Letters to Editor

Free radicals and cardiac anaesthesia

Sir,

We read with interest the special article by Hatwalne on “Free radical scavengers in anaesthesiology and critical care”. This discussion holds equal importance in cardiac anaesthesia and here, we highlight the role of free radicals in cardiac anaesthesia.

Oxidative injury in cardiac surgery is integral to ischaemia-reperfusion of the myocardium. Cardiopulmonary bypass (CPB) can initiate a systemic inflammatory response from blood contact with extracorporeal surfaces. Besides release of various
stress hormones, cytokines and chemokines, etc., it causes release of reactive oxygen species (ROS). These mediators may cause consumptive coagulopathy, interstitial fluid shifts, generate a host of microemboli and result in temporary dysfunction of nearly every organ.[2]

**In ischemia**

Ischaemia results in adenosinetriphosphate (ATP) depletion. This inhibits ATP-driven Na⁺–K⁺ pumps, increasing intracellular [iNa⁺]. Intracellular [iH⁺] is also increased and there is inhibition of mitochondrial oxidation of nicotinamide adenine dinucleotide phosphate (NADPH). Increased [iH⁺] enhances Na⁺–H⁺ exchange to retain normal intracellular pH, but raised [iNa⁺]. This augments [iCa²⁺] via Na⁺–Ca²⁺ exchange. High [iCa²⁺] degrades proteins and phospholipids. Source of free radicals in ischemia is mainly from neutrophils and mitochondria.[3]

**In reperfusion**

On reperfusion, extracellular [H⁺] is rapidly washed-out to normal levels. This raises [iCa²⁺] by Na⁺–H⁺ and Na⁺–Ca²⁺ exchange. Reperfusion also causes burst of ROS generation (hydroxyl, superoxide, hydrogen peroxide, peroxynitrite, etc.) as oxygen is abundantly supplied. Both [iCa²⁺] and free radicals injure the myocardium. Polyunsaturated fatty acids in cell membranes can undergo oxidation by free radicals. Thus, endothelial dysfunction is more prominent during reperfusion than ischemia. Consequently, myocardial stunning and infarction can occur. CPB induced activated leukocytes may release copious cytotoxic ROS. Use of leukocyte depleted blood, therefore, may mitigate myocardial, pulmonary and vascular endothelial injury. The antioxidant enzymes system, including glutathione reductase, superoxide dismutase and catalase are activated by myocardial ischaemia-reperfusion. However, these may be inadequate to buffer the large surge of free radicals produced during CPB.[2]

**Role of free radical scavengers**

Free radical scavengers (antioxidants, enzymatic scavengers, iron chelators) may be potentially useful therapeutic adjuncts in oxidative injury. High dose vitamin C and E scavenge free radicals, decrease cell membrane lipid peroxidation and indices of myocardial injury. This reflects in improved haemodynamics and shorter intensive care unit stays. High dose N-acetylcysteine before or during CPB acts as a free radical scavenger and reduces neutrophil oxidative burst response and elastase activity. Allopurinol (xanthine oxidase inhibitor) and mannitol reduce free radicals generation during reperfusion. Other antioxidants studied are methionine, reduced glutathione, mercaptopropionyl glycine, superoxide dismutase with polyethylene glycol, catalase, desferrioxamine, methylene blue, thiopentone, tranexamic acid, calcium channel blockers and mitochondrial co-enzyme.[3]

**In off-pump coronary artery bypass**

OPCAB avoids CPB and aortic cross-clamping. It decreases ROS induced injury.[4] However, ischaemia-reperfusion injury to myocardium does remain a concern during bypass grafting.

**In preconditioning**

The stimuli of short ischaemia and reperfusion trigger a signalling cascade of intracellular events that attenuates ischaemia-reperfusion injury (“Ischaemic preconditioning”). These signals include release of adenosine, bradykinin, opioids, norepinephrine, ROS, inhibitory G (guanine) - proteins and protein kinase-C (PKC). ROS act as double edged sword. ROS released in small amount during sublethal oxidative stress act as signalling molecule in triggering early and delayed cardioprotection. PKC (derived from mitochondria) is activated by ROS. It leads to phosphorylation and activation of the sarcolemmal and mitochondrial K₅ATP channels. This confers cardioprotection during ischemia-reperfusion. This "early pre-conditioning" lasts for 2-3 h. "Late pre-conditioning" appears after 12-24 h and lasts up to 72 h. Late pre-conditioning depends on gene transcription and de novo protein synthesis. Pharmacologic agents that mimic ischaemic preconditioning include adenosine, adenosine agonists, K₅ATP Channel openers (pinacidil, nicorandil), delta-opioids, volatile anaesthetics and nitroglycerine.[5]

**References**

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2. Clermont G, Vergely C, Jazayeri S, Lahet JJ, Goudeau JJ, Lecour S, et al. Systemic free radical activation is a major event involved in myocardial oxidative stress related to cardiopulmonary bypass. Anaesthesia 2002;57:80-7.
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4. Raja SG, Dreyfus GD. Off-pump coronary artery bypass surgery: To do or not to do? Current best available evidence. J Cardiothorac Vasc Anesth 2004;18:486-503.

5. Klomer RA, Rezkalaa SH. Preconditioning, postconditioning and their application to clinical cardiology. Cardiovasc Res 2006;70:297-30.

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