

# The Effect of Preoperative Creatinine Clearances on Postoperative Oxygenation in Coronary Artery Bypass Grafting: A Cohort Study

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Received: 14 Jan. 2018; Accepted: 19 Nov. 2018

**Abstract-** End-stage kidney disease has a high prevalence in patients undergone Coronary Artery Bypass Grafting (CABG) and could cause a wide spectrum of morbidities, due to deep water and electrolyte or acid-base impairments. The aim of this study was to assess the effect of low Creatinine Clearances (CICr) on arterial oxygenation defect, as common post-CABG morbidity. The study was conducted as a prospective cohort, the pure on pump CABG patients were grouped based on their preoperative CICr to groups A (CICr $\geq$ 60) and B (CICr $<$ 60). Postoperatively, the PaO<sub>2</sub>/FiO<sub>2</sub> values in 1 hour after ICU admission and 4 hours after extubation, intubation time duration, duration of ICU stay and high concentration oxygen demand were compared. Among 229 patients who remain in the study, 121 were in group A, and 108 in B group. Except for age, weight, height, BMI, and pump time, other demographic and independent variables were similar between two groups. The higher values of PaO<sub>2</sub>/FiO<sub>2</sub> and PaO<sub>2</sub>, 1 hour after ICU admission and 4 hours after extubation in group B, were not statistically significant, while SpO<sub>2</sub> value, 1 hour after ICU admission was higher in group B (98.19 $\pm$ 1.37) in compare with group A (97.78 $\pm$ 1.57) ( $P=0.040$ ). Intubation time duration (10.85 in A vs. 12.79 in B;  $P=0.306$ ), duration of ICU stay (39.04 in A vs. 43.09 in B;  $P=0.114$ ) and high concentration oxygen demand (2.5% in A vs. 3.8% in B;  $P=0.089$ ) were similar between groups of study. Lower Preoperative CICr values do not deteriorate post-CABG arterial oxygenation.

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*Acta Med Iran* 2018;56(12):750-756.

**Keywords:** CABG; Creatinine clearances; PaO<sub>2</sub>/FiO<sub>2</sub>; Oxygenation

## Introduction

Coronary Artery Bypass Grafting (CABG) is a common method in the management of coronary artery diseases, which mandates employment of board spectrum of resources and facilities. Usually, shortage of these facilities and resources works as a limiting factor to perform that (1). In this regard, CABG complications could seriously affect the clinical course of the disease, and the level of essential postoperative medical care, hospital length of stay, and resources wasting.

Post-CABG respiratory complications, ranging from a benign, subclinical situation in the majority of cases to an Acute Respiratory Distress Syndrome (ARDS) in 2%

of patients, are one of most important early complications of CABG (2-4). ARDS is lethal even in up to 50% of cases and will affect overall hospital length of stay and recovery time, and wasting resources (5). Its frequency and consequences remain unchanged, despite recent great advances in medical care technology (6). Arterial oxygenation is regarded as a major diagnostic criterion for ARDS, as well as an indicator for monitor success of treatment.

In other hand Chronic Kidney Diseases (CKD) is a known risk factor for the development of cardiovascular diseases (CVD) especially, Ischemic Heart Diseases (IHD) (7), as the Coronary Artery Diseases (CAD) is 20 times more common among End Stage Renal Disease

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(ESRD) patients than overall community (8-10) and simultaneous incidence of CVD and CKD could lead to higher mortality and worse prognosis (7), as the highest mortality rate in CVD patients occurs in those who have simultaneous ESRD (11-13). The previous studies confirmed that renal dysfunction could deteriorate the results of Percutaneous Coronary Interventions (PCI) and CABG in different ways (14,15).

Activation of active phase reactants during CABG surgery (16-18) could hasten the renal function and progress to Acute Kidney Injury (AKI), which is more common in CKD patients and could predispose patients to increased risk of morbidity and mortality, too (19). High mortality and morbidity of synchronized CAD and CKD along with the importance and frequency of respiratory complication in CABG patients encouraged us to assess the relationship between CKD and respiratory failure. Considering the important roles of arterial oxygenation in the assessment of respiratory failure, and Creatinine Clearances (CICr) in the monitoring of CKD, pushed us to consider them as assessable, routine, and acceptable assessment tools in this study.

The aim of this study was to compare post-CABG oxygenation impairment in patients with CICr in the normal range ( $\geq 90$ ) or mild CKD ( $90 > \text{CICr} \geq 60$ ) with patients who have moderate ( $60 > \text{CICr} \geq 30$ ) or severe ( $30 > \text{CICr} \geq 15$ ) disease, when dialysis was considered as exclusion criteria.

## Materials and Methods

A prospective cohort was conducted in winter 2012, by engaging patients who were a candidate to have on-pump CABG two months' period in Tehran Heart Center /Tehran University of Medical Sciences. According to the inclusion and exclusion criteria, it was assumed that between 200-300 patients had been engaged in the study.

During the study course, all CABG candidates who were intubated in operation theater included in the study, when approved that they had none of the following criteria in preoperative phase: hemodynamic instability, Intra-Aortic Balloon Pump (IABP), respiratory distress, uncontrolled pulmonary disease,  $\text{PaCO}_2 > 45$  mmHg,  $\text{PaO}_2 < 60$  mmHg, Forced Expiratory volume of Second one/Forced Vital Capacity ( $\text{FEV}_1/\text{FVC}$ )  $< 60\%$ ,  $\text{FEV}_1 < 60\%$ , Vital capacity (VC)  $< 50\%$ , Body Mass Index (BMI)  $> 40$ , systolic Ejection Fraction (EF)  $< 30\%$ , pre-operative transfusion, Inotropic or corticosteroid medication in recent admission, ESRD that needs

dialysis, severe neurologic or consciousness defects, non-clear medical history or laboratory test results, those who needed other surgeries simultaneously, or had other significant cardiac co-morbidities including, severe valvular or congenital anomalies.

Unscheduled extra operation along with CABG, pneumonia or other preoperative or postoperative infections in the ICU (Intensive Care Unit) according to patient charts or hospital infection surveillance records, any neurologic or consciousness defects, reoperation and death during 12 hours after extubation and failure to do assessment and tests in approximate 30 minutes around the scheduled time, were considered as exclusion criteria, too.

Age, gender, height, weight, pump time, cross-clamp time, preoperative EF, Creatinine of 24 hours before surgery,  $\text{FEV}_1/\text{FVC}$ , smoking history ( $> 5$  pack. year), opium dependency (regular use) history, controlled history of COPD (chronic obstructive lung disease), Diabetes Mellitus (DM), intubation time, ICU length of stay (ICU-LOS), postoperative inotrope and IABP use and Arterial Blood Gas (ABG) variables, including; (Arterial partial pressure of Oxygen )  $\text{PaO}_2$ , (Arterial partial pressure of carbon dioxide )  $\text{PaCO}_2$ , (Potential of Hydrogen) pH, (Saturation of oxygen in arterial blood sample)  $\text{SpO}_2$ , (base excess) BE, along with simultaneous (Fraction of inspired oxygen)  $\text{FiO}_2$  and  $\text{PaO}_2/\text{FiO}_2$  in one hour after ICU admission, and 4 hour after extubation, and Oxygen therapy with nasal cannula or reservoir mask (as used routinely in 4 hours after extubation) was recorded by one experienced open heart ICU nurse in each working shift, in a specially designed questionnaire for all patient.

Partial unification of methods and staff was applied by following hospital protocols or routines in anesthesia techniques and choice medications, applying lung recruitment before sternal closure, ICU care and apply Open Lung Concept in ICU. All patients were transferred from Operation Theater to the ICU on the same floor by anesthesia technician by bag ventilation, while monitored, and had headed up about  $30^\circ$  when there was not any contraindication. ICU care was supervised by inward intensivist in collaboration with the surgeon. Ventilation and extubation were done according to a routinely written protocol of hospital and "Open Lung Concept"(20).

Patient selection and CABG indications, preoperative management, anesthesia, surgery, all were performed randomly by those who were not engaged directly in the study and were blind to that.

CICr was calculated by Cock Croft and Gault

formula;

$$\text{Male ClCr} = \frac{(140 - \text{age}) \cdot (\text{Body weight}(\text{ kg}))}{72 (\text{serum Creatinine}(\text{mg} / 100\text{ml}))}$$

$$\text{Female ClCr} = (\text{Male ClCr}) \cdot (0.85)$$

According to ClCr of 24 hours before surgery, patients were divided into two main groups; group A which had  $\text{ClCr} \geq 60$  and group B with  $\text{ClCr} < 60$ . ClCr is a good estimate of Glomerular Filtration Rate (GFR). Therefore, group A should include patients with normal kidney function ( $\text{GFR} \geq 90$ ) or mild CKD ( $90 > \text{GFR} \geq 60$ ), and group B consists of moderate CKD ( $60 > \text{GFR} \geq 30$ ) or severe CKD ( $30 > \text{GFR} \geq 15$ ) (Harrison textbook of internal medicine 2013).

To calculate  $\text{PaO}_2/\text{FiO}_2$  4 hours after extubation, according to oxygen requirement and oxygen supplementation of 8-12 lit/min oxygen administration via reservoir face mask (M group) or 3-6 lit/min via nasal cannula (N group), and assumption of oxygen concentration in the central oxygen system and patient's dead space, we estimate  $\text{FiO}_2$  0.8 for group M group and 0.4 for N group.

Age, gender, height, weight, pump time, cross-clamp time, preoperative EF, Creatinine of 24 hours before surgery, FEV1/FVC, smoking history (>5 pack. year), opium dependency (regular use) history, controlled history of COPD, DM, postoperative inotropic and IABP use and Arterial Blood Gas (ABG) variables, including;  $\text{PaO}_2$ ,  $\text{PaCO}_2$ , pH,  $\text{SpO}_2$ , BE, along with simultaneous  $\text{FiO}_2$  and was recorded for by one experienced open heart ICU nurse in each working shift, in a specially designed questionnaire for all patient.

$\text{PaO}_2/\text{FiO}_2$  in one hour after ICU admission, and 4 hours after extubation, Oxygen therapy with a nasal cannula or reservoir mask in 4 hours after extubation, intubation time duration and ICU-LOS, were considered as mean outcomes of the study, to be compared between group A and Group B.

### Statistical method

We used SPSS version 20 for statistical analysis. We reported data as mean, SD, frequency, and percentage stepwise linear regression used for adjusting confounder

variables including t-test, ANOVA, linear regression.

### Results

Among 257 included patients, 28 patients had one or more exclusion criteria. Mean age of study population was  $60.66 (\pm 9.35)$  (range 39-85) years, mean Body Mass Index (BMI) was  $27.19 (\pm 3.93)$  (range 17.63-39.26)  $\text{kg.m}^2$  and 169 (74.4%) were males.

When 229 study patients were grouped based on their preoperative ClCr to groups A ( $\text{ClCr} \geq 60$ ) and B ( $\text{ClCr} < 60$ ); the group A encompassed 121 patients and group B 108 patients.

Frequencies of independent parametric and non-parametric variables and comparing them between two groups of study are presented in table 1. Values of age ( $56.08 \pm 7.78$  years in group A vs.  $65.79 \pm 8.32$  years in group B;  $P=0.000$ ) and pump time ( $64.66 \pm 17.97$  min. in group A vs.  $72.36 \pm 28.83$  min. in group B;  $P=0.029$ ) were lower in group A compared with group B. While, height ( $167.40 \pm 9.35$  cm in group A vs.  $160.02 \pm 9.78$  cm in group B;  $P=0.000$ ), weight ( $78.37 \pm 9.78$  kg in group A vs.  $66.77 \pm 10.51$  kg in group B;  $P=0.000$ ), and BMI ( $28.14 \pm 3.81$   $\text{kg.m}^2$  in group A vs.  $26.11 \pm 3.82$   $\text{kg.m}^2$  in group B;  $P=0.000$ ) values were higher in group A. In univariate analysis, other independent variables were not significantly different between the two groups.

Comparison ABG and other dependent variables in 1 hour after ICU admission and 4 hours after extubation between groups, in a univariate analysis, did not show a significant difference between groups of study except for  $\text{SpO}_2$  in 1 hour after ICU admission, ( $97.78 \pm 1.57$  in group A vs.  $98.19 \pm 1.37$  in group B;  $P=0.040$ ).

In multivariate analysis using stepwise linear regression for  $\text{PaO}_2/\text{FiO}_2$  as the dependent variable, only the BMI, cross-clamp time, and sex remained in the model their coefficients were: -5.214, -1.179 and -26.771, respectively (Table 3).

Need to use of reservoir mask than the use of nasal cannula oxygen 4 hours after extubation had no significant difference between 2 groups. The nasal cannula was used more for oxygenation especially in group B (80.2% in group B and 69.4% in group A).

Table 1. Comparison the independent parametric and nonparametric variables between groups

Variable	Total	Range	Group A	Group B	P*	
	Mean ( $\pm$ SD) or n (%)		Mean ( $\pm$ SD) or n (%)	Mean ( $\pm$ SD) or n (%)		
Parametric variables	Age (years)	60.66 ( $\pm$ 9.35)	39-85	56.08( $\pm$ 7.78)	65.79 ( $\pm$ 8.32)	0.000
	Height (cm)	163.96 ( $\pm$ 10.11)	138-192	167.40 ( $\pm$ 9.35)	160.02 ( $\pm$ 9.78)	0.000
	Weight (kg)	73.00 ( $\pm$ 11.65)	43-117	78.37 ( $\pm$ 9.78)	66.77 ( $\pm$ 10.51)	0.000
	BMI (kg/m <sup>2</sup> )	27.19 ( $\pm$ 3.93)	17.63-39.26	28.14 ( $\pm$ 3.81)	26.11 ( $\pm$ 3.82)	0.000
	Cross Clamp time (minutes)	41.18( $\pm$ 14.52)	15-108	39.17 ( $\pm$ 12.27)	43.25 ( $\pm$ 16.22)	0.060
	Pump time(minutes)	68.35( $\pm$ 24.37)	27-270	64.66 ( $\pm$ 17.97)	72.36 ( $\pm$ 28.83)	0.029
	Preoperative EF%	48.52 ( $\pm$ 8.46)	30-70	48.05 ( $\pm$ 8.24)	48.99 ( $\pm$ 8.76)	0.412
	Preoperative FEV1/FVC	88.65 ( $\pm$ 9.40)	60-101	89.69( $\pm$ 8.85)	87.47 ( $\pm$ 9.89)	0.087
	Sex (male)	169 (74.4%)	-	94 (77.7%)	75 (70.8%)	0.232
	Diabetic	67 (29.6%)	-	37 (30.8%)	30 (28.3%)	0.678
	Controlled COPD	8 (3.5%)	-	6 (5.0%)	2 (1.9%)	0.206
	Opium addiction	35 (15.5%)	-	-	-	-
	Nonparametric variables	Smoking	86 (38.1%)	-	47 (39.2%)	39 (36.8%)
Postoperative balloon pump 1 hours after ICU admission		4 (1.9%)	-	1 (0.9%)	3 (2.9%)	0.269
Inotrope 1 hours after ICU admission		43 (20.1%)	-	19 ((17%)	24 (23.5%)	0.231
Postoperative balloon pump 4 hours after extubation		2 (1.2%)	-	0 (0%)	2 (2.3%)	0.170
Inotrope 4 hours after extubation		10 (5.8%)	-	4 (4.8%)	6 (6.8%)	0.578

\*P&lt; 0.05 considered to be statistically meaningful

Table 2. Comparison ABG and other dependent variables in 1 hour after ICU admission and 4 hours after extubation between groups

Variable	Total	Group A	Group B	P	
ABG 1 hours after ICU admission	PH	7.3( $\pm$ 0.073)	7.37 ( $\pm$ 0.07)	7.37 ( $\pm$ 0.08)	0.671
	PaO <sub>2</sub>	132.37( $\pm$ 37.82)	131.04 ( $\pm$ 39.02)	133.75 ( $\pm$ 34.73)	0.589
	PaCO <sub>2</sub>	33.96( $\pm$ 5.66)	34.08 ( $\pm$ 5.56)	33.12 ( $\pm$ 6.44)	0.237
	BE	-4.86( $\pm$ 3.02)	-4.77 ( $\pm$ 3.09)	-4.95 ( $\pm$ 3.41)	0.680
	SpO <sub>2</sub>	97.945( $\pm$ 1.22)	97.78 ( $\pm$ 1.57)	98.19 ( $\pm$ 1.37)	0.040*
	PaO <sub>2</sub> /FiO <sub>2</sub>	264.805( $\pm$ 22.1)	259.10 ( $\pm$ 22.1)	270.51( $\pm$ 22.01 )	0.291
	PH	7.365( $\pm$ 0.41)	7.37 ( $\pm$ 0.048)	7.36 ( $\pm$ ) 0.049	0.531
ABG 4 hours after extubation	PaO <sub>2</sub>	95.28( $\pm$ 22.2)	92.67 ( $\pm$ 21.57)	97.89 ( $\pm$ 24.75)	0.134
	PaCO <sub>2</sub>	35.98( $\pm$ 4.9)	36.01 ( $\pm$ 4.59)	35.95 ( $\pm$ 5.07)	0.931
	BE	-7.905( $\pm$ 5.7)	-11.70 ( $\pm$ 7.81)	-4.11 ( $\pm$ 4.47)	0.359
	SpO <sub>2</sub>	96.295( $\pm$ 1.7)	96.51( $\pm$ 1.66 )	96.08( $\pm$ 1.99 )	0.125
	Estimated PaO <sub>2</sub> /FiO <sub>2</sub>	234.075( $\pm$ 20.4)	228.14 ( $\pm$ 22.1 )	240.01( $\pm$ 22.1 )	0.198
	high concentration oxygen demand (reservoir mask)	7(6.3)	3 (2.5%)	4 (3.8% )	0.089
	Intubation time duration e (hours)	11.96( $\pm$ 2.1)	10.85 ( $\pm$ 2.1)	12.97 ( $\pm$ 2.2 )	0.306
ICU length of stay (hours)	41.065( $\pm$ 11.2)	39.04 ( $\pm$ 11.1 )	43.09( $\pm$ 11.1 )	0.114	

ABG; arterial blood gas, ICU; Intensive care unit, PaO<sub>2</sub>; Arterial partial pressure of Oxygen, PaCO<sub>2</sub>; Arterial partial pressure of carbon dioxide, pH; Potential of Hydrogen, SpO<sub>2</sub>; Saturation of oxygen in an arterial blood sample, BE; base excess, FiO<sub>2</sub>; Fraction of inspired oxygen

**Table 3. Multivariate analysis using stepwise linear regression for predicting PaO<sub>2</sub>/FiO<sub>2</sub> as the dependent variable<sup>a</sup>**

Model	Unstandardized Coefficients		Standardized Coefficients	T	Sig.
	B	Std. Error	Beta		
(Constant)	442.749	40.647		10.893	.000
3 Body Mass Index	-5.214	1.291	-.312	-4.039	.000
cross clamp time min.	-1.179	.323	-.278	-3.650	.000
Sex	-26.771	11.174	-.185	-2.396	.018

<sup>a</sup> Dependent Variable: PaO<sub>2</sub>/FiO<sub>2</sub> 4hours after extubation

## Discussion

In this article, we assessed the effect of postoperative Creatinine Clearances on Coronary Artery Bypass Grafting postoperative oxygenation.

Serum creatinine level is one of the most important tools for detecting the perioperative renal function as an adverse outcome in cardiac surgery (21,22). Serum creatinine measurement is a clinically accepted, feasible, and inexpensive and can predict the risk factor for postoperative renal injury. So, creatinine has a role in risk predicting models after cardiac surgery and creatinine can enhance cardiac surgery outcome (23,24).

To our knowledge, this is the first study to report the effect of preoperative Creatinine Clearances on Coronary Artery Bypass Grafting postoperative oxygenation.

Moreover, our results highlight that by *t*-test analysis, independent variables had no significant difference between the two groups except some variables as age, height, BMI, pump duration.

The Creatinine Clearances is calculated by Croft–Gault equation which using age and weight, therefore the statistical difference for these two variables couldn't be effective in results.

In comparison between ABG parameters in one hour after ICU entrance and 4 hours after extubation, only SPO<sub>2</sub> level was significantly higher in B than A, in one hour after ICU entrance. These differences were correlated with the difference in the ratio of PaO<sub>2</sub>/FI<sub>2</sub>, PaO<sub>2</sub> level and FI<sub>2</sub> level in 2 groups, but it seems that these difference had no valuable clinical significant, but they are in favor of a reverse correlation between oxygenation and ClCr level (with 60 cut off).

The pao<sub>2</sub>/fio<sub>2</sub> ratio was between 200-300 (ARDS to acute lung injury) in both groups and also in group B was higher than group A (with no significant difference) at one hour after ICU entrance and 4 hours after extubation. Therefore, at least ClCr have no negative effect on oxygenation.

In an article by Najafi *et al.*, the effect of ClCr on outcome was evaluated in 11884 adult CABG patients. 7856 patients (66.1%) had normal kidney performance with ClCr >60 ml/min and Creatinine level equal or less than 1.1 mg/dl, but 706 patients (9.5%) had an occult renal failure with ClCr <60 ml/min and Creatinine level equal or less than 1.1 mg/dl. The results of this study indicated that the side effects after CABG such as need to longtime mechanical ventilation (more than 72 hours), mortality, renal failure, atrial fibrillation, intra-aortic balloon pump (IABP) and hospital length of stay more than 7 days were significantly more common in patients with occult renal failure (10). Association of the worst respiratory outcome with ClCr >60 ml/min in this study does not essentially mean the oxygenation disturbance in them.

In another study by Legare *et al.*, the association between renal failure and longer mechanical ventilation duration after CABG was demonstrated (25). Another study by Filsoofi has a similar result (26). In both of these studies, mechanical ventilation (more than 72 hour) was the assessment tool to evaluate the effect of ClCr on the respiratory situation. By integrating our results with findings of upper mentioned studies, it seems that longer mechanical ventilation in patients with ClCr should not be due to oxygenation disturbance.

There are several mechanisms which could affect both renal function and respiratory function during cardiac surgery, including; the balance between oxygen delivery and oxygen consumption, initiating the inflammatory cascade by different mechanisms and hemodynamic changes, iatrogenic, metabolic or drug toxicities (27-29).

Renal dysfunction could affect fluid and electrolyte balance and or clearance or detoxification of different drug metabolites or toxins. In another hand partial transient cardiac dysfunction and asthenia after on-pump cardiac revascularization could hasten the overall capacity of fluid and electrolyte justification. Theoretically, fluid overload could increase pulmonary congestion and increase the effects of activated

inflammatory cascade on lung tissue.

It is important to know that in our study, for patients with preoperative ClCr to groups A ( $ClCr \geq 60$ ) only BMI, cross-clamp time and sex can predict the PaO<sub>2</sub> at 4 hours after extubation. It is documented that arterial oxygenation can be effected in obese patients who undergo bariatric surgery (30,31). There is no doubt that oxygenation during cardiac surgery is related to aortic cross-clamp time (ischemic time) (32).

Finally, the comparison of the results of this study and the previous studies strongly suggest that the reported respiratory failure in patients with lower ClCr in CABG patients is not due to deterioration of oxygenation and also, lower preoperative ClCr values do not deteriorate post-CABG arterial oxygenation.

So, we recommend further studies to find more detailed risk models to predict ABG and other dependent variables during cardiac surgery.

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