

## Post-operative new-onset atrial fibrillation and its association with high serum lactate levels in off-pump coronary artery bypass patients

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### ABSTRACT:

**Background:** Atrial fibrillation accounts for 15-50% of all the complications after a coronary artery bypass operation, making it the most common cause of mortality and morbidity. Off-pump CABG reduces the development of new onset atrial fibrillation by decreasing the inflammatory reaction, tissue trauma, and necrosis. Increased serum lactate levels are a direct marker for poor prognosis in post-operative bypass patients. In Pakistan, there is a scarcity of data related to off-pump CABG and new onset AF. Hence, there is a need to evaluate the incidence, causes, and effects of off-pump CABG on POAF.

**Objective:** The objective of this study was to determine the frequency of new-onset atrial fibrillation in post-operative off-pump coronary artery bypass patients and compare the frequency of POAF in patients with and without hyperlactatemia.

**Methodology:** This descriptive case study was carried out in the adult cardiac surgery operation theatre and ICU at the Armed Forces Institute of Cardiology/National Institute of Heart Diseases. It was carried out over a period of six months from 27-12-2018 to 26-06-2019. A total of 100 patients were included in the study. Their serum lactate levels were checked pre and post-procedure. Statistical analysis was used to determine the frequency of developing AF in the first 48 hours and its relation with lactate levels.

**Results:** The mean age of the patients was  $59.1 \pm 7.8$  years. 78% of the patients were males, while females were only 22%. The mean BMI was  $28.4 \pm 3.0$  kg/m<sup>2</sup>. The majority of patients suffered from triple vessel disease (79%). LMS was found to be in 18 patients (18%). Atrial fibrillation was found in 16 patients (16%). Post-operative hyperlactatemia in the first 24 hours was present in 51 patients (51%).

**Conclusion:** Through this study, we established that off-pump CABG is a safer procedure as it can reduce the incidence of new-onset atrial fibrillation in post-operative patients.

**Keywords:** Atrial fibrillation, High serum lactate levels, Off-pump coronary artery bypass.

### INTRODUCTION:

Coronary artery disease is one of the most common cardiovascular diseases affecting the world population. It is a major cause of death in both developed and developing countries. According to the W.H.O., approximately 17.9 million deaths occur each year due to CAD<sup>1</sup>.

The central role in the management of ischemic heart disease is played by coronary revascularization<sup>2</sup>. It helps in relieving angina by restoring blood flow to the cardiac muscles. Coronary revascularization not only decreases the

need for medication but also improves the quality of life. It also improves the prognosis of the disease and decreases the socio-economic burden on the patient. Coronary revascularization not only helps patients with mild coronary atherosclerosis but also those patients whose left main or three vessels are affected<sup>3</sup>. The first milestones in coronary revascularization were surgical. Endarterectomy was used to remove the plaques of fatty substances from the vessel. This was followed by an anastomosis between the donor vessel and the coronary artery. In the beginning, these operations were performed on a beating heart without the use of cardiopulmonary bypass<sup>4</sup>.

With the advancement of medical and surgical skills, cardiopulmonary bypass (CPB) was introduced in cardiovascular surgery. This improved the surgical field for proper exposure and high quality anastomosis could be performed<sup>5</sup>. CABG, along with CPB, proved to be a far superior modality of treatment in cardiac arrest when compared to medical treatment and percutaneous trans-luminal coronary angioplasty (PTCA)<sup>6</sup>. Worldwide, CABG is performed on approximately 800,000 patients per year<sup>7</sup>. Conventional bypass surgery is now replaced by novel methods that will decrease the post-operative complications and assure good results, thus leading to less perioperative morbidity, faster recovery, shorter hospital stay, and reduced costs. Off-pump CABG on a beating heart helps to reduce the size of the surgical incision, trauma to skin, soft tissue, and bone. Thus, decreasing perioperative infections results in fast recovery<sup>8</sup>.

Patients undergoing CABG are already in a high-risk group with atherosclerosis and systemic low-grade inflammation. The processes of aortic clamping, reperfusion, anesthesia, and micro embolization further enhance this inflammatory process. Furthermore, on-pump CABG is not only a risk for micro-emboli development; it also causes inflammation in the whole body. The complement system of the body is activated when the blood comes in contact with the surface of the CPB circuit, resulting in inflammation<sup>9</sup>. Inflammation has been proposed to be a key factor in recognizing early onset post-operative complications like myocardial infarction, AF, stroke or low-output syndrome. Recent studies have shown that off-pump CABG decreased the inflammatory response in the body<sup>10</sup>.

Marked metabolic acidosis, with consequent catecholamine secretion and myocardial sensitization, directly causes supraventricular and ventricular arrhythmias. Approximately, 10-20% of patients undergoing cardiac surgery develop hyperlactatemia<sup>11</sup>. Perioperative hyperlactatemia can be caused by hypoxic or non-hypoxic factors. However, elevated lactate levels in the blood are often used to determine tissue hypoxia<sup>12</sup>.

New post-operative atrial fibrillation (POAF) occurs in about 15-50% of unselected patients undergoing cardiac surgery<sup>13</sup>. Release of catecholamines and surgical stress leads to the activation of the sympathetic system which then results in arrhythmias. The sympathetic system can also be activated by decreased blood volume, decreased blood pressure, blood loss, pain, and trauma to the tissues<sup>14</sup>. Studies show a direct relationship between POAF and elevated inflammatory markers like white blood cells, interleukins, blood lactate levels and C-reactive protein (CRP)<sup>15</sup>. Surgical intervention has been postulated to play a key role in atrial fibrillation in patients with a history of AF. A key role is played by the direct and prolonged contact of blood with the CPB machine, which causes oxidative stress and the production of pro-inflammatory molecules. These then cause the activation of endothelial cells, leucocytes, release of NADPH, nitrous oxide and reactive oxygen species (ROS)<sup>16, 17</sup>.

The highest prevalence of POAF was found in valve surgery combined with CABG i.e., up to 50%, whereas isolated valve surgery accounts for 40% and isolated CABG comprises only 30% of cases<sup>18</sup>. The most critical time for the development of POAF is between days 2 to 4 post-operatively, in which 90% of cases are reported<sup>19</sup>.

Patients who develop new-onset atrial fibrillation lose 30% of their pumping capability, which leads to increased morbidity and an increased length of ICU stay. A few studies have pointed out the association of post-operative atrial fibrillation with increased lactate levels. This study aims to answer this hypothesis in off-pump CABG surgery, and if it exists, better management to control the metabolic profile can help alleviate this problem and help patients in the post-operative setting.

## **MATERIALS AND METHODS:**

### **DATA COLLECTION PROCEDURE:**

A descriptive case study was conducted in the adult cardiac surgery operation theatre and ICU at the Armed Forces Institute of Cardiology/National Institute of Heart Diseases over a period of six months (Dec 2018-June 2019) after approval from the hospital ethical committee. A total of 100 patients were included in the study. All participants in

the study signed a written informed consent. All test expenses were borne by the hospital administration and not by the patient. All participants of both genders, aged 20 to 70 years, undergoing off-pump CABG, with or without hyperlactemia, were included in the study. Participants with recurrent revascularization (PCI or CABG), a history of supraventricular arrhythmias, an ejection fraction of less than 30%, and CKD (creatinine more than 2.0) were excluded. Non-probability consecutive sampling was used to calculate the sample size. With the help of the WHO sample size calculator, the population proportion of postoperative atrial fibrillation (POAF) in patients undergoing cardiac surgery was calculated to be 15%, with absolute precision of 7% and a confidence level of 95%. The sample size came to be 100 patients.

Serum lactate levels were checked pre and post procedure (at 0 hours, 6 hours, 12 hours and 24 hours). The frequency of developing atrial fibrillation in the first 48 hours after shifting to ICU and its relation to lactate levels were found by statistical analysis.

### DATA ANALYSIS PROCEDURE

Statistical analysis was performed using SPSS 23. A mean and standard deviation were calculated for quantitative variables, i.e., age and lactate levels. Frequency and percentage were calculated for qualitative variables, i.e., gender, new-onset atrial fibrillation and hyperlactatemia. Hyperlactatemia was compared between the two groups by the Chi-square test. Effect modifiers like age, gender, and co-morbidity were controlled by stratification. A post-stratification chi-square test was applied. P value  $\leq 0.05$  was taken as significant.

**RESULTS:** Among 100 recruited patients, the mean age was  $59.1 \pm 7.8$  years. Out of the total, 78 patients were males (78%), while 22 were females (22%). A mean BMI of  $28.4 \pm 3.0$  kg/m<sup>2</sup> was observed. Out of 100 patients, single vessel disease was found in 6 patients (6%), double vessel disease in 15 patients (15%), and triple vessel disease in 79 patients (79%). LMS was found in 18 patients (18%). The frequencies of comorbidities were as follows: diabetes 50 (50%), hypertension 52 (52%), renal parenchymal disease 16 (16%), thyroid disease 4 (4%) and COPD 18 (18%). POAF was found in 16 patients (16%). Hyperlactatemia was present in 51 patients (51%) within the first 24 hours post-operatively (Table1). The patients who developed POAF were further stratified according to demographics and clinical features. The most significant results were found in relation to hyperlactatemia ( $p=0.008$ ) (table 2). Those patients who developed hyperlactatemia 24 hrs post-operatively ( $n=51$ ) were further stratified for age, gender, and comorbidities (table 3).

Table 1: Patients demographics and clinical characteristics.

Variable	Number	Percentage	Mean $\pm$ SD
Age (years)			
$\leq 50$	18	18.0	59.1 $\pm$ 7.8
51 -71	82	82.0	
Gender			
Male	78	78.0	
Female	22	22.0	
BMI (kg/m <sup>2</sup> )			
< 25	11	11.0	28.4 $\pm$ 3.0
> 25	89	89.0	
Vessel disease			
Single vessel disease	6	6.0	
Double vessel disease	15	15.0	
Triple vessel disease	79	79.0	
Left main stem coronary artery			
Yes	18	18.0	
No	82	82.0	
Co-morbidities			
Diabetes	50	50.0	Total is not 100% as there were multiple responses
Hypertension	52	52.0	
Renal parenchymal disease	16	16.0	
Thyroid disease	4	4.0	

COPD	18	18.0	
New onset of atrial fibrillation			
Yes	16	16.0	
No	84	84.0	
Hyperlactatemia first 24 hours postop			
Yes	51	51.0	
No	49	49.0	

Table 2: Demographic and clinical stratification of patients with regards to POAF

Variable	POAF		Total	P value
	Yes	No		
Age				
≤ 50	2	16	18	0.532
51-70	14	68	82	
Total	16	84	100	
Gender				
Male	12	66	78	0.752
Female	4	18	22	
Total	16	84	100	
Hyperlactatemia				
Yes	13	38	51	0.008
No	3	46	49	
Total	16	84	100	
Diabetes				
Yes	9	41	50	0.585
No	7	43	50	
Total	16	84	100	
Hypertension				
Yes	7	45	52	0.471
No	9	39	48	
Total	16	84	100	
Renal parenchymal disease				
Yes	5	11	16	0.069
No	11	73	84	
Total	16	84	100	
Thyroid disease				
Yes	0	4	4	0.373
No	16	80	96	
Total	16	84	100	
COPD				
Yes	3	15	18	0.932
No	13	69	82	
Total	16	84	100	

Table 3: Demographic and clinical stratification with regards to hyperlactatemia.

Variable	Hyperlactatemia	POAF		Total	P value
		Yes	No		
Age (years)					
≤ 50	Yes	1	7	8	0.867
	No	1	9	10	

Total		2	16	18	
>50	Yes	12	31	43	0.006
	No	2	37	39	
Total		14	68	82	
Gender					
Male	Yes	10	29	39	0.012
	No	2	37	39	
Total		12	66	78	
Female	Yes	3	9	12	0.364
	No	1	9	10	
Total		4	18	22	
Diabetes					
Yes	Yes	8	15	23	0.004
	No	1	26	27	
Total		9	41	50	
No	Yes	5	23	28	0.375
	No	2	20	22	
Total		7	43	50	
Hypertension					
Yes	Yes	4	22	26	0.685
	No	3	23	26	
Total		7	45	52	
No	Yes	9	16	25	0.001
	No	0	23	23	
Total		9	39	48	
Renal Parenchymal disease					
Yes	Yes	5	1	6	0.001
	No	0	10	10	
Total		5	11	16	
No	Yes	8	37	45	0.172
	No	3	36	39	
Total		11	73	84	
Thyroid disease					
Yes	Yes	-	3	3	*
	No	-	1	1	
Total		-	4	4	*No statistics are computed because POAF is a constant
No	Yes	13	35	48	0.006
	No	3	45	48	
Total		16	80	96	
COPD					
Yes	Yes	2	8	10	0.671
	No	1	7	8	
Total		3	15	18	
No	Yes	11	30	41	0.007
	No	2	39	41	
Total		13	69	82	

**Table 4: Proportion of POAF in cardiac surgery patients (Binomial Test)**

		Category	N	Observed Prop.	Test Prop.	Exact Sig. (1-tailed)
Post-operative Atrial fibrillation	Group 1	Yes	16	0.16	0.05	0.000
	Group 2	No	84	0.84		
	Total		100	1.00		

**DISCUSSION:**

Atrial fibrillation (AF) is one of the most common complications after CABG and accounts for one quarter to one third of all patients<sup>20</sup>. On-pump CABG is associated with a high systemic inflammatory response and end organ damage, resulting in high post-operative morbidity and mortality. In contrast, with the use of off-pump CABG, inflammatory reactions and cardiac damage can be significantly decreased<sup>21</sup>.

In this study, we established a relationship between off-pump CABG and a decrease in new onset atrial fibrillation in post-operative patients. In our study, 16% of patients developed POAF, which is consistent with a study performed by Ascione et al., who found that 56 patients (28%) developed POAF after on-pump CABG, whereas only 11 patients developed it after off-pump CABG<sup>22</sup>. Lee et al., found in their study that POAF is a risk factor in the elderly (>65 years)<sup>23</sup>. We found in our study that the majority of those patients who developed POAF were above 50 years of age (14) whereas only 2 patients were below 50 years of age. We also found in our study that POAF is more common in males (12%) as compared to females (4%). Similarly, in another study, the proportion of male patients was 69 (71.1%) and females was 28 (28.8%)<sup>24</sup>.

Gramlich et al., found that people with high BMI are more susceptible to develop cardiac abnormalities, and the risk increases many folds during cardiac surgery. They postulated that it is due to an increase in right ventricular mass, elevated inflammatory markers, and a decrease in oxidative factors required for proper healing of heart<sup>25</sup>. We also observed that 89% of patients in our study had a BMI greater than 25.

A systemic review and meta-analysis of 5 randomized control trials performed by Spadaccio and Benedetto revealed that most patients who underwent bypass surgery had triple vessel disease<sup>26</sup>. The results of our study were consistent with their observations. We also found that 79% of our patients had triple vessel disease, whereas only 6% had single vessel disease.

Persistent elevated lactate levels are a marker of hypoxia and tissue damage. Mak et al., found in their study that 78% of the mortality cases had persistent hyperlactatemia. They also found that among 469 post-operative patients, 144 developed high lactate levels<sup>27</sup>. In our study, hyperlactatemia occurred in 51% of patients within 24 hours post-operatively. We also found that the only significant relationship occurred between POAF and hyperlactatemia ( $p > 0.008$ ).

Off-pump CABG offers reduced post-operative morbidity and mortality due to a reduction in inflammatory response as compared to conventional CABG<sup>28</sup>. In our study, only 16 patients (16% of total) developed POAF with off-pump CABG.

New techniques like off-pump CABG and minimally invasive direct coronary artery bypass (MIDCAB) are now the preferred methods to treat patients with coronary artery blockage. However, it has yet to be found whether MIDCAB is better in the prevention of POAF than median sternotomy and if POAF depends upon the use of CPB. In a study conducted by Stamou et al., at Washington Hospital over a span of 10 years, MIDCAB yielded a better post-operative outcome. They found that in MIDCAB, there were fewer incidences of AF and post-operative hospital stays. Although those who developed AF had a higher post-operative hospital stay along with high morbidity and mortality<sup>29</sup>.

**CONCLUSION:**

In the present study, we established that off-pump CABG could reduce the incidence of new-onset atrial fibrillation in post-operative off-pump coronary artery bypass patients as it is a less invasive procedure.

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