Effect of the type of cardiopulmonary bypass pump flow on postoperative cognitive function in patients undergoing isolated coronary artery surgery

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Abstract

Objective: Pulsatile flow, generated by a pump during cardiopulmonary bypass, has been accepted as more physiological in coronary artery bypass grafting surgery (CABG). Therefore, we aimed to investigate the effects of pulsatile and nonpulsatile flow on postoperative cognitive function and to review relationship with the biomarkers S100β and neuron-specific enolase (NSE).

Methods: Patients who underwent isolated CABG were included this prospective, randomized, double-blind study, which was performed between March 2010 and December 2010. Patients were divided into two groups: pulsatile (Group I, n=20) and nonpulsatile (Group II, n=20) flow. Blood samples were collected 1 day before surgery and in the sixth postoperative hour for the analysis of S100β and NSE. In addition, Mini-Mental State Examination (MMSE) was performed during preoperative period and on third postoperative day. Outcomes were determination of effects of pump flow type on cognitive function and relationships with concentrations of S100β and NSE.

Results: Forty patients were included. No differences were observed between the groups with respect to complications, mortality, S100β (Group I: 1.9±0.2 μ/L; Group II: 2.0±0.2 μ/L), NSE (Group I: 12.5±0.8 μ/L; Group II: 12.4±0.7 μ/L), MMSE scores [Group I: 25 (23–27); Group II: 25 (23–27)], and postoperative cognitive dysfunction (POCD) ($p>0.05$). No correlation was observed between MMSE scores and concentrations of S100β ($r=-0.032$) and NSE ($r=-0.423$) ($p>0.05$).

Conclusion: There was no difference between types of pump flow for POCD and no relationship between cognitive dysfunction and S100β and NSE concentrations. Pump flow type does not affect NSE concentrations. *(Anatol J Cardiol 2016; 16: 875-80)*

Keywords: pulsatile flow, nonpulsatile flow, S-100 beta protein, neuron-specific enolase, cognitive dysfunction

Introduction

The type of flow generated by a heart and lung machine has been an important research issue related to heart surgery. The proposal that pulsatile circulation is more suitable for the body and more physiologically relevant has divided researchers into two main groups. The first group advocates the superiority of pulsatile flow over nonpulsatile flow (1, 2), and the second group holds that both types of flow produce the same clinical results (3, 4).

Neurological complications that develop due to cardiac surgery are a serious cause of morbidity. Many neurological complications can develop after surgery, such as fatal brain damage, epileptic seizures, visual fi eld defects, postoperative cognitive dysfunction (POCD), stroke, primitive reflexes, spinal cord injury, and peripheral neuropathies (5). POCD is the most frequently observed complication, with an incidence of 30–79% (5). The wide range in the reported incidence of this complication occurs as a result of differences in study design and in descriptions of POCD.

POCD is typically diagnosed using neuropsychological clinical tests (6). However, serum biomarkers that can aid in diagnosis have been a topic of study because no test or set of tests is accepted as the gold standard for identifying POCD. For this reason, S100β and neuron-specific enolase (NSE) are the most studied biomarkers in this field (7, 8).

Cardiopulmonary bypass (CPB) is regarded as a risk factor for POCD (9, 10). However, although pulsatile flow is generally accepted as superior to nonpulsatile flow due to its similarity to human physiology, the type of flow generated by the heart and

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lung machine should be discussed in terms of POCD. For this reason, we aimed to examine the effect of the 2 flow types (i.e., pulsatile and nonpulsatile) generated by a heart and lung machine on biomarkers of POCD.

Methods

Patients

This prospective, randomized study was performed between March 2010 and December 2010 after receiving approval from the local ethics committee and consent from the participating patients. Forty patients were randomly divided into 2 groups with the help of a computer-generated numbers table: Group I (n=20) was the pulsatile flow group and Group II (n=20) was the nonpulsatile flow group. Patients who underwent isolated coronary artery bypass grafting surgery (CABG) with CPB and had graduated from at least high school were included in the study. Patients with a history of carotid lesion, diabetes mellitus, valvular disease, liver and renal failure, an ejection fraction <55%, transient ischemic attack, the use of psychiatric medication, previous surgery for another reason, or a cognitive function disorder [Mini Mental State Examination (MMSE) score ≤24] were not included in the study. Also, geriatric patients (age>65 years) were excluded.

Anesthesia and extracorporeal circulation

After standard monitoring, anesthesia induction was provided using 3–7 mg/kg of sodium thiopental, 1 mcg/kg of fentanyl, and 0.08–0.1 mg/kg of vecuronium; anesthesia was maintained using desflurane and vecuronium. A central vein catheter, rectal temperature probe, and urinary catheter were placed. During CPB, a Jostra Maquet HL20 heart and lung machine (HL20-486; Lund, Sweden) that can generate both pulsatile and nonpulsatile flows, a Monolyth membrane oxygenator with a cardiotomy reservoir (Sorin Biomedical, Italy), and polyvinyl chloride tubing were used to provide extracorporeal circulation. As usual, CPB was started in non-pulsatile flow in both groups; in the pulsatile flow group, it was transformed to pulsatile flow in aortic cross-clamping period. After cross-clamping, it was switched to nonpulsatile flow again. Nonpulsatile flow CPB was performed at 60–80 mm Hg mean pressure. Flow rates were maintained between 1.2 and 2.4 L/m^2/min depending on the weight. Pulsatile flow was generated by making temporal changes in the speed of the handles of the roller pump. Prior to the initiation of CPB, 300–400 U/kg of heparin were injected, and additional doses were given when the activated clotting time was >480 s. Moderate systemic hypothermia (31–33°C) was applied to the patients. Cardiac arrest was provided via the infusion of potassium-enriched cold blood cardioplegia. While all distal anastomoses were performed using a cross-clamp, proximal anastomoses were performed using the conventional technique after the cross-clamp was removed. CPB was terminated when the body temperature reached 37°C, and heparin was neutralized with protamine.

Clinical monitoring and blood samples

The patients were observed in the intensive care unit (ICU) of the cardiovascular surgery clinic during postoperative period, and blood pressure measurements and changes in rhythm during electrocardiography (ECG) were recorded. Blood samples were collected from all patients on 2 occasions to analyze S100β and NSE prior to surgery and after surgery during the sixth postoperative hour. The MMSE was applied to evaluate cognitive condition preoperatively and on third postoperative day. The MMSE was applied and evaluated by the same researcher (S.Ö.). Postoperative complications (i.e., stroke, POCD, low cardiac output, atrial fibrillation, acute lung injury, and inotropic support) and the length of stay in ICU and in the hospital were recorded. POCD was defined as deterioration in cognition temporally associated with surgery and a 25% decline in MMSE scores (6). S100β and NSE were measured using the electrochemiluminescence method in the Roche/Hitachi Cobas e601 device (Roche/Hitachi, Indianapolis, IN, USA).

The primary outcome of the study was to determine the effects of pulsatile and nonpulsatile pump flow and the relationship of these types of flow with S100β and NSE.

Statistical analysis

The Statistical Package for the Social Sciences 16.0 package software (SPSS Inc., Chicago, Illinois, USA) was used for the statistical analysis of the data. The number of patients required in the study was determined to be 36, according to the MMSE results obtained from 5 patients in each group. However, 40 patients were included in the study in anticipation that some patients would discontinue participation in the study. The normality of the distribution was tested using the Kolmogorov–Smirnov Z test, and the homogeneity of the variables was evaluated using the Levene and Welch tests. The data were presented as the mean±standard deviation, the median (interquartile range), or the percentage. Potential differences between groups were evaluated using the independent samples test, and the Mann–Whitney U test was used to evaluate nonparametric data. The Wilcoxon and paired samples tests were used to identify differences between preoperative and postoperative values. Spearman's Rho correlation test was applied to identify correlations between variables. A p value of <0.05 were accepted as statistically significant.

Results

This study included a total of 40 patients, including 20 patients in Group I and 20 patients in Group II. A flow chart of the study design is presented in Figure 1. Mortality was not observed in either group. Differences were observed among the groups in terms of individual data (i.e., age, gender), the duration of CPB, the number of vessels to which anastomoses were applied, the length of time of aortic cross-clamp, and the presence of fever (p>0.05, Table 1).

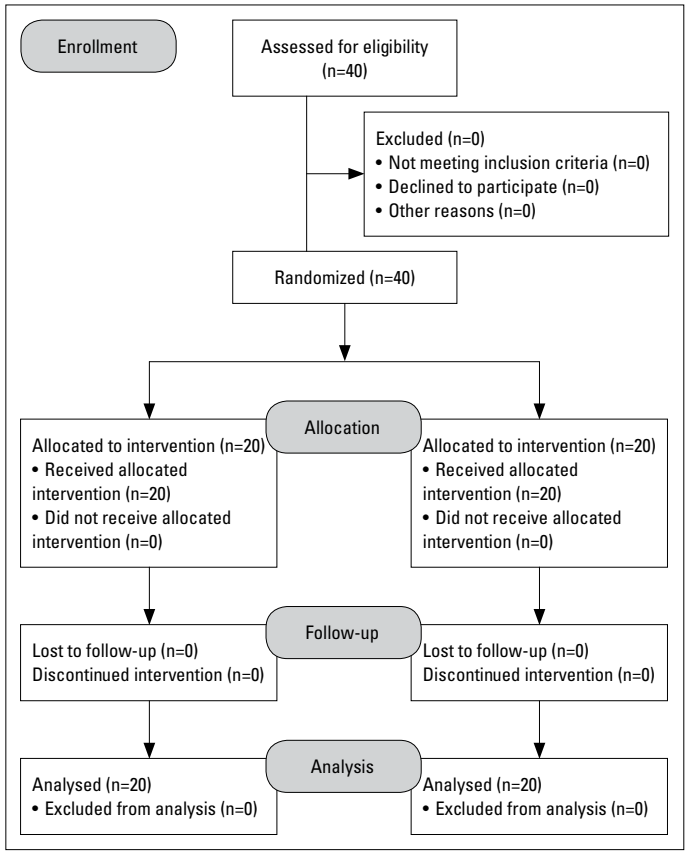

Figure 1. Flow diaphragma of research

Table 1. Comparison of demographical data, CPB time, ACCT, and temperature

	Group I (n=20)		Group II (n=20)		*P*
ACCT, min	79.6±7.5		78.7±7.9		0.763
	80.5 (60–90)		78.5 (60–90)		
CPB time, min	109.8±7.9		109.5±7.6		0.806
	110.5 (90–121)		109.5 (90–119)		
Temperature, °C	32.5±0.6		32.6±0.5		0.799
	33 (31–33)		33 (31–33)		
Age, years	55.75±4.78		56.50±6.39		0.659
	55.00 (47–62)		58.50 (47–65)		
	n	**%**	**n**	**%**	
Sex					
Male	15	75	16	80	0.799
Female	5	25	4	20	

ACCT - aortic cross-clamp time; CPB - cardiopulmonary bypass. Data are presented as mean±standard deviation and median (range); °C - centigrade degree. *Independent samples test, and the Mann–Whitney U test

The NSE and S100β measurements and the MMSE scores that were used to evaluate the cognitive function of the patients were similar between the groups in both the preoperative and postoperative periods (p>0.05, Table 2). Significant differences in NSE and S100β concentrations and MMSE scores were observed for both groups in the intragroup comparison (i.e., the comparison of the preoperative and postoperative periods) (p<0.05). Although MMSE scores decreased after surgery and the NSE and S100β concentrations increased, a significant correlation was not observed between MMSE scores and the tested biomarkers (Table 3). Moreover, there was no correlation between POCD and the biomarkers NSE and S100β (Table 4).

No differences were observed between groups in terms of the duration of stay in the intensive care unit (3.00±0.79 days in Group I, 3.20±0.77 days in Group II) and in the hospital (7.05±1.32 days in Group I, 7.40±1.35 days in Group II) during the postopera-

Table 2. Comparison of NSE, S100β, and MMSE scores

	Preoperative	Postoperative	P^a	P^b	P^c
NSE (μg·L^{-1})					
Group I (n=20)	4.1±0.2	12.5±0.8	p<0.001		
	4.2 (3.7–4.6)	12.6 (11.1–13.8)			
Group II (n=20)	4.0±0.2	12.4±0.7	p<0.001	0.858	0.843
	4.0 (3.7–4.6)	12.1 (11.4–13.8)			
S100β (μg·L^{-1})					
Group I (n=20)	0.1±0.06	1.9±0.2	p<0.001		
	0.2 (0.01–0.3)	1.9 (1.6–2.3)			
Group II (n=20)	0.1±0.06	2.0±0.2	p<0.001	0.643	0.137
	0.2 (0.01–0.3)	1.9 (1.6–2.4)			
MMSE					
Group I (n=20)	28.1±1.5	25.1±1.4	p<0.001		
	28 (26–31)	25 (23–27)			
Group II (n=20)	27.9±1.6	24.8±1.5	p<0.001	0.587	0.521
	28 (26–31)	25 (23–27)			

a - comparison of variables within the groups (preoperative-postoperative); b - comparison of preoperative variables; c - comparison of postoperative variables. MMSE-mini mental state examination; n - number of patients in each group; NSE - neuron specific enolase. Data are presented as mean±standard deviation and median (range). *Independent samples test and the Mann–Whitney U test between groups; Wilcoxon and paired samples tests between preoperative and postopera-

Table 3. Relationship between NSE, S100β, and MMSE scores

		Group I (n=20)		Group II (n=20)	
		r	*P*	r	*P*
Preoperative	P1	-0.374	0.105	-0.122	0.607
MMSE-NSE	P2	-0.419	0.066	-0.194	0.411
Postoperative	P1	-0.397	0.083	-0.119	0.617
MMSE-NSE	P2	-0.423	0.063	-0.184	0.437
Preoperative	P1	-0.043	0.856	0.198	0.404
MMSE- S100β	P2	-0.018	0.94	-0.274	0.243
Postoperative	P1	-0.066	0.781	0.185	0.434
MMSE-S100β	P2	-0.032	0.894	-0.256	0.276

P1 - preoperative; P2 - postoperative; NSE - neuron specific enolase; MMSE - mini

Table 4. Correlation between biomarkers and postoperative cognitive dysfunction

	r	*P*
Preoperative NSE	-.05	0.47
Preoperative S100β	-.05	0.5
Postoperative NSE	.1	0.2
Postoperative S100β	-.06	0.4
NSE - neuron specific enolase; * Spearman's Rho correlation test		

tive period (p>0.05). Stroke and low cardiac output were not observed in either group. No differences were observed between groups in terms of pulmonary infection (Group I, 10%; Group II, 10%) and the need for intra-aortic balloon pumps (Group I, 15%; Group II, 15%) (p>0.05). Postoperative inotropic support was provided to five patients in Group I and 8 patients in Group II (p>0.05). POCD was observed in 15% of the patients (3 patients in Group I and 3 patients in Group II) (p>0.05).

Discussion

In this study, we found that there was no differences between pump flow in context of mortality and morbidity such as POCD, length of stay in intensive care unit or hospital, stroke, pulmonary infection, need for intra-aortic balloon pump, and postoperative inotropic support. On the other hand, there was no difference in levels of S100β and NSE. Also, there was no correlation for POCD with these biomarkers. To our knowledge, our study was the first trial that demonstrated no significant effect of pump flows on NSE concentrations.

Pulsatile flow has been reported to be superior to nonpulsatile flow because pulsatile flow provides an environment that is similar to human vascular physiology in normal circumstances. However, some studies reported no significance difference between pulsatile and nonpulsatile flow (11). These findings stand in contrast to studies that indicated that pulsatile flow (12) is better in terms of neurological destruction.

Because no standard description or diagnosis criteria have been defined for POCD, which is an endemic neurological complication after heart surgery, many neuropsychological tests cannot be applied and the obtained test results can be evaluated differently (8). A set of several tests is generally used. The main reason for this approach is that no test has been described as the gold standard (5). We chose MMSE because this test is a frequently used neuropsychological test, and we accepted a 25% decrease in the number of points obtained during the postoperative period in comparison to the obtained preoperative values as POCD. Baranyi et al. (13) and Gottesman et al. (14) used a single neuropsychological test in their studies; these approaches were similar to that used in our study. The absence of a definitive neuropsychological test has necessitated the examination of biomarkers in parallel to clinical tests (7, 15, 16). For this reason, we compared the effect of 2 different heart and lung machine flow types on 2 biomarkers and MMSE scores in our study.

After testing, we observed that MMSE scores decreased postoperatively for all patients, but this reduction was at least 25% only in six patients (15%). In parallel with this finding, early POCD was diagnosed in 3 patients in each group. No differences were observed between groups in terms of POCD. The findings we acquired from clinical tests were consistent with the results of the study performed by Murkin et al. (11).

Martin et al. (17) divided the risk factors for POCD after cardiac surgery into 3 main groups: preoperative factors (i.e., age, education level, diabetes mellitus, renal failure, and hypertension), intraoperative factors (i.e., the duration of surgery, hyperglycemia, temperature, and cardiopulmonary bypass), and postoperative factors (i.e., hypoxia and temperature). We designed our study to account for possible POCD risk factors. We did not include patients who had active associated diseases. We observed that the other potential factors were similar in the 2 groups at the time of surgery. The intraoperative mean blood pressure was not below 50 mm Hg in either group.

Previous studies of POCD examined biomarkers in relation to clinical tests (7, 15, 16). The 2 most thoroughly studied biomarkers are NSE and S100β. Previous studies demonstrated that various factors can affect NSE and S100β measurements. Although hemolysis, which is an important problem during CPB, does not affect S100β, this process increases NSE concentrations (18). On the other hand, while S100β is not affected by heparin and protamine, this marker decreases in patients with carotid lesions (19, 20). While aspiration of the cardiotomy area causes an increase in S100β concentrations during surgery, this technique does not affect NSE concentrations (21). In addition, Snyder-Ramos et al. (22) proposed that a positive correlation exists between troponin I and S100β; therefore, heart tissue could be an important source of the S100β. It has been difficult to interpret the relationships between these two biomarkers and POCD because NSE is affected by hemolysis and the S100β protein can originate from different tissues.

The effect of pulsatile and nonpulsatile flow on S100β is debated. Bayram et al. (9) indicated that the main difference occurred in parallel with the use of CPB, rather than the type of flow. In contrast to these studies, Kusch et al. (23) concluded that the mean S100β concentration increased to a lower extent with a pulsatile flow than with a nonpulsatile flow. However, a significant difference in S100β concentrations was not observed between groups in our study. In contrast, postoperative S100β concentrations increased in comparison to preoperative values. Although NSE, which is the second biomarker that we investigated in our study, exhibited an increase during the postoperative period in comparison to baseline values, a significance difference was not observed among the groups. According to our literature review, our study is the first study to examine the effect of the flow types generated by a heart and lung machine on NSE. We observed that in addition to the studied biomarkers, the observed decrease in MMSE scores and the associated

incidence of POCD were not dependent on the flow type. Moreover, in contrast to Isgro et al. (24), no correlation was observed between the reduction in MMSE scores and the increase in NSE concentrations.

Different results were obtained from previous studies that investigated the relationship between NSE, POCD, and S100β. While Rasmussen et al. (7) concluded that there was no relationship between POCD, S100β, and NSE in patients who underwent non-cardiac surgery, those authors obtained different results for patients who underwent cardiac surgery (15, 16). Those researchers indicated that NSE was related to POCD during the early period after cardiac surgery, in contrast to non-cardiac surgery; however, POCD that developed after 3 months was not related to NSE or S100β. We postulated that this difference between non-cardiac and cardiac surgeries could be affected by factors such as hemolysis, which affect the concentration of NSE. Moreover, in our study, we chose to limit the inclusion of patients in the study to more effectively identify the laboratory or clinical complications that affect S100β and NSE concentrations and organ function failure. As a result, we found no significant correlation for POCD between flow types (25) and biomarkers (15) in contrast to the existing literature.

Study limitations

Our study had 3 limitations. First, this study only applied 1 test for detecting cognitive function failure. Second, this study collected preoperative and postoperative measurements rather than measuring the biomarker concentrations serially. Third, we examined only early period POCD. We chose to apply only 1 test to more effectively identify the relationship between NSE, S100β, and POCD, which was the primary outcome of our study. In POCD studies, the inconsistency of patients in the context of the tests increased with increased study duration.

Conclusion

We demonstrated that the type of flow generated by the heart and lung machine does not affect early period POCD and that pulsatile flow was not superior to nonpulsatile flow in context of POCD, in contrast to the generally accepted belief. In addition, NSE and S100β concentrations were not effective markers for identifying POCD. At the same time, both S100β and NSE were unaffected by the type of flow (pulsatile vs. nonpulsatile).

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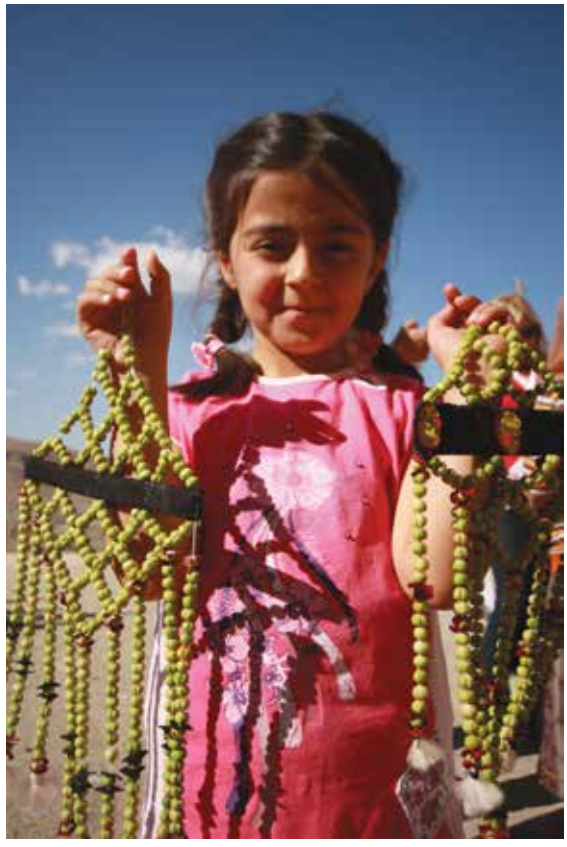

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