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Lower Perfusion Pressure during Hypothermic Cardiopulmonary Bypass Is Associated with Decreased Cerebral Blood Flow and Impaired Memory Performance 6 Months Postoperatively

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ABSTRACT

Objectives: We undertook to determine the influence of perfusion pressure during hypothermic cardiopulmonary bypass (CPB) on cerebral blood flow (CBF) and cognitive memory outcome at 6 months postoperatively.

Methods: Nineteen patients who underwent hypothermic nonpulsatile CPB for elective coronary artery bypass (CAB) surgery were evaluated by ^{133}Xe measurement of the CBF and by the Incidental Memory Assessment for evaluating cognitive memory (IMTscore), both at baseline before the operation (T_1) and again at 5 to 6 months postoperatively (T_2).

Results: Overall, the mean CBF fell significantly from 39 ± 5 mL·(100 g)$^{-1}$·min^{-1} at T_1 to 33 ± 3 mL·(100 g)$^{-1}$·min^{-1} at T_2 ($P < .001$). The decrease in CBF from T_1 to T_2 (ΔCBF_{2-1}) correlated with a significant reduction in the IMTscore from T_1 to T_2 ($\Delta IMTscore_{2-1}$) ($P < .001$) and with a mean arterial pressure during CPB (MAP_{CPB}) of <60 mm Hg ($P = .05$). Cluster analysis of ΔCBF_{2-1} and $\Delta IMTscore_{2-1}$ demonstrated that the patients with the greatest decrease in CBF showed the greatest decrease in IMTscore, whereas cluster analysis of ΔCBF_{2-1} and MAP_{CPB} indicated that patients with a perfusion pressure maintained at a mean of <60 mm Hg during CPB were prone to a greater decrease in later postoperative CBF.

Conclusion: This study demonstrated that a MAP_{CPB} of <60 mm Hg during CPB was associated with a significant decrease in CBF 6 months after CAB surgery and with an associated decrease in memory performance.

INTRODUCTION

Despite advances in surgical and perfusion techniques, the incidence of permanent cerebral complications following cardiac operations remains high, at 3% to 6% for severe permanent neurologic lesions [Murkin 1995; D'Ancona 2003] and up to 36% for persistent cognitive dysfunction despite good cardiac results [Newman 2001]. Although a great deal of information is available, the causes of neurologic and cognitive complications following cardiac surgery are still a matter of debate, even though increasing evidence favors hypoperfusion and cerebral embolization from the aorta and CPB circuitry as etiologic [Bokeriia 2009].

The hemodynamic impact of cardiopulmonary bypass (CPB) on the cerebral circulation has been widely investigated. Arterial hypotension and/or low cerebral blood flow (CBF), macro- and microparticulate cerebral embolism, air embolism, and brain hyperperfusion during CPB have all been suggested as possible causes of cerebral impairment [Murkin 2006; Bokeriia 2009]. Although many studies have examined CBF during and immediately after CPB, however, only a few have dealt with CBF at a greater interval after cardiac surgery [Henriksen 1984; Treasure 1989]. Nevertheless, even in these few studies conflicting results have been reported. Whereas Henriksen [1984] found a significant decrease in CBF as a late consequence of CPB, Treasure et al [1989] found no decrease in CBF, even in the patients demonstrating cognitive impairment. In light of these results, we undertook to evaluate the long-term effects of hypothermic CPB on CBF and cognitive memory outcomes.

MATERIALS AND METHODS

Patient Population

Twenty-four consecutive patients (22 male and 2 female) with a mean (±SD) age of 61 ± 7 years who were to undergo routine elective coronary artery bypass (CAB) surgery with hypothermic CPB were considered eligible for the study according to the following inclusion and exclusion criteria. Only patients between the ages of 50 and 70 years, with a cardiac ejection fraction >50%, and with a left ventricular end-diastolic pressure <12 mm Hg were entered into the study. Patients with a history of cerebrovascular disease, diabetes, untreated hypertension, preexisting occlusive disease of the carotid arteries, and a history of previous psychiatric disorders

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were excluded from the study. Nineteen healthy volunteers were selected as an age-matched control group for CBF comparison in the preoperative phase. All patients gave written informed consent to enter the study, which was approved by our institutional Ethics Committee.

Intraoperative Management

All patients were premedicated with 2 mg flunitrazepam given orally and 0.1 mg fentanyl given intramuscularly 1 hour before the operation. In the operating room, 1 radial artery catheter, 1 peripheral intravenous catheter, and 1 central venous catheter were inserted after endotracheal intubation. The electrocardiogram, arterial blood pressure, and rectal and nasopharyngeal temperatures were monitored continuously. After induction of anesthesia with fentanyl (10 µg/kg), pancuronium was given at a dosage of 0.1 mg/kg, and patients were connected to a Siemens-Elema 900 D Servo ventilator (Elema-Schonander, Solma, Sweden) and mechanically ventilated with 50% nitrous oxide and oxygen until shortly before CPB, when nitrous oxide was discontinued for the remainder of the surgery. Anesthesia was maintained with repeated doses of fentanyl (10 µg/kg): before skin incision, before sternotomy, at the start of CPB, and before the end of CPB. A total dose of 50 to 60 µg/kg fentanyl was given to each patient. Barbiturates and volatile agents were avoided.

Timing of Assessments

For each patient admitted to the study, CBF and cognitive memory examinations were performed after admission to the hospital but before surgery (T_1), and at a mean of 164 ± 11 days postoperatively (T_2).

CBF Measurement

CBF studies were performed with a 32-channel Cerebrograph, with 16 probes for each hemisphere (Novo Diagnostic Systems, Handsun, Denmark). Fifteen to 20 mCi of ^{133}Xe were injected intravenously, and the gamma activity of the tracer was recorded for 11 minutes after the injection. A biexponential analysis was then performed on the clearance curves of the head, according to the Obrist model. The mean CBF (expressed in milliliters per 100 g per minute) was determined from each detector and was reported as the mean flow from all detectors. The mean preoperative CBF was compared with the mean CBF of an age-matched control group in our laboratory. The mean arterial blood pressure (MAP), the arterial carbon dioxide tension ($PaCO_2$), the hemoglobin (Hb) concentration, and the cerebral delivery of oxygen (CDO_2), which was expressed as the product of the arterial oxygen content and the CBF, were determined at each CBF measurement.

CPB Management

CPB was conducted in a nonpulsatile mode with a Cobe roller pump (Cobe Laboratories, Lakewood, CO, USA) and a hollow-fiber membrane oxygenator (Dideco D703; Mirandola, Modena, Italy). A 40-µm air-trapping filter (Dideco D734; Mirandola) and a 20-µm cardiac suction-line filter (Dideco D742; Mirandola) were used. The system was primed with crystalloid solution (1700 mL) and 18% mannitol (200 mL). A pump flow of 2.4 $L \cdot min^{-1} \cdot m^2$ was maintained during normothermia and moderate hypothermia (27°C, nasopharyngeal and rectal). An intermittent infusion of Buckberg blood cardioplegic solution, which was cooled to 8°C during cardiac arrest and warmed to 37°C for reperfusion before aortic declamping, was used for myocardial protection. Rewarming was continued until the rectal temperature reached 35°C with maintenance of the arterial blood inflow temperature at ≤37°C. Blood gas management was directed to maintain the blood pH at 7.40 and the $PaCO_2$ at 40 mm Hg measured at 37°C according to the α-stat principle. Arterial blood gas monitoring was made via serial sampling during lung ventilation and continuously on the arterial line during CPB (CDI 300; Cardiovascular Devices, Irvine, CA, USA). The perfusion pressure was maintained between 50 and 70 mm Hg during CPB. Arterial hypotension was treated with metaraminol, and hypertension was treated with sodium nitroprusside. The mean of all MAP values collected during CPB (MAP_{CPB}) was also reported.

Variables at Cerebral Blood Flow (CBF) Examinations*

	Time 1 (Baseline)	Time 2 (6 mo)	*P* (Time 1 versus Time 2)
CBF, $mL \cdot (100\ g)^{-1} \cdot min^{-1}$	39 ± 5	33 ± 3	<.001
Hemoglobin, g/dL	13 ± 1	13 ± 1	NS
$PaCO_2$, mm Hg	36 ± 3	38 ± 4	NS
MAP, mm Hg	106 ± 12	110 ± 10	NS
CDO_2, $mL \cdot (100\ g)^{-1} \cdot min^{-1}$	6.6 ± 1	5.8 ± 1	.006

*NS indicates not statistically significant ($P > .05$); $PaCO_2$, arterial carbon dioxide tension; MAP, mean arterial blood pressure; CDO_2, cerebral delivery of oxygen.

Neuropsychological Examination

All patients underwent a battery of cognitive memory tests shortly before CBF measurements. These tests included the following: (1) the Posner test, a computerized test to assess the efficiency of the attentional system in the dynamic component; (2) the Warrington Recognition Memory Test, which evaluates the efficiency of the long-term memory system; (3) the Incidental Memory Assessment (IMT), a test used to evaluate the ability to learn new information without intention; (4) the Tower of London test, which measures the ability of an individual to plan a complex task and execute it; (5) the verbal fluency test, which is used to evaluate the ability to assess the semantic memory store; (6) the Raven test, used to evaluate cognitive and intellectual ability based on visuospatial ability; (7) the digit span test, which evaluates the efficiency of the short-term memory store; and (8) the Zung test, a questionnaire used to measure the presence of depressive symptoms in a patient.

Statistical Analysis

The Shapiro-Wilk *W* test was used to verify the normal distribution of variables. Statistical analysis was carried out

with SAS software (SAS Institute, Cary, NC, USA). Differences between the 2 CBF measurements were evaluated with the Student *t* test for paired data. The relationships between CBF and other variables were ascertained as follows: A multiple linear regression model for change in CBF was carried out by stepwise variable selection with the decrease in CBF from T_1 to T_2 (ΔCBF_{2-1}) as the dependent variable and all of the other variables as independent variables for both intraoperative variables and again for CBF–co-incident variables. The CBF–co-incident variables considered in the model were the differences between the T_2 and T_1 values for MAP (ΔMAP), Hb (ΔHb), CDO_2 (ΔCDO_2), $PaCO_2$ ($\Delta PaCO_2$), and neuropsychological scores. The analysis was repeated with CPB flow, MAP_{CPB}, CPB time, and nasopharyngeal temperature as the intraoperative variables. Finally, a cluster analysis was carried out among the variables statistically correlating with ΔCBF_{2-1}. All summary data are reported as the mean ± SD; statistical significance was assumed for *P* values <.05.

RESULTS

Five patients (3 male and 2 female) refused to complete the study after the first CBF measurement and were excluded from analysis. The data presented and the statistical analyses are for the 19 patients who completed all the examinations.

Clinical Course

The mean CPB duration was 137 ± 26 minutes, and the mean aortic clamp time was 86 ± 23 minutes. The MAP_{CPB} was 60 ± 6 mm Hg, the pump flow rate was 2.2 ± 0.1 L·min^{-1}·m^2, and the Hb concentration was 9 ± 1 g/dL. None of the patients underwent reoperation for postoperative bleeding, and none had detectable neurologic complications prior to T_2 assessment.

Other Variables

The Hb concentration was 13 ± 1 g/dL at T_1 and 13 ± 1 g/dL at T_2. The $PaCO_2$ value was 36 ± 3 mm Hg at T_1 and 38 ± 4 mm Hg at T_2. The MAP value was 106 ± 12 mm Hg at T_1 and 110 ± 10 mm Hg at T_2. The Hb, $PaCO_2$, and MAP values for the 2 measurement periods did not differ. The CDO_2 was 6.6 ± 1 mL·(100 g)$^{-1}$·min^{-1} at T_1 and decreased significantly to 5.8 ± 1 mL·(100 g)$^{-1}$·min^{-1} at T_2 (t = –3.206; P = .006) with a final mean decrease (ΔCDO_2) of 0.8 ± 1 mL·(100 g)$^{-1}$·min^{-1}, primarily because of decreased CBF (see below and the Table).

CBF and Cognitive Memory

The mean CBF at T_1 (CBF_1) was 39 ± 5 mL·(100 g)$^{-1}$·min^{-1} and was significantly different significantly from that of the age-matched control group (38 ± 10 mL·(100 g)$^{-1}$·min^{-1}). The

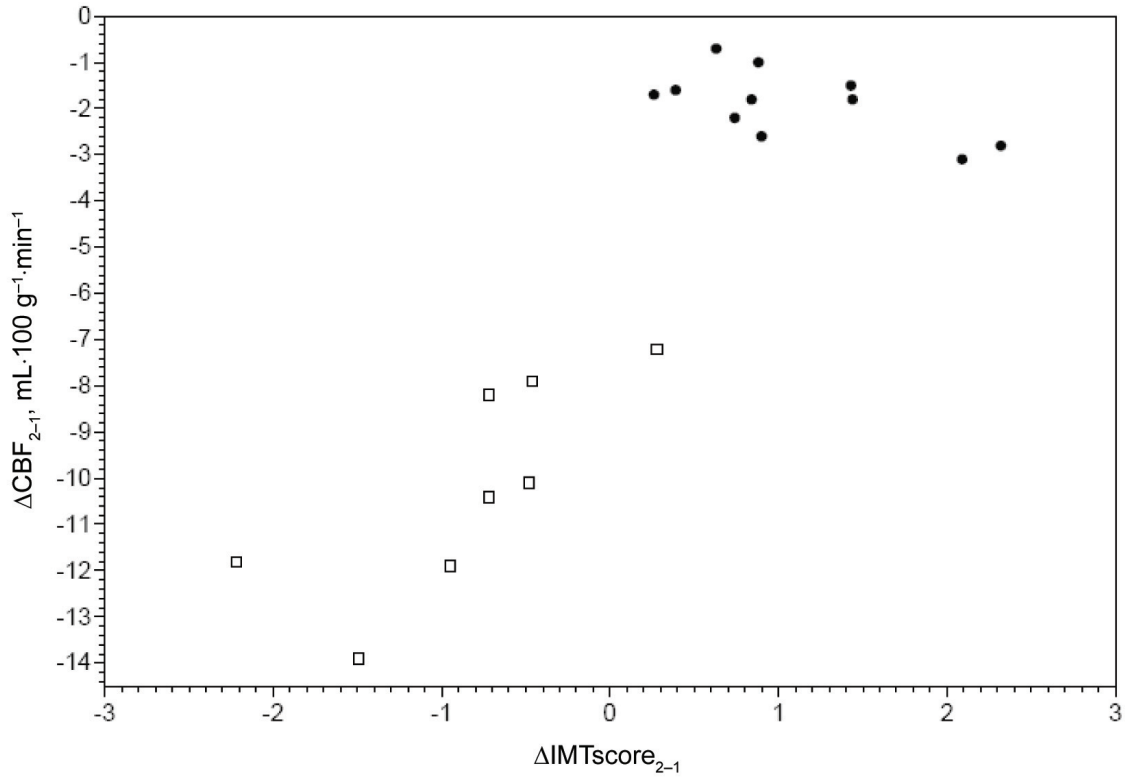

Figure 1. Cluster analysis demonstrating the relationship between ΔCBF_{2-1}, the decrease in the cerebral blood flow (CBF) from before the operation (T_1) to 5 to 6 months postoperatively (T_2), and the change in the Incidental Memory Assessment score from T_1 to T_2 ($\Delta IMTscore_{2-1}$). The figure shows the relationship between the decrease in IMT score and lower CBF values in cluster 2 patients (open squares) and the minimal decrease in CBF and an unchanged or improved IMT score in cluster 1 patients (closed circles).

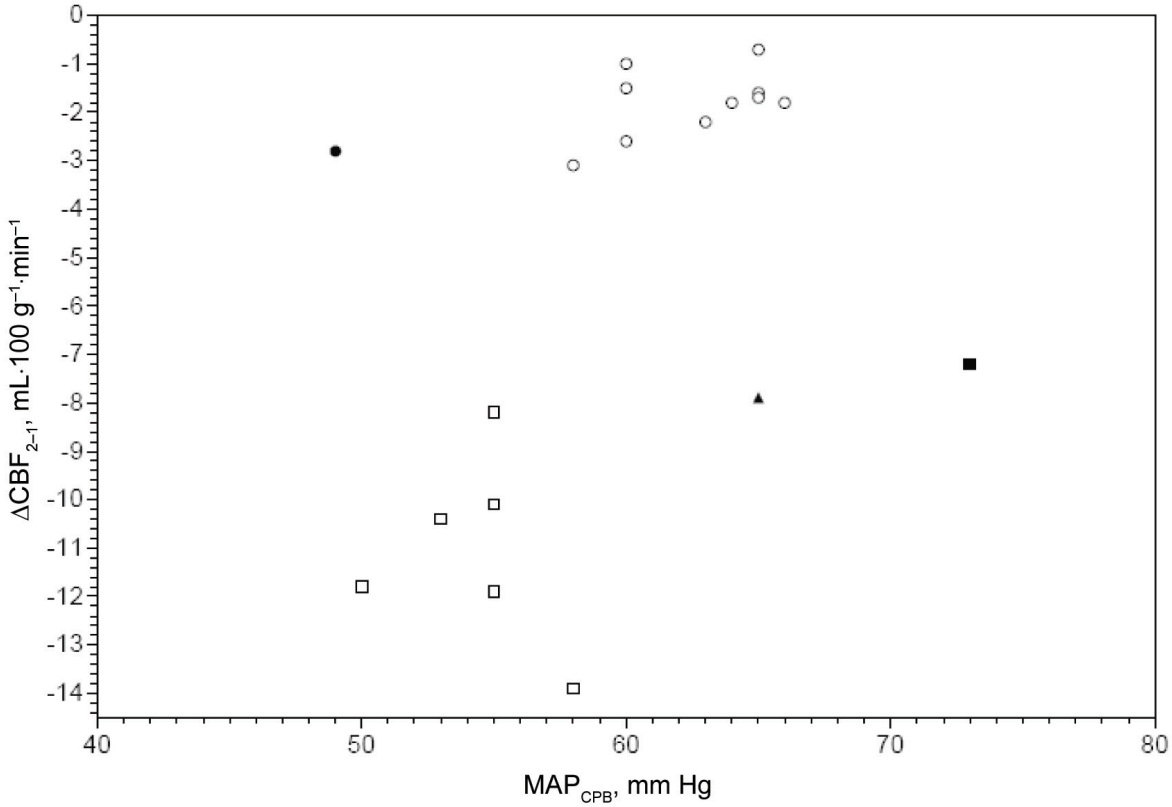

Figure 2. The relationship between ΔCBF_{2-1}, the decrease in the cerebral blood flow (CBF) from before the operation (T_1) to 5 to 6 months postoperatively (T_2), and the mean arterial pressure during cardiopulmonary bypass (MAP_{CPB}). Patients in cluster 1 (open circles, n = 10) had a mean MAP_{CPB} >60 mm Hg and had minimal change in postoperative cerebral blood flow (CBF), whereas patients in cluster 2 (open squares, n = 6) had a mean MAP_{CPB} <60 mm Hg and showed a significant decrease in CBF. The closed triangle, closed circle, and closed square represent outliers that do not fit into either of the 2 clusters.

mean CBF at T_2 (CBF_2) fell significantly to 33 ± 3 mL·(100 g)$^{-1}$·min^{-1} from the mean CBF_1 (t = –5.238; P < .001), with a mean percent decrease of 13% ± 10% (Table 1). Multiple stepwise linear regression analysis showed that the variance of ΔCBF_{2-1} was explained by only 2 variables, the change in the IMT score from T_1 to T_2 ($\Delta IMTscore_{2-1}$) (r^2 = 0.69; P = .0001) and MAP_{CPB} (r^2 = 0.20; P = .05). When cluster analysis of ΔCBF_{2-1} and $\Delta IMTscore_{2-1}$ was performed, the patient samples split into 2 subgroups of 11 and 8 patients (Figure 1), whereas cluster analysis of ΔCBF_{2-1} and MAP_{CPB} split the patients into 2 subgroups of 10 and 6 patients, with 3 patients remaining as outliers (Figure 2).

DISCUSSION

The major finding of this study is that CAB surgery with relative hypotension during CPB appears to cause a long-lasting reduction in CBF averaging 13%, which correlates with a long-term decrease in memory performance. Similar observations of decreased CBF have been made previously. Henriksen [1984] found a reduction in postoperative CBF of approximately 5% in a sample of 11 patients investigated 11 months after cardiac surgery. The author referred to this reduction as possible neuronal cell loss correlated with the duration of CPB [Henriksen 1984], but the author conducted no formal neurologic or cognitive assessments to corroborate his hypothesis. In another study of CBF in 59 CAB patients, Treasure et al [1989] found a significant reduction in CBF 2 weeks after surgery that returned to the preoperative level by 8 weeks postoperatively despite persistent neuropsychological dysfunction in a subset of these patients. Unfortunately, these authors did not evaluate CBF in patients presenting with cognitive dysfunction separately from the group as a whole; thus, it is difficult to compare their results with the findings of the present study. Most recently, Chernov et al used brain single photon emission computed tomography (SPECT) and neuropsychological testing 1 day before, 10 to 14 days after, and 6 months after CAB surgery in 65 patients who underwent CAB with CPB and in 43 patients who underwent off-pump CAB [Chernov 2006]. They observed that CAB with CPB was accompanied by short-term and long-term cognitive dysfunction in 96% and 55% of the cases, respectively. These investigators also found CBF to be decreased in 68% of the patients in the early period after CAB surgery, and CBF remained significantly decreased from the baseline value at the 6-month follow-up in 55% of the cases [Chernov 2006]. These results are very similar to our observations.

Preoperative clinical conditions (such as insulin-dependent diabetes, untreated hypertension, and cerebrovascular diseases) and intraoperative management including the use of bubble oxygenators, absence of an arterial filter, pH-stat blood gas management, and global hypoperfusion during CPB have all been associated with an increased risk of neurologic morbidity after CPB. Therefore, as has recently been recommended [Shann 2006], we selected our inclusion/exclusion criteria and intraoperative management techniques to minimize these confounders. During CPB, we used a hollow-fiber membrane oxygenator, a venous blood filter, and an air-trapping filter in the arterial line—all techniques designed to decrease the generation of microgaseous and microparticulate emboli. In addition, our patients were managed with the α-stat method and within the range of MAP in which pressure-flow autoregulation has been demonstrated to remain intact [Murkin 1987]. The correspondence between the preoperative CBF values measured in our patients and those of age- and sex-matched control individuals from our laboratory corroborates the validity of our techniques for CBF determination.

Nevertheless, some of our patients experienced a significant reduction in CBF, along with an impairment in memory performance. We observed 2 distinct CBF responses: One group had a minimal change in CBF, and the other experienced a substantial decline. To our knowledge, this finding is the first such demonstration linking late postoperative memory impairment with physiological evidence of decreased CBF.

Disturbances in memory are cognitive deficits that have been reported by a number of investigators after CAB grafting and can persist even late postoperatively [Murkin 1995; Newman 2001]. To what extent such disturbances can be directly attributable to CPB versus progression of the underlying disease remains controversial [Selnes 2007; Knipp 2008; Gerriets 2009]. In addition to the cerebral embolic load, memory dysfunction as an expression of a diffuse brain injury is possibly due to decreases in tissue cerebral microcirculatory perfusion, as has recently been shown to occur in the lingual microcirculation during CPB [den Uil 2008].

In our series of cognitive tests, memory decline was revealed as a long-lasting impairment that occurred primarily in the group of patients with more pronounced CBF decline. Thus, on the basis of the present results, it is likely that the CBF decrease observed at 6 months after surgery is etiologic with respect to postoperative memory dysfunction. This interpretation is in agreement with the data of Nishimura et al [1998], who used SPECT and found a decrease in CBF in the hippocampal areas in 3 of 13 patients after cardiovascular surgery (the hippocampus is a key brain area related to memory formation and retrieval). There is also some experimental support for increases in the expression of both pro- and anti-apoptotic genes during CPB [Sato 2002], particularly during hypothermic circulatory arrest, results that again show hypothalamic regions to be particularly vulnerable [Chock 2006].

As seen in Figure 1, the results of the cluster analysis, which was carried out by taking into account the variables ΔCBF_{2-1} and $\Delta IMTscore_{2-1}$, demonstrate 2 distinct patterns of association. Of the 11 patients showing a relatively small decrease in CBF (averaging 5%), memory and other cognitive domains were unimpaired and even demonstrated a small improvement in performance. Improved scores on memory performance tests in patients who have undergone cardiac surgery have previously been reported and are likely related to decreased stress after hospital discharge, the learning effect, and related phenomena [Meyers 1994].

The remaining 7 patients constituted a second group (also in Figure 1) who, in contrast, demonstrated both a marked decrease in CBF averaging 24% and significant reductions in memory scores in all but one of the patients. Notably, the one patient who did not experience any cognitive decline did demonstrate a significant CBF decrease. This patient in fact showed a slightly increased memory score, possibly because the decrease in CBF was the lowest among those of the patients belonging to this group. We cannot explain the preserved memory and overall cognitive functioning in this patient, but it is plausible that other factors in addition to decreased CBF acted in synergy to influence cognitive performance.

The other remarkable finding of the present study was the correlation between the CBF decrease detected at follow-up and MAP values maintained during the bypass procedure. Not surprisingly, this correlation was not high ($r^2 = 0.20$), but the fact that there was an association at all does reiterate that intraoperative management can have an impact that is detectable long after the procedure.

Cluster analysis of the variables ΔCBF_{2-1} and MAP_{CPB} has split the sample into 2 main subgroups, with 3 patients remaining as outliers (Figure 2). Six patients with mean MAP_{CPB} values of <60 mm Hg showed a greater decrease in CBF than the 9 patients in whom MAP_{CPB} was maintained at values between 60 and 70 mm Hg. Again, there were outliers, with 2 patients demonstrating significant decreases in postoperative CBF, notwithstanding mean MAP_{CPB} values of 65 and 74 mm Hg, whereas 2 other patients showed minimal decreases in postoperative CBF despite mean MAP_{CPB}values close to 50 mm Hg.

Alterations in systemic perfusion during CPB have been proposed as possible causes of impaired cerebral perfusion that give rise to deterioration of cerebral function. Animal studies have demonstrated that during hypothermic CPB, CBF becomes perfusion pressure dependent at MAP values of approximately 50 mm Hg [Schwartz 1995; Ploch 1998]. These findings are consistent with our observations. Accordingly, if MAP_{CPB} is kept below this critical value, the patients may be prone to cognitive deficit in the postoperative period. Newman et al [1994] demonstrated that cognitive impairment after cardiac surgery may be due to an inadequacy in the cerebral oxygen supply during CPB when the compensatory vasodilatory mechanism is impaired or collateral perfusion is interrupted. Our data show that in 6 patients of our series, a MAP_{CPB} between 50 and 60 mm Hg was probably inadequate to meet cerebral metabolism, given the remarkable CBF decrease detected late postoperatively. In addition, these patients were also among those who showed memory impairment at follow-up. These results are not inconsistent with those of Gold et al [1995], who found a higher incidence

of adverse neurologic outcomes at 6 months after cardiac surgery in patients maintained at a MAP_{CPB} between 50 and 60 mm Hg.

After exploring our results, we hypothesize that in patients with MAP_{CPB} values <60 mm Hg, this relative hypotension caused decreased microcirculatory perfusion that led to subclinical neurologic damage that was responsible for later memory impairment and attendant decreases in CBF. On average, patients maintained at a MAP_{CPB} >60 mm Hg had a lower incidence of neurologic complications, a finding consistent with results reported by others [Gold 1995].

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