EDITORIAL ARTICLE

# Myocardial protection: The eternal search for an ideal cardioplegia solution and adjuvants added for superior myocardial protection during cardio pulmonary bypass

Sandeep Kumar Kar

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## INTRODUCTION

The basis of myocardial protection rests on the principle of selective metabolic modulation of energy production during the period of ischemia, where utilization of glucose thorough the glycolytic pathway is more superior, favourable and energy efficient than Beta oxidation of fatty acids. This is preferential metabolic shift encouraging energy efficient bio-energetics to play on the role in Myocardial Protection through substrate modification for energy production in the heart, during the period of cardiopulmonary Bypass (CPB).

### Metabolic modulation with additives and adjuvants added to cardioplegia solution

This principle of metabolic modulation is effectively utilised, while formulating the Cardioplegia solutions which is administered during the period of Aortic Cross Clamping in CPB. To achieve further efficient energetics by reducing metabolic demands further, hypothermia <22 degree Centigrade has a synergistic action [1]. The four important caveats that target Cardioplegia designing incudes, substrate repletion, wash out of metabolites and products, Efficient buffering with buffers added to Cardioplegia solutions with wide range of Pka (buffering capacity) in the alkalotic side, as desirably found in histidine (in blood cardioplegia) or histidine can be added to crystalloid Cardioplegia to provide equivocal cardioprotection [2]. Lastly effective scavenging of free radicals, generated during the period of Aortic Cross Clamping and reperfusion by addition of suitable free radical scavengers [3].

The source for repletion of high energy phosphates in the form of nucleoside precursors, or energy repletion of Kreb Cycle intermediates through addition of neo-glucogenic amino acids act as effective adjuvants [4]. Numerous studies have effectively shown that insulin along with glucose administration in the hypothermic heart, just before Cardioplegia (blood or crystalloid) administration results in excellent myocardial protection, measured postoperatively, in terms of echocardiographic contractility indices and lower serum levels of markers of ischemic myocardial injury.

### Combating cytotoxicity

Two Lethal Cations namely ($Na^+$, $Ca^{2+}$) are the culprit agents implicated in causing myocardial edema and specifically $Ca^{2+}$ is the offender in initiating the cascade of calcium mediated cytotoxicity (at the mitochiondrial level of the myocyte). Maintainence of osmolarity greater 370 mili osmol per litre but less than 400 mili osmol per litre helps in maintain the appropriate level of $Na^+$. Use of $Ca^{2+}$ blockers as an adjuvant to the Cardioplegia solution, effectively counteracts calcium mediated cytotoxicity, therby conferring better myocardial protection, measured in terms of superior contractility indices on echocardiography [5].

### New insights into cardioplegia research

The addition of $Na^+$ - $H^+$ exchangers inhibitors like Amiloride and Cariporide to the Cardioplegia solution effectively tackles the culprit Na+ ion (implicated in causing myocardial edema), but at the cost of intracellular acidosis, which is effectively buffered by histidine present in blood or histidine being added to crystalloid Cardioplegia [6].

From 2004 onwards, there has been extensive research on the use of adenosine, along with lignocaine/ procaine to induce depolarization arrest in the myocardium with minimal extracellular $K^+$ concentration which effectively inactivates the rapidly firing voltage gated $Na^+$ Channels along with use dependent sodium channel blockade achieved by the addition of the local anaesthetic. This form of Cardioplegia is called Adenocaine [7]. Beta blockers have been consistent in reducing myocardial oxygen demand and providing myocardial protection in chronic heart failure, this property of beta blocker is effectively harnessed with addition of continuous esmolol infusion to Cardioplegia solution to produce diastolic arrest in addition to beta blockade induced heart rate reduction and reduction of myocardial resting oxygen demand with minimal extracellular $K^+$ concentration [8].

### Mitigating reperfusion injury with restorative cardioplegia

In CPB after the release of aortic cross-clamp, inflammatory mediators are released into the circulation that cumulatively depress myocardial contractility. Therefore reperfusion Cardioplegia solutions are designed (Hot Shot) Cardioplegia solution, which serves in washing out of the metabolites and as adjuvant added to the reperfusion solution are many free radical scavengers like Super Oxide Dismutase (SOD), Catalase, Desferroxamine, Glutathione and along with the addition of histidine buffer to counteract the problem of reperfusion acidosis.

The prolonged exposure of the arrested and cross-clamped heart to Cardioplegia solution containing little or no calcium may induce calcium ($Ca^{2+}$) hunger in the myocardium on reperfusion with calcium containing solutions, characterized by rapid inflow of calcium ions that that overwhelms the calcium sequestering capacity of the sarcoplasmic reticulum, initiating a cascade of calcium mediated cytotoxic mitochondrial injury, appropriately termed as the Calcium Paradox which never actually happens; due to contamination of the myocardium in cross-clamped state with calcium containing blood from the Noncoronary colleterals [4].

### Routes of cardioplegia delivery and newer research to combat inflammation

Apart from additives and adjuvants to increase the potency of the Cardioplegia, the route of delivery of the Cardioplegia, by combination of antegrade (aortic root, ostial). Conduit plegia and graft plegia in onpump coronary artery bypass with retrograde Cardioplegia through the coronary

*Department of Cardiac Anaesthesiology, Institute of Postgraduate Medical Education and Research, Kolkata, India.*

*Correspondence: Sandeep Kumar Kar, Assistant Professor, Department of Cardiac Anaesthesiology, Institute of Postgraduate Medical Education and Research, Kolkata, India, Tel: +919477234900; e-mail: sndpkar@yahoo.co.in*

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sinus forms a state of the art complete myocardial protection during CPB.

Last but not the least the exposure of the blood to the extracorporeal circuit induces a Systemic Inflammatory Response Syndrome (SIRS) characterized by massive exudation of inflammatory mediators like interleukins 6, interlukin 8, Tumour necrosis factor and complement activation. Cardiopulmonary bypass is known to mediate systemic inflammatory response in the absence of immune complexes mainly via the alternative pathway, contributing to postoperative organ damage through the activation of complement. During the complement activation by inflammation, C5b–9 (terminal membrane attack complex), a trans membrane channel leading to tissue injury, is formed from the C5b produced by cleavage of C5, which is effectively blocked with pexelizumab, a recombinant humanized single-chain monoclonal antibody to C5, proves to be a novel strategy to mitigate reperfusion mediated cytotoxicity [9].

## CONCLUSION

The eternal search for adjuvant and better myocardial protective agents that can be added to cardioplegic solution and the search for novel substate repletion during the period of ischemia to replete the energy pool of the cardio-myocyte, promoting effective and efficient energetics with minimal oxygen consumption still continues, and the ideal Cardioplegia solution is still in the state of evolution i.e. descent with modification.

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