Introduction

Acute kidney injury (AKI) post cardiopulmonary bypass (CPB) is well known yet incompletely understood, entity that has significant implications on both short- and long-term outcomes ***(Thakar et al., 2003).***

The development of AKI after CPB is associated with a significant increase in infectious complications, an increase in length of hospital stay, and greater mortality when compared with patients without AKI-CPB ***(Thakar et al., 2003).***

The etiology of acute kidney injury occurring after cardiac surgery is multifactorial, and not limited to ischemia and nephrotoxin administration. One particular problem is that both anemia and blood transfusion are risk factors for AKI, and neither are generally avoidable in high-risk heart surgery ***(Vermeulen et al., 2010).***

Certain etiological factors are peculiar to the cardiac surgery setting, such as routine use of cardiopulmonary bypass, and various degrees of hypothermia, which is probably nephroprotective from an ischemia point of view, but which also worsens hemolysis from the pump and thus may actually exacerbate the problem ***(Vermeulen et al., 2010).***

The pathophysiology of postoperative AKI in cardiac surgery is resulting from a combination vascular and tubular

injury. A variety of events occur in the perioperative period that could individually and cumulatively result in renal dysfunction. During cardiopulmonary bypass (CPB), the kidneys are exposed to interruptions and alterations in blood flow due to changes in pump flow and the lack of pulsatility, which can lead to ischemia-reperfusion injury ***(Huijuan Mao et al., 2013).***

Postoperative kidney function deterioration has been shown to be an important predictor of morbidity and mortality. In addition, the mortality rate in cardiac surgery associated acute kidney injury (CSA-AKI) when renal replacement therapy (RRT) is required is considerably higher for patients not requiring RRT ***(Kumar et al., 2012).***

The unacceptably high morbidity and mortality of AKI/CPB, despite the advent of RRT and intensive care unit care, highlight the importance of this problem. Perioperative management strategies include identifying high-risk patients, optimizing cardiac output and renal perfusion pressure, and avoiding nephrotoxins. Using the off-pump surgical technique when applicable or minimizing the time undergoing CPB may also help improve the overall incidence of AKI-CPB ***(Hilker et al., 2010).***

Early detection and determination of cause may be improved by using biomarkers for example (serum cystatin c, neutrophil gelatinase associated lipocalin (NGAL), and urinary neutron-1). Finally, understanding CPB-induced inflammation and cell damage, modulating the inflammatory pathways, and

improving CPB technology may reduce the incidence and severity of AKI-CPB ***(Ray et al., 2010).***

AIM OF THE WORK

The aim of this work is to review the current medical literature regarding the etiology, pathology, and advances in management of AKI following cardiac surgery with cardiopulmonary bypass.

Chapter I:

Etiology and epidemiology of acute kidney injury following cardiac surgery with cardiopulmonary bypass

Epidemiology of AKI post cardiac surgery by CPB

Incidence of AKI post cardiac surgery.

The incidence of AKI following cardiac surgery has historically been difficult to determine. Mild renal injury (creatinine rise <25%) may occur in as many as 50% of patients undergoing cardiac surgery. Moderate kidney injury has been reported in 8-15% of patients, while up to 5% of patients develop renal failure requiring dialysis following cardiac surgery ***(Shaw et al., 2008).***

Mortality and morbidity AKI post cardiac surgery.

Once renal failure progresses and a patient becomes dialysis dependent, mortality rates rise considerably and are often reported to be above 50 % ***(Chertow et al., 2002).***

Even with the progress of modern medicine and implementation of newer dialysis technology, the mortality associated with postoperative renal failure has not noticeably improved ***(Ympa et al., 2005).***

One may suggest that this is because renal failure in itself is often not the primary problem, but only a sign of significant low cardiac output and multi-organ failure, however, this is likely not the case. Other authors have proposed that the high mortality associated with renal failure is not related to RRT itself, rather it predisposes patients to other morbidities ***(Levy et al., 2006).***

It was reported that patients whose hospitalizations were complicated by sepsis, coagulopathies, respiratory, or neurologic failure, were more likely to die during their hospitalization, while it was rare for patients with uncomplicated renal failure not to survive ***(Levy et al. 2006).***

Some authors suggest that patients with AKI following cardiac surgery were more likely to suffer myocardial infarction, require reoperation for bleeding, and develop endocarditis or mediastinitis ***(Chertow et al., 2007).***

Patients with AKI requiring RRT demonstrate substantially elevated mortality rates, even patients with milder renal dysfunction not requiring RRT show decreased survival and worse outcomes compared to those without postoperative AKI ***(Stafford-Smith et al., 2009).***

Although it may be intuitive that morbidity will increase with severe renal dysfunction, it is less obvious that a modest

rise in creatinine can negatively affect quality of life and life expectancy ***(Stafford-Smith et al., 2009).***

Financial cost and hospital stay.

In addition to increasing mortality, acute kidney injury prolongs ICU stay and increases the proportion of patients discharged to a nursing care facility. This data suggests that the ill- effects of acute kidney injury are not simply a sign of sicker patients with other comorbid conditions, rather AKI is an independent predictor of morbidity and mortality following cardiac surgery ***(Lassnigg et al., 2008).***

As a result, all efforts must be made to identify patients at risk for AKI, focusing on prevention of renal dysfunction rather than simply treating it once the injury has occurred ***(Lassnigg et al., 2008).***

Risk factors of acute kidney injury post cardiac surgery with CPB.

Renal failure is defined as a 50% rise in serum creatinine, while others define it arbitrarily as a doubling of the creatinine, and yet others include only dialysis dependent patients in their analyses ***(Bellomo et al., 2004).***

The RIFLE and AKIN criteria were developed by panels of experts to provide a uniform definition of acute kidney injury and facilitate recommendations for patients suffering from renal failure ***(Mehta et al., 2007).***

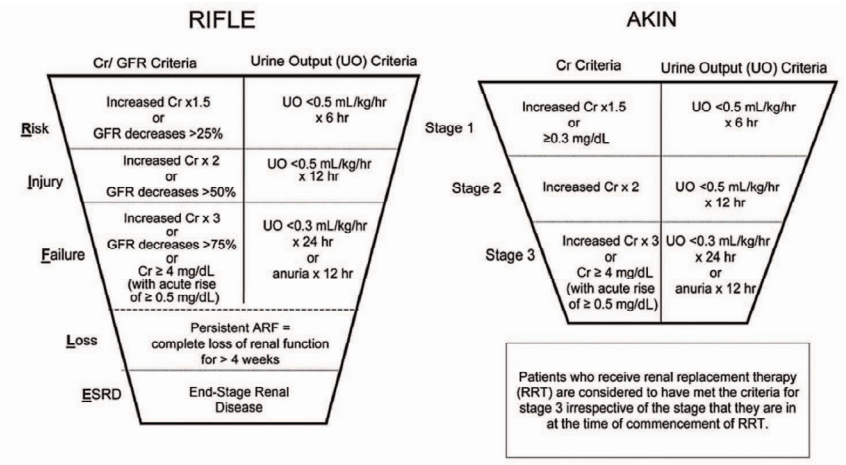

Fig. (1): RIFLE and AKIN criteria ***(Cruz et al., 2009).***

Risk factors for post-cardiac surgery AKI include variables that contribute to or are related to the underlying pathophysiology of AKI. Unlike nephropathies that reflect a single source of insult (e.g., contrast-induced nephropathy),

post-cardiac surgery AKI reflects the cumulative consequences of numerous potential perioperative insults that may or may not be relevant to any particular patient ***(Stafford et al., 2008).***

But Common consequences of all AKI are tubular and vascular cell dysfunction, necrosis, and apoptosis. Although interventions remain elusive to influence trigger mechanisms of the reflexive common pathway of AKI, there is better understanding of the direct effects of some specific cardiac surgery renal insults. In the absence of proven broadly applicable protective interventions, the major thrust of an effective approach to perioperative renal protection involves identifying specific sources of insult for an individual patient that can be changed, and minimizing them ***(Stafford et al., 2008).***

It can be hypothesized that AKI post cardiac surgery results from preoperative comorbid status, the type of surgical procedure, and immediate postoperative course ***(Waikar et al., 2008).***

Risk factors common to heart surgery candidates, including advanced age, diabetes, hypertension, and metabolic syndrome are also predictors of kidney disease, and one out of five patients meet criteria for chronic renal dysfunction preoperatively (e.g., GFR<60ml/min) ***(Waikar et al., 2008).***

Little is known about the effects of cardiopulmonary bypass (CPB) on normal renal physiology. During standard CPB, cardio-renal relationships are approximately preserved; renal blood flow is highly related to pump flow and perfusion

pressure, but falls from 25% to 12-13% of total flow, while perfusion pressure stands as the primary predictor of urine output ***(Stafford et al., 2008).***

Notably, no studies have addressed the intactness of renal autoregulatory reflexes during CPB such as myogenic and tubular glomerular feedback; these normally protect the glomeruli from overload by restricting renal blood flow at higher pressures (e.g., >80mmHg) ***(Stafford et al., 2008).***

Preoperative Risk Factors

Regarding the preoperative risk factors of AKI, advanced age is consistently associated with increased risk of AKI, regardless of the clinical setting ***(Waikar et al., 2008).***

In cardiac surgery, baseline renal function is likely the most important determinant of postoperative AKI, particularly severe AKI requiring dialysis ***(Thakar et al., 2003).***

Additionally, the cardiovascular status of the patient also influences the postoperative AKI risk. For example, functional status of congestive heart failure, presence of peripheral vascular disease, and preoperative use of intra-aortic balloon pump have all been associated with increased risk of AKI ***(Thakar et al., 2003)***.

Other comorbid conditions such as diabetes, along with the extent of glycemic control are also independently associated with development of AKI after surgery ***(Mangano et al., 2004).***

Chronic medications may influence perioperative AKI risk. Long-term diuretic therapy and angiotensin-converting enzyme inhibitors (ACEIs) have been associated with AKI. Although ACEIs can precipitate AKI with renal artery stenosis, neither isolated continuation of these agents preoperatively or the presence of renal artery stenosis independently predict post cardiac surgery AKI ***(Ho et al., 2012).***

Table (1): Risk factors of acute kidney injury post cardiac surgery with CPB ***(Stafford et al., 2008).***

Preoperative factors	Intra-operative factors	Postoperative factors
• Chronic disease Chronic renal disease Diabetes mellitus Chronic cardiac failure Aortic and peripheral vascular disease Chronic liver disease • Advanced age • Female sex • Genetic predisposition • Acute conditions Hypovolemia Sepsis PreoperativeIntra aortic ballon pump(IABP) Multiple organ dysfunction syndrome	• Type of surgery Cardiac Aortic Peripheral vascular Non-renal solid organ transplantation • Cardiac surgery Prolonged cardiopulmonary bypass (CPB) time Combined procedures Emergency surgery Previous cardiac surgery • Aortic surgery Aortic clamp placement Intra-operative radiocontrast	• Acute conditions Acute cardiac dysfunction Hemorrhage Hypovolemia • Sepsis • Rhabdomyolysis • Intra-abdominal hypertension • Multiple organ dysfunction syndrome • Drug nephrotoxicity

Preoperative renal dysfunction has consistently been the most predictive of postoperative renal complications. A preoperative creatinine between 175 and 350mmol/L is associated with a 10-20% risk of postoperative dialysis, while patients with a creatinine greater than 350mmol/L may have a 25-28% risk of dialysis ***(Thakar et al., 2003).***

It is essential to remember that preoperative renal dysfunction may not be obvious when looking at the creatinine alone. It is paramount to calculate the creatinine clearance for all patients, but particularly for those in extremes of age and body habitus ***(Thakar et al., 2003).***

Finally, genetic predispositions to AKI have been reported more recently. It was found that patient with the inherited Apo lipoprotein epsilon-4 allele were less likely to develop AKI compared to patients with other forms of the allele ***(Portilla et al., 2008).***

A risk index was developed based on preoperative risk factors to predict postoperative need for dialysis. Female sex, type of surgery (valve replacement with or without coronary-artery bypass grafting), preoperative cardiovascular status, and preoperative renal function were identified as significant predictors of postoperative AKI ***(Thakar et al., 2008).***

This clinical score (Table 2) discriminates predicted probability of AKI between <1% and >20%, based on a simple bedside risk-assessment tool ***(Candela et al., 2008).***

Table (2): Preoperative Risk Score for AKI after CPB.

RISK FACTOR	POINTS
Female sex	1
Chronic obstructive pulmonary disease	1
Insulin dependent diabetes mellitus	1
Left ventricular ejection fraction<35%	1
Congestive heart failure	1
Prior surgery	1
Emergency surgery	2
Preoperative intra-aortic balloon pump	2
Preoperative creatinine value 1.2 to<2.1 mg/dl	2
Preoperative creatinine value >2.1 mg/dl	5
Surgery type Valve replacement only 1 Coronary artery bypass graft+ valve replacement Other	 1 2 2

(Thakar et al., 2006)

Intraoperative Risk Factors

Several intraoperative risk factors have been associated with AKI. These factors are difficult to quantify, unless they were meticulously recorded during the surgery, and may still

represent as surrogate for unmeasured events during the surgical procedure ***(Boyle et al., 2006).***

In cardiac surgery intraoperative risk factors for postoperative renal failure include use of intra-aortic balloon pump, the need for deep hypothermic circulatory arrest, low-output syndrome, low urine output during cardiopulmonary bypass (CPB), need for pressors before CPB, number of blood transfusions during surgery ***(Boyle et al., 2006).***

Extreme CPB anemia (hematocrit less than 20%) is associated with postoperative AKI, but the alternative, transfusion, is also implicated. To avoid unnecessary transfusion, preoperative optimization (e.g., oral ferrous sulfate therapy, erythropoietin), intraoperative cell salvage and antifibrinolytic use, avoidance of unnecessary hemodilution and anemia tolerance is advocated, but the threshold for transfusion to minimize AKI and other adverse outcomes of cardiac surgery is controversial and an optimal target hematocrit yet to be determined ***(Stafford et al., 2008).***

One risk factor, which has consistently been linked with AKI is the use of and duration of exposure to CPB circuit. In those patients undergoing on-pump surgery, the risk of AKI seems to increase beyond a threshold of 100 to 120 minutes of bypass time ***(Thakar et al., 2003).***

Exposure to CPB circuit may promote a pro- inflammatory state which is deleterious to renal perfusion, given a certain set of preoperative risk factors ***(Orime et al., 2005).***

Inflammation is an important contributor to cardiac surgery related AKI. Circulating proinflammatory cytokines are part of the systemic inflammatory response to surgical trauma and CPB. In addition, local release of cytokines related to kidney ischemia/reperfusion is mediated by nuclear factor kappa B (NFB) activation ***(Stafford et al., 2008).***

Notably, renal dysfunction also influences the course and magnitude of any inflammatory responses since filtration is a primary clearance mechanism for many cytokines (e.g., interleukin 6, interleukin 1β, tumor necrosis factor-α) ***(Stafford et al., 2008).***

Embolism, low output syndrome, and exogenous catecholamines can all contribute to renal ischemia/reperfusion during cardiac surgery. These changes cause necrosis, and apoptotic cell death. Apoptotis instigates more local inflammation and injury. Experimentally, caspase or NF-B inhibition attenuates ischemia-reperfusion mediated AKI ***(Stafford et al., 2008).***

Intraoperative detection demonstrates numerous emboli, particularly during aortic manipulation (e.g., unclamping).Renal atheroembolism is sometimes a dominant source of cardiac surgical AKI and often observed at autopsy. Atheroma burden and emboli counts predict AKI, and aortic filter devices routinely