Introduction

In cardiac surgery, the extent of systemic inflammatory response is closely associated with patient's outcome. A systemic inflammatory response syndrome (SIRS) may develop after operations using cardiopulmonary bypass (CPB). This pathophysiologic entity reflects a hyperdynamic circulatory state including an increased cardiac output in the presence of reduced systemic vascular resistance (SVR), requiring treatment by vasoconstrictive agents and fluid replacement. In historic patients suffering from SIRS, subsequent lactic acidosis occurred in the greater part of them with increasing risk for multi-organ failure and postoperative infectious complications. Harmful effects of CPB have been reported repeatedly. **(Cremer et al., 1996*)***

Open heart surgery is associated with acute perioperative changes in plasma levels of neurohormonal stress factors. A remarkable rise in cortisol levels in the early postoperative phase has been shown in patients, with a partial recovery toward baseline values observed 24 hours postoperatively. **(Akhlagh et al., 2010*)***

The release of pro and anti-inflammatory cytokines mediates the inflammatory cascade. Interleukin- 6 (IL-6) and C-reactive protein (CRP) are markers of systemic inflammation. **(Bartoc et al., 2000*)***

In addition, the immune system and the nervous system communicate both directions and it has been suggested that nociception and proinflammatory cytokines play a mutual up-regulatory role. Thus, increased production of proinflammatory cytokines may exacerbate pain, and vice versa. Therefore, it is conceivable that effective pain management may affect the immune responses during the postoperative period. **(Beilin et al., 2007*)***

Low dose ketamine demonstrated anti-inflammatory effect in some studies but could not decrease inflammatory mediators according to other reports. It has been shown that small doses of ketamine exert analgesic action in the early stages of formation of pain stimuli. Therefore, it may be helpful to induce pre-emptive anesthesia and reduce narcotic consumption. The question of whether ketamine, in addition to its useful effect as a pain reliever, may attenuate the immunosuppressive effect of opioids in patients exposed to surgery is of interest to the clinician. ***Roytblat and colleagues*** have reported a decline in serum IL-6, an activator of the inflammatory cytokine cascade, in patients undergoing coronary artery bypass surgery. High blood lactate levels accompanied with metabolic acidosis are common among critically ill patients with systemic hypoperfusion and tissue hypoxia. Therefore, blood lactate level in type A lactic acidosis is related to the total oxygen deficiency and the extent of tissue hypoperfusion. So, we evaluated the effect of low dose of ketamine on stress markers and tissue perfusion in patients undergoing on-pump coronary artery bypass surgery (CABG) in a prospective, randomized and controlled trial. **(Cho JE et al., 2009)**

Dexmedetomidine a selective alpha 2 adrenergic agonist can attenuate the stress response to surgery by its sympatholytic effect secondary to activation of central alpha 2 adrenergic receptors, leading to reduction in blood pressure and heart rate., and more recently, it was proven that it has anti-inflammatory properties. ***(*Bulow et al., 2014)**

Aim of the Work

The aim of this work is to evaluate the potential effects of intravenous infusion of ketamine versus dexmedetomidine on attenuation of stress responses during coronary artery bypass grafting (CABG) operation.

Review of Literature

Surgical stress response:

Since 1932, when Cuthbertson first described the systemic response to lower-limb injury, our understanding of surgical physiology had been grown significantly, resulting in improved perioperative management, decreased complications, more efficacious analgesia, and faster recovery times. Better control of the stress response to surgery and optimum fluid management results in shorter functional recovery and hence decreased Hospital admission duration. **(Herndon et al., 2012)**

Surgical stress response is the physiologic response to surgery which have three key components:

1. Sympathetic nervous system activation.
2. Endocrine response with pituitary hormone secretion and insulin resistance.
3. Immunologic and hematologic changes including cytokine production, acute phase reaction, neutrophil leukocytosis, and lymphocyte proliferation. **(Sato et al., 2010)**

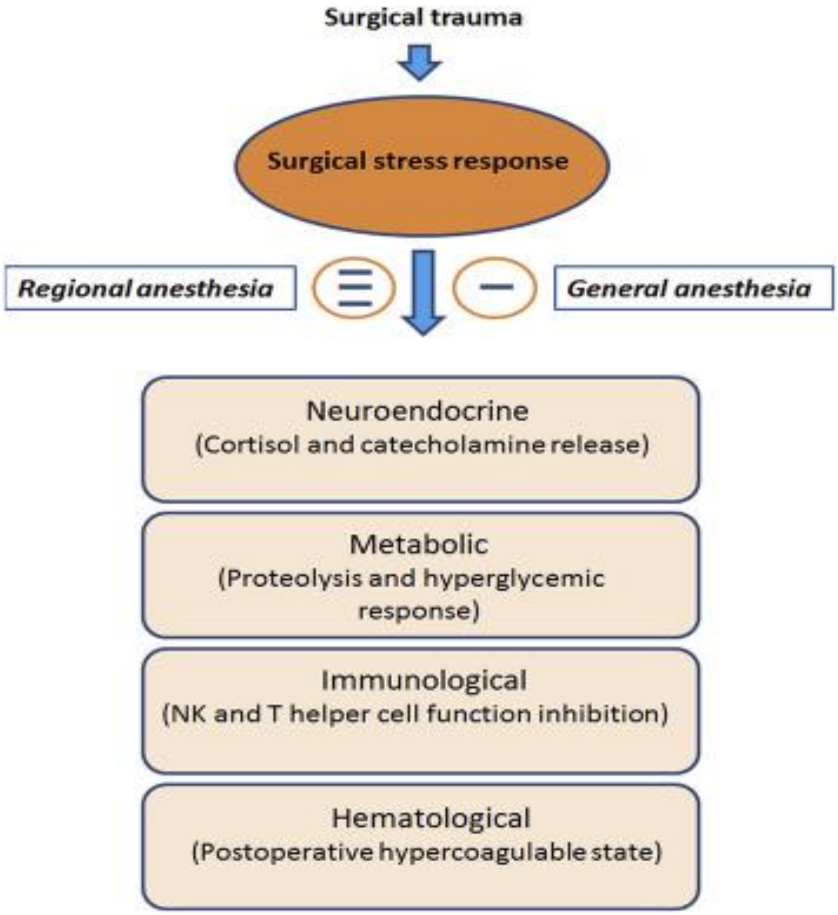

Figure (1): Demonstration of the relationship between surgical trauma and the multisystem effects of the surgical stress response. These are dampened to a greater extent (indicated by a greater number of minus markers in the figure) by regional anesthesia in comparison to general anesthesia. NK = natural killer. (**Ata et al., 2010)**

1. <u>Sympathetic Nervous System:</u>

The sympathoadrenal response to surgery results from an increased secretion of catecholamine from the adrenal medulla, results in tachycardia and hypertension that directly affect functions of numerous organs. Gluconeogenesis is stimulated results in hyperglycemia, and water is retained to maintain fluid volume and cardiovascular homeostasis by aldosterone hormone stimulation. **(Kulp et al., 2010)**

2. Endocrine Response:

It includes changes in pituitary secretion which affects hormone secretion from other glands. The overall metabolic result is increased catabolism, which mobilizes substrate to provide energy. Specifically, ACTH that stimulates cortisol secretion from the adrenal cortex resulting in hyperglycemia, also arginine vasopressin is stimulated which retains water, also insulin secretion by the pancreas is often diminished. Cortisol secretion is also stimulated by surgery which results in protein breakdown, gluconeogenesis in the liver, and increased lipolysis. Hyperglycemia is related to the intensity of the surgical injury, so hyperglycemia seen in cardiac surgery is much more severe than seen in minor surgical procedures such as herniorrhaphy. **(Jeschke et al., 2008)**

3. Humoral response:

Scientific evidences strongly suggest that systemic inflammation is an important cause of mortality and morbidity after cardiac surgical procedures. However, all interventions targeting inflammatory response failed to demonstrate any clinical benefit in large clinical trials. At this point, the question exists whether efforts to improve outcomes through suppression of inflammation are wise, at least until the pathophysiology is better understood. **(Morgan et al., 2009)**

Inflammatory response to cardiac surgery is caused by cardiopulmonary bypass with exposure of blood to non-physiologic surfaces, surgical trauma, anesthesia, changes in body temperature, increased intestinal permeability to endotoxins, and ischemia/reperfusion injury. This results in a complex immunologic reaction and interactions between numerous pathways including complement, cytokines, arachidonic acid metabolites, endothelins, platelet-activating factors, endothelial, and leukocyte adhesion molecules that stimulate the production of reactive oxygen species. **(Elahi et al., 2006)**

The clinical manifestations of this reaction includes postoperative complications such as respiratory failure, wound infections, myocardial damage with contractile dysfunction, renal impairment, coagulopathy, neurologic dysfunction, and altered liver function with an increased mortality. **(Murkin, 2010)**

A subtype of inflammatory response to surgery related to endotoxins has been reported to have adverse effects on the pulmonary, renal, cardiac, and vascular systems. It affects the coagulation system and may be both antihemostatic, thus potentially explaining bleeding, and prothrombotic effects which accounts for some cases of postoperative stroke, deep vein thrombosis, and pulmonary emboli with Circumstantial evidence also indicating that systemic inflammation may worsen neurologic injury. **(Ho et al., 2009)**

Infections are probably not caused by the direct effects of inflammation, but rather secondary effects on host immunity may predispose to this complication. Widespread activation of the complement system results in depletion of complement factors, which are crucial to the effective opsonization of bacterial pathogens, systemic activation and degranulation of neutrophils render these cells less capable of destroying bacteria by phagocytosis. The sources of infecting bacteria may arise from translocation across the patient's gut, surgical wounds (sternum and lower extremity) and the respiratory tract. Infections of prosthetic heart valves are less common but represent a devastating complication. **(Dieleman et al., 2012)**

Role of Cardiopulmonary bypass

Cardiopulmonary bypass (CPB) replaces the functions of the heart and lungs during cardiac surgery, allowing the heart to be opened and operated on. The first successful human intracardiac operation was performed by Gibbon Jr in 1953, using a mechanical extracorporeal pump oxygenator. Despite the long time since the first CPB surgery and numerous studies about CPB pathophysiological side effects, the complex mechanisms involved in the responses of blood and tissues to cardiopulmonary bypass are still unclear. **(Okamura et al., 2010)**

CPB leads to reductions in immunoglobulin levels through denaturation & reduced antibody production by B lymphocytes (plasma cells). Cell-mediated immunity is also affected which is revealed by decreased T-lymphocyte function after cardiac operations. Thus, reduced antibody levels, as well as reduced B- and T-cell function in the post-CPB period, may lead to increased infection rates after cardiac surgical procedures. **(Bunge et al., 2014)**

Although it has been shown that coronary artery bypass grafting (CABG) surgery compared with medical management alone showed that conventional CABG with

CPB improves mortality and improves symptoms in patients with severe coronary artery diseases, but risks of transfusions (30–90%), mortality (2–6%), stroke (2%), atrial fibrillation (30%), and neurocognitive dysfunction (50–60%) still occur with on-pump CABG. These adverse consequences have been largely attributed to the extracorporeal blood circulation (ECC) on cardiopulmonary bypass circuit, general systemic effects (including exacerbated inflammatory response resembling the SIRS), hypothermic cardiac arrest, aortic cannulation, and cross-clamping. Consequently, it may be of interest to study the potential benefit of specific anesthetic drugs exhibiting an anti-inflammatory mechanism. **(Ascione et al., 2003)**

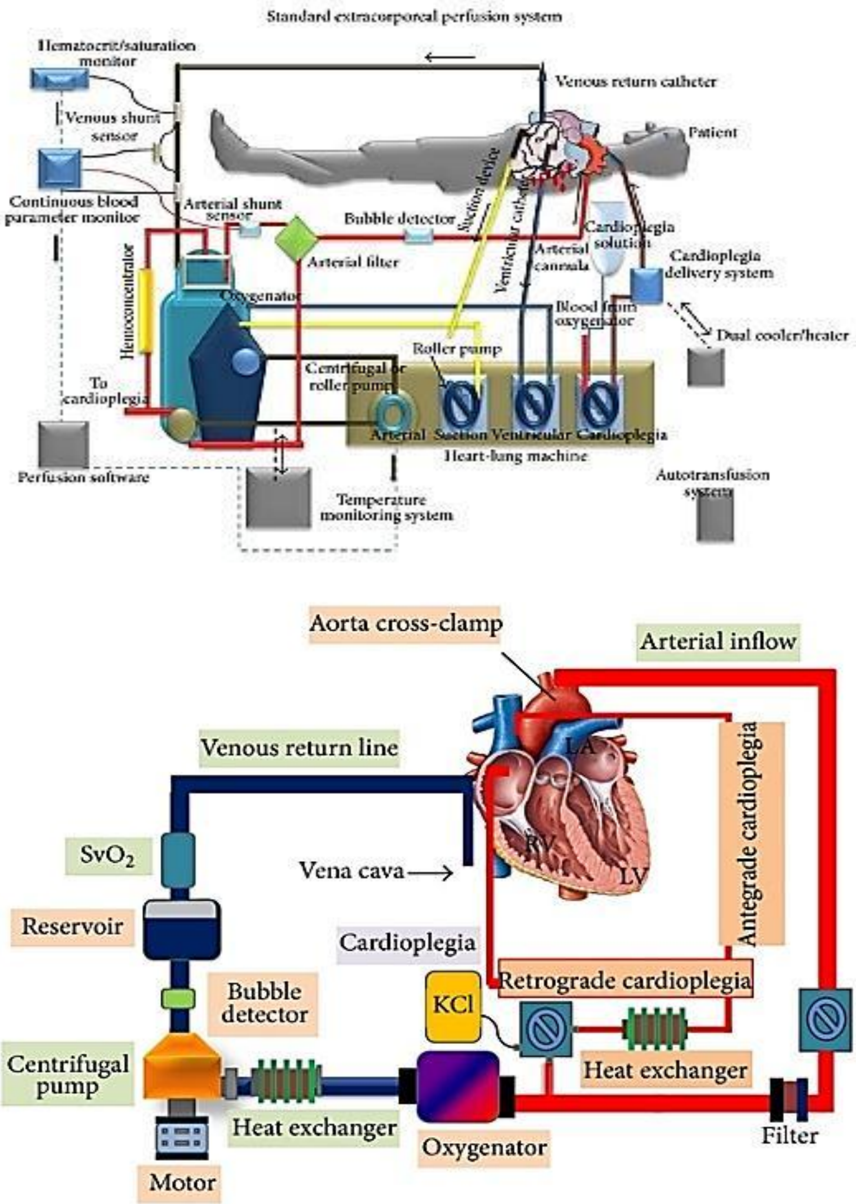

Figure (2): Overview of a standard extracorporeal circulation system (upper panel) and a detailed view of a heart undergoing artery bypass grafting surgery (lower panel). Cardiopulmonary bypass is achieved by gravity drainage of blood from the vena cava into a reservoir, followed by its pumping through a heat exchanger, oxygenator, and filter, followed by its return to the arterial system, usually the ascending aorta, by means of a centrifugal or roller pump. The heart is excluded from the patient's circulation by a single venous cannula inserted into the right atrium and advanced into the inferior vena cava, or by dual catheters placed into the superior and inferior vena cava. An aortic cross-clamp is placed between the anterograde cardioplegia catheter and the arterial inflow catheter to separate the heart from the circulation and allow cardioplegic arrest. When the heart is isolated from the circulation, total cardiopulmonary bypass is present, and ventilation of the lungs is no longer necessary to maintain oxygenation. The bypass pump produces nonpulsatile flow into the patient's aorta by either a centrifugal or roller pump. Myocardial preservation is achieved by decreasing myocardial oxygen consumption by infusing cardioplegia solutions containing potassium into the aortic root, which in the presence of a distally cross-clamped aorta and competent aortic valve ensures diversion of the solution into the coronary arteries. Alternatively, the cardioplegia solution may be administered in retrograde fashion through a cannula placed into the coronary sinus. An additional route for infusion of cardioplegia solutions is directly into newly placed bypass grafts. Cardioplegia solutions may also contain many additives, including blood, insulin, glucose, aspartate, glutamate, calcium, magnesium, nitroglycerine, and superoxide dismutase. None of these additives are definitively better than cold blood cardioplegia with a short cross-clamp time. **(Okamura et al., 2010)**

Evidences suggest that morbidity of cardiopulmonary bypass can be partly attributed to the generalized inflammatory response induced by blood contact to non-endothelial surface during extracorporeal circulation. Balance between the oxidative inflammatory cascade and the anti-inflammatory feedback mechanisms has a role which originates hypothesis that total perioperative values of inflammatory markers are probably less important to predict morbidity. **(Farina et al., 2012)**

The inflammatory response to cardiopulmonary bypass can be divided into 2 phases: “early” and “late”:

Early phase results of the direct blood contact with non-endothelial surfaces.

Late phase is triggered by ischemia/reperfusion injury and endotoxemia. **(Schaer et al., 2013)**

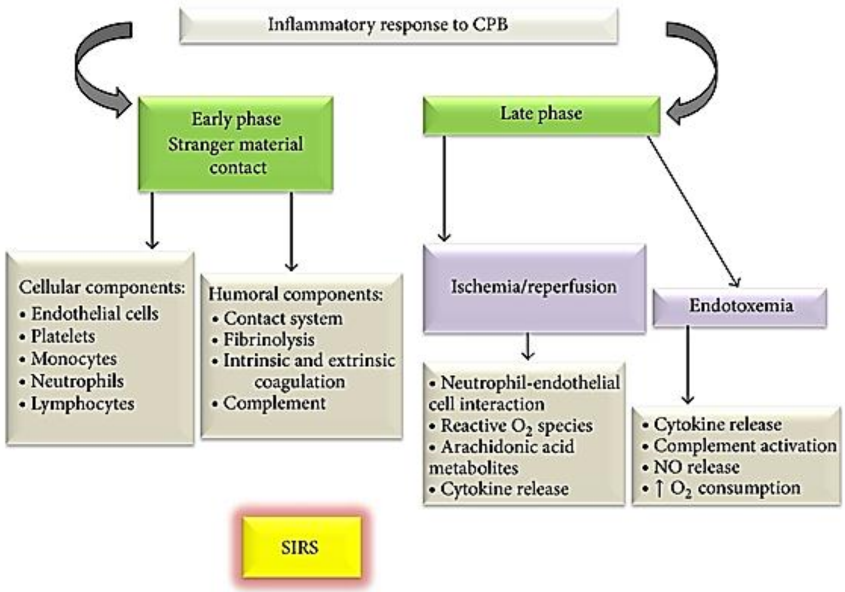

Figure (3): The inflammatory response to cardiopulmonary bypass is divided into 2 phases: "early" and "late" phases. The first phase is induced by the contact with xenosurfaces and the late phase is more related to oxygen reperfusion after ischemia and endotoxemia. **(Vermeulen et al., 2011)**

In the early phase, coagulation becomes favorable, which can be reduced by giving heparin before cardiopulmonary bypass initiation. When heparinized blood comes into CPB circuit plasma proteins are adsorbed onto the circuit wall, leading to whole-body inflammatory response, associated with tissue edema, coagulopathy, and organ dysfunction. But a second phase of inflammatory response is related to ischemia/reperfusion injury and release of endotoxins from intestinal microflora. **(Warren et al., 2009)**