Preservation of static and dynamic cerebral autoregulation after mild hypothermic cardiopulmonary bypass†

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Background. Dysfunction of cerebral autoregulation might contribute to neurological morbidity after cardiac surgery. In this study, our aim was to assess the preservation of cerebral autoregulation after cardiac surgery involving cardiopulmonary bypass (CPB).

Methods. Dynamic and static components of cerebral autoregulation were evaluated in 12 patients undergoing coronary artery bypass graft surgery, anaesthetized with midazolam, fentanyl, and propofol, and using mild hypothermic CPB (31–33°C). Arterial pressure (ABP), central venous pressure (CVP), and blood flow velocity in the middle cerebral artery (CBFV) were recorded. The cerebral perfusion pressure (CPP) was calculated as a difference between mean ABP and CVP. Rapid decrease of CPP was caused by a sudden change of patients' position from Trendelenburg to reverse Trendelenburg. Cerebral vascular resistance (CVR) was calculated by dividing CPP by CBFV. Index of static cerebral autoregulation (CAstat) was calculated as the change of CVR related to change of CPP during the manoeuvre. Dynamic rate of autoregulation (RoRdyn) was determined as the change in CVR per second during the first 4 s immediately after a decrease in CPP, related to the change of CPP. Measurements were obtained after induction of anaesthesia, and 15, 30, and 45 min after termination of CPB.

Results. No significant changes were found in CAstat or RoRdyn after CPB. Significant changes in CVR could be explained by concomitant changes in body temperature and haematocrit.

Conclusion. Autoregulation of cerebral blood flow remains preserved after mild hypothermic CPB.

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Adverse neurological events with serious impact on morbidity and mortality remain one of the major clinical problems in cardiac surgery.1 Although the relationship between these complications and cerebral autoregulation in the perioperative period has not been assessed, interference with cerebral blood flow (CBF) autoregulation during cardiopulmonary bypass (CPB) might be harmful in terms of neurological morbidity.2 Various degrees of disturbances of cerebral autoregulation during CPB have been found using 133Xe clearance3,4 and transcranial Doppler (TCD) ultrasonography.5,6 Studies on this subject involving patients in the postoperative period remain scarce.7

As little is known about the preservation of cerebral autoregulation after CPB, in routine, perioperative management of patients undergoing cardiac surgery does not take into consideration its possible derangement. TCD has been validated previously as a non-invasive means for the assessment of cerebral autoregulation. This method uses the measurement of cerebral blood flow velocity (CBFV) as surrogate measure of CBF.8–10 It enables the evaluation of the ‘static component’ of cerebral autoregulation, when CBFV is measured before and then after the change of arterial pressure (ABP). In addition, the rate of response of the change in cerebral vascular resistance (CVR) to the rapid change in ABP, that is its ‘dynamic component’, can also be evaluated. The evaluation of both components of cerebral autoregulation is important, as they may respond to pathological conditions differently.11

Our objective was to evaluate the static and dynamic aspects of cerebral autoregulation in the immediate post-bypass period in the group of patients undergoing coronary artery bypass grafting with mild hypothermic CPB.

Methods

The study protocol was approved by the institutional ethics committee. All patients gave written informed consent. Fourteen consecutive patients undergoing coronary artery bypass grafting with preserved left ventricular function (left ventricular ejection fraction more than 40%) were recruited. Patients with known neurological disorder, significant arrhythmias and those receiving i.v. vasoactive medication were excluded. In addition, patients with difficulties in obtaining CBFV waveforms by TCD monitor were excluded.

The absence of significant cerebrovascular disease was confirmed by preoperative Duplex examination. Symmetry of CBFV waveform between right and left middle cerebral artery was confirmed in all patients.

All patients received diazepam 7.5–10 mg orally 1 h before the operation. We used midazolam 0.05–0.1 mg kg\(^{-1}\) and fentanyl 10 µg kg\(^{-1}\) for induction of anaesthesia. Neuromuscular block was achieved by pancuronium 0.1 mg kg\(^{-1}\). Lungs were ventilated using volume-controlled mode with inspired oxygen concentration of 1.0, tidal volume 7–8 ml kg\(^{-1}\) and a ventilatory frequency adjusted to keep end-tidal carbon dioxide within the range of 4.4–4.8 kPa. Normocarbia was confirmed by arterial blood gas analysis. Anaesthesia was maintained with propofol infusion 2–4 mg kg\(^{-1}\) h\(^{-1}\) and additional administration of fentanyl (total dose 15–17 µg kg\(^{-1}\)). The use of volatile anaesthetics or vasoactive drugs was avoided during the operation.

The CPB circuit was primed with lactated Ringer solution. Non-pulsatile pump flow of 2–2.5 litre min\(^{-1}\) m\(^{-2}\) was maintained throughout the bypass period. The patients were not actively cooled. Membrane oxygenators were used. Alpha-stat strategy was used. \(P_aO_2\) was maintained in the range of 4.7–5.3 kPa, uncorrected for temperature. The haematocrit (Hct) was maintained at more than 20% with transfusion of packed red cells when necessary. Rectal and nasopharyngeal temperatures were monitored. After completion of distal anastomoses the patients were warmed up to a rectal temperature of 35°C. Patients in need of vasoactive medication or intra-aortic balloon pump support were excluded from the study.

Assessment of cerebral autoregulation was performed after the induction of anaesthesia but before the beginning of the operation, and 15, 30, and 45 min after termination of CPB. Maximal CBFV waveform in the left middle cerebral artery, acquired by TCD monitor (WAKI 2-TCTO\(^{®}\), Atys Medical, France), ABP and central venous pressure (CVP) waveforms were recorded on the hard drive of desktop computer using Grass PolyVIEW\(^{®}\) software with the sampling frequency of 100 samples per second. An abrupt decrease of ABP was caused by a rapid change of patients’ position from Trendelenburg position (15° head down) to reverse Trendelenburg (40° head up). At least 5 min of stable ABP were allowed before each manoeuvre. Arterial blood gases and Hct values in blood samples were drawn immediately before the beginning of the manoeuvre before CPB and then 30 min after its termination. Nasopharyngeal temperature was continuously recorded.

Waveform data recordings were analyzed off-line by an investigator blinded to the patients’ identity and timing of events.

The mean ABP, CVP, and average maximal CBFV (CBFVavr) were measured during the 4 s, starting 8 s after the beginning of the change in ABP. Cerebral perfusion pressure (CPP) was calculated as a difference between mean ABP and CVP, assuming that intracranial pressure was lower than CVP. Values of CPP and CBFVavr were normalized to their respective values during the 4 s immediately preceding the manoeuvre. CVR before and after the manoeuvre was calculated as a ratio of CPP and CBFVavr.

For the evaluation of static autoregulation index of static cerebral autoregulation (CAstat) was calculated as the percentage change of CVR related to the change of CPP over the entire period of the manoeuvre.\(^3\)

Rate of dynamic autoregulation (RoRdyn) was determined as described by Aaslid and colleagues;\(^1\) the CVR curve was obtained by dividing the respective values of CPP to CBFV during the first 4 s from the beginning of the ABP change. The slope of the line of best fit for this curve characterized the rate of the change of CVR over this time. The RoRdyn was defined as a ratio of this slope to the change of CPP over this time.

Possible influence of CPB on parameters characterizing CBF was assessed by ANOVA for repeated measures (General Linear Model, SPSS software). Post hoc Sidak test was used when within-subject effects were found to be significant (\(P<0.05\)).

Spearman’s correlation coefficient was calculated for the differences between the values of CVR, Hct, and nasopharyngeal temperature before CPB and 30 min after its discontinuation.

The presence of neurological deficit was assessed by routine neurological examination performed every day during the first 2 days after operation.

Results

A total of 10 male and four female patients were studied. Their mean age was 64 (range 49–78) years, and their mean body weight was 73 (range 60–85) kg. Eight patients suffered from arterial hypertension, and five from non-insulin dependent diabetes mellitus. Ten of them received beta-blockers as part of their usual medication, nine were treated by nitrates, three by calcium channel blockers, and four by ACE-inhibitors. The mean CPB time was 87 (sd 24) min with average aortic clamp time of 45 (14) min. During CPB the minimal nasopharyngeal temperature was 31.4 (1.1)°C, and during re-warming it reached 37.9 (0.6)°C. Two patients were excluded from the study, one as a result of the inability
to obtain CBFV waveform, and the other because of massive inotropic support and use of intra-aortic balloon pump after termination of CPB.

The values of indices characterizing CBF and cerebral autoregulation are shown in Table 1. Changes of physiological variables during operation are shown in Table 2. The duration of change in CPP was 4.6 (0.16) s, and the magnitude of the change was 13.0 (5.1) mm Hg during the manoeuvre.

The values of ABP, CVP, end-tidal carbon dioxide, and $P_{aCO_2}$ did not change significantly after CPB when compared with the baseline. CVR was decreased after CPB; this was also reflected by a significant increase in the CBFVavr. Despite these changes in CVR, no significant changes in the state of cerebral autoregulation (neither static nor dynamic) were found.

A significant decrease in Hct value was observed after CPB. Nasopharyngeal temperature was increased 15 and 30 min after CPB, but then returned to the pre-bypass value. There were no significant correlations between changes in CVR and changes in Hct or nasopharyngeal temperature; the correlation between the differences in the maximal and minimal values of nasopharyngeal temperature and those of CVR during the experiment was significant (r 0.62, P=0.03).

No patients suffered from gross neurological deficit after the operation.

**Discussion**

Autoregulation of cerebral blood flow is a sensitive mechanism, which can be impaired by various pathological conditions. As its disruption makes cerebral blood flow mainly dependent on pressure, it has the potential to affect the extent of brain damage by even subtle changes in systemic haemodynamics. Thus, the knowledge about possible changes in cerebral autoregulation may have an impact on various aspects of perioperative management of patients undergoing open heart surgery. Although the influence of such methods of CPB conduct, as pH-stat vs alpha-stat approach of pH management on the cerebral autoregulation was studied extensively, scarce data exist concerning changes in cerebral autoregulation in the postoperative period.

We were careful to eliminate any factors related to anaesthetic management that are known to influence cerebral autoregulation. We avoided hypercapnia, hypotension, and the use of halogenated inhalation agents; all these factors are known to affect cerebral autoregulation. The anaesthetic technique used in our study is not known to interfere with cerebral autoregulation even when the agents are used in relatively high doses. No vasoactive drugs were used in this study during the period of observation.

A common component in many protocols for the evaluation of cerebral autoregulation is the comparison of CBFV, recorded by means of TCD, with ABP recordings, in which high degree of correlation between the two variables corresponds to impaired autoregulation. However, finding an easy and clinically applicable way to evaluate autoregulation is not simple.

In our study we used a modification of the well known method of dynamic cerebral autoregulation as described by Aaslid and colleagues. Our methodology differed from the original in the way the rapid decrease of ABP was achieved. Aaslid and colleagues used the release of large tourniquet cuffs applied on both thighs; this would have interfered with the surgical preparation of the patient before coronary bypass for harvesting saphenous veins.

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### Table 1

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<th>Changes of TCD measured variables and indices of cerebral autoregulation during the operation. All variables are presented as mean (SD).</th>
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<tbody>
<tr>
<td>Before CPB</td>
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<tr>
<td>CBFVavr, cm s$^{-1}$</td>
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<tr>
<td>CVR, mmHg cm$^{-1}$ s$^{-1}$</td>
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<tr>
<td>Change of CPP, mm Hg</td>
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<td>CAstat, %</td>
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<td>RoRdyn, s$^{-1}$</td>
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### Table 2

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<tr>
<th>Changes of physiological variables during the operation. All variables are presented as mean (SD).</th>
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<tr>
<td>Before CPB</td>
</tr>
<tr>
<td>Nasopharyngeal temperature, °C</td>
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<tr>
<td>Haematocrit, %</td>
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<tr>
<td>Mean ABP, mm Hg</td>
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<tr>
<td>End-tidal CO$_2$, kPa</td>
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<td>$P_{aCO_2}$, kPa</td>
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rate of decrease of ABP was lower than that described by using the original method. However, RoRdyn is defined as the rate of change in CVR related to the magnitude of the concomitant change in ABP, therefore the precise absolute time interval for this change is less important. During the first 4 s after the change in ABP, CVR changed in approximately linear fashion. This fact is in accordance with the findings of a previously described method. It was also shown that the autoregulation process in humans is usually complete within 5–6 s. For analysis of dynamic aspect of cerebral autoregulation we analysed the changes in CVR and BP during the first 4 s after the beginning of change in ABP.

The minimum detectable difference between means for the comparison between two points of time in our study was 0.15 s for RoRdyn, and 24.3% for CAsstat with the power of 0.9 and P<0.05.

The results of assessment of static and dynamic autoregulation in this study are in agreement with the previous studies, performed in healthy volunteers, as well as those performed under propofol anaesthesia but without CPB.

In our study we did not find any impairment of cerebral autoregulation after mild hypothermic CPB in patients undergoing ‘uncomplicated’ coronary artery surgery. Our findings confirm the results of previous study, which had evaluated the response of CBF, measured by 133Xe clearance, to changes in ABP and PaCO₂. This study had shown preservation of static autoregulation and carbon dioxide reactivity in patients undergoing CPB in conditions similar to ours. In addition, we have not found changes in dynamic aspect of cerebral autoregulation. However, the situation may be different in other groups of patients presenting for cardiac surgery under different CPB conditions. The present study may serve as point of reference for evaluating other groups of patients in different clinical situations.

The fact that CVR decreased without any changes in cerebral autoregulation after CPB deserves special comment. The same phenomenon was observed by other investigators using not only TCD, but also Kety-Schmidt method of CBF measurement. The most probable explanation for a decrease in CVR was the concomitant decrease in blood viscosity. Hemodilution has been shown to increase CBF. Although we also observed a significant decrease in Hct after termination of CPB, we could not find a correlation between individual changes of Hct and CVR. Another cause for a decrease in CVR after CPB may be the elevation of brain temperature during the re-warming with corresponding increase in cerebral metabolic rate. The correlation between the maximal changes in nasopharyngeal temperature during the experiment and in CVR was statistically significant indeed.

The other limitation of the present study is our ability to assess only the major changes in cerebral blood flow autoregulation. It is possible that we were not able to detect the disruption of autoregulation in certain regions around very small foci of cerebral infarcted tissue, which are currently held responsible for subtle neuropsychological dysfunction detected by special neurophysiological tests. We did not perform this evaluation. However, no gross neurological deficit was observed in our group of patients.

Our study has shown that cerebral autoregulatory mechanisms remain preserved after mild hypothermic CPB in patients anaesthetized with midazolam, fentanyl, and propofol. Our data may be used as reference to further studies of effect of different CPB conditions, such as deep hypothermia, deep hypothermic circulatory arrest, and CPB in neonates, on the preservation of cerebral autoregulation.

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