CAN OBESITY AND OXIDATIVE STRESS LEAD TO ACUTE KIDNEY INJURY AFTER CARDIAC SURGERY?

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Abstract: Cardiopulmonary bypass (CPB) revolutionized cardiac surgery and contributed immensely to improved patients' outcomes [1, 2]. It is accepted that CPB exposes patients to non-physiological conditions during which organs are subjected to severe functional alterations. These leads to activation of different coagulation, proinflammatory, survival cascades, and oxidative stress [3–5]. Despite significant development over the years, oxidative stress and inflammation remain major concern when using CPB [6, 7].
Obesity in patients undergoing cardiac surgery increases oxidative stress, endothelial dysfunction, and inflammation, [8,9] and systemic markers of these processes, including F2-isoprostanes, IL-6, and plasminogen activator inhibitor (PAI)-1, increase rapidly and probably are related with development of acute kidney injury (AKI). AKI complicates the recovery of up to 30% of patients undergoing cardiac surgery. Moreover, it promotes systemic and sternal wound infection, is associated with myocardial injury and postoperative arrhythmias, and increase in the odds of death at 30 days. [10–13]. Despite the advances in surgical techniques, anesthesia, and intensive care that led to reduced perioperative mortality and shorter duration of hospitalization, the mortality associated with AKI after cardiac surgery have increased [5]. These findings could be explained in part by the growing prevalence of obesity due to the fact that the latter is proven to be associated with higher AKI incidence [14–17].
Keywords: obesity, cardiopulmonary bypass, acute kidney injury

1. INTRODUCTION

The presence of atherosclerotic coronary artery disease requiring intervention is associated with evidence of oxidative stress and inflammation prior to surgery which can be markedly accentuated during CPB [18]. Furthermore, patients undergoing cardiac surgery tend to have other
coexisting morbidities such as diabetes, renal and lung diseases which are related with abnormal redox state and oxidative stress. CPB initiates multiple processes that impact both cellular and noncellular contents of blood. The repeated passage of blood through the non-endothelised extracorporeal circuit triggers the activation of polymorphonuclear leukocytes (mainly neutrophils) which are believed to be a prime source of ROS (Reactive Oxygen Species) during cardiac surgery. The main forms of cardiac ROS are superoxide ($O_2^{-\cdot}$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($\cdot OH$), and peroxynitrite ($ONOO^-$). Although hydrogen peroxide is not a free radical it is considered a ROS due to its highly reactive nature.
During CPB, ischemic injury occurs when the blood supply to tissue is suboptimal and accompanied by cellular adenosine triphosphate depletion due to its degradation by hypoxanthine [15, 19]. Reperfusion after a period of ischemia plays a role in oxidative stress by initiating a series of biochemical events that result in the generation of excessive amount of ROS. Reduction of oxygen leads to the production of the superoxide anion, which is able to penetrate through cell membranes where it is converted into other more toxic oxygen species. CPB, ischemia and reperfusion injury during surgery can cause substantial myocardial stress leading to the generation of proinflammatory mediators and ROS resulting in damage to proteins, lipids, and DNA which impact on postoperative cardiac functional and outcomes [18]. Ischemia leads to reduction in mitochondria energy production due to the lack of oxygen and nutrients. This is followed by fall in ATP, decrease in intracellular pH, and a rise in intracellular concentrations of Na^+ and Ca^{2+} [15, 19]. Furthermore, cardiac myocytes exposed to ischemia react by producing proinflammatory cytokines and the consequent activation of leukocyte adhesion cascade allowing neutrophils to accumulate in the myocardium, adhere to the myocytes, and release ROS and other proteolytic enzymes. Moreover, reperfusion can lead to irreversible myocardial damage due to mitochondrial dysfunction driven by cytosolic Ca^{2+} loading and generation of ROS [20, 21]. ROS can also stimulate the opening of the

mitochondrial Permeability Transition Pore (mPTP) leading to further ROS production and generating a positive feedback loop of ROS formation and mPTP opening [22–25]. The opening of mPTP can also result in mitochondrial swelling, mitochondrial membrane damage, and cell death via either apoptosis or necrosis [25, 26].

2. MATERIALS AND METHODS

For a period of two years 225 patients with average age 71yr. (57 - 76) were included in this study and all of them were operated in elective manner. Surgery included on-pump CABG only. BMI rates were from 22 kg/m^2 up to 36 $kg/m^{2.}$ All patient included in this study had no history of renal diseases of any type. To measure the level of oxidative stress, antifibrinolysis and inflammation blood was sampled 24 hours before surgery and 2 hours after surgery. Plasma F_2-isoprostane was measured to evaluated the oxidative stress, PAI -1(plasminogen activator inhibitor) to evaluated antifibrinolysis and IL – 6 for the inflammation. To define is there AKI after surgery we use Acute Kidney Injury Network (AKIN) consensus criteria for AKI diagnosis.

3. RESULTS

Our study shows that F_2-isoprostane median concentration were higher prior surgery in patients who developed AKI after surgery with 15.3% compare with patient whiteout AKI. Concentration of IL-6 and PAI -1 before surgery did not show different between AKI and non-AKI group. Interest data were analyzed two hours after surgery, F_2-isoprostane was 23,6%, IL-6 was 23,4% and PAI -1 was 36,7% higher in AKI group compare with non-AKI.
Fifty-eight patients (25.7%) developed stage I AKI after cardiac surgery, defined using Acute Kidney Injury Network (AKIN) consensus criteria for AKI diagnosis: at least a 0.3-mg/dl (26.5-mmol/L) or 50% increase in serum creatinine within 72 hours of surgery.19 Patients who developed this criterion for AKI stayed in the hospital longer (9.2 days versus 7.5 days), were more likely to develop postoperative atrial fibrillation (39.1% versus 22.4%), were more likely to develop pneumonia (10.3% versus 2.3%), and had an increased risk for death at 30 days (5.6% versus 0.9%) than patients who did not develop AKI. Nineteen of these 58 patients developed stage II AKI, defined as a 100% increase in serum creatinine within 72 hours of surgery, and four patients developed stage III AKI, defined as a 200% increase in serum creatinine within 72 hours of surgery.

Characteristic	No AKI (n=167)	AKI (n=58)
Age (yr.)	60 (57–74)	62 (57–76)
Women (n)	78	27
Diabetes (n)	68	28
Smoking (n)	53	21
Hypertension (n)	158	76
BMI (kg/m2)	27.0 (22.0–36.0)	29.1 (26.0–35.0)
Cardiopulmonary bypass time (min)	114 (91–148)	117 (91–162)
Aortic cross-clamp time (min)	90 (68–113)	91 (64–125)
Left ventricular ejection fraction (%)	57 (48–67)	55 (46–60)

4. DISCUSSION

Data shows that BMI is an independent risk factor for AKI after cardiac surgery and perioperative marker of oxidative stress (plasma concentrations of F2-isoprostanes) predicts AKI after cardiac surgery. In conclusion, increased BMI predicts an increased risk for AKI after cardiac surgery, and increased oxidative stress may partially account for the risk for AKI associated with
obesity. Therapies that reduce intraoperative oxidative stress might reduce the incidence, severity, and associated morbidity of AKI after cardiac surgery.

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