# Relationship Between Extracorporeal Perfusion Pattern and Ischemic Brain Lesions

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## ABSTRACT

**Background:** We aimed to investigate the post-procedure effect of pulsatile and non-pulsatile flow utilized in cardiopulmonary bypass on brain ischemia among patients undergoing coronary artery bypass grafting (CABG) surgery. **Methods:** A total of 80 patients undergoing elective CABG between April 2012 and January 2013 were separated into two groups. While pulsatile flow was implemented during cardiopulmonary bypass in 40 patients, non-pulsatile flow was used in the remaining 40 cases. Formation of new ischemic lesions in the brain was evaluated by Diffusion-weighted magnetic resonance imaging (DW-MRI), performed prior to and after the operation. **Results:** No statistically significant differences were found between the two groups in terms of demographic values and concomitant diseases. New focal lesions were detected in 7 of 40 patients subjected to pulsatile flow (17.5%) and in 4 of 40 cases subjected to non-pulsatile flow (10%). Although the number of new lesions detected on brain diffusion MRI in the non-pulsatile flow patient group was lower in terms of the number of patients and the number of lesions, no statistically significant differences were determined between the two groups. **Conclusions:** Magnetic resonance imaging evidence of brain injury were similar after pulsatil-pump and nonpulsatil-pump coronary artery bypass grafting surgery.

**Keywords:** Coronary artery bypass grafting, diffusion-weighted magnetic resonance imaging, pulsatile flow, nonpulsatile flow

## INTRODUCTION

Coronary artery bypass grafting (CABG) is a type of surgery which is known to be associated with adverse neurological outcomes. With improvements in cardiac surgery, anesthesia and cardiopulmonary bypass (CPB) techniques, the reported frequency of stroke after coronary artery bypass grafting varies between 1.5% and 6%[1]. Following coronary artery bypass graft surgery, some studies using magnetic resonance imaging (MRI) have demonstrated new small ischemic brain lesions in patients without apparent neurological deficits[2]. Diffusion-weighted magnetic resonance imaging (DW-MRI) of the brain is especially sensitive and can depict ischemic areas that may not be evident clinically or with conventional MRI[3]. Diffusion-weighted MRI is superior to conventional MRI and allows for sensitive and early detection of ischemic brain lesions[4].

Pulsatile CPB is considered to be more physiological than nonpulsatile flow as it provides a lower systemic vascular resistance and higher oxygen consumption. The pulsatile energy ensures the patency of the vascular bed, improves microcirculation and enhances diffusion[5–7].

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There are a few studies demonstrated the beneficial effect of PF in reducing the incidence of stoke or renal failure. The evidence is insufficient to recommend for or against routinely providing the pulsatile profusion to reduce the incidence of stroke or renal failure[8]. We aimed to investigate the post-procedure effect of pulsatile and non-pulsatile flow utilized in cardiopulmonary bypass on brain ischemia among patients undergoing coronary artery bypass grafting (CABG) surgery .

## Methods

Forty patients undergoing elective CABG between April 2012 and January 2013 were separated into two groups. Patients diagnosed with carotid stenosis on the preoperative Carotid artery lesions detected by Doppler ultrasound, cases with lesions on diffusion MRI and aortic plaque formation detected in the perioperative period were the exclusion criteria from the trial. During the cardiopulmonary bypass, pulsatile flow was performed in 40 patients, while non-pulsatile flow was performed in the remaining 40 cases. Brain diffusion MRI was performed on all patients during the preoperative and the postoperative periods.

This prospective study included any patient undergoing elective CABG with no contraindications for MRI (including allergy to gadolinium-DTPA, presence of pacemaker, aneurysm clips, and/or a history of shrapnel injury); no concomitant cardiovascular surgical procedures were contemplated.

Neurological examination was applied to subjects to investigate neurological condition and the presence of a stroke using the The National Instute of Health ( NIH ) Stroke Scale .

The patients had to be able to provide written consent. Informed consent was obtained from all subjects before the first MRI. Our protocol consisted of obtaining the brain MRIs within one week before and after the surgery. The trial was approved by the institutional research and ethical commitee at our institution.

### *Surgical Procedure*

After premedication, anesthesia was induced with midazolam (70 mg/kg) and fentanyl (10 μg/kg). Muscle relaxation was achieved with pancronium bromide (0.1–0.2 mg/kg).

Anesthesia was supported by inhalation of isoflurane 0.5% to 1% (Abbot Laboratories, North Chicago, IL, USA). The extra corporeal circuit consisted of a roller pump (Stöckert Instrumente, Munich, Germany) with a non-pulsatile and pulsatile running mode, a hollow fiber membrane oxygenator (D 708 simplex III, Dideco, Mirandola, Italy). Patients were heparinized before initiation of CPB with 300 IU/kg, and additional doses were given to maintain an Activated Clotting Time (ACT) of more than 480 seconds. Extra-corporeal circulation was initiated with a flow of 2.4 to 2.6 L/m2/min.

### *Neuroimaging Studies*

All 40 patients undervent preoperative and postoperative brain MRI examination. Preoperative studies were made one day before operation and postoperative studies were made 72 hours after the operation. Brain MRI examination consisted of DWI series.

DWI was performed by use of single-shot , multislice, spin-echo, diffusion—weighted echo planar imaging of whole brain with B value 0, 1000 The paremeters of DWI are: TR 4200 msn , FOV 22 cm , NEX 2 , Matrix 160 100 slice thicknes 4.5 mm in axial plane total of 25 slices.

All examinations were evalueted by two experienced radiologists. The consensus was obtained for the presence and number of the lesions. The radiologists were blinded to the outcome and the identity of all patients. The abnormal number of signal hyperintensty were calculated on DWI images.

### *Statistical method*

The SPSS 11 (SPSS 11.0 (SPSS Inc., USA) was used for statistical analysis. Age, CPB, and aortic cross clamp scores were compared by the Independent Samples T test. Diabetes mellitus, hypertension, hyperlipidemia, and number of the patients who had new ischemic brain lesions were compared by the chi-square tests. A p value less than 0.05 indicated statistical significance.

## Results

In patients undergoing elective CABG, pulsatile flow was performed in Group 1 and non-pulsatile flow was performed in Group 2 during the cardiopulmonary bypass. No statistically significant differences were found between the two groups in terms of parameters evaluated in the preoperative and the postoperative periods, namely age, gender, diabetes mellitus, hyperlipidemia, hypertension, duration of aortic cross clamp and duration of cardiopulmonary bypass (Table

1, Table 2). New focal lesions were detected with diffusion MRI in 7 of 40 patients subjected to pulsatile flow and in 4 of 40 patients subjected to non-pulsatile flow, hence, 11 patients from the total of 80 patients (Table 3). The number and location of the new ischemic brain lesions are shown below (Figure 1).

**Table 1 Demographic profile of the patients (PF: pulsatile flow, NPF: nonpulsatile flow)**

| | PF(N=40) | NPF(N=40) | p value |
|---|---|---|---|
| ***Gender*** | F:8(20%)M:32(80%) | F:10(25%)M:30(75%) | 0.881 |
| ***Age (Mean±STD)*** | 56.50±8.54 | 60.91±8.26 | 0.765 |
| ***Diabetes Mellitus*** | 17 ( 42.5 %) | 20 (50%) | 0.501 |
| ***Hyperlipidemia*** | 12 (30%) | 12 (30%) | 1.000 |
| ***Hypertension*** | 20(50%) | 18(45%) | 0.890 |

**Table 2 Duration of cardiopulmonary bypass (CPB) and cross clamp (X-clamp) (PF: pulsatile flow, NPF: nonpulsatile flow)**

| | PF | NPF | p value |
|---|---|---|---|
| ***X-clamp (Mean±STD)*** | 50.95±16.68 | 59.09±13.50 | 0.89 |
| ***CPB (Mean±STD*** | 91.95±27.04 | 108.68±29.48 | 0.63 |

**Table 3 Total number of new ischemic brain lesions following coronary artery bypass surgery (PF:pulsatile flow, NPF:nonpulsatile flow)**

| ***New ischemic lesion*** | **PF** (N=40) | NPF(N=40) | p value | Total (N:80) |
|---|---|---|---|---|
| ***No. of the patients*** | 7 (17.5%) | 4(10%) | 0.330 | 11 (13.7%) |

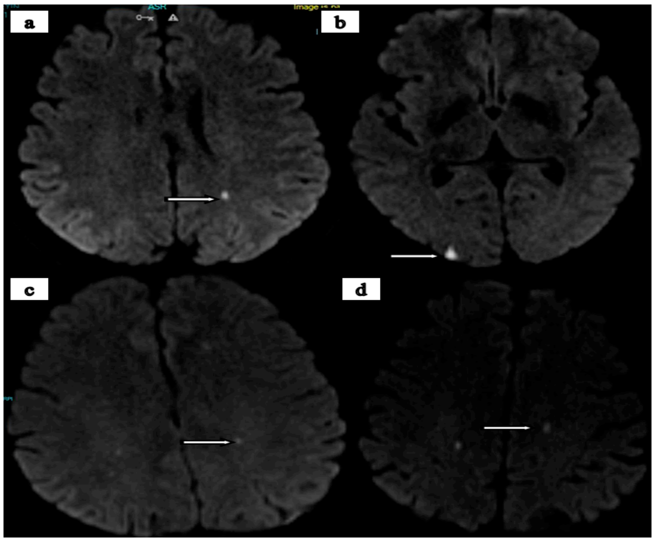


**Figure 1:**
**a)** restricted diffusion in left posterioparietal white matter
**b)** right occipital cortical
**c)** bilateral centrum semiovale
**d)** Bilateral foci of restricted diffusion in centrum semiovale white matter

None of the participating subjects had any neurological complaints or symptoms before surgery. NIH stroke scale score was 0 in all cases. After surgery, the neurological examination of the subjects that had new ischemic lesions in DWI and subjects with no lesions monitored as normal and the NIH score was 0.

Although the number of the patients with new ischemic lesions detected with brain diffusion MRI was lower in the non-pulsatile flow group, the difference was statistically insignificant. There were multiple ischemic lesions in both groups (Table 4).

## Discussion

CABG may be associated with neurological complications. The incidence of such complications is 0.4% to 5.7% for stroke, 10% to 28% for delirium, and 33% to 83% for persistent cognitive dysfunction and behavioral changes. Several risk factors for postoperative stroke have been postulated, including hypertension,

**Table 4 Location and number of the ischemic lesions (PF: pulsatile flow, NPF:nonpulsatile flow)**

| GROUP | No. of the ischemic lesions | Location of the ischemic lesions |
|---|---|---|
| *PF 1* | 5 | Bilateral occipital lobe, Right frontal lobe cortical-subcortical 20mm, left posterior parietal occipital subcortical 15mm and right caudate nucleus |
| *PF 2* | 2 | Right cerebellum cortical-subcortical |
| *PF 3* | 4 | Bilateral centrum semiovale, right frontal white matter |
| *PF 4* | 2 | Right occipital cortical, right frontal white matter |
| *PF 5* | 3 | Left cerebellum cortical-subcortical |
| *PF 6* | 2 | Left posterior parietal occipital subcortical |
| *PF 7* | 2 | Right centrum semiovale |
| *NPF 1* | 5 | Bilateral centrum semiovale, left frontal, bilateral posterior parietal white matter |
| *NPF 2* | 3 | Bilateral posterior parietal white matter and left centrum semiovale |
| *NPF 3* | 2 | Right occipital cortical |
| *NPF 4* | 2 | Left cerebellum cortical-subcortical |

diabetes mellitus, carotid stenosis, previous stroke, and age of ≥65 years[9]. In the current trial, no significant difference was found in terms of the preoperative risk factors. Postoperative stroke was not observed in any of the patients. All the patients were observed to be asymptomatic.

Clinically recognized cerebral infarction occurs in 2% to 6% of patients (1–3). It's presumably due to macroemboli arising from the cardiac chambers or cardiopulmonary bypass circuit or from atheromatous debris within the aortic arch. A shower of small embolic particles combined with decreased washout from cerebral hypoperfusion can produce a clustering of ischemic lesions in a watershed distribution. Several different mechanisms have been postulated to explain cerebral dysfunction after CABG, including cerebral hypoperfusion, cerebral edema, activation of inflammatory processes, and cerebral microembolism derived from air, atheromatous debris, small clots or particulate matter from the bypass circuit or lipid particles[10]. Atherosclerotic disease of the aorta is a known risk factor for stroke after cardiac surgery[11].

We believe that the new focal lesions observed in the current trial are due to emboli originating from the aorta or the heart during the operation, or due to the circulation of the heart-lung machine pump. We currently use filters in the arterial line in order to prevent embolic events originating from the heart lung machine. In order to prevent cardiac emboli, all the patients are subjected to preoperative echocardiography.

Several preoperative risk factors are significant in the development of delirium or stroke following CABG. In a prospective study of 456 patients undergoing CABG, we identified five preoperative factors associated with stroke: increasing age, history of previous stroke, hypertension, diabetes mellitus, and presence of a carotid bruit. The only significant intra-operative factor was the cardiopulmonary bypass time[9]. In the current trial, no statistically significant differences were found between the two groups in terms of the preoperative demographic data and concomitant diseases. The durations of cardiopulmonary bypass were also similar.

The presence of new ischemic brain infarcts, detected by diffusion-weighted magnetic resonance imaging

(DW-MRI), have been reported in considerable number of patients after cardiac surgery[12]. Clinically silent infarction may be far more frequent and could contribute to long-term cognitive dysfunction in patients after cardiac procedures. Using diffusion-weighted magnetic resonance imaging we document the occurrence, vascular distribution, and procedural dependence of silent infarction after cardiac surgery with cardiopulmonary bypass[1].

DWI is more sensitive than computerised tomography and conventional MRI sequences for the detection of early signs of ischemia, disclosing areas of brain infarction within a few hours after symptom onset in ≈95% of acute stroke patients[13]. In our study, DWI was performed in the pre- and the post-operative periods in all patients.

In a previous trial, new focal lesions were detected with diffusion MRI in the postoperative period in 5 of 16 patients (31%) following off-pump CABG. Ischemic lesions found at DW-MRI are seen after off-pump CABG at a rate similar to that reported for CABG with cardiopulmonary bypass[3]. In another trial, 32 new ischemic lesions were found with postoperative diffusion-weighted MRI in 13 of 29 patients undergoing the CABG operation[4]. New lesions were detected with diffusion MRI in 4 of 13 patients (31%) undergoing CABG in another similar trial[14]. In the current trial, in 11 of a total of 80 patients (13.7%), namely in 7 of 40 patients subjected to pulsatile flow (17.5%) and in 4 of 40 patients subjected to non-pulsatile flow (10%), new ischemic lesions were detected with postoperative diffusion-weighted MRI.

The controversy over the benefits of pulsatile and non-pulsatile flow during cardiopulmonary bypass procedures continues. The evidence is insufficient to recommend for or against routinely providing the pulsatile profusion to reduce the incidence of stroke[15]. In a trial conducted on 995 patients subjected to pulsatile perfusion and on 905 patients subjected to non-pulsatile perfusion during bypass, the pulsatile perfusion group was observed as having a higher incidence of early postoperative mortality (2.6% versus 1.5%) and cerebrovascular events (3.1% versus 1.3%)[16].

Medline database was used to search all of the literature on pulsatile vs. nonpulsatile perfusion published between 1952 and 2006. We found 194 articles related to this topic in the literature. Based on our literature search, we determined that pulsatile flow significantly improved blood flow of the vital organs including brain, heart, liver, and pancreas; reduced the systemic inflammatory response syndrome; and decreased the incidence of postoperative deaths in pediatric and adult patients. We also found evidence that pulsatile flow significantly improved vital organ recovery in several types of animal models when compared with nonpulsatile perfusion. Several investigators have also shown that pulsatile flow generates more hemodynamic energy, which maintains better microcirculation compared with nonpulsatile flow.

Although these studies suggest that pulsatile flow is superior to non-pulsatile flow during and after open-heart surgery in pediatric and adult patients[17], in the current trial, new focal lesions were detected in clinically asymptomatic brains in 7 of 40 patients subjected to pulsatile flow and in 4 of 40 patients subjected to non-pulsatile flow during cardiopulmonary bypass. Nevertheless, the difference between the two groups was statistically insignificant.

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