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Comparison of Renal Function in Coronary Artery Bypass Graft Surgery with Pulsatile versus Non-pulsatile Perfusion: A Randomized Clinical Trial

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ABSTRACT

Background: Despite numerous studies on tissue perfusion, capillary circulation, and their related factors, there is still no consensus on the utilization of pulsatile versus non-pulsatile perfusion methods to provide proper perfusion in patients undergoing Coronary Artery Bypass Graft (CABG) surgery.

Objectives: This study aimed to compare the effects of pulsatile versus non-pulsatile perfusion methods on renal function in patients undergoing CABG surgery in Shahid Mohammadi hospital, Bandar Abbas, Iran in 2018.

Methods: In this randomized clinical trial, 50 patients aged > 18 years who underwent CABG surgery were randomly divided into a pulsatile and a non-pulsatile group (n = 25 in each group). The two groups were compared in terms of laboratory findings including the plasma levels potassium, sodium, creatinine, and blood urea nitrogen, Glomerular Filtration Rate (GFR), urinary output, and ejection fraction.

Results: The results revealed a significant difference between the two groups regarding the trend of GFR changes during the study (P = 0.01). Accordingly, postoperative GFR increased more in the pulsatile group than in the non-pulsatile group. Moreover, creatinine and blood urea nitrogen levels reduced in the pulsatile group compared to the baseline. However, no significant differences were observed in the mean levels of potassium, sodium, and creatinine, urinary output, and ejection fraction in the two groups before and after the surgery.

Conclusions: According to the results, pulsatile method was preferred to the non-pulsatile perfusion method due to its positive effects on creatinine and blood urea nitrogen levels as well as on GFR during and after the CABG surgery.

1. Background

Atherosclerosis and clogged arteries in large and vital arteries lead to many disorders in the circulatory system. Cardiovascular diseases are the leading cause of death worldwide. Compared to other diseases, the coronary artery disease is responsible for more deaths, disabilities, and economic losses in both developed and developing countries (1, 2).

Today, Coronary Artery Bypass Graft (CABG) surgery is one of the most important treatments in patients with coronary artery disease (3). During heart surgery, arterial blood flow can be obtained using both pulsatile and non-pulsatile perfusion methods (4). Bypass surgery is usually performed in two ways. The 'on-pump' method uses a heart-lung replacement device known as a heart pump, which creates blood flow. This method uses a cardioplegia solution to cause cardiac arrest. As a result, the operation is performed on a stopped heart and the pump performs the functions of the heart and lungs at the same time (5). In the second method, the operation is performed on a beating heart without using the heart pump, which is called 'off-pump' surgery. Over the past few decades, the pulsatile perfusion method has been more widely used due to its similarity with the normal heart flow as well as its beneficial

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effects on hemodynamics, metabolism, organ function, and hormonal responses (4, 5). However, some studies have shown that pulsatile perfusion did not improve myocardial and organ functions, reporting no significant differences between pulsatile and non-pulsatile perfusion methods (6, 7). Pulsatile perfusion is like the blood flow that is physiologically established by the human heart in the body. The advantages of using this type of blood flow during cardiac surgery include more appropriate microvascular blood flow (8), more stable hemodynamic symptoms, better protection for vital organs, better oxygen supply, better clinical outcomes in pediatric heart surgeries (9), and lower postoperative complications and mental disorders (10). In the non-pulsatile perfusion method, on the other hand, blood flows continuously to the body. The advantages of this method include less damage to blood cells or less hemolysis compared to pulsatile blood flow (11).

Despite many studies on tissue perfusion, there is still no consensus on the use of pulsatile versus non-pulsatile method to create a proper perfusion during coronary artery surgery. Since the blood flow in the human body is pulsatile, the non-pulsatile blood flow of the pump during cardiovascular surgery may lead to impaired blood flow in tissues.

2. Objectives

the present study aims to evaluate the effects of pulsatile and non-pulsatile perfusion methods on renal function and biochemical parameters in patients undergoing CABG surgery.

3. Patients and Methods

This randomized controlled clinical trial was performed on 50 patients scheduled for CABG surgery in Shahid Mohammadi hospital, Bandar Abbas, Iran from September 2019 to January 2020. Based on a similar study (12) and considering the confidence interval of 95% and power of 80%, a 50-subject sample size was estimated (n = 25 in each group).

The participants were selected via convenience sampling based on the inclusion and exclusion criteria. The inclusion criteria were being a candidate for CABG surgery and aging above 18 years. Patients with a history of myocardial infarction during the last two weeks, off-pump surgery, emergency surgery, uncontrolled diabetes, abnormal liver function, and decreased level of preoperative consciousness were excluded from the study. Then, the participants were randomly allocated to pulsatile and non-pulsatile groups (n = 25 in each group) according to the table of random numbers. The trained nurse, laboratory technicians, and the statistical consultant were blinded to the study arms.

In both groups, anesthesia was induced according to the standard protocol by the intravenous injection of 3 mg/kgPropofol (BRUAN, Melsungen, Germany) and 0.1 mg/kg Fentanyl (DarooPakhsh Company, Tehran, Iran). To reduce the surgical technique error, all procedures were performed by a single surgical team. Cardiopulmonary bypass perfusion was performed using S3 and S5 models of Stokert roller pump (Liva Nova, England, and Wales). Median sternotomy was also performed for all the participants. In doing so, the left internal mammary artery and the greater saphenous vein were harvested as conduits. Then, 3 mg/kg heparin was administered and after two minutes, cannulation of the ascending aorta and the right atrium was done in the standard manner. When the activated prothrombin time reached 480 seconds, the pump was started. In the pulsatile group, the pulsatile mode was activated using the internal ECG mode at 60 beats/min. In the non-pulsatile group, continuous flow was provided by the roller pump. In both groups, the mean blood pressure was adjusted at 50 - 60 mmHg, and the core body temperature was lowered to 30 ºC. After clamping the ascending aorta, cold cardioplegic solution was infused with a potassium concentration of 20 meq/lit as the initial dose to induce cardiac arrest. Cardioplegia was administered after every distal anastomosis with a potassium concentration of 10 meq/lit. Just after completing distal anastomoses, the aortic clamp was removed, and rewarming was started. Proximal anastomosis was performed while the heart was beating. After checking the biochemical and blood gas parameters and considering hemodynamic parameters, weaning off the pump oxygenator was started. Hemostasis was done, a temporary pacemaker wire was inserted, tubes were drained, and sternotomy was closed routinely.

The participants' demographic characteristics including age, sex, Body Mass Index (BMI), history of smoking, Chronic Obstructive Pulmonary Disease (COPD), renal failure, chronic diseases such as diabetes mellitus, hypertension, and dyslipidemia, and atrial fibrillation were recorded. The serum potassium and sodium levels were measured preoperatively, during the operation, and 24 hours after the surgery. Creatinine and Blood Urea Nitrogen (BUN) levels and the urinary output were also measured preoperatively, 24 hours after the surgery, and at discharge. In addition, Glomerular Filtration Rate (GFR) was assessed and recorded before the surgery and at discharge. Ejection Fraction (EF) was also evaluated before and five days after the surgery. Sodium and potassium levels were measured using an "Ion Selective Electrode" (ISE) by an electrolyte analyzer. BUN and creatinine levels were also measured via light absorbance by Auto-Analyzer BT3000. GFR was calculated by an online GFR calculator (eGFR CALCULATOR) on www.ukidney.com. Urinary output was measured using standard measure pots and was recorded in the chart every 24 hours. Finally, EF was assessed 24 hours before and five days after the surgery by a single cardiologist using General Electric (GE) VIVID 7 DAIMENTION. After all, the two groups were compared concerning the need for postoperative inotropic support, duration of hospitalization, length of ICU stay, need for pump balloons, stroke, and postoperative mortality.

3.1. Ethical Consideration

This trial has been registered in the Iranian Registry of Clinical Trials (code: IRCT20200825048509N1). The research proposal was reviewed and approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran (code: IR.SSU.MEDICINE.REC.1398.121). Informed consent was obtained from all the participants after providing them with a full

explanation about the purpose, steps, benefits, and possible complications of the study on the day before surgery.

3.2. Statistical Analysis

Statistical analysis was performed using the SPSS software, version 21 (IBM Armonk, NY, USA). Quantitative variables were reported as number (percentage) and mean ± Standard Deviation (SD). Student's t-test, chi-square test, and repeated measures ANOVA were used to compare the two treatment methods. $P \leq 0.05$ was considered statistically significant.

4. Results

Out of the 53 participants who were initially entered into the study, three people were excluded due to unwillingness to cooperate and excessive hypotension during the surgery. Finally, the data of 50 participants were analyzed (n = 25 in each group) (Figure 1).

The mean age of the participants was 52.28 ± 10.9 years, and their mean BMI was 24.43 ± 4.6 kg/m2. Among the participants, 42% were female and 58% were male. The two groups were homogeneous in terms of sex, age, BMI, history of smoking, dyslipidemia, renal failure, and COPD. Atrial fibrillation was not reported in any of the study groups. However, the frequency of the participants with a history of hypertension was higher in the pulsatile group than in the non-pulsatile group (Table 1).

Despite the increase in the intraoperative mean levels of potassium compared to preoperative levels in both groups, no significant difference was observed in the trend of potassium changes during the surgery. Additionally, the mean levels of sodium decreased in the two groups during and after the surgery compared to the baseline, but the difference between the two groups was not statistically significant. Moreover, GFR values increased in both groups at discharge, and a significant difference was found between the two groups regarding the trend of GFR changes during the study (P = 0.01). Accordingly, the increase in postoperative GFR was more prominent in the pulsatile group than in the non-pulsatile group. The results also revealed a significant decrease in creatinine and BUN levels in the pulsatile group compared to the baseline. Furthermore, an increase was observed in the mean urinary output in both groups 24 hours after the surgery as well as at discharge compared to the baseline. No significant difference was detected between the two groups in this respect. The results also showed no significant difference between the two groups concerning the EF changes pre- and post-operatively (five days after the surgery) (Table 2). The trend of changes in the mentioned parameters has been depicted in Figure 2.

Although the need for postoperative inotropic support and length of ICU stay were lower in the pulsatile than in the non-pulsatile group, these differences were not statistically significant. However, the duration of hospitalization was significantly shorter in the pulsatile group compared to the non-pulsatile group (P = 0.005). No cases of stroke, postoperative mortality, and need for pump balloons were reported in any of the study groups. There was also no significant difference between the two groups in terms of the intubation duration (days) (Table 3).

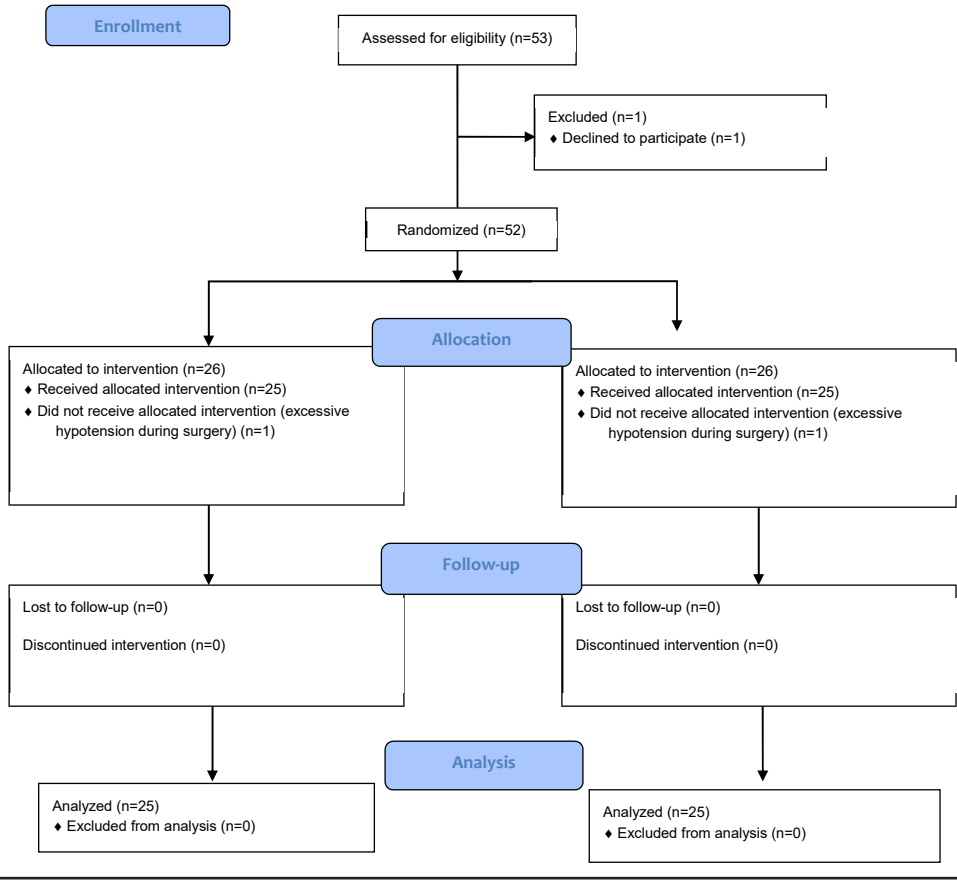

Figure 1. The CONSORT Diagram of the Study

Table 1. Demographic Characteristics and Clinical Findings of the Participants in the Two Groups before the Surgery (n = 25 in Each Group)

Variables	Pulsatile group	Non-pulsatile Group	P-value
Sex*			
Male	14 (56)	15 (60)	
Female	11 (44)	10 (40)	0.77
Age (yr)**	59.04 ±11.50	57.52 ± 10.51	0. 63
BMI (kg/m^2)**	25.14 ± 4.40	23.88 ± 4.80	0.34
Dyslipidemia*	11 (44)	15 (60)	0.26
Renal failure*	4 (16)	1 (4)	0.16
Hypertension*	19 (76)	10 (40)	0.01
DM*	12 (48)	10 (40)	0.57
COPD*	1 (4)	1 (4)	1.000
Smoking*	14 (56)	10 (40)	0.26

* Data have been presented as n (%); chi-square test. ** Data have been presented as mean ± SD; student's t-test.
Abbreviations: BMI, body mass index; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease.

Table 2. Comparison of the Two Groups Regarding Biochemical Parameters before, during, and after the Surgery (n = 25 in Each Group)

Variables	Pulsatile Group	Non-pulsatile Group	P-value*
Potassium			
Preoperative	4.33 ± 0.79	4.66 ± 0.76	0.23
Intraoperative	5.58 ± 0.90	5.65 ± 0.75	
Postoperative	4.06 ± 0.51	4.49 ± 0.56	
Sodium			
Preoperative	139.32 ± 2.80	138.56 ± 3.25	
Intraoperative	136.28 ± 3.16	135.28 ± 3.3.74	0.93
Postoperative	138.08 ± 2.67	137.40 ± 2.63	
GFR			
Preoperative	71.00 ± 30.53	78.84 ± 26.37	0.01
At discharge	88.07 ± 33.37	81.41 ± 33.03	
Creatinine			
Preoperative	1.12 ± 0.35	0.98 ± 0.22	0.05
24 h after the operation	1.28 ± 0.33	1.25 ± 0.28	
At discharge	0.93 ± 0.28	0.98 ± 0.17	
BUN			
Preoperative	20.08 ± 9.10	15.08 ± 3.82	0.01
24 h after the operation	23.12 ± 9.13	18.96 ± 4.02	
At discharge	17.80 ± 6.68	15.96 ± 3.93	
Urinary output			
Preoperative	73.60 ± 32.48	91.08 ± 41.4	0.32
24 h after the operation	85.40 ± 36.37	109.64 ± 63.26	
At discharge	81.68 ± 33.08	97.68 ± 32.44	
EF			
Preoperative	47.16 ± 8.88	47.52 ± 10.8	0.41
Postoperative (five days after the surgery)	60.12 ± 7.63	59.08 ± 8.07	

Data have been presented as mean ± SD. * Repeated measures ANOVA.
Abbreviations: GFR, glomerular filtration rate; BUN, blood urea nitrogen; EF, ejection fraction.

Table 3. Comparison of the Two Groups Regarding the Duration of Hospitalization, Length of ICU Stay, Intubation Duration, Need for Inotropic Support, Need for pump balloon Implantation, Stroke, and Death after Surgery (n = 25 in Each Group)

Variables	Pulsatile Group	Non-pulsatile Group	P-value
Need for inotropic support*	8 (32)	14 (52)	0.08
Need for pump balloon implantation*	0	0	-
Stroke*	0	0	-
Death*	0	0	-
Duration of hospitalization (days)**	7.96 ± 1.13	8.88 ± 1.05	0.005
Length of ICU stay (days)**	5.6 ± 1.08	6.16 ± 1.31	0.1
Intubation duration (days)**	1 ± 0.00	1 ± 0.00	1.000

* Data have been presented as n (%); chi-square test. ** Data have been presented as mean±SD; student's t-test.

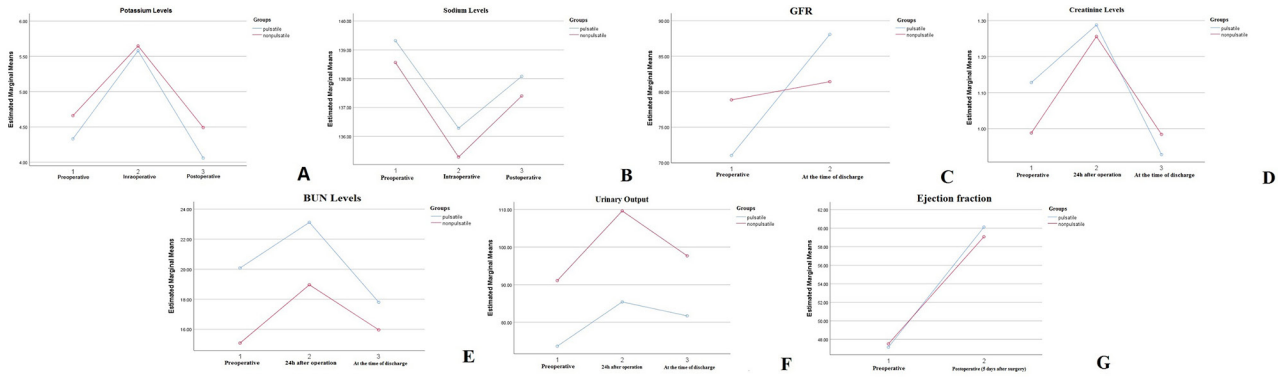

Figure 2. Changes in Biochemical Parameters in the Two Study Groups (A: Potassium, B: Sodium, C: Glomerular Filtration Rate, D: Creatinine, E: Blood Urea Nitrogen, F: Urinary Output, G: Ejection Fraction)

5. Discussion

CABG is one of the most important treatment methods for coronary artery disease, especially in patients suffering from multiple vessel disease (3). The most popular method for handling the heart and lung during CABG is the use of the "Cardio-Pulmonary Bypass" (CPB) machine (13). This method provides surgeons with a silent, bloodless field for making precise anastomoses. "On-pump cardiac surgery" may be associated with some complications, one of the most important of which being acute renal failure that significantly increases mortality and morbidity (14). The outflow of blood, hemolysis, hypothermia, and non-pulsatile perfusion may be the causes of renal dysfunction (15). This study aimed to evaluate the effects of pulsatile versus non-pulsatile perfusion method on renal function and blood electrolyte during on-pump CABG surgery. The results revealed no significant difference between the two methods in terms of blood levels of potassium and sodium, urinary output, and EF. However, a significant decrease was observed in GFR and creatinine and BUN levels in the pulsatile group compared to the non-pulsatile group. Conlon PJ et al. performed a study on 2672 patients undergoing CABG and reported kidney damage in only 0.7% of the patients. Nonetheless, this procedure was associated with 28% mortality in the patients suffering from kidney disease compared to 1% in those without kidney damage (16). In patients with acute renal failure, the mortality rate increased to 88% after cardiac surgery (17). Compared to pulsatile or normal perfusion, non-pulsatile perfusion activates the sympathetic nerves, resulting in vasoconstriction, and increases afterload due to the lack of stimulation of arterial occlusion receptors (18). Adademir et al. (2012) evaluated the effects of pulsatile and non-pulsatile flow cardiovascular bypass on renal function of 85 patients with normal preoperative renal function using urinary neutrophil gelatinase-associated lipocalin and interleukin-18 as the markers of renal injury. Neutrophil gelatinase-associated lipocalin and interleukin-18 levels were measured via Enzyme-Linked Immunosorbent Assay (ELISA) 2, 12, and 24 hours after the cardiovascular bypass. The results indicated no significant difference between the study groups in terms of preoperative renal function tests. However, interleukin-18 levels measured 12 h after the surgery were significantly lower in the pulsatile perfusion group compared to the non-pulsatile group ($P < 0.05$). Overall, they reported a better kidney protection in the pulsatile perfusion group than in the non-pulsatile group (19). Amouzegar et al. also conducted a research in 2017 and showed no significant difference between the study groups in terms of urinary output, which was in line with the present study findings (20). Furthermore, Presta et al. disclosed that although pulsatile perfusion was a safe method during coronary heart surgery, there was no significant difference between the pulsatile and non-pulsatile groups with respect to urinary output and BUN level (21). In the current study, however, GFR significantly increased in the pulsatile group than in the non-pulsatile group postoperatively. Alkan et al. conducted a study to compare the effects of pulsatile and non-pulsatile perfusion methods on vital organs' functions. They found no significant difference between the two groups concerning creatinine levels (22). Similar results were also obtained in another study on the relationship between pulsatile perfusion and acute renal failure (23).

Although non-pulsatile perfusion is the most common method during open cardiac surgery, evidence has suggested better cardiac, renal, and pulmonary outcomes in patients undergoing pulsatile perfusion (24). The results of the present study showed no significant difference between the study groups regarding the need for inotropic support. However, the findings of a prior investigation demonstrated that the pulsatile perfusion method reduced the duration of hospitalization (5).

The present study had some limitations, one of which being the small sample size. Besides, patients with previous chronic renal diseases were omitted, and the efficacy of pulsatile pump perfusion in case of low cardiac output or emergencies could not be evaluated. Therefore, further studies are recommended to assess the effect of the pulsatile perfusion method in patients with underlying cardiac and renal diseases.

5.1. Conclusion

According to the results, pulsatile perfusion method is preferred to the non-pulsatile method due to its positive effects on BUN levels and GFR during and after the CABG surgery.

5.2. Clinical trial Registration Code

IRCT20200825048509N1.

5.3. Ethical Approval

This trial has been registered in the Iranian Registry

of Clinical Trials (code: IRCT20200825048509N1). The research proposal was reviewed and approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran (code: IR.SSU.MEDICINE.REC.1398.121).

5.4. Informed Consent

Informed consent was obtained from all the participants after providing them with a full explanation about the purpose, steps, benefits, and possible complications of the study on the day before surgery.

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Authors' Contribution

Study concept and design: S.J.; analysis and interpretation of the data: S.S., Sh.M., M.T, and H.M; drafting of the manuscript: S.S., Sh.M., M.T, and H.M; critical revision of the manuscript for important intellectual content: S.J. and Sh.M.; statistical analysis: S.J. All authors read and approved the final manuscript.

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