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THE EFFECT OF PULSATILE AND NON-PULSATILE EXTRA CORPOREAL PERFUSION ON CEREBRAL OXYGEN SATURATION IN CARDIOPULMONARY BYPASS PATIENTS
(FLOW TYPE ON CEREBRAL OXYGENATION)

Kardiyopulmoner Bypass Hastalarında Pulsatil ve Pulsatil Olmayan Ekstra Korporeal Perfüzyonun Serebral Oksijen Satürasyonuna Etkisi
(Akım Türünün Serebral Oksijenasyona Etkisi)

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Abstract

Aim: The flow type generated by a heart-lung machine is important in cardiopulmonary bypass. The use of pulsatile flow versus non-pulsatile flow during cardiopulmonary bypass has been a controversy among clinicians. We compared the effect of non-pulsatile and pulsatile flow during cardiopulmonary bypass on cerebral oxygenation.

Materials and Methods: We conducted a retrospective study of 50 adult patients who underwent coronary artery bypass graft surgery at our university hospital, with near infrared spectroscopy used to compare differences in cerebral oxygenation between the pulsatile and non-pulsatile flow type.

Results: There was no difference between the effect of pulsatile and non-pulsatile flow on the saturation of hemoglobin (SpO2), nor on the partial pressure of oxygen (pO2) and carbon dioxide (pCO2). The near infrared spectroscopy results were not different between the two flow types.

Conclusion: There was no effect of the flow type generated by a heart-lung machine (pulsatile or non-pulsatile) on cerebral oxygenation in adult patients.

Keywords: Cardiopulmonary bypass, Perfusion, Near infrared spectroscopy.

Öz

Amaç: Kalp akciğer makinesi tarafından oluşturulan akım türü kardiyopulmoner bypassta önemlidir. Kardiyopulmoner bypass sırasında pulsatil akıma karşı pulsatil olmayan akımın kullanılması klinisyenler arasında bir tartışma konusu olmuştur. Kardiyopulmoner bypass sırasında pulsatil olmayan ve pulsatil akımın serebral oksijenasyon üzerindeki etkisini karşılaştırdık.

Materyal ve Metot: Üniversite hastanemizde koroner arter bypass greft cerrahisi yapılan 50 erişkin hastanın pulsatil ve pulsatil olmayan akım tipi arasındaki serebral oksijenasyon farklarını karşılaştırmak için kullanılan yakın kızılötesi spektroskopi ile retrospektif bir çalışma yaptık.

Bulgular: Pulsatil ve pulsatil olmayan akımın SpO2, pO2, pCO2 üzerindeki etkileri arasında anlamlı bir fark yoktu. Yakın Kızılötesi Spektroskopisi verilerinde her iki akım türü arasında anlamlı bir fark yoktu.

Sonuç: Erişkin hastalarda kalp-akciğer makinesi (pulsatil veya pulsatil olmayan) tarafından üretilen akım tipinin serebral oksijenasyona etkisi yoktu.

Anahtar Kelimeler: Kardiyopulmoner bypass, Perfüzyon, Yakın kızılötesi spektroskopisi.

INTRODUCTION

The flow type generated by a heart-lung machine is important in cardiopulmonary bypass treatment [1]. Until recently, the use of pulsatile flow during cardiopulmonary bypass was constrained by inadequate clinical experience, technological limitations (such as the inability of the pulsatile pump to generate sufficient pulsatility) and clinical concerns related to hemolysis. However, as the technology of bypass machines has improved, clinical experience in using pulsatile flow has been accumulating [2], although the advantages of either type of flow (pulsatile or non-pulsatile) during cardiopulmonary bypass has remained an issue of clinical controversy [3-5].

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Non-pulsatile blood flow has the advantage of being a robust technical method while pulsatile flow mimics the natural flow of a beating heart[6]. In adults, pulsatile flow improves pulmonary, hepatic and renal functions, while in children, pulsatile flow decreases the need for inotrope agents and cerebral oxygenation[3]. Moreover, pulsatile flow lowers pulmonary vascular resistance and edema formation, and improves microcirculation and metabolism compared to non-pulsatile flow. Despite these known advantages of pulsatile flow, there is currently no substantive evidence of its superiority of non-pulsatile flow[4]. Moreover, there have been reports that non-pulsatile flow causes an activation of inflammatory mediators, capillary collapse and microvascular shunting which leads to a hemodynamic energy decrease[7]. These negative effects of non-pulsatile flow might be related to the 60-80 mmHg mean arterial pressure required, compared to a pressure 10% above baseline being needed to generate a pulsatile flow [4].

The differential effects of pulsatile and non-pulsatile flow might be important to consider for patients who are at risk of adverse perioperative outcomes after coronary artery bypass surgery, due to various etiological factors, including embolic events and cerebral hypoperfusion[8]. During cardiopulmonary bypass cerebral perfusion may be impaired due to venous congestion, embolic events in the arterial system, carotid stenosis, and technical difficulties related with the cannulas used[6]. Hence, flow type selection is crucial in these patients to improve cerebral oxygenation and outcomes. Therefore, our goal was to compare the effect of non-pulsatile and pulsatile flow during cardiopulmonary bypass on cerebral oxygenation using near infrared spectroscopy (NIRS), which has been approved by the by United States Food and Drug Administration since 1993 for the measurement cerebral oximetry[9, 10].

MATERIAL AND METHODS

Statement of ethics

Our study was approved by our institutional Research Ethics Board (2018.137.10.02) and patients provided informed consent prior to surgery.

Study design and patient selection

This was a retrospective analysis of patients who underwent coronary artery bypass graft surgery under cardiopulmonary bypass at our university hospital. Patients were selected over a 3 month period (August, September, November 2018) of observation by a researcher not involved in the study. Patients who had known carotid stenosis and those who underwent an emergency procedure were excluded. The identified patients were classified into the pulsatile and non-pulsatile group, based on the flow type of cardiopulmonary bypass used. After classification, 20 patients were randomly selected from each group, using a computer-based selection, for enrollment into the study.

Surgical approach

The flow type, pulsatile or non-pulsatile, was selected based on each surgeon’s preference, taking into consideration of the patients’ medical condition. All operative procedures were performed under a standard protocol involving anesthesia induction and maintenance, heart-lung machine components, prime composition, cardioplegia solution, and postoperative care. Routine anesthesia preparation of coronary artery bypass graft surgery was as follows. After the pre-operative visit, proper sedation was maintained with morphine and diazepam on the morning of the surgery. In the operation room, all the patients were monitored using 5-way electrocardiography, non-invasive blood pressure, peripheric oxygen saturation and NIRS of cerebral oxygenation. Two peripheral venous access points were obtained using an 18 gauge venous cannula. Following Allen test, radial artery cannulation and monitoring was completed and anesthesia induced as follows: diazepam, 20 mg; lidocaine 2%, 100 mg; fentanyl, 3.5 mcg kg^{-1}; and rocuronium, 0.6 mcg kg^{-1}, all introduced intravenously. Following successful intubation, a 3-way right internal jugular venous catheter was inserted under ultrasound guidance. An esophageal temperature probe and urinary catheter were placed. Anesthesia was maintained using 4L of 60% oxygen and 40% air mixture with sevoflurane 1.0 MAC.

Following median sternotomy, the left internal mammary artery was mobilized and the saphenous venous graft was prepaid. A roller pump heart-lung machine, consisting of a bubble oxygenator and venous reservoir was used in all cases. A primary solution consisting of 1000 ml of ringer lactate was used, with 20% mannitol, 10 ml calcium gluconate, sodium bicarbonate and 5000 units of heparin, with a total hematocrit target of 25%. After heparinization (dosage, 3 mg kg^{-1}, intravenous) cannulation was started if the activated coagulation time (ACT) was sufficiently long (at least 480 s). Arterial cannulation was performed on the ascending aorta, with a two-stage venous cannulation performed on the right atrium. Cardiopulmonary bypass was initialed under mild systemic hypothermia (32°C). After cross clamping of the aorta, 10 mL kg^{-1} of cold cardioplegic solution, prepared with blood and consist of plegisol, potassium and magnesium, was injected, with repeated doses (5 ml kg^{-1}) repeated every 20 min. In the pulsatile group, pulsatile flow, at a 10% base flow with 65 beats per min, was maintained during aortic clamp. In the non-pulsatile group, pump flow was maintained at a mean arterial pressure of 60-80 mmHg and 2.3-2.5 L m$^{2-1}$ min^{-1}.

Distal anastomosis and proximal anastomosis were performed under cross clamp and side clamp, respectively. Following the anastomosis, the patient was gradually warmed and cardiopulmonary bypass terminated when a core temperature of 37°C was reached, and hemodynamic and laboratory parameters reached normative values. Protamine sulfate was infused and decannulation was performed. Following deheparinization control ACT measurement, arterial blood gas control was repeated before transport to the intensive care unit. All the hemodynamic parameters, including NIRS, were recorded.

NIRS monitoring

NIRS monitoring for cerebral oxygenation is routinely performed during coronary artery bypass graft surgery under cardiopulmonary bypass at our hospital. The self-adhesive NIRS pads, which contain both the emitter and sensor of near infrared light, are applied to the skin of the forehead for cerebral oximetry. Two wavelengths of light are used, 700 and 850 mm. These wavelengths are used in commercial devices and provide the maximum separation between the absorption spectra for oxyhemoglobin and deoxyhemoglobin [9, 10]. Regional cerebral oxygen saturation ($rScO_2$) is measured, reflecting the saturation of oxygen in veins (70-80%), arteries (20-25%) and capillaries (5%) [11]. Unlike pulse-oximetry, cerebral oximetry by NIRS does not differentiate arterial and venous blood, providing global information on regional oxygen supply and demand [9]. As the basal measurements differ in each patient, basal NIRS measurements were save and used for continuous monitoring, with a change >25% being indicative of a possible neurological event resulting from decreased cerebral oxygenation [12].

Statistics analysis

Categorical data were described as numbers (%), with continuous data reported as the mean±standard deviation (SD) for normally distributed data and the median (interquartile range) for non-normal distributions. Normality of the distribution was evaluated using the Kolmogorov Smirnov test.

Age, height, weight, the duration of aortic clamping, total bypass, and temperature were compared between the pulsatile and non-pulsatile groups using an independent t-test. The effects of diabetes type I and II (DM) and of non-pulsatile and pulsatile flow on left and right NIRS spectra were evaluated, as well as values of the hemoglobulin saturation (SpO2), partial pressure of oxygen (pO2) and carbon dioxide (pCO2), and the hematocrit, over time, using a two-way repeated measure analysis of variance (ANOVA). Multiple comparisons were evaluated using Tukey's test in the case of parametric tests. Pearson's chi-square was used to compare the differences between categorical variables, in 2x2 tables.

All analyses were performed using R-3.5.2 (for Windows. The R-project for statistical computing), Jamovi project (2018), Jamovi (Version 0.9.5.12) [Computer Software], (Retrieved from https://www.jamovi.org) and JASP Team (2018), JASP (Version 0.9) [Computer software] software. "R Commander" and" RcmdrPlugin.KMggplot2" packages were used in the creation of the graphics. For all tests, significance was set at a p-value of 0.05.

RESULTS

The study group included 25 patients in each group, with a mean age of 61.18±9.35 (range, 43-80) years. Of these, 16 (32%) had DM and 33 (66%) hypertension (HT). Between-group comparisons of the baseline and surgical variables (sex, age, height, weight, DM, HT, aortic clamp time, total bypass, and temperature values) are reported in Table I. Only the rate of HT was higher in the non-pulsatile than pulsatile flow group (p=0.037). In patients who underwent non-pulsatile flow, the aortic clamping (p=0.020) and total bypass time (p=0.044) were higher than those in the pulsatile flow group.

Table I. Comparison of the demographic and clinical features among patients in the pulsatile and non-pulsatile groups

	Flow		
	Non-Pulsatile	**Pulsatile**	**p**
Sex (Male / Female)	14 (46.7) / 11 (55.0)	16 (53.3) / 9 (45.0)	0.564*
Age	62.4 ± 8.7	59.9 ± 10.0	0.484**
Height	166 ± 10.1	167.4 ± 7.7	0.565**
Weight	76 ± 15.6	74.3 ± 12.6	0.939**
Diabetes Mellitus (+)	9 (56.2)	7 (43.8)	0.544*
Hypertension (+)	20 (60.6)	13 (39.4)	**0.037***
Aortic clamp time	56.2 ± 22.2	44.1 ± 18.6	**0.020****
Total bypass time	86.7 ± 29.9	72.0 ± 25.4	**0.044****
Temperature	32.8 ± 1.2	33.1 ± 0.5	0.539**

Categorical data are reported as a number (%) and continuous data as the mean±standard deviation. *: Chi-squared test; **: independent group t-test; was used for independent groups. P-values reported in bold type are significant (p<0.05).

The effects of non-pulsatile and pulsatile flow on measured (right and left) NIRS values and hematocrit, over time, are reported in Table II, with no between-group differences identified. An influence of DM on pO2 was identified (p=0.002), with no effect on other variable identified. Specifically, DM was associated with a higher pO2 at the 20th and 40th min, compared to initial values.

Table II. Effect of flow type and diabetes mellitus (DM) on right and left NIRS, pO2, pCO2, and hematocrit values at the initial and 20th and 40th minute

	Flow					DM			
	General	**Non-Pulsatile**	**Pulsatile**	P^{β}	$P^{€}$	**(+)**	**(-)**	p^{β}	$p^{¥}$
NIRS Left									
Initial	61.26 ± 9.10	60.96 ± 7.47	61.56 ± 10.63	**<0.001**	0.703	58.25 ± 9.88	62.68 ± 8.49	**<0.001**	0.502
20th min.	55.58 ± 7.66	56.04 ± 6.25	55.12 ± 8.96			54.06 ± 6.17	56.29 ± 8.25		
40th min.	57.94 ± 7.65	58.16 ± 6.56	57.72 ± 8.74			56.13 ± 7.13	58.79 ± 7.84		
NIRS Right									
Initial	61.18 ± 9.01	60.56 ± 8.60	61.80 ± 9.54	**<0.001**	0.948	59 ± 10.2	62.21 ± 8.35	**<0.001**	0.413
20th min.	55.98 ± 7.61	55.60 ± 6.35	56.36 ± 8.82			55.5 ± 7.21	56.21 ± 7.89		
40th min.	58.40 ± 8.44	57.72 ± 8.24	59.08 ± 8.76			56.38 ± 7.49	59.35 ± 8.8		
PO2									
Initial	138.34 ± 81.15	142.24 ± 85.42	134.44 ± 78.22	**<0.001**	0.868	87.63 ± 31.88	162.21 ± 86.51	**<0.001**	**0.002**
20th min.	247.70 ± 45.85	247.04 ± 53.91	248.36 ± 37.21			239.25 ± 46.6	251.68 ± 45.65		
40th min.	211.84 ± 52.22	217.44 ± 61.86	206.24 ± 40.94			220.88 ± 54.66	207.59 ± 51.31		
PCO2									
Initial	38.40 ± 4.33	38.68 ± 4.46	38.12 ± 4.27	**<0.001**	0.417	38.81 ± 4.68	38.21 ± 4.21	**<0.001**	0.969
20th min.	31.83 ± 4.18	31.74 ± 4.04	31.92 ± 4.41			31.97 ± 3.89	31.76 ± 4.37		
40th min.	31.95 ± 3.90	31.24 ± 3.65	32.66 ± 4.07			32.19 ± 4.09	31.84 ± 3.86		
SPO2									
Initial	96.40 ± 4.45	95.84 ± 5.95	96.96 ± 2.11	**N/A**	N/A	93.50 ± 6.69	97.76 ± 1.76	**N/A**	N/A
20th min.	99.12 ± 0.33	99.16 ± 0.37	99.08 ± 0.28			99.06 ± 0.25	99.15 ± 0.36		
40th min.	99.00 ± 0.29	98.96 ± 0.35	99.04 ± 0.2			98.94 ± 0.44	99.03 ± 0.17		
Hematocrit									
Initial	41.56 ± 6.11	41.16 ± 5.86	41.96 ± 6.45	**<0.001**	0.914	41 ± 7.01	41.82 ± 5.73	**<0.001**	0.283
20th min.	22.36 ± 5.23	21.8 ± 5.69	22.92 ± 4.78			21.88 ± 5.68	22.59 ± 5.08		
40th min.	23.12 ± 4.42	22.4 ± 5.16	23.84 ± 3.50			22.88 ± 4.22	23.24 ± 4.57		
Final	25.62 ± 3.48	25.28 ± 4.17	25.96 ± 2.65			26.5 ± 3.46	25.21 ± 3.45		

N/A: Not available. β: Change over time, €: Flow*Time common interaction probability (p) value, ¥: DM*Time common interaction probability (p) value. A two-way analysis of variance with repeated measures was used. Descriptive statistics are presented as mean±standard deviation. Significant p-values are reported in bold (p <0.05).

The time-dependent changes in NIRS (right and left) values, pO2, pCO2, SpO2 and hematocrit were also investigated, with a significant change over time identified (p<0.001 for each). The right and left NIRS values were significantly lower, than initial values, at the 20th and 40th min, with values at the 40th min being higher than those at the 20th min. The pO2 was higher at the 20th and 40th min, compared to initial values, while the pCO2 and hematocrit values at these two time points were lower than initial values.

DISCUSSION

There is ongoing controversy regarding the superiority of pulsatile flow over non-pulsatile flow during cardiopulmonary bypass [3], with some studies reporting benefits of pulsatile flow on hemodynamics, metabolism, organ function, microcirculation, and histology, while others not findings these benefits [3, 13-18]. Previous studies have used NIRS as an outcome measure to compare pulsatile and non-pulsatile flow. In their study, Tovedal et al. [6] reported on effects of these two flow types in 20 patients, 10 with carotid stenosis and 10 without. Both flow modes were applied for each patient during aortic cross-clamping, thereby, providing an internal control. No improvement in NIRS was provided by the pulsatile flow, for each case and no improvement on NIRS was found by pulsatile flow but only the mean arterial pressure was significantly lower during pulsatile than non-pulsatile flow. Zhao et al. [19] compared NIRS values for the two flow types among children who underwent cardiac surgery for the correct of a tetralogy of Fallot, with 20 children in each group. They reported a higher rSO2 for the pulsatile than non-pulsatile group during the cross-clamp period. In their study of 111 pediatric patients, Su et al. [16] reported decreases in rSO2, from baseline, at all time points in the group receiving pulsatile flow perfusion. Of note, this study included 77 patients in the pulsatile group and 34 in the non-pulsatile. Our study, which included 25 patients in the non-pulsatile group and 25 in the pulsatile group, did not identify any differences in rSO2 between the two flow types. In their review of the literature between 1952 and 2006, Ji and Undar [4] provided evidence of significantly improved blood flow to the vital organs (brain, heart, liver, and pancreas), reduced systemic inflammatory response syndrome, and decreased incidence of postoperative mortality, in both pediatric and adult patients, treated with pulsatile versus non-pulsatile flow. Our study did not identify a significant difference in cerebral oxygenation between the two flow types.

Grubhofer et al. [5] used NIRS to measure cerebral oxygenation parameters, such as oxyhemoglobin (HbO2), deoxyhemoglobin (Hb) and oxidized cytochrome aa3 (CtO2), during elective cardiac surgery, with no evidence of superior benefit of pulsatility versus non-pulsatility identified. They concluded that pulsatile flow does not improve cerebral oxygenation, which supports our study findings.

Pulsatile flow has been shown to improve renal function during and after cardiopulmonary bypass surgery. Hökenek et al. [20] reported significantly lower values of cystatin C, creatinine and blood urea nitrogen values for the pulsatile than non-pulsatile group, on day 3 post-surgery.

They also reported a significant difference between the groups in terms of urine output during cardiopulmonary bypass, and a lower incidence rate of acute kidney injury. Kim et al. [20] also showed a substantially higher renal tissue perfusion flow with pulsatile than non-pulsatile bypass in an experimental animal model. Poswal et al. [21] compared hematological parameters, clotting profile, renal parameters, hepatic function tests, and hemodynamic variables between pulsatile and non-pulsatile flow among patients who underwent cardiopulmonary bypass. Creatinine clearance and urine output were better in the pulsatile than non-pulsatile flow group, while the coagulation profile, renal function parameters and liver function tests were not significantly different between the two groups.

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CONCLUSIONS

Although some previous studies have reported a clinical benefit of pulsatile over non-pulsatile flow during cardiopulmonary bypass, we did not find a significant difference between these two flow types with regard to NIRS spectra, SpO2, pCO2, pO2, and hematocrit values. Our findings underlie the continued controversy regarding the possible advantages of pulsatile over non-pulsatile flow, with future studies warranted for evidence to guide practice. Moreover, with rapid advances in technology, new pulsatile pumps may be developed that will mimic the natural flow generated by the native heart.

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