# COMPARISON OF RENAL FUNCTION IN ANEMIC AND NON-ANEMIC PATIENTS UNDERGOING CARDIOPULMONARY BYPASS

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## Abstract

***Background:*** Cardio Pulmonary Bypass (CPB) utilizes hemodilution, but in anemic patients, it results in further reduction in Hemoglobin (Hb) concentration, which causes a decrease in oxygen-carrying capacity, which leads to renal hypoxia and leading to renal injury.

***Methods:*** Sixty consecutive patients aged 18-60 years with normal preoperative renal function undergoing CPB were included. Pre and postoperative outcome measures were documented.

***Results:*** A total of 60 patients were included in the study. Out of which, 25 were anemic, and 35 were non-anemic. The anemia group had a statistically significant increase in both urea and serum creatinine levels ($p<0.05$ respectively) after CPB, but the non-anemia group had only a statistically significant increase in urea ($p<0.05$), but the serum creatinine increase was not significant ($p=0.343$). Renal injury was equal in both groups.

***Conclusions:*** Renal injury is equal between non-anemic and anemic groups; it implies that preoperative borderline anemia alone is not the only independent predictor of renal injury

***Keywords:*** *Anemia, Cardiopulmonary bypass, Acute renal injury*

**Introduction:** Cardiopulmonary bypass (CPB) is a technique that temporarily supports or mimics the function of the heart and lungs during various cardiothoracic surgical procedures. CPB is used in coronary artery bypass surgery, cardiac valve surgery, thoracic aorta surgery, and thoracic organ transplantation. This technique requires the cannulation of large veins to drain deoxygenated blood into the bypass machine (heart-lung machine or pump-oxygenator), which then returns oxygenated blood to circulation via an arterial duct. Cardiopulmonary bypass provides a stable and relatively bloodless surgical field while maintaining adequate tissue perfusion (1).

The assumption that renal injury from CPB is multifactorial. CPB is known to result in altered intrarenal blood pressures, release of systemic inflammatory mediators, formation of microemboli and hemolysis of RBC all of which may contribute to multiorgan dysfunction that can be manifested as myocardial dysfunction, renal dysfunction and respiratory dysfunction (2).

The incidence of CPB-AKI ranges between 15-30%, depending on the complexity of the procedure (3). Defining AKI is quite complex ranging from 25% increase in baseline serum creatinine (serum Cr) to the need for hemodialysis (4). An integral multidisciplinary strategy (KDIGO cardiac surgery) has been adopted as a tool with high sensitivity and good prognostic value to classify postoperative AKI after cardiac surgery (5). KDIGO defines AKI as serum creatinine increase by 0.3 mg/dl in 48 h or rises to at least 1.5-fold from baseline within 7 days. Stages of AKI can be determined based on the changes in serum creatinine or urine output (6). CPB is a common risk factor for acute kidney injury postoperative and is associated with increase in a significant increase in infectious complications, an increase in length of hospital stay and a greater mortality rate when compared to patients without AKI-CBP (4). This occurs because the mean arterial pressure (MAP) is kept low (50–70 mm Hg) during CPB, the kidney is unable to auto regulate its perfusion or maintain renal blood flow (RBF) (7). CPB utilizes hemodilution, which leads to decreased vascular resistance while reducing the oxygen carrying capacity. Reduced perfusion leads to renal hypoxia, a condition where the outer renal medulla is particularly vulnerable to reduced oxygen delivery without a reduced oxygen demand (8). The mechanism of postoperative renal injury in patients with normal preoperative renal function with CPB is due to hypo perfusion, loss of pulsatile perfusion, development of systemic inflammatory response syndrome and inappropriate hemodilution, leading to prerenal injury (9).

According to the World Health Organization (WHO), anemia is defined as hemoglobin (Hb) levels <12.0 g/dL in women and <13.0 g/dL in men and can vary based on ethnicity and altered physiological status (10). The risk of anemia in cardiac surgery patients could be due to CPB associated hemodilution, therapeutic phlebotomy and surgical blood loss (11). Common causes for preoperative anemia in cardiac surgery patients are hospital-acquired anemia, iron deficiency anemia, and anemia due to chronic disease this could be associated with higher morbidity and mortality rates, prolonged intensive care unit (ICU) and hospital stays and lead to increased health care costs (12). Therefore hospital and ICU stay length was evaluated as a secondary factor to understand the type and severity of morbidity in anemia and non-anemia group after surgery.

**Material and Method:**

**Study Design:** The study is a prospective observational study that was performed in the department of cardiovascular, thoracic surgery, at the Kasturba Medical College, Manipal, Karnataka, India. The study protocol was approved by the institutional review board at the KMC, Manipal; patients who underwent CBP during the study period were included and grouped based on their preoperative Hb levels. Patients were excluded if they had acute or chronic kidney disease, had to undergo emergency surgery, or were less than 18 y of age. Study included 60 participants and were divided into 2 groups. The first group included patients who had preoperative Hb level <12gm/dL and <13gm/dL for women and men respectively as anemic and second group included patients with preoperative Hb level >12gm/dL and >13gm/dL for women and men respectively as non-anemic.

**Sample Size Calculation**

Sample size evaluation was conducted for different groups for ANOVA test and was calculated using the following formula.

$$n = \frac{2\,((Z_{1-\alpha}/2 + Z_{1-\beta})^2)\,\sigma^2\,[1+(m-1)\,\rho]}{md^2}$$

$Z_{1-\alpha}/2$ = 1.96 (for 5% Level of significance)

$Z_{1-\beta}$ = 0.84 (80% power)

d = 0.4 (Clinically significant difference from pre and post)

σ = 1 (Standard Deviation)

m = 2 (Number of measurements)

ρ = 0.3 (Intra class correlation coefficient)

Hence the calculated sample size is N=32 in each group

Sample size: 25 in anemic and 35 in non-anemic

**Parameter Observed**

Study include total 60 cases who underwent CPB surgery. The mean age group of our study is 47.34±11.24 years and 47.88±10.56 years in non-anemic and anemic group respectively. Occurrence and frequency of AKI was determined from pre and post serum creatinine and urea levels. The mean pre serum creatinine levels were 0.89±0.13mg/dL and 0.90±0.18mg/dL and the mean pre serum urea level were 25.94±9.51mg/dL and 25.56±9.19mg/dL in non-anemic and anemic group respectively, which indicate creatinine and urea levels were in normal range and subjects did not show presence of kidney disorder before surgery. Multivariable regression was used to assess the association between preoperative Hb concentrations and a primary outcome of postoperative acute kidney injury (AKI) and secondary outcomes of ICU and hospital length of stay (LOS) following CPB supported surgery.

**Statistics:**

The data collected was analysed using the EZR (32 bit) version 1.37 software for statistical significance. Continuous data are expressed as mean ± SD and categorical data are presented as number (percentage). Independent t-test is performed to evaluate the comparison between anemic and non-anemic groups. Paired t test was performed to compare pre and post renal parameters. A p value of $<0.05$ was considered as statistically significant.

**Study definitions:**

World Health Organization (WHO) defines anemia as hemoglobin (Hb) levels of 12.0 g/dL in women and 13.0 g/dL in men. AKI is defined by the RIFLE criteria using the maximal change in serum Cr during the first seven perioperative care days compared with baseline values before surgery. This was analysed using the peak perioperative creatinine level within 48 h of surgery. CPB was defined as mechanical circulatory support used with central or peripheral cannulation during transplantation. Postoperative acute renal failure (ARF) was defined by a need for renal replacement therapy at least once perioperative.

**Results:**

Among the subjects undergoing surgery with CPB during the study period, 60 met our inclusion criteria and were included in the study. These patients were grouped based on their preoperative Hb as anemic and non-anemic. According to WHO guidelines patients with Hb levels <12gm/dL and <13gm/dL for women and men respectively were anemic (41.6%) and patients with Hb level >12gm/dL and >13gm/dL for women and men respectively were non-anemic (58.3%).

**Table 1: Clinical parameter comparison between anemia and non-anemia groups**

| | | **Non – Anemia** | **Anemia** | |
|---|---|---|---|---|
| | | **N=35** | **N=25** | |
| **Parameters** | **Group** | **Frequency(Percent)** | **Frequency(Percent)** | **P value** |
| **Gender** | Female | 16 (45.7) | 11 (44) | 1.000 |
| | Male | 19 (54.3) | 14 (56) | |
| **HTN** | No | 28 (80) | 20 (80) | 1.000 |
| | Yes | 7 (20) | 5 (20) | |
| **DM** | No | 32 (91.4) | 22 (88) | 0.686 |
| | Yes | 3 (8.6) | 3 (12) | |
| **Parameters** | | **Mean ± SD** | **Mean ± SD** | **P value** |
| **Age** | | 47.34 ± 11.24 | 47.88 ± 10.56 | 0.852 |

Demographic details (Gender and age) and presence of any comorbid conditions were obtained from individual patient before they underwent surgery. Among the total study population females were 27 (45%) and 33 (55%) were males with a mean age of 47.34 ± 11.24 in non-anemia and 47.88 ± 10.56 in anemia group. Hypertension and Diabetes mellitus were found to be less common comorbidity presenting only in 20% and 10% of the total population respectively.

**Table 2: Surgical Procedures in anemia and non-anemia groups**

| Sl. no | Surgical Procedures | Anemic n=25 | Non anemic n=35 |
|---|---|---|---|
| 1 | Aortic valve replacement (AVR) | 4 (16%) | 8 (22.85%) |
| 2 | Mitral valve replacement (MVR) | 5 (20%) | 7 (20%) |
| 3 | Double valve replacement (DVR) | 3 (12%) | 7 (20%) |
| 4 | Aortic valve replacement + Coronary artery bypass grafting | 3 (12%) | 3 (8.57%) |
| 5 | Mitral valve replacement + Tricuspid valve repair | 2 (8%) | 2 (5.71%) |
| 6 | Mitral valve repair | 5 (20%) | 2 (5.71%) |
| 7 | Bentall | 1 (4%) | - |
| 8 | Aortic valve replacement + Right lung lobectomy | 1 (4%) | - |
| 9 | Pulmonary thromboembolectomy+ Tricuspid valve repair | 1 (4%) | - |
| 10 | Mitral valve repair+ Tricuspid valve repair+ Atrial septal defect closure | - | 1 (2.85%) |
| 11 | Atrial septal defect closure | - | 2 (5.71%) |
| 12 | Aortic valve replacement + Ventricular septal defect closure | - | 1 (2.85%) |
| 13 | Pericardial window drainage + Mitral valve replacement | - | 1 (2.85%) |
| 14 | Coronary artery bypass grafting + Left ventricular clot removal + pulmonary endarterectomy | - | 1 (2.85%) |

Most of the patients underwent CPB supported cardiac surgery like AVR (20%) and MVR (20%) followed by DVR (16.4%) of the total population. CPB supported pulmonary surgery were infrequent < 2% of the total population. Among anemic group MVR or repair surgery were performed more. Among non-anemic group AVR, MVR and DVR were performed more in comparisons with anemia group. Type of surgery may have an independent association with urgency and need for perioperative RRT.

**Table 3: Outcome parameter comparison between anemia and non-anemia groups**

| | **Non - Anemia** | **Anemia** | |
|---|---|---|---|
| | **N=35** | **N=25** | |
| **Parameters** | **Mean ± SD** | **Mean ± SD** | **P value** |
| **Pre Creatinine** | 0.89 ± 0.13 | 0.90 ± 0.18 | 0.815 |
| **Post Creatinine** | 0.93 ± 0.23 | 1.03 ± 0.30 | 0.143 |
| **Pre Urea** | 25.94 ± 9.51 | 25.56 ± 9.19 | 0.877 |
| **Post Urea** | 30.94 ± 9.42 | 32.08 ± 9.19 | 0.643 |

Comparable increase in post creatinine and urea levels were observed in anemia and non-anemia groups. Preoperative Hb wasn't much of a crucial factor in determining frequency and degree of kidney injury during perioperative care since both groups showed similar variations.

**Table 4: Comparison of Pre & Post parameters in Anemia group**

| **Pre & Post Primary Parameters Of Anemia group** | | |
|---|---|---|
| **Parameters** (n=25) | **Mean ± SD** | **P value** |
| **Pre Creatinine** | 0.90 ± 0.18 | **0.013** |
| **Post Creatinine** | 1.03 ± 0.30 | |
| **Pre Urea** | 25.56 ± 9.19 | **<0.001** |

| | | |
|---|---|---|
| **Post Urea** | 32.08 ± 9.19 | |

Anemia group being a vulnerable group for perioperative AKI should be closely monitored for any fluctuations in serum creatinine and urea levels. A significant increase in serum urea ($p<0.001$) and serum creatinine (p 0.013) was observed. These altered levels did not show any significant clinical effects (p= 0.343).

**Table 5: Comparison of Pre & Post parameters in Non- Anemia group**

| **Pre & Post Primary Parameters Of Non Anemia group** | | |
|---|---|---|
| **Parameters (n=35)** | **Mean ± SD** | **P value** |
| **Pre Creatinine** | 0.89 ± 0.13 | 0.343 |
| **Post Creatinine** | 0.93 ± 0.23 | |
| **Pre Urea** | 25.94 ± 9.51 | **0.0113** |
| **Post Urea** | 30.94 ± 9.42 | |

Insignificant increase in post Creatinine levels was seen in non-anemia group (p 0.343) when compared to anemia group (p 0.013). Statistically significant increase in post urea levels were seen in non-anemia group (p 0.0113). Elevated serum urea indicated presence of renal injury or disease.

**Table 6: Secondary Outcome parameter comparison between anemia and non-anemia groups**

| | **Non - Anemia** | **Anemia** | |
|---|---|---|---|
| | **N=35** | **N=25** | |
| **Parameters** | **Mean ± SD** | **Mean ± SD** | **P value** |
| **Hospital Stay** | 5.63 ± 1.59 | 6.76 ± 2.17 | **0.023** |
| **ICU Stay** | 1.09 ± 0.28 | 1.44 ± 0.71 | **0.010** |

Hospital and ICU lengths of stay provide clear and continuous data on severity of morbidity and can be accounted as an alternative to data complication. Perioperative care resource utilization increases on longer stay which in turn increases the heath care cost. Length of stay was increased in anemia group when compared to non-anemia group and may varied since postoperative complication care was crucial for anemic group.

**Discussion:**

In the current study, we evaluated the effects of CPB on renal perfusion, filtration, and excretion in patients undergoing surgery to compare renal injury in anemic and non-anemic groups. In the present study total number of 60 subjects with mean age of 47.56±10.87 years were enrolled based on inclusion and exclusion criteria. Among these participants 25 were grouped as anemic and 35 as non-anemic based on their preoperative Hb levels. Both groups were compared based on their demographic details, BP and glucose levels (Table 1) and type of surgery undergone (Table 2).

Pre and post serum creatinine and urea levels were examined to analyse the degree of renal injury after the CPB supported surgery. In a recent retrospective study conducted by Fu et al; (13) he recognized that a small change in the preoperative creatinine and low CPB target temperature level may not alter the CKD stage but does suggest significant odds of developing severe postoperative prerenal AKI after cardiac surgery. Our study revealed equal amount of injury in both groups and it was not statistically significant (Table 3). Anemic group showed statistically significant increase in serum creatinine and urea ($p<0.05$ respectively) after CBP where as non-anemic group showed only significant increase in urea ($p<0.05$) (Table 5) which indicated presence of kidney injury or disease. According to LucaDe Santo et al; (11) and Robert Sickeler et al; (5) preoperative anemia was considered as an independent predictor for highly prevalent feature that independently predicted AKI. Our study results differed since degree of kidney injury were similar in case of anemic and non-anemic groups.

CPB associated acute renal failure is one of the major risk factors for mortality as explained by an observational study conducted by Christina. M et al; postoperative mortality of 19% and 63% of renal dysfunction patients without the need for dialysis and patients undergoing dialysis respectively in study of 2222 CABG participants (14). Conflicting results were seen in our study where renal parameters were analysed independently which showed only significant increase in post parameters when compared to baseline (Table 4-5). Even though there was statistically significant rise in post serum creatinine levels no significant clinical effects were observed (p=0.343).

A study conducted by Navis et al; (15) found a significant decline in renal function with a fall in GFR of 33±4% below baseline after 12 months and 42±9% after 30 months which was found to be slightly larger in patients undergone CPB supported liver transplant were associated with significantly more rates of AKI (61.44% versus 36.5.3%, P < 0.01), postoperative ARF, and increased 30-day mortality (16) than heart transplant (15). Another study by Raul et al; (2) reported the differences in risk factors according to the degree of preoperative renal function which was a predictor of AKI seen in CKD stages 3-4 patients (Serum Cr < 60 mL/min/1.73 m2 BSA).

Few studies have estimated that up to 30% of cardiac surgery patients develop clinically relevant kidney injury and may require to necessitate dialysis or consider renal replacement therapy (RRT) (17). Preventive measures like volume and electrolyte balance and acid–base balance should be taken to avoid mortality (18) which directly attributes to severe ARF (approximately 1% to 2% of patients) and confers an approx. 8 times increase in the odds of mortality in the ICU (19) even when adjusted for comorbidity during perioperative care. In our study hospital and ICU stay were prolonged in anemic patients when compared to non-anemic which indicates higher level of morbidity in anemic groups (Table 6).

One-third of patients undergoing cardiac surgery are prone to preoperative anemia and is associated with increased mortality and morbidity. Presence of preoperative anemia gives an indicator for the need of homogenous blood transfusion (red blood cells, platelets, fresh frozen plasma, or cryoprecipitate) before surgery to avoid postoperative complications and decrease morbidity and mortality rate (19,20). Currently, there are not many optimal approaches to prevent prerenal AKI in vulnerable patient group. Few strategies to increase oxygen delivery by increasing renal perfusion can be achieved by increasing CPB flow and/or MAP (21). Alternative strategies like temperature reduction (cooling) or reducing the reabsorption of filtered solute with diuretics or natriuretic peptides to reduce oxygen demand can be considered (22).

**Limitations:**

- Unequal gender distribution is the major limitation in our study due to constricted time limit.
- Unequal number of subjects in both the groups, since it is a time bound study.

**Conclusion:**

Despite more widespread applications of percutaneous coronary and valvular interventions, the need for using CPB despite their perioperative complications remains the standard approach for certain cardiac and pulmonary surgery because some patients are not eligible for percutaneous procedures or may not be tolerated in some (14). Selective utilization of CPB in an emergency of bleeding maybe resuscitative and is most effective when applied in a well planned and executed manner (23) (24).

**Reference:**

1. El-Sherief AH, Wu CC, Schoenhagen P, Little BP, Cheng A, Abbara S, et al. Basics of Cardiopulmonary Bypass: Normal and Abnormal Postoperative CT Appearances. RadioGraphics. 2013 Jan;33(1):63–72.
2. Lombardi R, Ferreiro A. Risk Factors Profile for Acute Kidney Injury after Cardiac Surgery Is Different According to the Level of Baseline Renal Function. Ren Fail. 2008 Jan;30(2):155–60.
3. Englberger L, Suri RM, Li Z, Casey ET, Daly RC, Dearani JA, et al. Clinical accuracy of RIFLE and Acute Kidney Injury Network (AKIN) criteria for acute kidney injury in patients undergoing cardiac surgery. Crit Care Lond Engl. 2011;15(1):R16.
4. Kumar AB, Suneja M. Cardiopulmonary bypass-associated acute kidney injury. Anesthesiology. 2011 Apr;114(4):964–70.
5. Sickeler R, Phillips-Bute B, Kertai MD, Schroder J, Mathew JP, Swaminathan M, et al. The risk of acute kidney injury with co-occurrence of anemia and hypotension during cardiopulmonary bypass relative to anemia alone. Ann Thorac Surg. 2014 Mar;97(3):865–71.
6. Ostermann M, Joannidis M. Acute kidney injury 2016: diagnosis and diagnostic workup. Crit Care Lond Engl. 2016 Sep 27;20(1):299.

7. Lannemyr L, Bragadottir G, Krumbholz V, Redfors B, Sellgren J, Ricksten S-E. Effects of Cardiopulmonary Bypass on Renal Perfusion, Filtration, and Oxygenation in Patients Undergoing Cardiac Surgery. Anesthesiology. 2017 Feb 1;126(2):205–13.
8. Ranucci M, Romitti F, Isgrò G, Cotza M, Brozzi S, Boncilli A, et al. Oxygen delivery during cardiopulmonary bypass and acute renal failure after coronary operations. Ann Thorac Surg. 2005 Dec;80(6):2213–20.
9. Richard F Davis, Glenn P. Cardiopulmonary bypass and mechanical support: Principles and practice. 4th ed. 369–381 p.
10. Cappellini MD, Motta I. Anemia in Clinical Practice-Definition and Classification: Does Hemoglobin Change With Aging? Semin Hematol. 2015 Oct;52(4):261–9.
11. De Santo L, Romano G, Della Corte A, de Simone V, Grimaldi F, Cotrufo M, et al. Preoperative anemia in patients undergoing coronary artery bypass grafting predicts acute kidney injury. J Thorac Cardiovasc Surg. 2009 Oct;138(4):965–70.
12. Nguyen Q, Meng E, Berube J, Bergstrom R, Lam W. Preoperative anemia and transfusion in cardiac surgery: a single-centre retrospective study. J Cardiothorac Surg. 2021 Dec;16(1):109.
13. Fu H-Y, Chou N-K, Chen Y-S, Yu H-Y. Risk factor for acute kidney injury in patients with chronic kidney disease receiving valve surgery with cardiopulmonary bypass. Asian J Surg. 2021 Jan;44(1):229–34.
14. Esper SA, Subramaniam K, Tanaka KA. Pathophysiology of Cardiopulmonary Bypass: Current Strategies for the Prevention and Treatment of Anemia, Coagulopathy, and Organ Dysfunction. Semin Cardiothorac Vasc Anesth. 2014 Jun;18(2):161–76.
15. Navis, Gerjan, Broekroelofs, Jan, Mannes, Gregor P.M. RENAL HEMODYNAMICS AFTER LUNG TRANSPLANTATION. Clin Transplant. 1996 Jun 15;61(11):1600–5.
16. Heid CA, Khoury MK, Maaraoui K, Liu C, Peltz M, Wait MA, et al. Acute Kidney Injury in Patients Undergoing Cardiopulmonary Bypass for Lung Transplantation. J Surg Res. 2020 Nov;255:332–8.
17. Rocha PN, Rocha AT, Palmer SM, Davis RD, Smith SR. Acute Renal Failure after Lung Transplantation: Incidence, Predictors and Impact on Perioperative Morbidity and Mortality. Am J Transplant. 2005 Jun;5(6):1469–76.
18. de Mendonça A, Vincent J-L, Suter PM, Moreno R, Dearden NM, Antonelli M, et al. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med. 2000 Jul 28;26(7):915–21.

19. Karkouti K, Wijeysundera DN, Yau TM, Callum JL, Cheng DC, Crowther M, et al. Acute Kidney Injury After Cardiac Surgery: Focus on Modifiable Risk Factors. Circulation. 2009 Feb 3;119(4):495–502.
20. Klein AA, Chau M, Yeates JA, Collier T, Evans C, Agarwal S, et al. Preoperative intravenous iron before cardiac surgery: a prospective multicentre feasibility study. Br J Anaesth. 2020 Mar;124(3):243–50.
21. Joles JA. Adjusting cardiopulmonary bypass flow or arterial pressure to maintain renal medullary oxygen. Kidney Int. 2019 Jun;95(6):1292–3.
22. Sgouralis I, Evans RG, Gardiner BS, Smith JA, Fry BC, Layton AT. Renal hemodynamics, function, and oxygenation during cardiac surgery performed on cardiopulmonary bypass: a modeling study. Physiol Rep. 2015 Jan;3(1):e12260.
23. Picone AL, Yendamuri S. Use of cardiopulmonary bypass in lung cancer surgery: focus on extended pulmonary resections for T4 non-small cell lung cancer. J Xiangya Med. 2018 Jun;3:24–24.
24. Muralidaran A, Detterbeck FC, Boffa DJ, Wang Z, Kim AW. Long-term survival after lung resection for non-small cell lung cancer with circulatory bypass: a systematic review. J Thorac Cardiovasc Surg. 2011 Nov;142(5):1137–42.