The Efficacy of Remote Ischemic Preconditioning in Prevention of Acute Kidney Injury Post Cardiac Surgery on Cardiopulmonary Bypass.

Thesis
Submitted for fulfillment of M.D degree in anesthesiology and intensive care

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DEDICATION

To all my family especially my parents for always believe in me, for their continuous love and their support in my decisions. Without whom I could not have made it here, to my wife, Raghdaa Ahmed. She was always there cheering me up and stood by me through the good times and bad, my lovely children Mena and Mohamed and to the souls of my beloved ones.
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<td>Acute kidney injury</td>
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<td>AKIN</td>
<td>Acute kidney injury network</td>
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<td>RIFLE</td>
<td>Risk injury failure end stage renal disease</td>
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<td>RIPC</td>
<td>Remote ischemic preconditioning</td>
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<td>NGAL</td>
<td>Neutrophil gelatinase-associated lipocalin</td>
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<tr>
<td>CPB</td>
<td>Cardiopulmonary bypass</td>
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<tr>
<td>CABG</td>
<td>Coronary artery bypass graft</td>
</tr>
<tr>
<td>Uosm</td>
<td>Urine osmolality</td>
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<tr>
<td>Una</td>
<td>Urinary Na</td>
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<tr>
<td>GN</td>
<td>Glomerulonephritis</td>
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<tr>
<td>ATN</td>
<td>Acute tubular necrosis</td>
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<td>GFR</td>
<td>Glomerular filtration rate</td>
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<td>Cystatin C</td>
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<tr>
<td>Kim1</td>
<td>kidney injury molecule 1</td>
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<tr>
<td>IL6</td>
<td>Interleukin 6</td>
</tr>
<tr>
<td>CRP</td>
<td>C Reactive protein</td>
</tr>
<tr>
<td>1-FABP</td>
<td>liver fatty-acid-binding protein</td>
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<tr>
<td>GST</td>
<td>Glutathione-S-transferase</td>
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<tr>
<td>IL-18</td>
<td>Interleukin 18</td>
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<tr>
<td>IABP</td>
<td>Intra-aortic balloon pump</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricle</td>
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<td>SIRS</td>
<td>Systemic inflammatory response syndrome</td>
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<tr>
<td>ARF</td>
<td>Acute renal failure</td>
</tr>
<tr>
<td>mTAL</td>
<td>Thick ascending limbs of loop of Henle</td>
</tr>
<tr>
<td>KPa</td>
<td>Kilo pascal</td>
</tr>
<tr>
<td>ADH</td>
<td>Antidiuretic hormone</td>
</tr>
<tr>
<td>CRF</td>
<td>Chronic renal failure</td>
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<tr>
<td>ATP</td>
<td>Adenosine tri phosphate</td>
</tr>
<tr>
<td>PMN</td>
<td>Neutrophils</td>
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<tr>
<td>M0</td>
<td>Macrophages</td>
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<tr>
<td>iNKT</td>
<td>Invariant natural killer T lymphocyte</td>
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<tr>
<td>ICAM-1</td>
<td>Adhesion molecules</td>
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<tr>
<td>TLRs</td>
<td>Toll like receptors</td>
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<td>Dendritic cells</td>
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<tr>
<td>IRI</td>
<td>Ischemia reperfusion injury</td>
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<td>TECs</td>
<td>Tubular epithelial cells</td>
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<tr>
<td>MHC</td>
<td>Major histocompatibility complex</td>
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<tr>
<td>ACE</td>
<td>Angiotensin converting enzyme inhibitors</td>
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<td>UO</td>
<td>Urine output</td>
</tr>
<tr>
<td>SCr</td>
<td>Serum creatinine</td>
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<td>ADQI</td>
<td>Acute Dialysis Quality Initiative</td>
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<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease</td>
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<td>Cr</td>
<td>Creatinine</td>
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<td>CKD</td>
<td>Chronic kidney disease</td>
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<tr>
<td>kDa</td>
<td>Dalton</td>
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<tr>
<td>(NF)-κB</td>
<td>Nuclear factor Kb</td>
</tr>
<tr>
<td>SV40</td>
<td>Simian vacuolating virus 40</td>
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<tr>
<td>ROS mitochondrial</td>
<td>Mitochondrial reactive oxygen species</td>
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<tr>
<td>MnSOD</td>
<td>Manganese superoxide dismutase</td>
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<td>HSP32</td>
<td>Heat shock protein 32</td>
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<td>Phosphorylated heat shock protein 27</td>
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<td>PAkt</td>
<td>Phosphorylated protein kinase B on serine-473</td>
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<td>Tumor necrosis factor-α</td>
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<td>Intercellular adhesion molecule-1</td>
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<td>Cyclic guanosine mono-phosphate</td>
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<td>Calcitonin gene-related peptide</td>
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<td>Cyclooxygenase 2</td>
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<td>JAK</td>
<td>Janus kinase</td>
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<td>Hypoxia-inducible factor 1a</td>
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<td>HSP</td>
<td>Heat shock protein;</td>
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<tr>
<td>Inos</td>
<td>Inducible nitric oxide synthase</td>
</tr>
<tr>
<td>m PTP</td>
<td>Mitochondrial permeability transition pore</td>
</tr>
<tr>
<td>Nrf2</td>
<td>Nuclear factor (erythroid-derived 2</td>
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<tr>
<td>STAT1/3</td>
<td>Signal transducer and activator of transcription</td>
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<tr>
<td>MAPK</td>
<td>Mitochondrial activated protein kinase</td>
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<tr>
<td>MnSOD</td>
<td>Manganese superoxide dismutase</td>
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<tr>
<td>NO</td>
<td>Nitric oxide</td>
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<tr>
<td>L-NAME</td>
<td>NG-nitro-L-arginine methyl ester hydrochloride</td>
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<tr>
<td>PKC</td>
<td>Protein kinases</td>
</tr>
<tr>
<td>KATP</td>
<td>ATP-dependent mitochondrial potassium channel</td>
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<td>pHSP27</td>
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Introduction

Acute kidney injury (AKI) post cardiac surgical incidence varies between 5% and 30%. Acute kidney injury is associated with an increased risk of mortality and morbidity, predisposes patients to a longer hospitalization, requires additional treatments, and increases the hospital costs, acute kidney injury is characterized by a progressive worsening course, being the consequence of an interplay of different path physiological mechanisms, with patient-related factors and as major causes by cardiopulmonary bypass.\(^1\)

Such that even after adjustment for patient comorbid conditions and surgical complications, the presence of AKI requiring dialysis therapy increases the risk of death by 8 times in this patient group. Furthermore, changes 0.5 mg/dL in serum creatinine level after cardiac surgery also contribute to a significant increase in mortality at 30 days post-surgery.\(^2\)

Several different injury pathways including exogenous and endogenous toxins, metabolic and neurohormonal factors, renal ischemia and inflammatory surgical response contribute to the development of AKI during cardiac and vascular interventions.\(^3\)

New classification criteria have been recently proposed because of the wide variation in AKI definitions with a difficult result comparison across studies and populations. The RIFLE (an acronym for risk, injury, failure, loss, end-stage kidney disease) criteria and the Acute Kidney Injury Network (AKIN) criteria have emerged as diagnostic tools for monitoring the severity and progression of postoperative AKI, and for
having accurately characterized the entire spectrum of postoperative renal dysfunction.¹

Remote ischemic preconditioning (RIPC) is a phenomenon in which a brief ischemia and reperfusion in distant tissues protects a critical target organ or tissue from a subsequent episode of lethal ischemia and reperfusion through either neuronal or humoral pathway, although the kidneys are not directly exposed to ischemia-reperfusion injury, RIPC might preserve kidney function in patients undergoing cardiac and vascular interventions through blocking free radical production and attenuating the inflammatory response involved in pathogenesis of AKI. This technique of RIPC has significant potential to decrease ischemic injury of other organs in patients undergoing cardiac and vascular interventions.³

The underlying mechanisms of RIPC are very complex and not yet fully defined. It has been hypothesized that RIPC predominantly involves systemic multi factorial anti-inflammatory, neuronal, and humoral signalling pathways, which may differ in response to various ischemic stimuli and are likely to interact with each other.⁴

Several studies have reported the validity of biomarkers such as blood urea nitrogen, serum creatinine, creatinine clearance, and an increase in urinary excretion of various proteins for diagnosing renal injury. However, the time required for these markers to rise significantly is very long. Unfortunately, the serum creatinine estimation which is routinely used in clinical practice increases significantly only days after renal tubular damage has occurred. Hence, it is a remarkably delayed and unreliable indicator of AKI. Also, these biomarkers are not specific for
the site of injury and may be indicators rather than predictors of kidney injury to potentially facilitate therapeutic intervention.\textsuperscript{5}

Neutrophil gelatinase associated lipocalin (NGAL) has been investigated extensively and would appear to be one of the most promising early AKI biomarkers. It measures tubular stress and is involved in the ischemic renal injury and repair process, NGAL increases dramatically in response to tubular injury and precedes rises in serum creatinine by more than 24 hours. \textsuperscript{1}
Acute kidney injury post-cardiopulmonary bypass

The risk of acute kidney injury after cardiac surgery varies between 5% and 30%, and 1%–5% of cardiac surgical patients who develop renal failure require dialysis so a method of prevention of this complication and early treatment strategies are urgently needed.  

Highlighting the importance of understanding the pathophysiology of AKI related to cardiac surgery done on CPB and applying specific therapies that are based on this fact in ongoing clinical trials.

Cardiac surgery, including coronary artery bypass (CABG) and valve surgery, remains one of the most common surgical procedures, the characteristics of those undergoing cardiac surgery have changed over time.

Increasingly, those referred for surgical evaluation are elderly and have multiple comorbid conditions. Although surgical outcomes also have improved over time but patients remain at risk for postoperative complications.

From clinical point of view  AKI can be grouped into three primary etiologies: prerenal, renal, and post renal ,all three etiologies will be discussed briefly here; however, renal etiologies , especially those from ischemic injury, will receive the bulk of the discussion in this chapter given the frequency with which they occur and the fact that they are the etiologies associated with frank renal tissue injury.
Renal etiologies of AKI are challenging to be evaluate because of the wide variety of injuries that can occur to the kidney. In general, it can be helpful to think of damage to the four major structures of the kidney when considering etiologies of intrinsic renal failure. These four structures are

1. The tubules.
2. The glomeruli.
3. The interstitial.
4. Vascular Damage

**Tubular Damage the main target in AKI in cardiac surgery**
Acute tubular necrosis (ATN) is the term used to designate AKI resulting from damage to the tubules. The two major causes of ATN are:

1. Ischemic – resulting from severe or protracted decrease in renal perfusion or hypoxia.
2. Nephrotoxic – resulting from a variety of exogenous compounds (e.g. aminoglycosides, amphotericin B, cis-platinum, radiocontrast media) and endogenous compounds (e.g. hemoglobin in hemolysis, myoglobin in rhabdomyolysis) that are toxic or potentially toxic to the kidney.\textsuperscript{10}

\textbf{Figure 2 Nephron structure}

Other structural targets of AKI not related to post-operative insult:

1. \textbf{Glomerular Damage} AKI from glomerular damage occurs in severe cases of acute glomerulonephritis (GN).

2. \textbf{Interstitial Damage} AKI from interstitial damage can result from acute interstitial nephritis due to an allergic reaction to a variety medications or infections.
3. **Vascular Damage** AKI from vascular damage occurs because injury to intrarenal vessels decreases renal perfusion and diminishes GFR. Causes of vascular injury include for example malignant hypertension, atheroembolic disease, preeclampsia/eclampsia).11

Ischemic kidney injury frequently occurs as apart of multiple organ failure and sepsis, so we review the major mechanisms of this dynamic process, which involves hemodynamic changes, inflammation, and endothelial and epithelial cell injury, followed by repair that can be adaptive and restore epithelial integrity or maladaptive, leading to CKD.

Better understanding of the cellular pathophysiological processes underlying kidney injury and repair will hopefully lead to the design of promising therapies to prevent the injury, fasten repair, and minimize the development of CKD.12

Renal ischemia/reperfusion injury (IRI), a common cause of AKI results from a generalized or localized impairment of O2 and nutrient delivery to, and waste product removal from, cells of the kidney.13

There is imbalance between local tissue O2 supply and demand and buildup of waste products of metabolism this imbalance lead to tubular epithelial cells undergo injury and if it is severe, death by apoptosis and necrosis (acute tubular necrosis) with organ functional impairment of water and electrolyte homeostasis and impair excretion of waste products of metabolism. There are numerous pathophysiological states and drugs that can end to generalized or localized ischemia.14
In this chapter, we illustrate the important components of the cellular pathophysiology in AKI associated with ischemia and also designate what is known about the repair process and how this process necrosis (acute tubular necrosis [ATN]), with organ functional impairment of water and electrolyte disturbances and reduced excretion of end products of metabolism.¹⁰

**Post-operative phase of AKI**

Postoperative AKI is characterized by a progressive worsening course with different phases the early one, being characterized by a vasomotor nephropathy with alterations in vasoreactivity and renal perfusion. The unavoidable consequence is prerenal azotemia, cellular adenosine triphosphate depletion, and oxidative injury, all leading to activation of bone-marrow derived and endothelial cells with a subsequent proinflammatory state.¹⁵

Then, inflammatory cells adhere to activated endothelium in the peritubular capillaries of the outer medulla, with medullary congestion and hypoxic injury to the proximal tubule, proliferation of tubule cells and re-differentiation are subsequently followed by functional reconstitution. The typical lesion observed in a patient affected by postoperative AKI is acute tubular necrosis, with granular casts in the urine.¹⁶

**Risk factors associated with AKI**

Although different studies have attempted to determine etiologic factors in its pathogenesis, postoperative AKI is the consequence of an
interplay of different pathophysiologic mechanisms, with patient related factors and cardiopulmonary bypass (CPB) as major causes.¹⁷

![Figure 3 Different phases of AKI](image)

Kidneys are prone to ischemic damage because of their peculiar blood circulation, in which renal medulla is normally perfused at a low O2 tension with a limited reserve; and CPB determines unavoidable alterations in blood flow by ischemia-reperfusion injury, low cardiac output, renal vasoconstriction, hemodilution, and loss of pulsatile flow during CPB. All these factors lead to an O2 supply/demand renal imbalance, with significant cellular injury.¹⁸
Table- 1  **Risk factors associated with AKI**

<table>
<thead>
<tr>
<th>Patient-Related</th>
<th>Procedure-Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>• COPD.</td>
<td>• Duration of CPB.</td>
</tr>
<tr>
<td>• DM.</td>
<td>• Cross-clamp time.</td>
</tr>
<tr>
<td>• Peripheral vascular disease.</td>
<td>• Off-pump or on-pump.</td>
</tr>
<tr>
<td>• Renal insufficiency.</td>
<td>• Non-pulsatile flow.</td>
</tr>
<tr>
<td>• Congestive heart failure.</td>
<td>• Hemolysis.</td>
</tr>
<tr>
<td>• LV ejection fraction &lt;35%.</td>
<td>• Hemodilution.</td>
</tr>
<tr>
<td>• Emergent surgery.</td>
<td></td>
</tr>
<tr>
<td>• Cardiogenic shock with (IABP).</td>
<td></td>
</tr>
<tr>
<td>• Left main coronary disease.</td>
<td></td>
</tr>
</tbody>
</table>

**Post-operative risk factor**\(^1^2\):

- Post-operative use of vasoactive drug.
- Hemodynamic instability.
- Nephrotoxic medications.
- Volume depletion.
- Sepsis/SIRS.
- The need for mechanical support further govern the degree of AKI.
Physiological background of control of renal blood flow control and the impact of hypoxia:

In the healthy patient, the kidney receives about 20% of the total cardiac output (about 1 liter/min), with an O2 delivery in excess of 80 ml/min/100 g tissue. The distribution of blood flow within the kidney is not uniform, with the cortex receiving more than 90% of total blood flow.19

On the other hand, O2 consumption usually does not exceed about 10% of total body utilization, such that there is a low arteriovenous O2 content difference (1.5 ml O2 per 100 ml blood). The low fraction of O2 extraction by the kidney should suggest that there is an adequate and ample O2 reserve.19

However, the kidney is highly sensitive to hypo perfusion, with acute renal failure (AKI) being a frequent complication of hypotension. This apparent paradox (of high blood supply and low extraction of O2, yet high incidence of renal damage to hypo perfusion) is related to the physiological gradient of intra-renal Oxygenation with the renal medulla able to function at ambient O2 tensions of 2-3 kPa. This low O2 tension results from the high O2 requirement for tubular absorptive activity of sodium and chloride.19

Although a high percentage of blood goes to the cortex (about 5 ml/min/g), the cortex extracts only about 18% of total O2 delivered to it. On the other hand, the medullary region has a far smaller blood flow (0.03 ml/min/g), but has a far greater extraction (of about 79% of the delivered O2).20
Medullary Oxygenation is normally strictly balanced by a series of control mechanisms, which match regional O2 supply and consumption. Failure of these controls renders the outer medullary region susceptible to acute or repeated episodes of hypoxic injury, which may lead to acute tubular necrosis (ATN) especially of the thick ascending limbs (the mTAL regions) and the straight proximal S3 segments, or to chronic tubulo-interstitial changes, respectively.21

As a result of the difference of flow and O2 requirement, the O2 tension in the cortex is about 50 mm Hg higher than that of the inner medulla. This explains why the mTAL region is extremely prone to hypoxic injury and why ATN can be induced by a 40-50% decrease in renal blood flow.20

Medullary hypoxic injury is characterized by necrosis of those renal tubules that are farthest away from the blood vessels. The main determinant of medullary O2 requirement is the rate of active reabsorption of salt and water in the mTAL region. When this process is inhibited by loop diuretics, there is an increase in the medullary tissue O2 partial pressure from 2 to about 4 kPa.22

There are a number of mediators, which can affect medullary blood flow and alter the degree of any ischemic injury.22

This mediators include23:

i) Vasodilators: adenosine, nitric oxide, prostaglandin E2, dopamine and urodilatin (an analogue of ANP).
ii) Vasoconstrictors: endothelin, angiotensin II, ADH (antidiuretic hormone or vasopressin).

iii) Tubulo-glomerular feedback: occurs when insufficient reabsorption of sodium by the renal tubules leads to glomerular afferent constriction so reducing filtration and hence the delivery and reabsorption of tubular solute.

iv) Medullary tubular growth factors: these include tumor necrosis factor, insulin-like growth factor I and epidermal growth factor.

**Pathophysiological mechanisms of AKI in post-CPB**

The kidney is uniquely prone to injury as a result of its and physiology and anatomy. Cardiac surgery provides a plethora of renal insults. The clinical picture is too compound to be a simple story of either hypo perfusion or ischemia-reperfusion injury.

(1) **Medullary ischemia & low mean arterial pressure**

Changing hemodynamics with the kidney, hemodilution and changes in renal vascular resistance cause redistribution of renal blood flow during CPB to maintain glomerular perfusion at the expense of worsening medullary oxygenation.

The renal tubular cells have a high metabolic requirement, resulting in an O2 extraction ratio of 80% in contrast to the myocardium, which extracts 65% of the available O2. Renal tubular cells, particularly the thick ascending limb of the loop of Henle, are therefore predominantly vulnerable to hypoxia. The renal response to reperfusion following a
Acute kidney injury post-cardiopulmonary bypass

hypoxic insult is vasoconstriction, more than hyperemic vasodilation, which is mediated by local pathway like adenosine pathways -the tubule-glomerular feedback mechanism. 25

This mechanism controls afferent glomerular arteriolar resistance to reduce glomerular filtration when the feedback mechanism is triggered. Under these situations the medullary counter-current exchange of O2 increases further reducing medullary Oxygenation, while the tubular cells increase their O2 consumption by reabsorbing electrolytes, particularly sodium.26

In the post-bypass patient hypovolemia or hypotension perpetuates these changes rather than allowing their resolution, the perioperative in medullary oxygenation links with postoperative renal impairments.25

Low mean arterial pressure below the limits of auto-regulation during cardiac surgery and/or CPB and impaired auto-regulation due to existing comorbidities such as advanced age, atherosclerosis, chronic hypertension, or chronic kidney disease (CKD), recent MI or severe valvular disease with impaired left ventricular function and reduced renal perfusion play an important role in causing AKI.7

Low perfusion pressure leading to prerenal failure and sooner or later cellular ATP depletion and oxidative injury (initiation phase). These developments lead to activation of bone marrow–derived cells, endothelial cells, and renal epithelial cells and a resulting proinflammatory state. Inflammatory cells adhere to activated endothelium in the peritubular capillaries of the outer medulla, leading to
medullary congestion and more hypoxic injury to the S3 segment of the proximal tubule which called (extension phase).\(^\text{12}\)

Besides, process of inflammatory mediators release leads to additional cellular injury. Tubule cells then begin the process of proliferation (maintenance phase) and re-differentiation. In due course, polarity and function are reconstituted (repair phase).\(^\text{7}\)

(2) Interstitial edema:

Renal ischemia causes swelling of renal cells and arrest of the active transmembrane Na-K pump, Na accumulates within the cells and water is then drawn in down the osmotic gradient. Glomerular capillary endothelial cell swelling causes further disturbances in the microcirculation within the kidney, so reperfusion may not reestablish normal blood flow.\(^\text{27}\)

(3) Tubular obstruction:

Hypoxia causes failing of tubule cell attachment to the basement membrane, resulting in sloughing of these cells and their collection within the tubular lumen, sometimes termed acute tubular necrosis ,this tubular obstruction causes leakage of glomerular filtrates into the interstitial tissue of the kidney, a phenomenon called tubular back leak.\(^\text{28}\)

Despite the GFR is reduced by a decrease in renal blood flow outside the auto regulatory range, tubular back leak results in a larger deterioration in renal function than the decrease in renal blood flow and GFR.\(^\text{29}\)
The dual effect of obstruction and compression on the kidney tubules by edema increases the intra-tubular hydrostatic pressure, which faces glomerular filtration pressure. \(^{30}\)

**(4) Nephrotoxins:**

The mechanism is a mixture of direct cytotoxicity, renal vasoconstriction, and tubular obstruction as hemolysis due to mechanical trauma of red blood cells causes the release of hemoglobin which is nephrotoxic and directly related to the development of AKI. \(^{7}\)

**(5) Ischemia-reperfusion injury:**

Both CPB per se and frank ischemia cause a release of free radicals, which continue to cause renal damage during reperfusion, this damage is not confined to the glomerulus and tubules, but also touches the renal microvasculature. \(^{31}\)

Prolonged bypass time and if total circulatory arrest are independent predictors of postoperative AKI. \(^{32}\)

The kidney has an adenosine-mediated ischemic preconditioning capacity, but no studies up till now have yet tried to evaluate this mechanism to reduce the incidence or severity of AKI. \(^{3331}\)

**(6) Renal vasoconstriction:**
Acute kidney injury post -cardiopulmonary bypass

The autonomic nervous system has an important role in the control of renal blood flow, the stress response to CPB and the administration of exogenous catecholamine both provide α-1 adrenoceptor-mediated vasoconstriction, and the use of inotropic agents is an independent risk factor for AKI. \(^{34}\)

In animals, renal vasoconstriction reduces GFR and increases the renal auto regulatory threshold, while similar effects can be seen in man, there doesn’t appear to be a renal auto regulatory mechanism during CPB, even though renal blood flow regulation in man may be more complex than previously thought. \(^{35}\)

\textbf{(7) Renal arterial embolization:}

Particulate micro emboli and the gaseous effect of CPB have a role in renal impairment during cardiac and aortic surgery but this becomes less problem since membrane oxygenators replaced bubble oxygenators. \(^{36}\)

Manipulation of the ascending aorta during surgery can produce atheromatous emboli release, and the risk of postoperative AKI increases with increasing severity of ascending aortic atheroma. \(^{37}\)

Thrombus, lipid droplets result from mediastinal suction, fragments of vessel wall, platelet-fibrin aggregates and endocarditic vegetation’s are other sources of micro emboli that may cause renal impairment. \(^{38}\)

Use of a cell saver may reduce the lipid embolic load, intra-aortic balloon counter pulsation is also associated with an increased risk of AKI probably as a result of plaque disruption during balloon deflation. \(^{39}\)
Remarkably, strategies designed to increase renal blood flow may actually deteriorate the embolic load offered to the kidney.  

Finally, CPB-related embolization should be mentioned in the occurrence of AKI by transcranial Doppler ultrasonography, recorded Doppler signals and emboli counts during CABG, along with the assessment of creatinine changes. Emboli counts were independently associated with post-operative AKI.  

(8) Systemic inflammatory response:

The CPB-induced systemic inflammatory response should be considered as one of the relevant determinants of postoperative AKI, with a final interstitial inflammation with tubular injury.  

Cardiopulmonary bypass also exposes blood cells to nonphysiologic surfaces and shear forces, leading to cell lysis.  

The subsequent mechanical destruction of erythrocytes determines a release of plasma free hemoglobin into the circulation, finally causing occlusion of renal tubules with hemoglobin casts and necrosis of tubular cells.  

The CPB itself provokes a cause organ dysfunction. systemic inflammatory response syndrome (SIRS) due to ischemia-reperfusion injury, endotoxemia, operative trauma, non-pulsatile blood flow, and pre-existing left ventricular dysfunction. Inflammatory mediators, such as endotoxin, IL-1b, IL-6, IL-8, and TNF-a, considerably owing to
Acute kidney injury post-cardiopulmonary bypass

Activation of neutrophils rise during CPB and vascular endothelium, elaboration of cytotoxic O2-derived free radicals, proteases, cytokines, and chemokines and increased platelet degranulation, and adherence. CPB activates factor XII (Hageman factor) to factor XIIa and also results in the activation of intrinsic coagulation system, the kallikrein system, the fibrinolytic system and complement cascade. 43

Pro-inflammatory mediators as tumor necrosis factor and cytokines released by CPB activate complement cascades producing a whole body inflammatory response, often mediated by endotoxins. 44

![Inflammation in CPB Diagram](image)

**Figure 4 Systemic inflammatory response syndrome with CPB**

Ischemia and/or reperfusion initiate changes in vascular endothelial cells, tubular epithelial cells and leukocytes that result in the loss of immune system homeostasis in the kidney, the ensuing inflammation leads to kidney parenchymal cell death and in severe cases AKI. 45
The inflammatory response can be mediated by two different, but related, arms of the immune system: innate and adaptive immunity as shown in the next figure.

**Figure 5  Inflammatory role of bone marrow-derived and kidney cells in AKI**

Ischemia-reperfusion induces changes in leukocytes, endothelial cells and tubular epithelial cells that result in kidney inflammation and mediate AKI. Bone marrow derived cells such as iNKT cells neutrophils (PMN) and macrophages (MØ) accumulate in the kidney, are activated and produce pro-inflammatory cytokines (i.e. IFN-production by iNKT cells and PMNs).\(^{46,45}\)

Endothelial cells are damaged by IRI leading to increased vascular permeability and expression of adhesion molecules such as ICAM-1 and fractalkine.\(^{47}\)
These changes facilitate the accumulation of leukocytes in the kidney. Renal dendritic cells produce cytokines and chemokines and traffic to the renal draining lymph node and present antigens to T cells. Tubular epithelial cells exhibit increased complement deposition and upregulate the expression of toll like receptors (TLRs) both of which mediate chemokine and cytokine production in the injured kidney.\textsuperscript{48}

Changes in each cell type directly or indirectly influence the other cells involved to promote inflammation after renal IRI. These interactions between kidney and bone marrow derived cells and between innate and adaptive immunity demonstrate the complex nature of the inflammation associated with AKI.\textsuperscript{49}

\textbf{Figure 6 Innate immune system response in AKI}

(9) CPB hypothermia and AKI

A correlation between AKI and CPB hypothermia has been also documented. The causative mechanism seems to be related to the increased metabolic demand, with the subsequent nephron damage due to
low perfusion temperatures as the result of hypo perfusion of the superficial cortex that occurs during rewarming and restoration of normothermia. A CPB perfusion temperature less than 27°C seems to be directly associated with AKI occurrence [40].

(10) Drugs that impact kidney auto-regulation.

Administration of drugs that impact kidney auto-regulation (e.g., ACE inhibitors, angiotensin receptor blockers, and radio contrast agents), may also precipitate AKI.50

CPB decreases the effective renal perfusion pressure up to 30% by altering the vasomotor tone and exposes the renal parenchyma to reduced O2 tension and contributes to ischemia–reperfusion The pre-renal state worsens in presence of injury cardiogenic shock and inotropic support or an intra-aortic balloon pump, and episodes of hypotension.43

(11) CPB associated hemolysis.

CPB is known to cause hemolysis due to cardiotomy suction, occlusive roller pumps, turbulent flow in the oxygenator, and blood return through cell savers which results in oxidative stress and renal tubular injury. Free iron released from heme leads to organic and inorganic O2 radical reactions, lipid peroxidation and the formation of damaging hydroxyl radicals with subsequent tissue damage.
Strategies to Prevent AKI during CPB

Several preventive strategies acting at preoperative, intraoperative, and postoperative levels have been proposed. However, these approaches are often controversial owing to the difficulty in targeting single pathways in the complex AKI pathophysiology.\(^{17}\)

Nephrotoxic medications or intravenous contrast may lead to tubular damage, with subsequent AKI. Contrast agents cause vasoconstriction-mediated medullary ischemia and direct cytotoxicity on glomerular cells. Should delay cardiac surgery beyond 24 hours of exposure to contrast agent and minimizing its use have significant potential to decrease AKI.\(^{51}\)

However, the most relevant preventive strategies have been focused on deleterious effects related to CPB use, such as hemodilution and non-pulsatile flow with regard to the flow characteristics during CPB. Pulsatile perfusion demonstrated superior renal protection, improving organ perfusion by reducing vasoconstrictive reflexes, optimizing O\(_2\) consumption, and reducing acidosis.\(^{7}\)

Presta and colleagues in 2010 demonstrated that pulsatile CPB preserves renal function better than standard linear CPB, even in elderly patients.\(^{52}\)

Poor O\(_2\) availability to the renal medulla during CPB may deteriorate renal function, causing ischemic and inflammatory organ injury. Ranucci and colleagues in 2015 observed that the lowest hematocrit and O\(_2\) delivery are independent AKI predictors at the cut-off
value of hematocrit less than 26% and O2 delivery less than 272 ml/min/1m² respectively.  

The detrimental hemodilution effects may be consequently reduced by increasing O2 delivery with an adequate increase pump flow [32].

Von Heymann and coworkers in 2014 observed that patients perfused at a pump flow greater than 3.0L/min/1m² are not prone to develop AKI if with a hematocrit on CPB below 20%. Although available measurements refer to cerebral flow only, CPB flow rates of 1.8 to 2.2L/min/1m² and a mean arterial pressure above 50 to 60 mm Hg are recommended for renal protection.

**Drug that may play role in renal protection**

In this setting, drugs increasing renal blood flow have been extensively tested for renoprotective effect, and it may even exacerbate renal tubular injury in the early postoperative period, whereas fenoldopam, increasing renal blood flow in a dose-dependent manner, has been repeatedly observed to reduce AKI after cardiac surgery.  

Atrial and brain natriuretic peptide and urodilatin (Urodilatin is a hormone that causes natriuresis through increasing renal blood flow. It is secreted in response to increased mean arterial pressure and increased blood volume from the cells of the distal tubule and collecting duct) improve natriuresis by increasing GFR as well by inhibiting sodium reabsorption by the medullary collecting duct, and they were found to mitigate renal dysfunction.
Diuretics may reduce AKI, preventing tubule obstruction and decreasing O2 consumption however, furosemide was not demonstrated to be renoprotective, and similar negative results have been observed for mannitol and other therapeutic agents attenuating the systemic CPB inflammatory syndrome with subsequent tubular injury have been intensively investigated, but also failed to reduce renal dysfunction. 58

Statins attenuate inflammation and oxidative stress, two of the mechanism responsible for AKI, but a recent meta-analysis of 30,000 cardiac surgery patients showed that statin had no renoprotective effects exist while N-acetylcysteine use trial show inconclusive data. 59

Off bypass surgery effect on AKI

The most incremental pathophysiologic mechanisms resulting in renal injury are related to CPB use, its theoretic elimination could reduce the spectrum of renal injury after CPB, with its undesirable effects but observational and randomized studies have shown controversial renal effects from the use of the off-pump coronary artery bypass graft technique, and available meta-analyses by Wijeysundera and colleagues in 2005 also presented contrary results. 60

Remote ischemic preconditioning trials in renal protection

Remote ischemic preconditioning offers a simple procedure with the potential to provide widespread and systemic protection from major organ injury in patients undergoing major vascular surgery. Accordingly, we sought to evaluate the clinical use of remote preconditioning in
providing myocardial and renal protection after elective open aortic artery aneurism repair.⁶¹

To date, whether RIPC can protect kidney function in patients undergoing cardiac and vascular interventions is still a controversial issue.³

The effect of RIPC on renal impairment was also investigated in multiple study most of them on animals and few on adult or pediatric ongoing cardiac or vascular surgery and will illustrate in the next chapters.⁴
Assessment of post-operative AKI.

Historically, classic ATN goes through an oliguric (UOP ≤ 400 mL/24 hours) phase of 1–2 weeks followed by a no oliguric (UOP > 400 mL/day) phase of 10–14 days with eventual recovery of renal function. This description however is not the rule as both prolonged oliguric phases and initial non oliguric phases are common.62

More than 30 different definitions used to define acute kidney injury (AKI), many of them are complex; however, the more commonly used were based on UOP and/or serum creatinine criteria. Where UOP has been used to define AKI, it is generally considered that a value less than 400–500 mL/day could be an indicator.63

Multiple definitions for AKI have obviously led to a great disparity in the reported incidence of AKI making it problematic or even impossible to compare the various issued studies focusing on AKI. Therefore, it became vital to establish a consensual and accurate definition of AKI that could ideally be used globally.64

AKI is conventionally established when the kidney’s major function (glomerular filtration) is decreased which indirectly measured by change in serum creatinine. But also prerenal factors, such as volume depletion, decreased effective circulating volume or alterations in the caliber of the glomerular afferent arterioles, all cause elevations in serum creatinine. Also post renal factors, such as urinary tract obstruction, similarly result in elevations in serum creatinine. So we can say that multiple of intrinsic renal diseases may result in a sudden rise in serum creatinine, mostly in
patients admitted to hospital. Other tests to distinguish these various forms of AKI, such as microscopic urine examination for casts and determination of fractional excretion of sodium, have been vague and have not enabled.65

**Glomerular Filtration Rate**

It is generally acknowledged that GFR is the most valuable overall index of kidney function in health and disease, and changes in SCr and UOP are surrogates for changes in GFR. In medical practice, a sudden decline GFR is surveyed from an increase in creatinine or oliguria. Perceiving the restrictions of the use of a decrease in kidney function for the early identification and accurate estimation of renal injury, there is a broad consensus and agreement that, while more sensitive and specific biomarkers are needed, changes in SCr and/or UOP form the basis of all diagnostic criteria for AKI. The first international interdisciplinary consensus criteria for diagnosis of AKI were the RIFLE criteria.55

**The RIFLE classification of AKI**

The Acute Dialysis Quality Initiative (ADQI) group in May 2002 in Vicenza (Italy) intensivists and nephrologists and came together over 2 days in a conference with the purpose of defining AKI. From this conference, the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification for AKI definition appeared to science, which was published in May 2004 in critical care [8].
The ADQI assembly considered that the ideal AKI definition would have to contain the following criteria:

1. Easy clinical applicability
2. Sensitivity and specificity
3. Consider baseline SCr variations
4. Consider the ‘acute-on-chronic’ phenomenon (which means the occurrence of an acute insult over a chronically injured renal function causing its deterioration).  

This definition should also put classification of AKI according to its severity (mild or severe) and its timing of occurrence (early or late AKI). By gratifying these criteria, this classification should allow the detection of patients whose kidney function was slightly affected (high sensitivity but low specificity) as well as patients with severe kidney function deterioration (high specificity with lower sensitivity).

The RIFLE classification is based on SCr and UOP determinants, and considers three severity classes of AKI (Risk, Injury and Failure), according to the variations in SCr and/or UOP, and two outcome classes (loss of kidney function and end-stage kidney disease).

Classification of patients using the criteria (SCr and/or UOP) which leads to the worst classification (maximum RIFLE), for example a patient was in the Risk class according to the UOP but in the Injury class according to SCr variation, then the worst criteria (SCr) should be used for classifying the severity of AKI in this patient.

The time-based pattern of the SCr and/or UOP variation is also important for defining AKI: the decline of renal function must be sudden
(1–7 days) and continuous (persisting >24 h). This definition is applied when the baseline SCr is recognized, but significant number of patients baseline SCr is unknown; in such situation and if there is no history of chronic kidney disease (CKD), baseline SCr should be estimated from the Modification of Diet in Renal Disease (MDRD) equation or formula, assuming a baseline glomerular filtration rate (GFR) of 75 mL/min/1.73m2.

**Table 2 RIFLE criteria of AKI**

<table>
<thead>
<tr>
<th>class</th>
<th>GFR criteria</th>
<th>UOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>SCr increase X 1.5 or GFR decrease &gt;25%</td>
<td>&lt;0.5 mL/kg/h X 6 hours</td>
</tr>
<tr>
<td>Injury</td>
<td>SCr increase X 2.0 or GFR decrease &gt;50%</td>
<td>&lt;0.5 mL/kg/h X 12 hours</td>
</tr>
<tr>
<td>Failure</td>
<td>SCr increase X 3.0 or GFR decrease &gt;75% or SCr &gt; 4 mg/dL with an acute rise ≥0.5 mg/dL</td>
<td>&lt;0.3 mL/kg/h X 12 hours</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent acute renal failure (complete loss of kidney function) ≥4 weeks</td>
<td></td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>End-stage renal disease &gt;3 months</td>
<td></td>
</tr>
</tbody>
</table>

**Strengths of the RIFLE classification**

RIFLE has been largely validated in terms of determining the incidence of AKI and its prognostic stratification in several settings of
hospitalized patients the RIFLE criteria was established for standardization the definition and stratification of AKI severity.\textsuperscript{69}

Moreover, it has been shown that the RIFLE makes the monitoring of the progression of AKI severity during hospital course more easy and RIFLE classes are strongly associated with increased lengths of stay, RRT requirement, renal function recovery and discharge from hospital to a care facility. \textsuperscript{70}

**Limitations of the RIFLE classification.**

Despite its clinical use, the RIFLE classification has a number of important limitations. \textsuperscript{696670}

**Issues concerning serum creatinine are:**

- The need for baseline SCr to define and classify AKI; this baseline value is frequently unknown in clinical practice \textsuperscript{70}
- When using the MDRD formula (if base line SCr unknown) has been validated in CKD patients with stable renal function, not in AKI patients.
- Multiple studies previously mentioned that only Scr should be used to define and stage AKI?
- The endogenous production and serum release of Scr are variable, and multiple factors like age, gender, diet, and muscle mass play a role in its level.
Assessment of post-operative AKI

- 10 to 40% of SCr elimination is performed by renal tubule and this mechanism is amplified as the GFR diminishes, thus, overvaluing renal function in AKI patients groups.
- Many medications inhibit tubular secretion of SCr (i.e. trimethoprim, cimetidine), causing a temporary increase in SCr.
- Various factors can affect with SCr determination (i.e. acetoacetate accumulated in DKA causing a false elevation in SCr).
- SCr is a marker of renal function, and not of renal lesion.

Issues concerning urine output

The decrease in the UOP is sensitive and frequent in AKI but also has some important limitations in defining and staging AKI.

- Sensitivity and specificity of UOP changed by the use of diuretics, and this issue is not specifically considered in the RIFLE classification.
- The UOP need bladder catheter in place, which, despite being common in ICU patients, is not so frequent in other hospitalized patients.
- It is possible that the predictive ability of UOP could be inferior to that of SCr, which can explain the difference in terms of mortality between the same classes defined by each one of those criteria, observed in studies that utilized both criteria to define and classify AKI, the capacity of the RIFLE (using both criteria) to predict mortality can be more stable.
Assessment of post-operative AKI

than the ability of this classification employing only SCr which verifies the clinical utility of using simultaneously both criteria as proposed by the ADQI work group.\textsuperscript{72,73}

- Lastly, the RIFLE classification does not provide any information the cause or the origin of AKI and the requirement for RRT are not considered in the RIFLE classification. In two studies that evaluated ICU patients with AKI necessitating continuous RRT, the RIFLE classification showed less acuteness in predicting mortality. One possible explanation for this phenomenon is that in both the studies, the clinical severity of patients was so high that it could not allow RIFLE to distinguish mortality according to AKI severity (i.e. between the three classes).\textsuperscript{74}

The Acute Kidney Injury Network (AKIN)

The Acute Kidney Injury Network (AKIN) working group in September 2005, in a meeting in Amsterdam put a new classification of AKI which is modification of the RIFLE classification; therefore, their strengths and limitations are very similar to those above-mentioned for the RIFLE however AKIN classification has some further benefits and limitations related to the modifications made the RIFLE classification.\textsuperscript{75}

The AKIN classification (Table 3) was published in March 2007 in critical care, and it is a later version of the RIFLE classification with some modifications: the diagnosis of AKI is only considered after achieving an adequate status of hydration and after excluding urinary obstruction; the AKIN classification only relies on SCr and not on GFR
Assessment of post-operative AKI

changes; baseline SCr is not necessary in the AKIN classification, and it requires at least two values of Scr obtained within a period of 48 h.

AKI is the sudden abatement within 48 hrs. of renal function, characterized by an increase in serum SCr of no less than 0.3 mg/dL or by a rate increment in SCr ≥50% (1.5× pattern esteem), or by a diminishing in the UOP (archived oliguria <0.5 mL/kg/hour for over 6 hour and classified to 3 stages:

Stage 1 compares to the danger class, yet it likewise considers a flat out increment in (0.3 mg/dL);

Stages 2 and 3 relate to damage and disappointment classes, separately;

Stage 3 additionally considers patients requiring RRT autonomously of the stage (characterized by SCr and UOP) they are in at the purpose of RRT start; the two result classes (loss of kidney capacity and end-stage kidney illness) were expelled from the characterization.

These adjustments in light of the combined proof that even little increments in SCr are connected with a poor anticipation, and in the great variability of assets and of the signs to begin RRT showed in various nations and healing centers .

It has been shown that the AKIN classification, like the RIFLE classification, allowed the identification and stratification of AKI in a large proportion of hospitalized patients and was independently associated with the outcome .

The AKIN classification could theoretically improve the RIFLE criteria sensitivity and specificity, although the advantages of the RIFLE
modifications have not been proven. In fact, the AKIN classification compared with the RIFLE classification did not exhibit a better prognostic acuity in terms of in-hospital mortality, although it enabled the identification of more AKI patients. 74 77

Table 3 Three stages of AKI according AKIN

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine level</th>
<th>UOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Increase in SCr by ≥0.3 mg/dL or ≥1.5-&lt;2.0 times baseline.</td>
<td>Less than 0.5 mL/kg per hour for more than 6 hours.</td>
</tr>
<tr>
<td>Stage II</td>
<td>Increase in SCr by ≥2.0-&lt;3.0 times baseline.</td>
<td>Less than 0.5 mL/kg per hour for more than 12 hours.</td>
</tr>
<tr>
<td>Stage III</td>
<td>Increase in SCr by ≥3.0 times baseline.</td>
<td>Less than 0.3 mL/kg per hour for 24 hours or anuria for 12 hours.</td>
</tr>
</tbody>
</table>

Strengths of the AKIN classification.

- First, the AKI definition is only considered after an adequate status of hydration is reached, therefore, the AKIN classification, unlike RIFLE, adds important information about the cause.
- Second, the AKIN classification does not need baseline SCr to define AKI, although it requires at least two SCr determinations within 48 hours.
- Third, the AKIN classification is based on SCr and not on GFR changes.
Limitations of the AKIN classification. 63

- First, the AKIN classification does not allow the identification of AKI when SCr elevation occurs in a time frame higher than 48 hours.
- Second, in the 3rd Stage of the AKIN classification includes three diagnostic criteria (SCr, UOP and RRT), and the exciting variability in decision of the beginning or cessation of RRT as well as in RRT modality used and in the dose of dialysis among different nephrologists, hospitals and countries could limit the prognostic acuteness of this classification.
**Neutrophil gelatinase-associated lipocalin**

**Neutrophil gelatinase-associated lipocalin as recent marker for acute kidney injuries assessment**

The need for a troponin-like biomarker for diagnosis of AKI like diagnose person present with symptoms of chest pain MI by troponin is needed, the objective measurement of structural biomarkers, such as troponin, that are released from damaged myocytes can rapidly identify acute myocardial. This has allowed for early therapeutic interventions and a good decrease in mortality over the past few years.\(^{78}\)

As AKI is largely asymptomatic disease and beginning the diagnosis in this increasingly common disorder currently depends on functional biomarkers such as serial serum creatinine measurements which unfortunately is a delayed and unreliable indicator of AKI for a multiple reasons.\(^ {79} \)

**Why creatinine is not a novel indicator for AKI?**

- Even normal serum creatinine is influenced by several non-renal factors such as age, gender, medications, hydration status, nutrition status, muscle metabolism, muscle mass, and tubular secretion.
- Presence of renal reserve make a number of acute and chronic kidney conditions can exist with no increase in serum creatinine owing to the it is estimated that over 50% drop in kidney function before serum creatinine rises.
- Serum creatinine concentrations do not accompanied with decrease in GFR in the acute setting, it takes several hours
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or days before a new equilibrium between the apparently steady state production and the decreased excretion of creatinine is established.

- An increase in serum creatinine represents a late indication of a functional change in GFR that lags behind important structural changes that occur in the kidney during the early-damage stage of AKI.  

Indeed, animal studies have recognized multiple interventional methods that can prevent or even treat AKI if initiated early in the course of disease, before the SCr even starts to elevate.  

The lack of early biomarkers has laden our ability to translate these promising interventional methods therapies to human AKI. Also lacking are reliable methods to assess effectiveness of protective or therapeutic interventions and early predictive biomarkers of drug toxicity.  

A troponin-like biomarker of AKI that is measured easily, not affected by other biological variables and able of both early detection and risk stratification represents a marvelous advance in the care of patients prone to renal injury, since the incidence of AKI hospitalized population is estimated 5–7%.  

Recently several biomarkers of AKI recently identified and studied. And the limitations of the conventional renal function markers (SCr and UOP) can be overwhelmed with the utilization of those new biomarkers. In fact, various urinary and serum markers of AKI have been identified and described such as neutrophil gelatinase-associated lipocalin, interleukin-18 and the kidney injury molecule-1.  

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These biomarkers start to elevate soon in AKI (1–3 days before the increase in Scr), and do exhibit a great sensitivity and specificity in AKI diagnosis with a good correlation with RRT needs, as well as with mortality, in several settings, namely in the post-operative period of cardiac surgery in ICU patients and in the contrast-induced nephropathy in children undergoing coronary angiography. 85

Although some authors have stipulated that an increase in postoperative serum creatinine levels must occur within 48 hours of surgery to ensure that AKI is related to the inciting event, these consensus criteria were not specific for cardiac surgical patients, because increase in serum creatinine can occur as late as 72 hours after cardiac surgery. 86

In recent years, several studies have shown that novel biomarkers can detect acute tubular injury earlier than serum creatinine in the setting of AKI. 87

For the past decade, there have been a host of investigations surrounding novel structural biomarkers of AKI because they may facilitate patient management and development of therapies. 88 89

Being able to predict whether AKI will progress could improve monitoring and care, guide patient counseling, and assist with enrollment into trials of AKI treatment. Biomarkers included urinary IL-18, urinary albumin to creatinine ratio, and urinary and plasma neutrophil gelatinase-associated lipocalin (NGAL) 90
Characteristics of an ideal AKI biomarker

- Being noninvasive and easy to perform on the bedside or in a normal clinical lab, using accessible samples such as blood or urine. With respect to the sample source, the majority of AKI biomarkers described thus far have been measured in the urine.\(^6^5\)
- Urinary biomarkers have many advantages, including the noninvasive during sample collection, the reduced number of interfering proteins and the potential for the development of patient self-testing kits, but also many disadvantages also exist in urine including the lack of samples from patients with severe oliguria and potential changes in urinary biomarker concentration induced by hydration status and diuretic therapy. Also commonly employed correction factor for urinary dilution is to express urinary biomarkers adjusted for urinary creatinine concentration in research studies, this correction may be inaccurate in the situation of AKI because creatinine production may be reduced in some forms of AKI.\(^9^1\)
- Diagnosis depends on serum level of biomarker have revolutionized many facets of medicine, as exemplified by the use of troponins for the early diagnosis of acute MI. Then again, plasma biomarkers may be confused by extra-renal sources as well as by subclinical changes in renal elimination. Thus, in the case of AKI, it is important and ideal to develop both urinary and plasma biomarkers.\(^9^2\)
- clinically applicable AKI biomarkers that should be rapidly and reliably measurable using standardized clinical assay methods.\(^9^3\)
- They should be sensitive to facilitate early detection with cut-off values and a wide dynamic range that allow for risk stratification.\(^8^3\)
In addition to aiding early diagnosis and prediction, the biomarkers should be highly specific for AKI, and enable the identification of AKI subtypes and etiologies, as well as differentiating AKI from chronic kidney disease.

Availability of accurate biomarkers that can distinguish pre-and post-renal conditions from true intrinsic AKI and also identifying the primary location of injury (proximal tubule, distal tubule, interstitium or vasculature) would represent a significant advance.¹⁶

Indicative for the duration of kidney failure whether AKI, chronic kidney disease or ‘acute-on-chronic’ kidney injury).³³

Identifying AKI etiologies (ischemia, toxins, sepsis or a combination)³³

Risk stratification and prognostication (duration and severity of AKI, need for renal replacement therapy, length of hospital stay and mortality).³³

Unsurprisingly, the pursuit of improved biomarkers for the early diagnosis of AKI and its outcomes is an area of intense contemporary research. For answers, we must turn to the kidney itself. Indeed, understanding the early stress response of the kidney to acute injuries has revealed a number of potential biomarkers.³³
What is NGAL?

Structural biology and source of serum NGAL

The recent journey of NGAL in medicine considered the most promising novel AKI biomarker. Expression & structure of NGAL was originally identified as a novel protein isolated from secondary granules of human neutrophils, and was subsequently demonstrated to be a 25-kDa protein covalently bound to neutrophil gelatinase.\(^{94\ 95}\)

Mature peripheral neutrophils lack NGAL mRNA expression, and NGAL protein is synthesized at the early myelocyte stage of granulopoiesis during formation of secondary granules. NGAL mRNA is normally expressed in a variety of adult human tissues as salivary gland, stomach, colon bone marrow, uterus, prostate, trachea, lung, liver and kidney.\(^{96}\)

Several of these tissues express the NGAL protein at very low levels when exposed to micro-organisms constitutively.

The promoter region of the NGAL gene contains binding sites for a number of transcription factors, including nuclear factor (NF)-κB.\(^{96}\)

This could explain the constitutive, as well as inducible, expression of NGAL in several of the non-hematopoietic tissues. Like other lipocalins, NGAL forms a barrel-shaped tertiary structure with a hydrophobic calyx that binds small lipophilic molecules, the major ligands for NGAL are siderophore; small iron-binding molecules.\(^{97}\)
Useful roles of NGAL comprises a critical component of innate immunity to bacterial infection, Siderophore are synthesized by bacteria to scavenge iron from the surroundings, and use specific transporters to recover the siderophore-iron complex, confirming their iron supply, the siderophore-chelating property of NGAL therefore purifies and make it a bacteriostatic agent. 98

Then again, siderophores produced by eukaryotes participate in NGAL-mediated iron shuttling, which is important to various cellular responses, such as proliferation and differentiation this property provides a likely molecular mechanism for the documented role of NGAL in enhancing the epithelial phenotype.99
During kidney organogenesis, NGAL induce epithelial differentiation of the mesenchymal progenitors, leading to the development of glomeruli, proximal tubules, Henle’s loop and distal tubules.\textsuperscript{100}

However, NGAL expression is also markedly induced in injured epithelial cells, including the kidney, colon, liver and lung. This is likely mediated via NF-κB, which is known to be rapidly activated in epithelial cells after acute injuries, and plays a central role in controlling cell survival and proliferation.\textsuperscript{101}

With regards to an injured mature organ, such as the kidney, the biological role of NGAL induction is to preserve of function, attenuate of apoptosis and enhance proliferative response.\textsuperscript{102}

This defensive effect is depends on the chelation of toxic iron from extracellular environments, and the regulation of delivery of siderophore and iron to intracellular sites, lastly NGAL is noticeably induced in a number of human cancers, where it often represents a predictor of bad prognosis.\textsuperscript{103}

The NGAL gene is known to be induced by a number of tumor-promoting factors like SV40 and polyoma virus, , hepatocyte growth factor, retinoic acid, phorbol esters, the transforming factor neu glucocorticoids and NF-κB .\textsuperscript{103}
The uptake of NGAL via receptors such as megalin intracellularly have evolved as illustrating mechanism, and for intracellular handling via endosomes. The subsequent molecular way taken by NGAL may be largely dependent on the type of molecule it is complexed with NGAL that is devoid of siderophore and iron (holo-NGAL) rapidly scavenges intracellular iron. 104

The depletion of intra-cellular iron results in a decrease in the mammalian cell’s proliferative ability and induce cell apoptosis but when NGAL is attach to siderophore and iron a rapid release of iron with regulation of iron-dependent molecular pathways which results in downstream induction of proliferation and epithelial transformation. 105

Studies recently aimed to prove these hypotheses hold promise for increase our knowledge of NGAL biology. Also NGAL as predictor of AKI Preclinical transcriptome profiling studies identified NGAL to be
Neutrophil gelatinase-associated lipocalin

one of the most upregulated genes in the kidney very early after acute injury in animal models.\textsuperscript{106}

NGAL the most highly induced proteins in the kidney after ischemic or nephrotoxic AKI in animal models this revealed by downstream proteomic analyses.\textsuperscript{107}

The easily and unanticipated detection of NGAL protein was in the urine and serum soon after AKI in animal studies has promote a number of translational studies to evaluate NGAL as a noninvasive biomarker in human AKI.\textsuperscript{108}

Many studies mainly cross-sectional study of adults with established AKI (serum creatinine is doubled) from variable causes, a marked increase in urine and serum NGAL was noted by western blotting when compared with normal controls.\textsuperscript{106}

Furthermore, the predictive power of urinary NGAL for AKI after cardiac surgery varied with baseline renal function, with optimal discriminatory performance in patients with normal preoperative renal function.\textsuperscript{109}

Despite plasma NGAL is freely filtered by the glomerulus, it is mostly reabsorbed in the proximal tubules by competent megalin-dependent endocytosis so the genesis and sources of plasma and urinary NGAL following AKI require further clarification.\textsuperscript{98}

The previous postulation arise after study of systemic injection of labelled NGAL, which becomes enriched in the proximal tubule but does
not appear in the urine in animals, thus any urinary excretion of NGAL is likely only when there is concomitant proximal renal tubular injury that precludes NGAL reabsorption and/or increases de novo NGAL synthesis.5

Genetic expression studies in AKI have revealed a rapid and huge (1000-fold) upregulation of NGAL mRNA in the thick ascending limb of loop of Henle and the collecting ducts, the resultant synthesis of NGAL protein in the distal nephron and secretion into the urine appears to comprise the major fraction of urinary NGAL.98

This over-expression of NGAL in the distal tubule and rapid secretion into the lower urinary tract is in concurrence with its function as an antimicrobial function, it is also consistent with the proposed role for NGAL in promoting cell survival and proliferation and also goes with the recent documentation of abundant apoptotic cell death in distal nephron segments in several animal and human models of AKI.110111

Surprisingly the kidney itself might not be a major source, since direct ipsilateral renal vein sampling after unilateral ischemia indicates that the NGAL synthesized in the kidney is not introduced efficiently into the circulation, but is abundantly present in the ipsilateral ureter ?.112

Now it well established that AKI results in a intensely increased NGAL mRNA expression in distant organs as the liver and lungs, and the over-expressed NGAL protein released into the circulation may constitute a wide systemic pool.113
Neutrophil gelatinase-associated lipocalin

NGAL also is an acute phase reactant and this contributions to the systemic pool in AKI source of NGAL as acute phase reactant may be released from neutrophils, macrophages and other immune cells. 

Another point should be evaluated is any decrease in glomerular filtration rate resulting from AKI would be expected to decrease the renal clearance of NGAL with subsequent accumulation in the systemic circulation as the rise in plasma NGAL after AKI and lower urinary level.

New biomarkers hold the promise of allowing clinicians to detect kidney injury earlier, to guide future therapy, and to better prognosticate of AKI, differential diagnosis of AKI.

Researches on serum NGAL

A number of studies have now implicated NGAL as an early diagnostic biomarker for AKI in common clinical situations. In prospective studies of children, with normal kidney function and no comorbid conditions, who underwent elective cardiac surgery, AKI (defined as a 50% increase in serum creatinine) occurred in 30% of the subjects, 2-3 days after surgery.

In contrast, NGAL measurements by ELISA revealed a 10-fold or more increase in the urine and plasma, within 2-6 h of the surgery in those who subsequently developed AKI. Both urine and plasma NGAL were excellent independent predictors of AKI for the 2-6-h urine and plasma NGAL measurements.
Neutrophil gelatinase-associated lipocalin

In a recent study of adults in the emergency department setting, a single measurement of urine NGAL at the time of initial presentation predicted AKI and reliably distinguished prerenal azotemia from intrinsic AKI and from chronic kidney disease (CKD). 117

Thus, NGAL is a useful early AKI marker that predicts development of AKI even in heterogeneous groups of patients with multiple comorbidities and unknown timing of kidney injury.118

Because of its high predictive properties for AKI, NGAL is also emerging as an early biomarker in interventional trials. For example, a reduction in urine NGAL has been employed as an outcome variable in clinical trials demonstrating the improved efficacy of a modern hydroxyethyl starch preparation over albumin or gelatin in maintaining renal function in elderly cardiac surgery patients.119

Furthermore, adults who developed AKI after aprotinin use during cardiac surgery displayed a dramatic rise in urine NGAL in the immediate post-operative period, attesting to the potential use of NGAL for the prediction of nephrotoxic AKI. 117

Not surprisingly, NGAL measurements as an predictor are currently implemented in multiple clinical trials formally listed in clinicalTrials.gov.
Remote ischemia preconditioning

Remote Ischemic preconditioning

Ischemic preconditioning intrinsic mechanisms brought to bear by organs exposed to toxic or ischemic insults, which protect them against a subsequent exposure to ischemia since described 20 years ago several trials to get best benefits from this phenomenon. Studies was started on cardiac ischemic preconditioning and its protective effect from reperfusion injuries and ischemic insult.

Remote ischemic preconditioning then appears to light and multiple studies done and still ongoing research to prove its effect on cardiac protection.

As renal injuries post cardiac bypass and surgery is a common clinical problem associated with significant mortality and morbidity as mentioned in previous chapter. A new strategy to reduce this damage is remote ischemic preconditioning (RIPC).

Ischemic injury to the kidney is associated with high morbidity and mortality. Improving the ability of the kidney to tolerate ischemic injury would have important implication.  

Ischemia-reperfusion injury (IRI) is the leading cause of acute kidney injury (AKI) and in a variety of other clinical settings other than surgery with cardiopulmonary bypass, like renal transplantation, and hypovolemic/septic shock.
Remote ischemia preconditioning

The mechanism of renal RIPC has not yet been elucidated but multiple trial on animal such rat and mice is going to study this effect.121

The underlying mechanisms of RIPC are very complex and not yet fully defined. It has been hypothesized that RIPC predominantly involves systemic multifactorial anti-inflammatory, neuronal, and humoral signaling pathways, which may differ in response to various ischemic stimuli and are likely to interact with each other.

The signaling mechanism underlying RIPC has been studied almost exclusively in the heart and has been attributed to both neurogenic pathways, as well as the release of biochemical messengers into the circulation. However, transmission may differ depending on the stimulus protocol, target organ and remote organ.122

On the animal studies various models of RIPC on organs have been used, mainly mesenteric ischemia and limb ischemia has been successful by the temporary occlusion of the infra-renal aorta, although this involved different species123
Remote ischemia preconditioning

Figure 9 Mechanisms of IPC in cardiac cells

Hypothetical scheme outlining the 2 phases of kinase cascade activation in response to IPC. During the preconditioning phase, mitochondrial reactive O2 species (ROS) were released and PKc was activated. These events reactivate the PI3K- Akt-p70S6K and MEK-1/2–ERK-1/2- p70S6K cascades, which comprise the reperfusion injury salvage kinase (RISK) pathway, at reperfusion.

In the cardiac cell as illustrated in previous figure risk pathway mediates cellular survival through several possible mechanisms, which may include inhibition of mitochondrial permeability transition pore (mPTP) opening.\(^1\)\(^2\)\(^3\)

The implication of the idea on the kidney started by applying ischemic preconditioning on the kidney directly on aortic surgery and on animals.

A significant amount of data, however, now exists in a number of organs to suggest that there may be intrinsic mechanisms brought to bear by organs exposed to toxic or ischemic insults, which protect them against a subsequent exposure to ischemia.
Remote ischemia preconditioning

While it is frequently stated that this phenomenon was first described in the heart, in fact there is almost a century of literature on the kidney that supports the concept that prior injury protects against a second insult susceptible to ischemic injury.

Kidney ischemic preconditioning

What are the mechanisms that account for kidney ischemic preconditioning?

Thus, the development of protocol of RIPC to diminish IRI-induced damage is crucial. In kidney of experimental models, different types of ischemic conditioning (IC) has been shown to confer protection to the kidney against IRI.¹²⁴
One or more brief episodes of sub-lethal, intermittent ischemia and reperfusion (IR) may be produced locally in the kidney (local IPC) or in a remote tissue (RIPC).

The underlying mechanisms of RIPC are very complex and not yet fully defined. It has been hypothesized that RIPC predominantly involves systemic multifactorial anti-inflammatory, neuronal, and humoral signaling pathways, which may differ in response to various ischemic stimuli and are likely to interact with each other point of convergence for a range of preconditioning triggers.\textsuperscript{4}

There are a number of possible explanations for ischemic preconditioning, as suggested in the studies conducted in the early part of the twentieth century.\textsuperscript{125}

Possible explanation may be the regenerating kidney protected because new tubular cells are dedifferentiated and less after the initial ischemia and when the initial insult is too short to induce cell death, since new cells would not be generated in these situations.\textsuperscript{125}

Furthermore, it cannot account for the protection seen in tubules isolated from kidneys after 24 h of obstruction where protection does not correlate with tubular proliferation, it is possible that the preconditioning influence is sufficient to change the differentiation status of the epithelial cell and this dedifferentiated status, similar to a phenotype that occurs in tissue culture, leads to resistance to hypoxic injury, just as epithelial cells, when placed into culture, are resistant.\textsuperscript{125}
Remote ischemia preconditioning

As seen in dividing cells they are less susceptible to oxidative stress, a feature of reperfusion, when compared with quiescent cells.¹²⁴

Most of local IPC multiple trials try to prove a multitude of pro survival pathways in the kidney, however, in contrast to local IC, few attempts have been made to investigate the underlying renal molecular mechanisms of RIPC and whether the renal responses to different.¹²⁴

Possible communication Pathways in RIPC

Neuronal and humoral pathways.

Neuronal and humoral pathways are linked together and their involvement are mostly based on the finding that blockade of the autonomic ganglion reversed the cardio-protective effects of RIPC when the preconditioning ischemic insult is performed via mesenteric artery occlusion, this concept appears to also apply to the RIPC associated neuroprotection in cerebral tissue, as was recently demonstrated.¹²⁶

Also adenosine receptors, particularly the subtype A₁, have been implicated as the mediators of neuroprotection in RIPC, likely through increased production of specific antioxidants and NO.¹²⁷

For the kidney, studies on RIPC signaling are sparse. We have recently demonstrated that the adenosine receptor antagonist 8-(p-sulphofenyl)theophylline, which has been effective in blocking RIPC in the heart, has no on renal RIPC by hind limb ischemia.¹²¹
Organ protection by remote ischemia may also be related to a catecholamine effect, because pretreatment with certain catecholamine can mimic the effect of preconditioning.128

**Possible Humoral pathway**

Other underlying mechanisms may include humoral factors, such as adenosine, bradykinin, erythropoietin, d 1-opioid, and free radicals, released into the systemic circulation, which subsequently protect the remote organ.129

**Possible Anti-Inflammatory Pathways**

Some studies suggested that protective effect of RIPC may be due to the beneficial anti-inflammatory or antioxidant effects, including decreased extracellular levels of noxious metabolites, such as protons and lactate. In support of this concept, RIPC reduced neutrophil activation through expression of neutrophil CD11b and platelet neutrophil complexes130 131

Moreover, protein kinases involved in TNF synthesis, mitogen-activated protein kinase (MAPK) – activated protein kinase 2, and MAPK kinase 8 were suppressed, whereas ischemic preconditioning activated TNF- R1, which promotes the production of manganese SOD, a strong antioxidant and protector against reactive O2 species132

Other immunologic changes include the suppression of genes encoding key proteins involved in cytokine synthesis, leukocyte
chemotaxis, adhesion, migration, exocytosis, innate immunity signaling pathways, and apoptosis.\textsuperscript{129}

\textbf{Role of Mediators of Kidney Recovery after RIPC}

\textbf{Nitric oxide (NO)}

Nitric oxide (NO) is considered a vital cytoprotective agent and may play an essential role in RIPC both as a trigger and mediator of RIPC. Supporting evidence for the role of NO in mediating the protection against ischemic injury arise from trials showing that inhibition of NOS isoforms by the non-selective NOS inhibitor L-NAME (NG-nitro-L-arginine methyl ester hydrochloride) results in upregulation of the protective effects of IPC, in addition, IPC was shown to induce NOS expression with a subsequent increase in the NO oxidation production of nitrite and nitrate.\textsuperscript{133}

Also if L-NAME is infused of before lower limb RIPC abolish its protective effects against sub-sequent abdominal adipocutaneous flap ischemia.\textsuperscript{134}

\textbf{De novo protein synthesis (cytoprotective proteins)}

although the exact mechanisms are not completely clear it has been speculated that one or more de novo proteins are capable of reactivating the RISK pathway, including heat shock proteins (HSPs), cyclooxygenase-2, manganese superoxide dismutase (MnSOD), inducible nitric oxide synthase (iNOS) and aldose reductase.\textsuperscript{135}
Remote ischemia preconditioning

Another protein ERK1/2 and Akt are persistently activated after days following ischemia and possibly participate in the long-term repair process after IRI independent of IC. 136

It is not clear whether RIPC is able to increase and maintain high levels of cytoprotective proteins in the kidney after the ischemic insult. Multiple studies was designed to evaluate the recovery capacity of the kidney after IRI and investigate whether RIPC offer additional protective effects against IRI-induced functional impairment, tissue inflammation, and fibrosis via the up-regulation of established cytoprotective proteins as mentioned previously.4

Protein kinases (PKC)

The current concept of signal transduction in IPC suggests activation of the signaling cascades through the phosphoinositide 3-kinase /Akt /endothelial nitric oxide synthase(NOS)/cyclic guanosine monophosphate / PKG pathways, eventually leading to the opening of the ATP-dependent mitochondrial potassium (KATP) channel, which is believed to be a downstream target of PKG/PKC activation.137

A number of studies have shown that the kidney may be dependent on MAPK phosphorylation to render immediate protection against IRI since phosphorylation is increased early after reperfusion, this may also be important for the recovery phase, although studies have reported conflicting results, this is possibly due to the variety of the signaling cascades and cellular processes influenced by MAPK.136 138
Remote ischemia preconditioning

As mentioned by Jang HS et al. Study underwent unilateral renal ischemia in mice for 37 minutes followed by 7 days of reperfusion Akt and ERK1/2 activation in response of ischemia with the recovery of renal function from day 3 to day 7 in which a sustained activation of ERK1/2 was observed up to 9 days.\textsuperscript{139}

Studies show suppression of ERK1/2 from day 1 after reperfusion resulted in increased tissue damage and a decreased proliferation of tubular epithelial cells, with increase in interstitial cell proliferation, extracellular matrix deposition, and TGF-β1 expression levels.\textsuperscript{124}

Another study show pAkt inhibition 4 hours prior to 35 minutes of bilateral renal ischemia in mice reduced kidney function, increased histopathological damage, and decreased tubular cell proliferation (24–48 hours after reperfusion).\textsuperscript{140}

Taken together, these findings indicate that ERK1/2 and Akt activation plays a significant role in the recovery phase following IRI. However, the precise role of MAPK and the importance of when these are active in the course of renal IRI have yet to be established.\textsuperscript{140}

**Heat shock proteins possible role**

HSP27, HSP32, and HSP70 are well-established cytoprotective proteins with diverse effects that counteract IRI-related damage, including anti-apoptotic, anti-oxidant, and anti-inflammatory effects as well as the ability to refold damaged proteins and stabilize the cytoskeleton of the cell.\textsuperscript{141}
Remote ischemia preconditioning

The expression and activation of these proteins make them sensitive to IRI it is noted that increased HSP27 protein expression has been detected up to 12 weeks after 30 minutes of ischemia in the mouse kidney and not only increases HSP27 phosphorylation but also increases HSP32 and HSP70 expression levels 7 days after reperfusion.\textsuperscript{142}

As discussed in the study by Park et al in 2014 this prolonged activation may be caused by persistent ongoing inflammatory activity, reactive O2 species generation, and epithelial cell de-differentiation.\textsuperscript{124}

**KIM-1 and NGAL Possible Role**

In the present study, we confirmed that this connection may be responsible for not only the increased HSP expression levels but also for KIM-1, NGAL, and iNOS regulation.\textsuperscript{143}

The up-regulation of iNOS and the accompanying increment in nitric oxide (NO) might have added to the practical recuperation that we saw, then again, abundance NO would bring about additional tissue harm.\textsuperscript{143}

Strangely, the expanded articulation of KIM-1 and NGAL may not just serve as markers of IRI-initiated tissue harm as an in vivo study demonstrated that the upregulation of KIM-1 on the surface of tubular epithelial cells after IRI empowers these cells to clear apoptotic and necrotic cells through phagocytosis. Nonetheless, ceaseless KIM-1 expression has likewise been connected to renal interstitial fibrosis. [149]
Remote ischemia preconditioning

Specifically, NGAL is fit for restraining apoptosis and empowering cell multiplication in proximal tubule cells. In rundown, our outcomes propose that chose cytoprotective proteins including MAPK, HSPs, iNOS, NGAL, and KIM-1 may take part in the recuperation stage after IRI. 102
Aim of the work

Our aim was to demonstrate if RIPC would improve post-operative renal outcome and reduce incidence of AKI or not and whether renal biomarker NGAL can predict early occurrence of AKI rather than the usual methods.
Patients and methods

- **Ethics committee:**
  - The study protocol was approved by the institutional ethical committee of Benha University hospitals.
  - Informed patient written consent was obtained from every patient before enrolment in the study.

- **Type of Study:** Prospective, controlled double blind and randomized study.

- **Methods of randomization:** Patients have been randomized into two equal group with online randomization program that used to generate random number list (http://www.randomizer.org/). Patient randomization numbers was concealed in opaque envelopes and was opened by the study investigator.

- **Methods of blindness:** Staff involved in the clinical care and members of the study group obtaining functional data was blinded to randomization for the period of data acquisition and analysis. Group allocation was revealed after the final statistical analysis.

- **Inclusion criteria:**
  - Age ranged between 18 - 60 years.
  - ASA physical status: II and III.

- **Type of operations:**
  - Cardiac surgical procedures with cardiopulmonary bypass.
Patients and methods

- **Site of study:** Benha university hospital.

- **Groups allocation:**
  Patients was randomly allocated into two equal groups:
  
  - **Group I** (Study group): consisted of 20 patients (Remote ischemic preconditioning group) the protocol of RIPC was induced by inflation of automatic blood pressure cuff above 200 mm Hg for 5-min on the lower limb to induce ischemia then permitted reperfusion for 5-min this cycle was repeated three times before initiation of cardiopulmonary bypass.
  
  - **Group II** (control group): consisted of 20 patients underwent placement of the blood pressure cuff around the lower limb with no inflation.

- **Exclusion criteria:**
  - Patients with airway and parenchymal lung disease.
  - Pulmonary hypertension more than 100 mmHg.
  - Immunodeficiency.
  - Haematological disorders.
  - Hepatic impairment.
  - Renal impairment.
  - Pregnancy.
  - Morbid Obesity.
  - Diabetic patient.
  - Patients with myocardial ischemia or infarction.
  - Patients with peripheral vascular disease.
  - Patient required deep hypothermic circulatory arrest.
  - Patients received drugs that interfere with the mechanism of RIPC i.e. sulfonylureas, nicorandil and propofol.
Patients and methods

Anesthetic Management:

- **In the preoperative room**
  - The patient lied in the semi sitting position (30 degrees to 45 degree).
  - Venous access: Wide bore I.V line (14-16 gauges) was inserted and blood sample taken for baseline ACT measurement.
  - Premedication (sedation) in the form of midazolam (0.01:0.02) mg /kg is given to the patient IV.
  - O2 supplementation (2-3) L/min via nasal cannula to avoid hypoxemia after pre-medication.
  - Pulse oximeter and non-invasive blood pressure cuff was connected to the patient.
  - Arterial line insertion: (the radial artery was the choice in all patients) after assessment the adequacy of the collaterals by Allen’s test then arterial sample taken and ABG(baseline) was measured.

- **At the operation room before the induction of anaesthesia patients were monitored by:**
  - **The 5 Lead ECG:** combined lead II (for rhythm) and V5 (for anterior ischemia) were used.
  - **Arterial Blood Pressure monitoring:**
    - Non Invasive Blood Pressure monitoring.
    - Invasive Blood Pressure monitoring: have been applied by conducting the arterial line to the pressure -tubing-transducer system which was flushed by heparinized saline (0.5-1 unit) of heparin per ml of saline.
  - **Pulse oximeter:** was placed over the finger of the patient.
Patients and methods

Induction of anaesthesia:

All patients had received the same general anaesthetic technique. Anaesthesia was induced with fentanyl (5-10) µg /kg, midazolam dose ranged from 5 to 10 mg with sleeping dose of thiopental sodium (1-3 mg/kg) according to patient hemodynamic and myocardial function. Endotracheal intubation was facilitated by pancrunium bromide 0.08 mg/kg with a suitable size tube.

Anaesthesia was maintained with inhaled isoflurane 1 MAC in 60% oxygen and pancrunium bromide 0.02 mg/kg was administrated every 30 minute in all patients to maintain muscle relaxation.

After induction of anaesthesia:

- Central Venous catheter was inserted in right internal jugular vein and monitored.
- Urinary catheter was inserted after the patient anesthetized to flow up urine output.
- Nasopharyngeal temperature probe was inserted and core temperature was monitored.

Laboratory monitoring:

Arterial Blood Gases (ABG) haematocrit, serum K, ca, glucose, and Mg were measured after the mechanical ventilation, on CPB and finally after weaning from CPB.

Also activated clotting Time (ACT) was measured after heparin by 5 min, on CPB and finally after weaning from CPB after reverse heparinising state with the antidote protamine sulphate.
Patients and methods

Parameters that have been used in our current study.

Primary outcome:

- **Level of Serum NGAL**: Was measured before operation (baseline) and 2 hours post cardiopulmonary bypass.

Secondary outcome measurements include the following:

- **Serum creatinine**: Was measured at baseline, 2h post-cardiopulmonary bypass and at 24, 48, 72 hours post bypass.
- **Estimated glomerular filtration rate**: Was measured at baseline, 2h after cardiopulmonary bypass and 24, 48, 72 hours post bypass.
- **Urine output**: Every 1 hour intraoperatively and every 6 hours postoperatively till 72 hours.
- **Degree of AKI**: According to acute kidney injury network criteria.
- **Total fluid intake given to patients**: Intraoperatively (pre CPB, on CPB and post CPB) then for the next three days postoperatively (amount and type).
- **Mean arterial blood pressure**: During the operation it was recorded every 1 hour intraoperative and for the next three days postoperatively every 6 hours.
- **Central venous pressure**: During the operation pre CPB, post CPB and every 6 hours from arrival of patient to ICU for the next 72 hours.
- **Operative time**: Was recorded from induction of anesthesia till skin closure.
- **Aortic cross clamp time (ischemic time)**: Was recorded from application of aortic clamp till aortic de-clamping.
Patients and methods

- **Cardiopulmonary bypass time:** Was recorded from connecting patient to extra-corporeal circulation till termination of cardiopulmonary bypass by re-establishing normal physiological function of the heart.

- **Duration of ICU stay:** Was recorded from transferring the patient from operating theatre to the ICU till discharge from ICU to the ward.

- **Dose of inotropic support requirements:** Inotropic support at each time was quantified by calculating the inotropic support.

**Statistical design:**

- Analysis of data was done by using SPSS version 16.
- Quantitative data was presented as mean ± Standard deviation.
- Qualitative data was presented as numbers and percentages.
- Quantitative data was analysed by using unpaired student t-test.
- Qualitative data was analysed by using chi-square test.
- P Value < 0.05 was considered statistically significant.
- P Value <0.01 was considered statistically highly significant.
- A sample size of at least ten patients was needed to have a power of least 80%, the two-sided α error of 5% level, and on the basis that from our previous studies we would expect a difference in serum NGAL of about 25 % between RIPC(Study) and control group at 2 hour after CPB . The effect size was 0.925.
Results

The current study shows the following results

There were no statically significant differences as regard the demographic data of the patients of the two group as shown in (table 4)

![Figure 11 Comparison between the two group regarding age](image)

**Table 4 Demographic data of both group**

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>37.8</td>
<td>11.77</td>
<td>37.15</td>
<td>8.63</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.1</td>
<td>14.11</td>
<td>66.1</td>
<td>12.46</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.7</td>
<td>15.57</td>
<td>169.9</td>
<td>14.7</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Sex M</td>
<td>14</td>
<td>70%</td>
<td>13</td>
<td>65%</td>
</tr>
<tr>
<td>F</td>
<td>6</td>
<td>30%</td>
<td>7</td>
<td>35%</td>
</tr>
<tr>
<td>ASA II</td>
<td>5</td>
<td>25%</td>
<td>4</td>
<td>20%</td>
</tr>
<tr>
<td>III</td>
<td>15</td>
<td>75%</td>
<td>16</td>
<td>80%</td>
</tr>
</tbody>
</table>
Results

There were 70% of patient Male (14) and 30% Female in group I while 65% Male (13) and 35% (7) Female in group II with no statistical difference between them also there were 8 patients (40%) (ASA II) and 12 (60%) (ASA III) in group I and of group II 7(35%) (ASA II) and 13 (65%) (ASA III), chi-Square test shows no statistical difference between the two group.

As regard the statistical analysis of the intraoperative measurement times (operative time, cross-clamping duration, total cardiopulmonary
bypass time and duration of ICU stay by days in table shows no statistical difference between two groups.

Table 5 Operative times of the two group

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Time of surgery (min.)</td>
<td>357.5</td>
<td>849.0</td>
<td>377.75</td>
<td>152.8</td>
</tr>
<tr>
<td>Total bypass time (min.)</td>
<td>135.5</td>
<td>229.4</td>
<td>128.25</td>
<td>717.8</td>
</tr>
<tr>
<td>cross clamping (min.)</td>
<td>76.75</td>
<td>15.15</td>
<td>79</td>
<td>312.5</td>
</tr>
<tr>
<td>Duration of ICU stay(Day)</td>
<td>3.8</td>
<td>1.76</td>
<td>3.6</td>
<td>1.14</td>
</tr>
</tbody>
</table>

Also ICU stay of group I was (3.8±1.76 days) and of group II was (3.6±1.14 days) and the analysis of the statistical difference was non-significant.

Figure 14 Comparison between the two-group regrading cross clamping time
Table 6 Serum Neutrophil Gelatinase Associated Lipocalin levels

<table>
<thead>
<tr>
<th>Serum NGAL (ng/ml)</th>
<th>Group I</th>
<th>Group II</th>
<th>Test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Baseline</td>
<td>125.05</td>
<td>17.056</td>
<td>130.15</td>
<td>17.37</td>
</tr>
<tr>
<td>2 hrs. post bypass</td>
<td>220.05</td>
<td>106.25</td>
<td>87.8</td>
<td>75.65</td>
</tr>
</tbody>
</table>

The statistical analysis of changes in serum NGAL level in blood preoperatively shows baseline serum NGAL level of group I (125.05±17.05 ng/ml) and of group II (130.15±17.37 ng/ml).

Then 2 hours post CPB serum NGAL level of group I was (220.05±106.25 ng/ml) and of group II was (187.8±75.65 ng/ml) the difference was statistically non-significant.

Figure 15 Comparison between the two group regrading serum NGAL level
**Results**

The Baseline creatinine serum level of group I was (0.99±0.18mg/dl) and of group II was (0.99±0.16 mg/dl) which is nearly the same mean.

**Table 7 Serum creatinine level of both group**

<table>
<thead>
<tr>
<th>Serum creatinine mg/ml</th>
<th>Group I</th>
<th>Group II</th>
<th>Test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Base line</td>
<td>0.99</td>
<td>0.18</td>
<td>0.99</td>
<td>0.16</td>
</tr>
<tr>
<td>2 hrs. post bypass</td>
<td>1.03</td>
<td>0.16</td>
<td>1.06</td>
<td>0.13</td>
</tr>
<tr>
<td>24 hrs. post bypass</td>
<td>1.21</td>
<td>0.69</td>
<td>1.1</td>
<td>0.45</td>
</tr>
<tr>
<td>48 hrs. post bypass</td>
<td>1.44</td>
<td>0.96</td>
<td>1.19</td>
<td>0.57</td>
</tr>
<tr>
<td>72 hrs. post bypass</td>
<td>1.5</td>
<td>1.39</td>
<td>1.25</td>
<td>0.99</td>
</tr>
</tbody>
</table>

After CPB by all creatinine serum level was statistically non-significant as shown in the next chart.

*Figure 17 Comparison between both groups as regard creatinine level*
As regard the monitoring of UOP as shown in table (pre bypass, on bypass, post bypass in 1st hour, 2nd hour, 3rd hour, 4th hour, 5th hour, 6th hour, 24 hours, 48 hours and 72 hours) post bypass to assess renal function show the following UOP values:

**Table 8 Urine output of the two group**

<table>
<thead>
<tr>
<th>UOP (ml)</th>
<th>Group I</th>
<th></th>
<th>Group II</th>
<th></th>
<th>Test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Pre bypass</td>
<td>182</td>
<td>61.61</td>
<td>170</td>
<td>61.56</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>0.54</td>
<td>0.61</td>
<td>0.61</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>On bypass</td>
<td>1585</td>
<td>308.26</td>
<td>1645</td>
<td>313.68</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>0.61</td>
<td>0.54</td>
<td>0.61</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Post bypass</td>
<td>945</td>
<td>334.78</td>
<td>882.5</td>
<td>425</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>0.66</td>
<td>0.52</td>
<td>0.51</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>1st hr.</td>
<td>122.75</td>
<td>24.99</td>
<td>112</td>
<td>20.60</td>
<td>1.48</td>
</tr>
<tr>
<td></td>
<td>1.48</td>
<td>0.14</td>
<td>0.14</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>2nd hrs.</td>
<td>111</td>
<td>21.43</td>
<td>118.5</td>
<td>22.71</td>
<td>1.07</td>
</tr>
<tr>
<td></td>
<td>1.07</td>
<td>0.28</td>
<td>0.28</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>3rd hrs.</td>
<td>120.5</td>
<td>19.53</td>
<td>117.75</td>
<td>24.41</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>0.39</td>
<td>0.69</td>
<td>0.69</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>4th hrs.</td>
<td>114</td>
<td>19.91</td>
<td>115.5</td>
<td>22.99</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>0.22</td>
<td>0.82</td>
<td>0.82</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>5th hrs.</td>
<td>117.5</td>
<td>24.47</td>
<td>121.5</td>
<td>22.01</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>0.54</td>
<td>0.58</td>
<td>0.58</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>6th hrs.</td>
<td>120.5</td>
<td>22.763</td>
<td>119.5</td>
<td>22.29</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>0.14</td>
<td>0.88</td>
<td>0.88</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>6 hrs.</td>
<td>1075</td>
<td>119.76</td>
<td>1017.5</td>
<td>126.98</td>
<td>1.47</td>
</tr>
<tr>
<td></td>
<td>1.47</td>
<td>0.14</td>
<td>0.14</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>12 hr.</td>
<td>1943</td>
<td>131.31</td>
<td>1890</td>
<td>255.8</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>0.82</td>
<td>0.41</td>
<td>0.41</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>24 hrs.</td>
<td>4385</td>
<td>727.1</td>
<td>4185</td>
<td>906.9</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>0.76</td>
<td>0.44</td>
<td>0.44</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>48 hrs.</td>
<td>4025</td>
<td>1292</td>
<td>3990</td>
<td>1266</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>0.08</td>
<td>0.93</td>
<td>0.93</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>72 hrs.</td>
<td>3430</td>
<td>1587</td>
<td>4005</td>
<td>1278</td>
<td>1.26</td>
</tr>
<tr>
<td></td>
<td>1.26</td>
<td>0.21</td>
<td>0.21</td>
<td>0.21</td>
<td></td>
</tr>
</tbody>
</table>

The following three charts also compare UOP in operation theatre and in the postoperative period of group and group II and both were statically insignificant.
Results

Figure 17 Comparison between both groups as regards UOP

Figure 18 Comparison between both groups as regards UOP

Figure 19 Comparison between both groups as regards UOP in the next 3 days
Results

Estimated glomerular filtration rate (EGFR) calculated by using Cockcroft-gault formula calculated, this formula uses UOP and serum creatinine. EGFR pre bypass, on bypass, post bypass in 1st hour, 2nd hour, 3rd hour, 4th hour, 5th hour, 6th hour, 24 hours, 48 hours, and 72 hours post bypass to assess renal function are showed in the next table.

**Table 9 Estimated glomerular filtration rate of the two group**

<table>
<thead>
<tr>
<th>EGFR</th>
<th>Group I</th>
<th>Group II</th>
<th>Test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Base line</td>
<td>99.351</td>
<td>76.19</td>
<td>5.79</td>
<td>5.031</td>
</tr>
<tr>
<td>2hrs.post bypass</td>
<td>96.68</td>
<td>14.11</td>
<td>90.2</td>
<td>15.16</td>
</tr>
<tr>
<td>24hrs. post bypass</td>
<td>97.15</td>
<td>33.41</td>
<td>80.46</td>
<td>31.64</td>
</tr>
<tr>
<td>48hrs. post bypass</td>
<td>89.1</td>
<td>34.60</td>
<td>86.85</td>
<td>32.52</td>
</tr>
<tr>
<td>72 hrs. post bypass</td>
<td>89.3</td>
<td>33.514</td>
<td>90.3</td>
<td>33.173</td>
</tr>
</tbody>
</table>

All the estimated GFR show no statistical differences between the two group.

![Figure 20 Comparison between both groups as regards EGFR](image)

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Results

Also fluid management in the next table is nearly the same during the scheduled time in the table and when analyzed statically show no differences

**Table 10 Fluid management of both group**

<table>
<thead>
<tr>
<th>Iv fluids (ml)</th>
<th>Group I</th>
<th></th>
<th>Group II</th>
<th></th>
<th>Test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>crystalloids pre bypass</td>
<td>860</td>
<td>336.2</td>
<td>875</td>
<td>358.2</td>
<td>0.13</td>
<td>0.89</td>
</tr>
<tr>
<td>crystalloid bypass</td>
<td>1500</td>
<td>0</td>
<td>1500</td>
<td>0</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>crystalloids post bypass</td>
<td>810</td>
<td>298.9</td>
<td>882.5</td>
<td>280.6</td>
<td>0.79</td>
<td>0.43</td>
</tr>
<tr>
<td>Blood product</td>
<td>367.5</td>
<td>240.2</td>
<td>402.5</td>
<td>260.8</td>
<td>0.44</td>
<td>0.66</td>
</tr>
<tr>
<td>crystalloids 1st day co1</td>
<td>4420</td>
<td>424.7</td>
<td>4420</td>
<td>607.3</td>
<td>1.08</td>
<td>0.28</td>
</tr>
<tr>
<td>crystalloids 2nd day</td>
<td>4008</td>
<td>956.7</td>
<td>4105</td>
<td>795.5</td>
<td>0.35</td>
<td>0.72</td>
</tr>
<tr>
<td>crystalloids 3rd day</td>
<td>3803</td>
<td>1234</td>
<td>4205</td>
<td>855.5</td>
<td>1.19</td>
<td>0.23</td>
</tr>
</tbody>
</table>

As regard statistical analysis of mean arterial blood pressure pre bypass, on bypass, post bypass first six hour analysis and postoperative 1st day 2nd day and 3rd day results showed in the following table and chart:

**Table 11 Mean arterial blood pressure**

<table>
<thead>
<tr>
<th>MAP (mm hg)</th>
<th>Group I</th>
<th></th>
<th>Group II</th>
<th></th>
<th>Test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre bypass</td>
<td>75.8</td>
<td>11.36</td>
<td>77.45</td>
<td>13.24</td>
<td>0.42</td>
<td>0.67</td>
</tr>
<tr>
<td>On bypass</td>
<td>74.25</td>
<td>12.79</td>
<td>70.75</td>
<td>9.08</td>
<td>0.99</td>
<td>0.32</td>
</tr>
<tr>
<td>1st hr. Post bypass</td>
<td>77.1</td>
<td>9.61</td>
<td>82.1</td>
<td>9.48</td>
<td>1.65</td>
<td>0.1</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th></th>
<th>2nd hr. Post bypass</th>
<th>3rd hr. Post bypass</th>
<th>4th hrs. Post bypass</th>
<th>5th hrs. Post bypass</th>
<th>6th hrs. Post bypass</th>
<th>1st day</th>
<th>2nd day</th>
<th>3rd day</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAPB</td>
<td>78.3</td>
<td>10</td>
<td>80.8</td>
<td>13.83</td>
<td>0.65</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mm Hg</td>
<td>0.51</td>
<td>0.65</td>
<td>10.12</td>
<td>5.43</td>
<td>0.14</td>
<td>5.99</td>
<td>76.25</td>
<td>80.8</td>
</tr>
<tr>
<td>Pre bypass</td>
<td>On bypass</td>
<td>2nd hr. Post bypass</td>
<td>3rd hr. Post bypass</td>
<td>4th hrs. Post bypass</td>
<td>5th hrs. Post bypass</td>
<td>6th hrs. Post bypass</td>
<td>1st day</td>
<td>2nd day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 21** Comparison between both groups as regards MAPB
Results

Table 12 Central venous pressure measurement of both group

| CVP (cmH2O) | Group I | | Group II | | Test | | p-value |
|-------------|---------|---|---------|---|------|---|
| Mean | SD | Mean | SD |
| Pre bypass | 4.6 | 2.68 | 4.45 | 2.89 | 0.17 | 0.86 |
| CVP Post bypass | 5.55 | 1.99 | 5 | 2.38 | 0.79 | 0.43 |
| CVP 1st 6hrs. | 5.55 | 2.06 | 6.4 | 1.19 | 1.59 | 0.12 |
| CVP 2nd 6hrs. | 6.15 | 1.18 | 6.45 | 1.54 | 0.69 | 0.49 |
| CVP 3rd 6hrs. | 5.8 | 1.96 | 5.95 | 2.65 | 0.2 | 0.83 |
| CVP 4th 6hrs. | 5.9 | 3.09 | 5.25 | 2.53 | 0.72 | 0.49 |
| CVP 2nd day | 6.75 | 2.86 | 5 | 3.39 | 1.76 | 0.08 |
| CVP 3rd day | 6.7 | 3.99 | 6.7 | 3.25 | 0 | 1 |

As regard statistical analysis of central venous pressure (CVP) pre bypass, post bypass 1st day every six hours then 2nd and 3rd day results show the following:

![Figure 13 Comparison between both groups as regards CVP](image-url)
As regard stastical analysis of inotropic support between the two groups results showed in the following table

**Table 13  Inotropic support of the two group**

<table>
<thead>
<tr>
<th>inotropic support</th>
<th>Group I</th>
<th>Group II</th>
<th>Test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenaline</td>
<td>Mean: 73, SD: 52.12</td>
<td>Mean: 70.5, SD: 54.13</td>
<td>0.14</td>
<td>0.88</td>
</tr>
</tbody>
</table>

There was no statistical difference between study and control group.
**Discussion**

The incidence of postoperative renal failure remains troublesome, and the pursuit of the optimal method of renal protection continues to be one of the top priorities in the management of patients undergoing open heart surgery.

Also, AKI after cardiac surgery is associated with adverse outcomes, such as prolonged intensive care and hospital stay, dialysis dependency and increased long-term mortality the pathogenesis of cardiac surgery-associated AKI is complex and multifactorial as mentioned in the first chapter.

These mechanisms of injury are likely to be active at different times with different intensities and may act synergistically. There is inadequate supply of randomized controlled trials for the prevention or treatment of cardiac surgery-associated AKI due to the lack of early predictive biomarkers.

Remote IPC protocols by repetitive short periods of cycles of IR may ameliorated the biochemical effects of IRI and biochemical changes with CPB, this may take place by inhibiting the IRI inflammatory effects, oxidative stress, proliferation of cells and apoptosis.144

Despite animal studies to date have demonstrated protective effect of RIPC against ischemia/reperfusion injury to the myocardium of animals and humans, a small number of studies investigates the potential of RIPC to protect the kidney.
Discussions

This current study conducted on 40 Patients scheduled for adult patient scheduled for open heart surgery on cardiopulmonary bypass using the previously described protocol of RIPC try to introduce RIPC as renoprotective against post CPB acute kidney injury.

The results were non-significant the as regarding serum NGAL serum NGAL level measured 2 hours post bypass of group I was (220.05±106.25 ng/ml) in and of group II was (187.8±75.65 ng/ml). Unpaired student t-test was used to analyze the difference and showed that t=1.1 and p-value=0.21 which was statistically non-significant.

Also results of serum creatinine and EGFR as conventional method for AKI assessment was statistically non-significant between the control and study group as mention in the previous chapter of results.

Clinical Evidence in addition to experimental evidence obtained from study on animal model show controversy about the effect of IPC on renal outcome while fewer research is going to study the effect of RIPC on renal outcome. This studies have different methodology, outcomes, aim and even molecular basis and explanations.

In our discussion we will illustrate what is going with our study and what is against.

Study went with our study by Walsh et al. in (2009) done on endovascular aneurysm repair. Lower limb ischemia was used as the RIPC stimulus, after 10 min, the cuff was deflated, and the procedure was repeated on the other leg. Outcome as predictor of renal insult was reduction in urinary albumin/ creatinine ratio and urinary retinol binding
protein. No differences in the rates of renal impairment between the study and control group. 145

Walsh et al. again in (2010) underwent another study on adult patient underwent elective open abdominal aortic aneurysm repair, the right common iliac clamping for 10 min after 10 min, the right iliac territory was reperfused and the clamp applied to the left common iliac artery for 10 min, no statistically significant differences in renal outcome indices (median urinary retinol binding protein, albumin/creatinine ratios, serum creatinine, or GFR values). 146

162 patient underwent elective cardiac surgery CABG was investigated by Rahman et al in (2010). Protocol of RIPC used three cycles of five min of upper-limb ischemia by cuff inflation to 200 mmHg separated by 5-min periods of cuff deflation. No significant differences in renal outcome indices (rates of dialysis, peak creatinine, and urinary albumin/creatinine ratio). 147

Cho et al. in 2011 investigated 120 patients underwent elective complex valvular heart surgery with RIPC consisted of 3 cycles of 10-min of lower limb ischemia and reperfusion by using an automated cuff inflator, no significant differences in serum levels of renal injury biomarkers or incidence of AKI between the study and control group. 148

Pedersen et al in 2012 also had investigated 113 children underwent surgery for complex congenital heart disease, intermittent leg ischemia through four cycles of 5-min BP cuff inflation to 40 mmHg above the systolic pressure and 5-min deflation. No statistically significant
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Differences in AKI incidence and levels of the renal biomarkers between the study and control group.  

Despite Huang et al. study in (2013) done on patient underwent laparoscopic partial nephrectomy and the RIPC consisted of three 5-min cycles of right lower limb ischemia and 5 min of reperfusion during each cycle RIPC decreased the rate of GFR reduction at 1 month compared with the control group but after 6 months no differences in the GFR reduction.  

Meta-analysis by Li, Lan et al showed that RIPC has no beneficial effect on the postoperative incidence of AKI, renal biomarkers, hemodialysis requirement, mortality, or hospital and ICU stays during cardiovascular interventions this meta-analysis and all above human studies go with our study.  

Although the majority of studies to date have demonstrated protection by IPC against ischemia/reperfusion injury to the myocardium of animals and humans, a small number of studies have investigated the potential of IPC to protect the kidney in animal models, the direct IPC application was associated with promising reno protection but RIPC has conflicting results.  

Kierulf-Lassen et al in 2015 studied on rats after 37 minutes of unilateral ischemia (direct IPC) of the kidney was associated at the molecular level with the up-regulation of established cytoprotective HSP levels but also persistent inflammatory and pro-fibrotic activities, also continuous ERK1/2 and Akt activation as well as increased iNOS expression may be involved in the repair process after IRI, but no
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protective effects were observed in response to RIPC which was elucidated by applying RIPC on the contralateral kidney between the study and control group.\textsuperscript{124}

Jiang et al in 2014 have demonstrated that the protective effects of RIC in limiting IRI in the rat kidney, but both KIM-1 and NGAL mRNA expression increased in response to IRI at day 7 reflecting damage to both proximal and distal tubules, and RIPC did not change these levels. Overall, the functional measurements and tissue damage markers suggest that RIPC did not provide a protective effect against IRI at days 3 and day 7.\textsuperscript{144}

Conflicting results of Ali et al in 2007 study which done on 82 patient underwent elective open abdominal aortic aneurysm repair two cycles of intermittent cross-clamping of the common iliac artery with 10-min ischemia and 10-min reperfusion showed that RIPC reduced the incidence of renal impairment between study and control group. This study used creatinine as end point of renal insults but the study was done on patient underwent elective open abdominal aortic aneurysm repair.\textsuperscript{152}

Zimmermann et al. in 2011 investigated 120 patient underwent elective cardiac surgery (CABG) with RIPC by applying thigh tourniquet for 5-min intervals to induce ischemia separated by 5-min intervals of reperfusion RIPC this cycle repeated 3 times. Decreased the rate of AKI in the study group when compared with the control group and this was against our study.\textsuperscript{153}

Also against our result the study done by Venugopal et al. in 2010 when 78 patient underwent elective cardiac surgery (CABG) in non-
discussions

Diabetic patients 3 cycles each 5-min of right forearm ischemia, induced by inflating a BP cuff to 200 mmHg, after 5 min of reperfusion RIPC decreased the incidence of AKI (AKI stages 1, 2, and 3 in RIPC group were 3%, 8%, and 0% compared with 25%, 0%, and 0% in control group, respectively (P=0.01).¹⁵⁴

While study done on animals has conflicting results when Wever et al in 2011 reported renoprotective effects of brief hind limb occlusion in rats, 61 Rats underwent either unilateral or bilateral RIPC, after 24 hours of reperfusion, renal function was improved in both the bilateral RIPC group and in the fractionated unilateral group, although bilateral RIPC was more effective than unilateral RIPC. Also the study report that treatment with the adenosine receptor blocker 8-(p-sulfophenyl) theophylline had no effect on fractionated or continuous RIPC but this study has different methodology and timing.¹⁵⁵

Also against our study song et al. in 2011, who investigated the effect of small intestinal RIPC on renal function in rats, 60 renal ischemic injury was induced by a 45-minute renal artery occlusion and reperfusion for 2 or 24 hours in rats with a previous contralateral nephrectomy, and RIPC was induced by three cycles of 8-minute ischemia and 5-minute reperfusion of the small intestine. Indeed, pretreatment with intestinal IPC significantly alleviated renal ischemic impairment.¹⁵⁶

A systematic review and meta-analysis on animals doesn’t go with our study as it indicates that IPC has an overall protective effect on the kidney, since it reduces serum creatinine, blood urea nitrogen (BUN) and renal damage in the study group when compared with control group as
assessed by histology after IRI, they found that IPC is more effective in reducing serum creatinine when the IPC stimulus is applied >24 h before index ischemia (late window of protection), a trend which was also observed for BUN and renal histology data.\textsuperscript{157}

Furthermore, serum creatinine and BUN data showed an effect of animal species on IPC efficacy: IPC was more effective when performed in mice vs. rats. They mentioned that no significant differences were observed for the variables site of preconditioning (local, remote or both) or IPC protocol (continuous vs. fractionated) but review indicates that their current clinical trials on RIPC may not be optimally designed, and further optimization may be necessary for successful translation to the clinical setting.\textsuperscript{157, 158}
Conclusion

This current study demonstrates that RIPC in patients underwent open heart surgery didn’t improve the renal outcome either through measured serum NGAL level nor the usual measurements as creatinine level and EGFR.

The future clinical studies should be designed to develop optimal RIPC procedures in accordance with operation type and elucidate the molecular mechanisms of RIPC.

Being more specifically research should study the under laying physiological mechanism behind this mechanism and trying different protocols of RIPC.
Summary

Renal impairment is crucial after cardiac surgery done on CPB. Unfortunately, AKI remains very high in such patients with poor outcomes. It is therefore necessary to find novel approaches to improve renal outcomes after cardiac surgery patients in order to simultaneously increase success rates and decrease complications and mortality.

Even with optimization of hemodynamics and oxygenation renal injury occur AKI still occur, a phenomenon known as ischemia reperfusion injury and CPB associated SIRS, which is incriminated to be responsible for AKI. This has prompted a search for cytoprotective mechanisms that make the renal less vulnerable to such damage.

Inducing non-lethal and brief ischemia before the period of prolonged ischemia has been considered as a tool for increasing the heart’s resistance to ischemia-reperfusion (I/R) injury.

Subsequently, preconditioning the heart with ischemia was shown to maintain its cardio-protective abilities even if the non-lethal ischemic stimulus was applied not directly to the targeted tissue, but to any distant site of the organism – hence the idea of remote ischemic preconditioning (RIPC).

The implication of the idea (RIPC) on the kidney started by applying ischemic preconditioning on the kidney directly on aortic surgery and on animals.
Summary

A significant amount of data, however, now exists in a number of organs to suggest that there may be intrinsic mechanisms brought to bear by organs exposed to toxic or ischemic insults, which protect them against a subsequent exposure to ischemia.

The aim of this study was to determine if RIPC could induce renal protection and improve post-operative renal outcome and reduce incidence of AKI. And whether renal biomarker NGAL can predict early occurrence of AKI rather than the usual methods.

So we started this prospective, randomized, controlled, double blind and clinical study and conduct it on 40 patients ASA II and III, age ranged between 18 and 60 underwent open heart surgery. These patients were randomly allocated by using randomization program at the website (www.randomizer.org) into two equal groups:

- **Group I** (Study group): consisted of 20 patient underwent remote ischemic preconditioning.
- **Group II** (control group): consisted of 20 patient didn’t underwent remote ischemic preconditioning.

Patients with airway and/or parenchymal lung disease, pulmonary hypertension more than 100 mmHg, Immunodeficiency, hematological disorders, hepatic or renal impairment, pregnancy, morbid obesity, diabetic, patients with myocardial ischemia or infarction, patients with peripheral vascular disease and patients receiving drugs that interfere with the mechanism of RIPC i.e. sulfonylureas, nicorandil or propofol were excluded of the study.
In the operative room same anaesthetic technique was used. The main outcome of our study was serum NGAL and it was measured before operation (baseline) and 2 hours post cardiopulmonary bypass, the secondary outcome measurements include age, sex, weight, height, ASA status, operative time, creatinine level, EGFR, cross clamping duration, cardiopulmonary bypass time, ventilation time, MAPB, CVP, ICU stay time and inotropic support.

The results were non-significant between the two groups as regarding serum NGAL, serum creatinine, EGFR, operative time, cross clamping duration and cardiopulmonary bypass time and hemodynamic parameters, duration of ICU stay and inotropic support.

In conclusion RIPC has no renoprotective effect in patient underwent open heart surgery with CPB however further studies are needed as recent study and other done study are conflicting in its results.
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إصابة الكلى الحاد تحدث في ما يصل إلى 40% من المرضى بعد جراحة القلب ويتطلب غسيل الكلى في 1% من الحالات. ويرتبط إصابة الكلى الحاد مع زيادة خطر الوفيات. وهي تحدث نتيجة تفاعل آليات الفيزيولوجية المرضية المختلفة، مع عوامل ذات صلة بالمريض وأسباب تتعلق بماكينة القلب الصناعي.

حتى بعد التعديل على ظروف المريض المرضية ومضاعفات الجراحية، فإن إصابة الكلى التي تتطلب الغسيل الكلوي يزيد من خطر الوفاة بنسبة 8 مرات في هذه الفئة من المرضى. ويعتبر الخلل الذي يصيب المسارات المختلفة في العمليات البيولوجية بما في ذلك تراكم السموم الخارجية والداخلية، واضطراب العمليات الهرمونية العصبية، نتيجة حالة الأنتهاكات المصاحبة للجراحة تسمى في تدهور وظائف الكلى.

وقد اقترحت معايير التصنيف الجديدة مؤخرا بسبب التباين الواضح في تعريفات تدهور وظائف الكلى. الكلى اهمها معيار ريفيل (RIFLE) ومعيار أكين (AKIN).

تعتبر عملية تهيئة الأنسجة لتحمل نقص الأكسجين ArrayList وقائيات تؤدي إلى تقليل ملوثات في المشاكل التي تصيب جسم الإنسان بعد عملية التروية، وبالرغم من أن عملية تهيئة العضو لتحمل نقص الأكسجين يتم عن طريق تطبيقه لنقص التروية غير المميت في النيج المستهدف.

على الرغم من أن الكليتين لا يتعرض مباشرة لإصابة نقص التروية، إلا أنه قد وجد انها تقلل من اضطراب الكلى ما بعد الجرحية وتعتبر الآليات الكامنة وراء تهيئة الأنسجة لتحمل نقص الأكسجين عن بعد معقدة جدا وغير محددة حتى الآن بشكل كامل.

وأفادت العديد من الدراسات صلاحية المؤشرات الحيوية مثل البولية والنيتروجين في الدم والكرياتينين في مصل الدم، كشفة الكرياتينين، وزيادة في إفراز البروتين من البروتينات المختلفة لتشخيص الإصابة الكلوية. ومع ذلك، فإن الوقت اللازم لهذه العلامات في الارتفاع بشكل ملحوظ طويلا جدا.

وحدثاً وجد أن نسبة المؤشر البيولوجي نيجال NGAL يرتفع في الدم قبل كل المؤشرات الحيوية الأخرى مما يساعد على تقييم فاعلية نقص التروية سريعاً.
سيتم الموافقة على بروتوكول الدراسة من قبل اللجنة الأخلاقية المؤسسية من المستشفيات الجامعية بينها وسيتم الحصول على موافقة خطية من كل مريض عده.

سيتم تقسيم المرضى إلى مجموعتين سيتم توزيعهم عشوائياً.

المجموعة الأولى: تتكون من 20 مريض ستتلقى تهيئة الأنسجة لنقص الأكسجين عن بعد.

المجموعة الثانية: تتكون من 20 مريض لن تتلقى تهيئة الأنسجة لنقص الأكسجين عن بعد.

وسيتم قياس نسبة نيجال (NGAL) في الدم لكل المجموعتين لقياس مدى فاعليته في قياس كفاءة تهيئة الأنسجة لنقص الأكسجين.

وسيتم قياس نسبة نجاح (NGAL) في الدم لكل المجموعتين لقياس مدى فاعليته في قياس كفاءة تهيئة الأنسجة لنقص الأكسجين عن بعد في تقليل نسبة خلل وظائف الكلى مابعد جراحات القلب المفتوح.
مدى فاعلية تهيئة أنسجة الجسم لنقص الدم والاكسجين عن بعد في الوقاية من أصابات الكلى الحادة بعد عمليات القلب المفتوح.

رسالة
مقدمه للحصول على درجة الدكتوراه في التخدير والعناية المركزة

مقدمة بواسطة

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