The effects of hypothermic cardiopulmonary bypass on Doppler cerebral blood flow during the first 24 postoperative hours

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Abstract

To provide understanding of influence of cardiopulmonary bypass (CPB) on cerebral blood flow (CBF), we investigated the effect of CPB on patients’ cerebral haemodynamic parameters. Twenty-three patients were prospectively enrolled. CBF was estimated by transcranial Doppler (TCD) to measure blood velocity in the middle cerebral artery (MVMCA), preoperatively (T0) and at four postoperative times (T1, T2, T3, T4). At times T2, T3 and T4, MVMCA remained at higher levels than T0 (P < 0.05). In the multivariate analysis PaCO2 was independently associated to MVMCA at times T1 and T2 (P = 0.03, P = 0.01, respectively) and temperature was independently associated with MVMCA at time T1 (P = 0.02). Thus, the present study showed an increase in CBF after CPB, that was correlated with raised temperature but not with decrease in haematocrit.

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1. Introduction

After cardiac surgery with cardiopulmonary bypass (CPB), a high incidence of neuropsychological impairment has been reported and new neurological deficits are also common [1]. Different associated factors have been identified to be responsible for or co-factors in the neurological deficit: the presence of significant carotid artery stenosis, cardiac valve surgery, repeated heart surgery and/or a history of stroke [2]. Other perioperative factors like material or air microembolisms [3] and already altered cerebral perfusion have also been incriminated.

Cerebral blood flow (CBF) auto-regulation is normally under tight control [4]. However, during CPB this regulation may be altered. Indeed, Stephan et al., using pH-stat acid-base management, have demonstrated that during systemic hypothermic non-pulsatile cardiopulmonary bypass, a luxury cerebral perfusion is observed with an increase in CBF contemporary to a decrease of cerebral metabolism [5]. Furthermore, during the rewarming period following CPB, an increased CBF has also been reported in studies using either transcranial Doppler (TCD) sonography [6,7] or a cerebral blood flow tracer [8,9]. The observed increase in CBF was not attributed to a luxury cerebral perfusion but to an increased cerebral oxygen consumption [7,10].

Because modification of cerebral blood flow during the immediate post CPB has not been systematically examined, we designed a prospective observational study to evaluate by repeated TCD, changes in CBF during the first 24 h after elective coronary artery surgery. We hypothesized that after CPB, the observed change in CBF could be explained by a decrease in haematocrit as well as to the rewarming. Moreover, as different degrees of correlation have been reported between TCD-derived CBF and the 133Xenon-clearance method, both techniques were compared postoperatively.

2. Materials and methods

Over a period of 6 months, 25 patients (20 men and five women) scheduled for elective coronary bypass surgery were prospectively enrolled in this clinical study and investigated by means of TCD and xenon cerebral blood flow (XCBF) methods. All patients had preoperative TCD cerebral blood flow measurements of the middle cerebral artery...
cross-clamping time was 96 ± 27.5 ± 2.8 respectively. Mean number of coronary grafts bypassed was presented an anamnetic hypertension or diabetes mellitus, time of 144 from the study. Mean age was 64 ± 10 years, mean aortic cross-clamping time was 96 ± 33 min with a mean bypass time of 144 ± 46 min. The mean bypass temperature was 27.5 ± 1.6 °C. Eleven patients (48%) and six patients (26%) presented an anamnetic hypertension or diabetes mellitus, respectively. Mean number of coronary grafts bypassed was 2.8 ± 0.6.

2.2. Pre-, peri- and postoperative management

Prior to transfer to the operating room, all patients received premedication with diazepam and morphine. General anaesthesia was induced and maintained with midazolam, fentanyl and pancuronium bromide, adjusted to body weight and elimination half time. All patients were monitored with a V-lead continuous ECG. A radial arterial and a central venous catheter, a nasogastric tube and a Foley catheter were inserted. A flow-directed pulmonary artery catheter (PAC) was introduced for clinical management. After anticoagulation with heparin 300–400 IU/kg to obtain an activated clotting time (ACT) higher than 600 s, systemic hypothermic (28 °C) nonpulsatile cardiopulmonary bypass (CBP) with cannulation of the aorta and the right atrium associated with cold cardioplegic-induced cardiac arrest were used. The nonpulsatile CBP flow was set at 2 l·min⁻¹·m⁻² and a mean arterial pressure (MAP) was maintained at 60 mmHg using vasoactive drugs (sodium nitroprusside or phenylephrine accordingly). A standard roller pump (Stöckert Instrumente, Munich, Germany), a hollow-fibre membrane oxygenator (D703A compact flow, Dideco, Mirandola, Italy) and a 40 μm arterial filter (Bentley, Irvine, CA) were used. ACT was maintained at a level > 600 s by additional administration of heparin during the bypass. The aim levels of arterial pH and PaCO₂ was at 7.40 and 5 kPa, respectively during the hypothermic phase of CPB. Blood gas samples were measured according to the alpha-stat method at 37 °C with a blood gas analyser (Nova Biomedical/Waltham, USA). Weaning from CBP was achieved with inotropic or vasopressor drug support when required. At the end of the bypass surgery patients were rewarmed up to 35 °C (rectal temperature). Heparin was antagonized by protamine 1 mg/100 IU heparin. At the end of surgery, the patients were transferred sedated to the surgical ICU.

The postoperative management consisted of rewarmin the patients using a convective device which generates heated air flow and weaning from mechanical ventilation followed by orotracheal extubation as early as possible. For all study period, blood temperature was measured using PAC. A fixed 2 mg·h⁻¹ nitrate infusion was administered to every patient who had undergone coronary artery revascularisation with an internal mammary artery. Shivering was treated with bolus injections of morphine sulfate or meperidine. Mean arterial blood pressure was aimed to be at a level between 60 and 90 mmHg with appropriated therapy, i.e. hypotension was initially treated by volume replacement with crystalloid infusions and catecholamines according to measured cardiac output. Hypertension was treated by nitroprusside infusions. Pain was controlled by morphine sulphate bolus injections and if required sedation was provided with intermittent bolus injections of midazolam until extubation. Haematocrit was maintained above 25% after surgery. Patients remained in bed until surgical drains were removed (usually 48 h postoperatively).

2.3. Study protocol

2.3.1. TCD measurements

An investigator trained in the transcranial Doppler sonography method (B.P.) performed a TCD measurement of both MCA (VMCA) flow velocity. Each measuring point was made after at least 15 min of supine rest, when a steady-state haemodynamic condition was achieved (change in blood pressure and/or cardiac output less than 10%). Duration of TCD measurement was 20 min per patient (10 min for each MCA side). The examiner looked for the maximal blood flow velocity with the probe hold by hand:

- before cardiac surgery (T₀);
- at ICU arrival (T₁);
- 2 h later (T₁ + 2 h; T₂);
- when body temperature reached 37 °C (T₃);
- and at 24 h after surgery (T₄).

T₁, T₂, T₃, and T₄ were respectively 166 ± 55, 293 ± 74 348 ± 105 and 1501 ± 81 min after the end of CPB. The flow velocity measurements were realized in the supine position. Doppler signals from MCA were measured over the temporal bone windows at a depth ranging between 40 and 60 mm using a 2-MHz pulsed TCD-2-64 B Doppler Ultrasound velocimeter (EME TCD-2-64, Ueberlingen,
Germany) with an integrated Fourier real-time frequency analyser. The ultrasound transducer was placed just above the zygomatic arch. The orientation and strength of the Doppler signal was adjusted to obtain the best possible signal. In each subject, a constant depth-range and angle of insonation were kept throughout the study. After individual adjustment of Doppler parameters, such as gain, sample volume and power of ultrasound, these were not changed over the study period. Maximum flow velocity was followed continuously with minimum angle between probe and vessel. At each side TCD measurement, the higher VMCA was recorded every 5 min over a 10-min duration and then averaged from this period. The Pulsatility Index (PI) was then calculated. The VMCA or PI values were obtained only during end-expiration to avoid respiratory fluctuations and all patients observed a sinus rhythm without arrhythmia. To minimize side differences, mean of the right and the left middle cerebral artery was calculated. Mean VMCA (MVMCA) was calculated as the average of the mean velocity of right and left middle cerebral arteries (see Table 2). Data were printed on a paper chart. Quality control of the data acquisition was assessed by a blinded investigator, the MD Neurologist TCD specialist of the Geneva University Hospital.

Concomitantly, clinical neurological status, haemodynamic data (systemic arterial pressure, central venous pressure, pulmonary artery pressure, pulmonary wedge pressure, and cardiac output) using bedside calibrated monitoring (Hewlett Packard Monitor M1092A; Meyrin, Switzerland), ventilatory parameters (Erica, Dräger, Lübeck, Germany) and blood gas exchange data (Nova Biomedical, Waltham, MA, USA) were recorded. Furthermore, demographic data and drug administration were also noted at each TCD point measurements. TCD measurements were performed under steady-state conditions. Specifically, no modification of drug dosage, depth of anaesthesia, chest therapy or endotracheal suction were allowed in the 30 min preceding or during TCD measurements. Mean of the cerebral ventilation and orotracheal extubation were conducted according to the clinical progress of each patient and the partial arterial pressure of carbon dioxide (PaCO2) which was maintained at similar levels. The first two TCD measurements were performed under intermittent positive pressure ventilation (IPPV) without spontaneous breathing. Thereafter, the ventilatory mode could vary in each patient according to clinical progress. Finally, seventeen patients were extubated at T1 TDC measurement.

2.3.2. Xenon cerebral blood flow measurement

XCBF was measured at ICU arrival (T1). Regional CBF was measured by the non-invasive intravenous 133Xenon method with ten extra Novo Cerebrograph 10a cranial cadmium telluride detectors (Novo Diagnostic Systems, Bagsvaerd, Denmark), five placed over each hemisphere. 133Xenon dissolved in normal saline (0.9%) at a dose of 10 mCi was injected into a central vein. Expired air recordings were obtained which adequately reflect the arterial xenon time course. From the clearance curves the Initial Slope Index was derived [14]. The CBF value is expressed as ml per 100 g brain tissue per minute.

2.3.3. Recorded data

The following data were recorded simultaneously to TDC measurement at each time period in the same order by a second blinded investigator: body temperature from pulmonary artery catheter (T°), haematocrit (Htc), blood gas data (pH, PaCO2, PaO2, except for time 0), cardiac output (CO, except for time 0), and ventilatory settings (ventilatory mode, respiratory frequency, tidal volume and minute volume, except for time 0). Duration of all data recording was 5 min. Haematocrit was determined from venous samples and analysed using an haematology analyser (SYSMEX NE 8000, TOA Medical Electronics, Kobe, Japan).

2.4. Data analysis

The data expressed as mean ± SD. Parametric tests were used only when variables passed normality test (* = 0.05). A one-way repeated-measures analysis of variances (ANOVA), followed by a Tukey–Kramer multiple comparison procedure when appropriate, was performed to compare the measured variables for the five, or four respectively, different time periods (T0, T1, T2, T3, T4). Variables associated with the MVMCA in the univariate analysis (defined as P < 0.1) were subsequently analysed in a multiple regression analysis independently in every time period. This multiple regression analysis was used to identify those variables which statistically correlate with the CBF velocities values. At T1, CBF values measured by TCD (MVMCA) was compared to XCBF using linear regression analysis. For this, GraphPad Prism version 3.00 for Windows (GraphPad Software, San Diego, CA, USA, http://www.graphpad.com) and StatView (SAS Institute 5.0.1, Cary, NC, USA) for PC were used. A P < 0.05 was considered statistically significant.

3. Results

The data were normally distributed. Haemodynamic parameters, pH, PaCO2, haematocrit and temperature changes are shown in Table 1. Doppler measurements were successfully obtained from both locations in all patients during every study period. PI remained stable for the four time points of study. Increased flow velocities were observed, in all patients except patients 2, 9, 13 and 16, at each time point after surgery compared to T1 (32% at T2 and > 50% at T3, T4, respectively). At times T2, T3 and T4 MVMCA remained at higher levels than preoperatively (the TCD data are summarized in Table 2 and Fig. 1).

A significant correlation between PaCO2 and MVMCA was found at T1 and T2 (r = 0.65, P = 0.0007; r = 0.53,
P = 0.009 respectively; Fig. 2a,b) but not at T3 and T4. A correlation between an increase in T8 and mean VMCA was found at T1, T2 and T3 (r = 0.58, P = 0.003; r = 0.34, P < 0.05; r = 0.36, P < 0.05, respectively) but not at T4. In the multivariate analysis PaCO2 was independently associated to MVMCA in time T1 and T2 (P = 0.03, P = 0.01, respectively) and T8 was independently associated to MVMCA in time T1 (P = 0.02). Other parameters: heart rate, blood pressure, central venous pressure, pulmonary artery pressure, pulmonary capillary occlusion pressure, cardiac output, pH, PaO2, haemoglobin, haematocrit, ventilatory mode-parameters and Glasgow score scale had no significant correlation with MVMCA or PI. The mean XCBF value expressed as ISI was 37.5 ± 12.8 ml/100 g brain tissue per minute. The correlation between XCBF and MVMCA was r = 0.51, P = 0.01 (Fig. 3).

4. Discussion

In the present study, TCD was used to assess changes in CBF during the first 24 postoperative hours after CPB. In the absence of significant haemodynamic changes besides a 17% decrease in mean arterial pressure, MVMCA is increased at T2 and thereafter in comparison to preoperative values. This increase was correlated with an increase in temperature but not with a decrease in haematocrit.

The haematocrit and CBF are inversely related [15], and different studies have demonstrated that a decrease in haematocrit correlates with an increase in Doppler blood velocity in the middle cerebral artery (VMCA) [16–17]. Because haemodilution is used during deep hypothermic cardiopulmonary bypass to reduce red cell rigidity and vascular resistance, the observed increase in MVMCA in the present study could have been attributed to the decreased viscosity. Nevertheless, MVMCA value at T1 did not change when compared to T0 whereas haematocrit had

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Table 1

<table>
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Table 2

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<tr>
<td>SD</td>
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<td>0.31</td>
<td>0.22</td>
<td>0.22</td>
<td>0.21</td>
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Fig. 1. Changes of mean ± SD absolute values of arterial pressure (MAP) and haematocrit (Htc) over time concomitantly with MVMCA. No significant relation was observed between MAP or Htc and the flow velocities. P < 0.05 vs. T0; **P < 0.001 vs. T0; *P < 0.05 vs. T1; **P < 0.001 vs. T1.
dropped from 41.4 to 30.9 ($P < 0.001$). This phenomena may be explained by a traumatized brain which does not respond to changes in haematocrit [18].

Different hypotheses can be proposed to explain the increased of MVMCA.

First, as suggested by Von Knobelsdorff et al. [7] and Croughwell et al. [10], during the rewarming period, concomitant to the awakening from anaesthesia, an increased CBF is observed accompanied by a decrease in cerebral venous blood O$_2$ saturation. Indeed, during this period, episodes of decreased O$_2$ saturation of the blood in the bulbus jugularis are observed [19]. In the absence of jugularis blood O$_2$ saturation measurement, which was refused by the ethical committee, we are not able to confirm this increased cerebral oxygen consumption. However, physiologically, brain temperature is 0.5–1 °C more than body core temperature, and this gap increases by several degrees during cooling and rewarming on CPB [20,21]. Moreover, Bissonette et al. have recently demonstrated, with a modified retrograde jugular bulb catheter, an important increase in brain temperature up to 6 h after termination of CPB; and this increase was 2–3 °C higher than mean core temperature [22]. Since the present study observed a positive correlation between increase in temperature and increase in MVMCA, we are tempted to discuss the possible link between the recorded increase in MVMCA and a post CPB observed cerebral hyperthermia. In the present study, we have used the pulmonary artery catheter to measure the temperature during the rewarming even if it may be assumed that it does not represent the temperature of brain. However, during both normothermia and hyperthermia, venous mixed temperature is the most closely parameter correlated to venous jugular bulb temperature [23]. Indeed, compared to temperatures from different sites (rectal, tympanic, oesophageal, skin surface and axilla temperatures respectively) the latter closely reflects brain temperature after CPB [22].

Second, the utilization of vasodilator drugs such as nitroglycerine during the postoperative period may be responsible for the observed increase in MVMCA. Nevertheless, the constant increase of MVMCA without change in the therapeutic dose do not address this hypothesis. Moreover, unchanged PI in our patients rules out nitroglycerine as drug playing the major role in the increase of MVMCA.

The potential methodological flaw in the current study could be the reliability of MVMCA to reflects and monitors CBF. Indeed, even though different studies have demonstrated a good correlation between CBF and TCD, they were not conducted in CPB surgery patients [24]. Weyland et al. demonstrated that the changes in cerebral perfusion associated with the rewarming period following CPB could

Fig. 2. (a,b) Linear regression analysis comparing change in PaCO$_2$ and MVMCA during time 1 and time 2. MVMCA, middle cerebral artery blood flow velocity.
not be accurately measured by TCD monitoring [8]. Conversely, Trivedi et al. found a good correlation between $^{133}$Xenon clearance technique and TCD [9]. The weak correlation ($r^2 = 0.26$) found in the present study at $T_1$ (2 h 46 min ± 0 h 55 min after the end of CPB and at $T^*$ = 35.6 ± 0.8), between CBF values obtained by intravenous $^{133}$Xenon method and TCD-derived may plead for the poor reliability of MVMCA to reflects and monitors CBF. However, in the present study, the arterial $^{133}$Xenon level was only estimated with end tidal measurements and this may have disturb the accuracy of CBF measurements as patients in the early postoperative CPB usually have shunts due to atelectases. The authors have compared TCD to this technique, because the $^{133}$Xenon clearance technique is the easiest to accomplish and the most widely used method available after CPB. Indeed, it also requires the shortest time, a factor of importance because physiologic factors (temperature, arterial carbon dioxide tension, haematocrit, depth of anaesthesia) which affect CBF often are changing after CPB [25]. And, as no methods measure accurately CBF and all measurements are relative approximations with inherent errors and limitations [25], the patient being its own control allows us to conclude that a significant change in MVMCA occurs when flow velocities were measured pre- and postoperatively after cardiac surgery with cardiopulmonary bypass.

A second limit of the present study is that, for each measuring time, the steady state (in term of shivering, pain and sedation, factors which influence cerebral metabolism and MVMCA) has been most likely influenced by medications which have been administered. However, as all these medications decrease cerebral metabolism, we may suspect that the observed increase in MVMCA is not related to their effects. Furthermore, it may even be supposed that increase in MVMCA would have been more important without the administration of these drugs. Finally, it should be kept in mind that there could be heterogeneity in this patient population, resulting in increased MVMCA variability.

In conclusion, the results of the present study demonstrate that during the postoperative period following CPB in haemodynamically stable patients with a normal neurological outcome, MVMCA value is increased after the fifth post-operative hour and does not return to preoperative values at 24 h. However, the present study design does not allow us to draw conclusions on the physiological mechanisms responsible for the observed increase in MVMCA, if this is not explained by the rewarming or PaCO2 value.

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References


