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Preconditioning, anesthetics, and perioperative medication

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Activation of endogenous signal transduction pathways, by a variety of stimuli including ischemic and anesthetic pre- and post-conditioning, protects myocardium against ischemia and reperfusion injury. Experimental evidence suggests that adenosine-regulated potassium channels, cyclooxygenase-2, intracellular kinases, endothelial nitric oxide synthase, and membrane bound receptors play critical roles in signal transduction, and that intracellular signaling pathways ultimately converge on mitochondria to produce cardioprotection. Disease states, and perioperative medications such as sulfonylureas and COX-2 antagonists, could have adverse effects on cardioprotection by impairing activation of ion channels and proteins that are important in cell signaling. Insights gained from animal and clinical studies are reviewed and recommendations given for the use of perioperative anesthetics and medications.

Key words: diabetes; ischemic preconditioning; K_{ATP} channels; sulfonylureas; COX-2 antagonists; volatile anesthetics; opioids.

INTRODUCTION

Anesthesiologists face an ever-growing population of aged patients who have significant co-morbidities such as diabetes and ischemic heart disease. Increasing attention has been paid to the identification and evaluation of perioperative interventions

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designed to decrease the risk of cardiovascular complications in these high-risk patients undergoing anesthesia and surgery. Emerging concepts in cardioprotection are based on experimental studies of ischemic and pharmacological preconditioning and on knowledge of activation of common signal transduction pathways. Strategies for clinical cardioprotection and their experimental basis are reviewed.

ISCHEMIC PRE- AND POST-CONDITIONING

In 1986, Murry, Jennings and Reimer[1] first described the ability of a "preconditioning" stimulus to protect myocardium against infarction. These investigators demonstrated that a brief period of coronary artery occlusion and reperfusion protected myocardium against infarction during a subsequent more prolonged period of ischemia and reperfusion. A distinguishing attribute of ischemic preconditioning (IPC) was the presence of a memory period, in which the heart remained resistant to infarction for a period of up to 2 hours after the initial preconditioning stimulus. This protection waned after 2 hours, but reappeared 24 hours later during a "delayed or late phase" of preconditioning.[2] Myocardial salvage after ischemic injury was also possible by intervening at the onset of reperfusion. Vinten-Johansen and colleagues[3] demonstrated that brief episodes of ischemia occurring during early reperfusion prevented myocardial necrosis after prolonged coronary artery occlusion and reperfusion. The magnitude of protection observed was similar to IPC and the phenomenon was termed ischemic "post-conditioning." Interventions performed at reperfusion to protect myocardium, such as post-conditioning, may be more clinically relevant because they do not depend upon foreknowledge that an ischemic event will occur. Pharmacological strategies designed to activate specific signal transduction pathways common to ischemic pre- and post-conditioning may also be advantageous because they avoid vascular and myocardial injury that could result from coronary artery occlusion.

VOLATILE ANESTHETICS AND CARDIOPROTECTION

The actions of volatile anesthetics to protect myocardium against reversible and irreversible ischemic injury have been known for nearly 3 decades.[4] Halothane decreased experimental myocardial infarct size[5] and recovery of stunned myocardium was enhanced by halothane or isoflurane in a chronically-instrumented, conscious dog model.[6] Early investigations attributed the beneficial effects of volatile agents to anesthetic-induced changes in loading conditions and consequent reductions of myocardial oxygen consumption. However, these actions were not entirely responsible for the cardioprotection observed. Recently, experimental evidence has clearly demonstrated that volatile anesthetics protected against ischemic myocardial damage by activating specific intracellular signal transduction pathways. Further, the activation of signaling cascades was dependent upon whether the anesthetic agent was present before or after the period of ischemia and reperfusion.

Pharmacological preconditioning with volatile anesthetics (termed anesthetic preconditioning, APC) was demonstrated by Kersten et al.[7] Dogs were anesthetized with 1 MAC isoflurane for 30 min and the anesthetic was discontinued 30 min prior to prolonged coronary artery occlusion and reperfusion, and yet, the myocardium remained resistant to infarction and myocardial infarct size was decreased by 50%. Anesthetic-induced reductions of myocardial oxygen consumption were not thought to play