a myocardial protective effect after reperfusion of the remote tissue [11].

Two types are as follows:

(1) Early RIPC – effect similarly decreases after a few hours. It is more effective than delayed when it is applied for cardioprotection. It is stronger and slows down the rate of ATP depletion [12].
(2) Late RIPC – it starts after 12–24 h. It is more effective than early in preventing the kidney injury following cardiac surgery [13].

Method of stimulating RIPC consists of three cycles of sphygmomanometer blood pressure 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. RIPC is supposed to protect myocardium primarily, but it protects other body organs such as kidney, liver, mesentery, brain, skeletal muscle, pancreas, and intestine [14].

The following theories are proposed [4]:

(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, and bradykinin which stimulate afferent neural pathway. Finally, these end up into heart and cardioprotection is achieved [15].
(3) Humoral hypothesis – endogenous substances such as bradykinin, adenosine, angiotensin?1, calcitonin gene-related peptide, and endocannabinoids release into bloodstream, reach to the cellular membrane receptor of cardiomyocyte, and stimulate various intracellular signaling pathways [16].
(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 an endogenous substance in the circulation. It is a potent chemotactic for neutrophils and is involved directly in RIPC. However in a recent study published by Cho *et al*. [17], they found that the cardioprotective effect of limb RIPC were abolished under propofol, sevoflurane, and carvedilol therapy.

As an alternative to RIPC, an interesting study by Tuter *et al*. [18] used intermittent systemic hypoxic-hyperoxic training for myocardial protection. For 4 days before the cardiac surgery, patients received a hypoxic mixture with 12% oxygen content followed by hyperoxic mixture of 35–40% taking safety measure of lowest accepted SpO_2 82% and maximum accepted heart rate of +50% during the procedure. This procedure was compared against RIPC group and control group regarding postoperative troponin and serum lactate. There was significantly lower troponin and serum lactate in intermittent systemic hypoxic-hyperoxic training and RIPC compared with the control group [18].

Myocardial protection during cardiopulmonary bypass

(1) Hypothermia.
(2) Cardioplegia.
(3) Decompression.

Hypothermia is known to decrease myocardial oxygen requirements during rest and also in the fibrillating and arrested heart. At 22°C, myocardial oxygen consumption is reduced from 80 to 0.3 ml/100 g/min. It also impedes the process resulting in apoptosis [1].

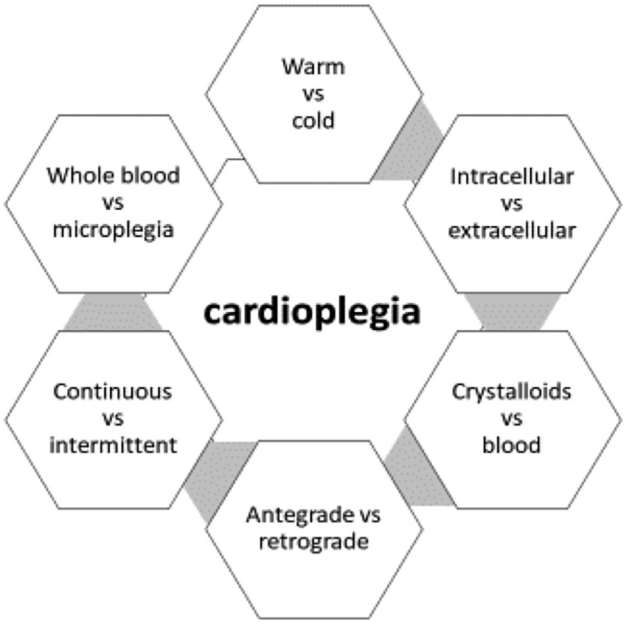
Hypothermia is applied locally by inserting ice directly on the myocardium or systemic hypothermia using the heat-cooler machine attached to the cardiopulmonary bypass. The deleterious effects of hypothermia include decreased production of ATP, paralysis of diaphragm by local ice affecting the phrenic nerve, oxygen delivery to tissues is decreased owing to an increase in hemoglobin affinity for oxygen, metabolic acidosis,

increased plasma viscosity, reduced erythrocyte deformability and subsequently lower flow through the microcapillaries, hypothermia-induced vascular spasm also impedes blood supply, platelet dysfunction, and coagulation defects [19].

Cardioplegia [20]

(1) Cardioplegia is an integral and essential method for myocardial protection for patients of all ages requiring cardiac surgery. Since its initial discovery by Lamb in 1985, cardioplegia has gone in and out of favor. Its components have been manipulated, and a variety of techniques have been used. Cardioplegic solutions provide myocardium protection by reducing oxygen demand to below 10%. Therefore, a reliable cardioplegic solution is mandatory for achieving successful myocardial protection. Yet, to this day, there continues to be a debate over what the ideal cardioplegic solution should be like.
(2) Cardioplegia solutions may be blood or crystalloids, warm or cold, continuous or intermittent (Fig. 1).
(3) The advantage of blood cardioplegia over the crystalloid cardioplegia is that blood provides better oxygen delivery by its hemoglobin content, buffering, free-radical scavenger (red blood cells and platelets), provide nutrients (amino acids and fatty acids), reduces myocardial edema, and has less volume overload.

Figure 1



Types of cardioplegia.

A combined antegrade and retrograde delivery for cardioplegia ensures the adequate protection to areas of myocardium distal to totally occluded coronary arteries and overcomes the less effective protection of right ventricle provided by the retrograde alone technique.

(1) Regarding the temperature of the cardioplegia, it may be cold (9°C), tepid (29°C), and warm (37°C). Early postoperative left ventricular function was best preserved after tepid cardioplegia with a decrease in ventricular rhythm disorders, need for postischemic DC shock, and blood loss [21].
(2) The mechanism of action of all different types of cardioplegia solutions used is to ensure diastolic arrest of the heart to ensure decreased wall tension and decreased myocardial oxygen consumption during arrest. This was achieved by potassium (K^+)-containing solutions, with potassium concentration range from 20 to 40 mEq/l. The high K^+ extracellular levels block Na-K ATPase and maintain the cells in the depolarized state. Examples include St Thomas cardioplegia and Buckberg blood cardioplegia.
(3) A recently introduced type of cardioplegia is the Del Nido cardioplegia. The single-dose, cold blood Del Nido cardioplegia, can be safely delivered antegrade or retrograde for longer redosing intervals. It is an acalcemic extracellular cardioplegia solution with the unique use of a sodium channel blocker causing polarization of the myocyte membrane. The unique formulation reduces energy consumption, blocks calcium entry into the intracellular environment, scavenges hydrogen ions, preserves high-energy phosphates, and promotes anaerobic glycolysis during myocardial arrest (Table 1).

Table 1 The Del Nido cardioplegia solution as described originally [22]

Ingredients	Volume (ml)	Role
Plasma-Lyte A	1000	Na 140 mmol/l; K 5 mmol/l; Mg 3 mmol/l; pH 7.4
Mannitol 20%	16.3	Osmotic pressure, free-radical scavenger
$MgSO_4$ 50%	4	Calcium channel blocker, improved myocardial recovery
$NaHCO_3$ 8.4%	13	pH buffer
KCl 2 mEq/l	13	Myocardial depolarization
Lidocaine 1%	13	Sodium channel blocker, hyperpolarizing agent

Table 2 Custodiol cardioplegia [23]

Ingredients	Concentration
Na	15 mmol/l
K	9 mmol/l
Mg	4 mmol/l
Ca	0.15 mmol/l
Histidine	198 mmol/l
Tryptophan	2 mmol/l
Ketoglutarate	1 mmol/l
Mannitol	30 mmol/l
pH	7.02–7.20

(4) The other type of cardioplegia is the intracellular crystalloid cardioplegia (Custodiol). It is a nondepolarizing cardioplegia with very low sodium and calcium content. Sodium depletion of the extracellular space causes a hyperpolarization of the myocyte plasma membrane, inducing cardiac arrest in diastole. A high histidine content buffers the acidosis caused by the accumulation of anaerobic metabolites during the long ischemic period, ketoglutarate improves ATP production during reperfusion, tryptophan stabilizes the cell membrane, and mannitol decreases cellular edema and acts as a free-radical scavenger [23] (Table 2).

Additives to cardioplegia

(1) Beta-blockers: the ultrashort-acting and cardioselective beta-blocker esmolol has a half-life of a few minutes, with rapid elimination after cessation of infusion. Clinical studies have shown that esmolol can be used to obtain minimal myocardial contraction during surgery while maintaining continuous normothermic coronary perfusion to avoid ischemia. The use of esmolol as a cardioplegic agent may be a beneficial alternative to standard techniques [24].
(2) Glucose-insulin-potassium: these are used frequently to protect and provide nutrition to the myocardium. However, the recent insulin trial failed to document benefit of insulin-cardioplegic solution in coronary revascularization surgery for high-risk patients [25].
(3) Antioxidants: these are used for protecting the heart from the oxygen free-radical generated during ischemia and to provide scavengers during the reperfusion phase. Reduced glutathione was shown to improve myocardial recovery. Moreover, iron-chelating agents such as deferoxamine have been used systemically and in cardioplegia to decrease lipid peroxidation and free-radical generation [20].
(4) Nitric oxide/L-arginine: nitric oxide exerts a myocyte protective role as an antiapoptotic factor and as a mediator in ischemic preconditioning. L-arginine increases nitric oxide release and increases myocardial pH recovery [20].
(5) Na^+/H^+ exchange inhibition: protons accumulating during ischemia are extruded at the time of reperfusion in exchange for sodium ions. The resulting sodium overload cannot be adequately handled by the sodium/potassium pump because it is inefficient owing to ischemia-induced shortage of energy. This excess of intracellular sodium is then extruded from cells through the sodium/calcium exchanger, which functions in a reverse mode. It brings calcium ions in the cells allowing a dangerous calcium overload, responsible for the ischemia/reperfusion tissue injury. GUARDIAN trial used cariporide, a Na^+/H^+ exchange inhibitor, at different dose but failed to demonstrate clinical benefit [26].

Ameliorating the reperfusion injury [1]

Ischemic postconditioning

Ischemic postconditioning is defined as interruption of reperfusion after completion of cardiac surgery. This may be applied by perfusion for 30 s followed by reocclusion for 30 s. This was found to decrease infarct size.

Volatile anesthetics have postconditioning effect that may be through inhibition of neutrophils-mediated reactive oxygen species generation.

Pharmacological postconditioning

(1) Antioxidants: glutathione peroxidase, superoxide dismutase, and vitamin E.
(2) Ionotropic stimulation: catecholamines.
(3) Endogenous cardioprotectants: adenosine acts through A1 and A3 myocyte receptor. nitric oxide reverses endothelial dysfunction and improves coronary flow.
(4) Metabolic stimulation by insulin and adenosine leads to rapid recovery of aerobic metabolism.
(5) $Na\text{-}H_2$-antiport inhibition: acidosis stimulates $Na\text{-}H_2$ sarcolemmal antiport which removes intracellular H_2 for Na. Intracellular hypernatremia activates Na-Ca exchanger system that extrudes Na for intracellular Ca.
(6) Cyclosporine A was found to be a potent inhibitor of MPTP. This pore remains closed during ischemia; however, during the early minutes of reperfusion, calcium overload and excessive

production of reactive oxygen species prompt opening of the MPTP, precipitating the collapse of its membrane potential followed by irreversible damage and cell death. A single bolus dose of 2.5 mg/kg was used and demonstrated reduced extent of myocardial injury in patients with acute ST-elevation myocardial infarction [27].

(7) Intralipid has recently been shown to be more effective than cyclosporine in an *in vivo* rat heart and isolated mouse heart experiment [28].

Markers of protection [29]

(1) Two excellent markers for determining the adequacy of myocardial protection are cardiac enzyme levels (CPK-MB : creatine kinase or troponin) and postoperative septal motion, as both depict muscle injury and correlate with early and late mortality. In contrast, the markers frequently utilized in studies, such as hospital or ICU length of stay, arrhythmias, inotropes, IABP and in-hospital or 30-day mortality, are poor indicators of the adequacy of myocardial protection.
(2) Cardiac enzyme release has been shown to directly correlate with muscle damage and outcomes. Even small elevations have been shown to be significant, and the higher the level, the more the deaths.
(3) The septum is a subendocardial structure, so it is more vulnerable to inadequate myocardial protection. It is easily seen on an echocardiogram, and its dysfunction indicates muscle injury from inadequate myocardial protection.

Future recommendations [5]

Combinations of interventions with solid preclinical information on mechanism of action, efficacy, and safety, and that are easily applicable are good candidates to be moved to clinical trials. Some promising examples of approaches to multitargeted cardioprotection include the following:

(1) A combination of RIC with a drug with a different mechanism of action – this is being tested in the COMBAT-MI trial (COMBin Ation Therapy in Myocardial Infarction) (NCT02404376).
(2) A combination of a drug that activates endogenous cardioprotective pathways [RISK (Reperfusion-Induced Salvage Kinase), SAFE (Survivor Activating Factor Enhancement), cGMP (cyclic Guanidine Mono Phosphate)/PKG (Protein Kinase G)] with a drug that inhibits cell death pathways.
(3) A drug targeting vascular injury/inflammation with a drug targeting cardiomyocyte death.

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Conflicts of interest

There are no conflicts of interest.

References

1 Scott T, Swanevelder J. Perioperative myocardial protection. Contin Educ Anaesthesia Crit Care Pain 2009; 9:97–101.
2 Rahimatoola SH. The hibernating myocardium. Am Heart J 1989; 117:211–222.
3 Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. N Eng J Med 2007; 357:1121–1135.
4 Annachhatre AS, Annachhatre SR. Preconditioning in cardiac anesthesia . . . . . where are we? Ann Card Anaesth 2019; 22:412–420.
5 Davidson SM, Ferdinandy P, Andreadou I, Bøtker HE, Heusch G, Ibáñez B, *et al.* Multitarget strategies to reduce myocardial ischemia/reperfusion injury: JACC review topic of the week. J Am Coll Cardiol 2019; 73:89–99.
6 Kloner RA, Arimie RB, Kay GL, Cannom D, Matthews R, Bhandari A, *et al.* Evidence for stunned myocardium in humans: a2001 update. Coron Artery Dis 2001; 12:349–356.
7 Jerome SN, Akimitsu T, Gute DCKR. Ischemic preconditioning attenuates capillary no-reflow induced by prolonged ischemia and reperfusion. Am J Physiol 1995; 268 (H):2063–2067.
8 Warltier DC, Kersten JR, Pagel PSGG. Anesthetic preconditioning: serendipity and science. Anesthesiology 2002; 97:1–3.
9 Schultz JJ, Hsu AKGG. Ischemic preconditioning and morphine?induced cardioprotection involve the delta (delta)-opioid receptor in the intact rat heart. J Mol Cell Cardiol 1977; 29:2187–2195.
10 Dershwitz M, Randel GI, Rosow CE, Fragen RJ, Connors PM, Librojo ES, *et al.* Initial clinical experience with remifentanil, a new opioid metabolized by esterases. Anesth Analg 1995; 81:619–623.
11 Kharbanda RK, Mortensen UM, White PA, Kristiansen SB, Schmidt MR, Hoschtitzky JA, *et al.* Transient limb ischemia induces remote ischemic preconditioning in vivo. Circulation 2002; 106:2881–2883.
12 Yang L, Wang G, Du Y, Ji BZZ. Remote ischemic preconditioning reduces cardiac troponin I release in cardiac surgery: a meta-analysis. J Cardiothorac Vasc Anesth 2014; 28:682–689.
13 Heusch G, Bøtker HE, Przyklenk K, Redington AYD. Remote ischemic conditioning. J Am Coll Cardiol 2015; 65:177–195.
14 Remote Preconditioning Trialists' Group, Healy DA, Khan WA, Wong CS, Moloney MC, Grace PA, *et al.* Remote preconditioning and major clinical complications following adult cardiovascular surgery: systematic review and meta-analysis. Int J Cardiol 2014; 176:20–31.
15 Ehrenfeld P, Millan C, Matus CE, Figueroa JE, Burgos RA, Nualart F, *et al.* Activation of kinin B1 receptors induces chemotaxis of human neutrophils. Biology 2006; 80:117–124.
16 Saxena P, Shaw OM, Misso NL, Naran A, Shehatha J, Newman MA, *et al.* Remote ischemic preconditioning stimulus decreases the expression of kinin receptors in human neutrophils. J Surg Res 2011; 171:311–316.
17 Cho YJ, Nam K, Kim TK, Choi SW, Kim SJ, Hausenloy DJ, *et al.* Sevoflurane, propofol and carvedilol block myocardial protection by limb remote ischemic preconditioning. Int J Mol Sci 2019; 20:269.
18 Tuter DS, Kopylov PY, Syrkin AL, Glazachev OS, Komarov RN, Katkov AI, *et al.* Intermittent systemic hypoxic-hyperoxic training for myocardial protection in patients undergoing coronary artery bypass surgery: first results from a single-centre, randomised controlled trial. Open Hear 2018; 5:1–8.
19 Van Pouk S, Steven K, Marcus AELM. Hypothermia effects on platelet function & hemostasis. Thromb J 2014; 12:31.
20 Nicolini F, Beghi C, Muscari C, Agostinelli A, Budillon AM, Spaggiari I, *et al.* Myocardial protection in adult cardiac surgery: current options and future challenges. Eur J Cardio-thoracic Surg 2003; 24:986–993.

21 Hayashida N, Weisel RD, Shirai T, Ikonomidis JS, Ivanov J, Carson SM, *et al.* Tepid antegrade and retrograde cardioplegia. Ann Thorac Surg 1995; 59:723–729.

22 Sanetra K, Pawlak I, Cisowski M. Del Nido cardioplegia – what is the current evidence? Polish J Cardiovasc Surg 2018; 15: 114–118.

23 Edelman JJB, Seco M, Dunne B, Matzelle SJ, Murphy M, Joshi P, *et al.* Custodiol for myocardial protection and preservation: a systematic review. Ann Cardiothorac Surg 2013; 2:717–728.

24 Bessho RCD. Myocardial protection with oxygenated esmolol cardioplegia during prolonged normothermic ischemia in the rat. J Thorac Cardiovasc Surg 2002; 124:340–351.

25 Rao V, Christakis GT, Weisel RD, Ivanov J, Borger MA. CG for the ICT (ICT) I. The Insulin Cardioplegia Trial: myocardial protection for urgent coronary artery bypass grafting. Thorac Cardiovasc Surg 2002; 123:928–935.

26 Theroux P, Chaitman BR, Danchin N, Erhardt L, Meinertz T, Schroeder JS, *et al.* for the GuarDIAN (GUARDIAN) I. Inhibition of the sodium-hydrogen exchanger with cariporide to prevent myocardial infarction in high-risk ischemic situations: main results of the GUARDIAN trial. Circulation 2000; 102: 3032–3038.

27 Muehlschlegel JD. Closing the pore on reperfusion injury: myocardial protection with cyclosporine. Anesthesiology 2014; 121:212–213.

28 Li J, Iorga A, Sharma S, Youn JY, Partow-Navid R, Umar S, *et al.* Intralipid, a clinically safe compound, protects the heart against ischemia-reperfusion injury more efficiently than cyclosporine-A. Anesthesiology 2012; 117:836–846.

29 Allen BS. Myocardial protection: a forgotten modality. Eur J Cardio-Thoracic Surg 2020; 27:263–270.