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EFFECTS OF NIMODIPINE ON CEREBRAL BLOOD FLOW AND NEUROPSYCHOLOGICAL OUTCOME AFTER CARDIAC SURGERY

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SUMMARY

Thirty-five patients undergoing cardiac surgery requiring cardiopulmonary bypass (CPB) were allocated randomly in a prospective double-blind study to receive either nimodipine 0.5 μg kg^{-1} min^{-1} or placebo. Cerebral blood flow (CBF) was measured during and immediately after CPB. Neuropsychological tests were performed 6 months after surgery to determine any relationship between ischaemic damage and CBF and administration of nimodipine. There were no differences in CBF between the nimodipine (n = 18) and placebo groups (n = 17). Significant changes in neuropsychological tests were found in six patients tested 6 months after surgery but there were no conclusive signs of ischaemic damage. The nimodipine-treated group performed better in tests of verbal fluency and visual retention, suggesting that some memory functions were preserved better in this group.

KEY WORDS

Brain: cerebral blood flow. Heart: calcium channel blocker, nimodipine.

The incidence of neurological sequelae after cardiac surgery varies from 1.3% to 79% [1–3]. Several studies have examined intraoperative factors associated with poor neurological outcome [4–7]. These include reduced cerebral perfusion pressure (CPP) during cardiopulmonary bypass (CPB) [5], and some postmortem studies have shown lesions in the boundary territories between major cerebral arteries, indicating hypotensive ischaemia [6]. Particulate or air emboli from the bypass circuit may also cause localized ischaemia [7].

Development of ischaemic damage has been linked to an increase in intracellular free Ca^{2+} during ischaemia reducing further cerebral blood flow (CBF) and inducing deleterious intracellular events including breakdown of phospholipids, production of free oxygen radicals and release of excitatory amines [8, 9].

The calcium channel blocker nimodipine has been reported to increase CBF both in regional cerebral ischaemia [10] and in the period of reduced flow after resuscitation from cardiac arrest in man [11].

This study was designed to determine if nimodipine has any influence on CBF during and shortly after CPB and if it reduces the incidence of cerebral damage as measured by neuropsychological testing.

PATIENTS AND METHODS

This prospective study was approved by the Institutional Ethics Committee, the Norwegian Council for Science and the Humanities and the Norwegian Medicine Control Authority. Informed consent to participate in the study was received from 39 patients undergoing replacement of the mitral or aortic valve, coronary artery bypass grafting (CABG), or any combination of these procedures. Patients with known cerebral, cerebrovascular or psychiatric disorders were excluded.

Neuropsychological tests were performed by the same neuropsychologist (B.T.O.) on the day before surgery and within 5 days and 6 months

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TABLE I. *Neuropsychological tests used, number of test variables and main function tested*

Test name	Number of variables	Tested function
Mental state		
Jacobs [12]	4	Organic mental screening
PASAT [13]	1	Information processing
Trail-making [14]	2	Conceptual shifting, verbal mediation, perceptual motor speed
Verbal fluency [15]	2	Word production, associative memory
Memory tests		
Bentons visual [16]	8	Visual retention test
Lurias methods [17]	7	Verbal learning, distractability
Verbal digit span [18]	2	Short memory test
Motor tests		
Digit symbol [19]	1	Motor speed, perception
Zazzo [19]	4	Motor speed, perseveration tendency

after surgery. Thirty-one test variables were used, testing mental state, memory, psychomotor performance and sustained attention (table I) [12–19].

All patients received pethidine 1 mg kg^{-1} and promethazine 0.5 mg kg^{-1} i.m. 1 h before operation. All anaesthetic procedures were performed by anaesthetists not involved in the study.

Anaesthesia was induced with fentanyl 0.01–0.02 mg kg^{-1} and diazepam 0.1–0.2 mg kg^{-1} and maintained with 50% nitrous oxide in oxygen and additional doses of fentanyl 0.2–0.4 mg and diazepam 2.5–5 mg as needed. Neuromuscular block was produced with pancuronium 0.1 mg kg^{-1} and maintained with additional doses of 2 mg when needed.

Ventilation of the lungs was adjusted to keep Pa_{CO_2} at 4.6–5.6 kPa at the actual patient temperature (oesophageal). A pulmonary artery and a radial artery catheter were used for measuring haemodynamic variables.

Hypotension, defined as a reduction in mean arterial pressure (MAP) of 20% less than pre-anaesthetic values, if it occurred before CPB, was treated with an infusion of crystalloids, while that during weaning from CPB and after CPB was treated with dopamine, adrenaline or both.

CPB was performed in a non-pulsatile mode using a roller pump (Polystan) and a bubble oxygenator (Polystan 011500). A 30-μm filter (Polystan standard) was used in the cardiotomy suction and a depth filter (Cobe, U.S.A.) in the arterial cannula. The pump flow was set initially at 2.4 litre min^{-1} m^{-2} and reduced to 2.0 litre min^{-1} m^{-2} during hypothermia (30 °C).

CBF was measured (fig. 1) after sternotomy and during hypothermic CPB (30 °C). An i.v. infusion of nimodipine 0.5 μg kg^{-1} min^{-1} or placebo (the solvent for nimodipine, each 10 ml containing ethanol 1.5 g, polyethylene glycol (400) 1.5 g, sodium citrate 0.02 g, citric acid 0.003 g and water 7 g) was thereafter started in a randomized, blinded fashion. Further measurements were performed 15 and 45 min later, after CPB when the circulation was stable and 15 min after the infusion had been discontinued.

In the first 10 patients (six nimodipine, four placebo) CBF before and after bypass was measured by xenon clearance. After i.v. injection of xenon-133 15–20 mCi, clearance was measured

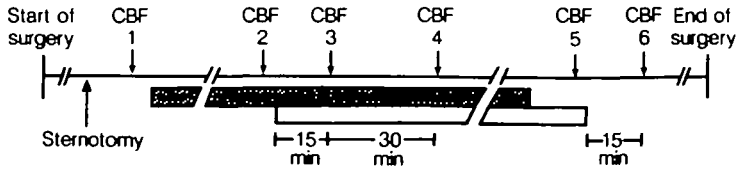

FIG. 1. Timing of cerebral blood flow (CBF) measurements in relation to start of surgery, cardiopulmonary bypass period (▨) and infusion of study drug (nimodipine/placebo) (□).

by five external scintillation detectors positioned over the right parietal hemisphere. An air detector sampled expired air for assessment of arterial and air xenon-133 activity using a Novo Cerebrograph 10a (Novo, Hadsund, Denmark). CBF was determined from the initial slope index as described by Risberg and colleagues [20]. During CPB, xenon-133 was injected in a catheter positioned in the right common carotid artery via the brachiocephalic trunk. CBF was then measured by the method of Olesen, Paulsen and Lassen [21]. All measurements were corrected for background or remaining activity and for changes in the xenon-133 *tissue:blood partition coefficient*, caused by variations in temperature and packed cell volume (PCV) [22].

The i.v. technique was abandoned after the first 10 patients as it was felt that the need for 11 min of surgery without diathermy was incompatible with optimal patient care. In the remaining patients, all CBF measurements were performed by the intra-arterial method, requiring only 1 min without diathermy.

Cerebral vascular resistance index (CVRI, mm Hg ml^{-1} 100 g^{-1} min^{-1}) was calculated from the cerebral perfusion pressure (CPP = MAP − CVP) and CBF.

Haemodynamic variables, blood-gas tensions and temperature were measured at the same intervals as CBF and 8, 16 and 24 h after surgery. In addition, the requirements for inotropic drugs were recorded.

Physiological variables between treated and untreated patients were compared with Mann–Whitney rank sum test. For statistical comparison of number of patients in defined groups, chi-square test was used. The Wilcoxon signed rank sum test was used for comparison of changes during the procedure. As this was a study primarily of CBF, power analysis was performed of possible effects on CBF and not on neurological outcome. In a previous study [23] mean CBF during CPB was 12 ml 100 g^{-1} min^{-1}. Nimodipine doubled CBF after cardiac arrest in man [11]. If CBF increased 50% with nimodipine in the present study, with SD = 4, 10 patients in each group would be sufficient for $P < 0.05$ with a power of 90%.

The neuropsychological tests were analysed with Student's *t* test, and correlation analysis for age, sex and education was performed on the differences before and after the operation. All values are mean (SEM).

TABLE II. *Patient data, cardiovascular state and operative details. AVR = Aortic valve replacement; MVR = mitral valve replacement.* *P < 0.05

	Nimodipine ($n = 18$)	Placebo ($n = 17$)
Age (yr)	62 (2)	59 (2)
Sex (M/F)	13/5	12/5
Hypertension	1*	5*
Previous myocardial infarction	6	8
Ejection fraction (%)	64 (3)	53 (5)
AVR-MVR/CABG	8/10	6/11

RESULTS

Four patients (two nimodipine, two placebo) were excluded as it was not possible to inject xenon-133 into the right carotid artery because of non-symptomatic stenosis, leaving 35 patients (18 nimodipine, 17 placebo). There were no significant differences in patient characteristics or type of surgery between the groups, except that significantly more patients in the placebo group were hypertensive (table II). Long term calcium channel blocker treatment was stopped at least 48 h before the operation in seven patients (three nimodipine, four placebo).

There were no significant differences between the two groups in haemodynamic variables, blood-gas tensions, PCV or temperature (table III), or in durations of surgery or CPB.

The CBF values obtained before and after CPB by the i.v. method [20] (21.5 (2.1) ml 100 g^{-1} min^{-1} and 30.4 (2.2) ml 100 g^{-1} min^{-1}) were not significantly different from those obtained by the intra-arterial method [21] (22.3 (1.5) ml 100 g^{-1} min^{-1} and 30.1 (1.7) ml 100 g^{-1} min^{-1}). The results from the two methods were therefore pooled.

There were no significant differences in CBF between the nimodipine group and the placebo group at any time (fig. 2) or in CVRI. CBF increased significantly with a concomitant decrease in CVRI during hypothermic CPB in both groups and remained increased after CPB in the nimodipine group. In the placebo group, CBF was not significantly different 15 min after discontinuation of the infusion from before CPB.

There were no significant differences in the need for inotropic drugs between the two groups during weaning from CPB or during the first 24 h after operation.

Seven patients did not undergo neuro-

TABLE III. *Mean arterial pressure (MAP), cardiac index (CI), systemic vascular resistance index (SVRI), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), pH,* P_{CO_2}, P_{O_2}, PCV AND OESOPHAGEAL TEMPERATURE IN PATIENTS GIVEN NIMODIPINE (n = *18*) (*N*) *or placebo* (n = *17*) (*P*) *during and 8, 16, 24 h after operation*

Variable	After sternot. pre-CPB	During CPB			After CPB		After operation		
		0 min	15 min	45 min	Immed.	15 min	8 h	16 h	24 h
MAP (mm Hg)									
N	77 (2)	60 (3)	58 (2)	57 (3)	77 (3)	80 (2)	78 (2)	73 (2)	79 (3)
P	82 (3)	58 (3)	65 (3)	64 (4)	86 (4)	84 (4)	84 (3)	79 (2)	86 (2)
CI (litre m^2)									
N	2.1 (0.1)	2.3 (0.1)	2.2 (0.1)	2.4 (0.1)	3.2 (0.4)	2.9 (0.3)	2.3 (0.3)	2.8 (0.3)	3.2 (0.4)
P	2.5 (0.2)	2.4 (0.1)	2.4 (0.1)	2.4 (0.1)	2.6 (0.2)	2.6 (0.3)	2.3 (0.1)	2.6 (0.1)	3.0 (0.2)
SVRI (dyn cm^{-5} m^2)									
N	2985 (273)	1968 (131)	2074 (137)	1857 (162)	1896 (237)	2220 (227)	2751 (225)	2131 (204)	2048 (213)
P	2747 (250)	1732 (103)	2150 (130)	2053 (168)	2465 (305)	2586 (354)	2967 (259)	2326 (157)	2102 (128)
CVP (mm Hg)									
N	6 (1)	3 (1)	2 (1)	3 (1)	10 (1)	10 (2)	9 (1)	9 (1)	9 (1)
P	5 (1)	3 (1)	3 (1)	2 (1)	10 (1)	10 (1)	8 (1)	8 (1)	10 (1)
PCWP (mm Hg)									
N	10 (1)	—	—	—	14 (1)	13 (1)	11 (1)	11 (1)	12 (1)
P	9 (1)	—	—	—	13 (2)	14 (1)	11 (1)	11 (1)	12 (1)
pH									
N	7.43 (0.01)	7.40 (0.01)	7.39 (0.01)	7.37 (0.01)	7.40 (0.01)	7.41 (0.01)	7.43 (0.01)	7.40 (0.01)	7.38 (0.01)
P	7.42 (0.01)	7.41 (0.01)	7.38 (0.01)	7.39 (0.01)	7.40 (0.01)	7.41 (0.01)	7.43 (0.01)	7.39 (0.01)	7.37 (0.01)
P_{CO_2} (kPa)									
N	4.6 (0.2)	4.8 (0.1)	5.3 (0.1)	5.5 (0.1)	4.8 (0.1)	4.8 (0.1)	4.9 (0.2)	5.2 (0.2)	6.1 (0.2)
P	4.5 (0.2)	4.7 (0.1)	5.1 (0.2)	5.0 (0.2)	5.0 (0.2)	4.9 (0.2)	4.7 (0.2)	5.4 (0.2)	6.6 (0.3)
P_{O_2} (kPa)									
N	22.2 (3.3)	23.9 (3.1)	30.4 (5.0)	23.9 (3.5)	29.1 (6.3)	29.1 (6.2)	23.1 (2.3)	16.1 (1.4)	14.4 (1.0)
P	23.1 (2.7)	20.2 (4.5)	23.6 (3.6)	30.8 (3.2)	32.7 (6.1)	32.7 (6.2)	27.4 (1.5)	17.8 (1.3)	16.0 (1.2)
PCV									
N	0.35 (0.01)	0.24 (0.01)	0.25 (0.01)	0.25 (0.01)	0.29 (0.01)	0.30 (0.02)	—	—	—
P	0.36 (0.01)	0.22 (0.01)	0.23 (0.01)	0.24 (0.01)	0.30 (0.01)	0.32 (0.01)	—	—	—
Temp. (°C)									
N	36.1 (0.2)	27.7 (0.4)	30.4 (0.5)	34.1 (0.9)	37.0 (0.1)	37.0 (0.1)	37.4 (0.2)	38.4 (0.2)	38.1 (0.1)
P	36.1 (0.1)	30.9 (0.7)	32.3 (0.7)	35.2 (0.9)	37.2 (0.1)	37.0 (0.1)	37.6 (0.1)	38.5 (0.1)	38.3 (0.2)

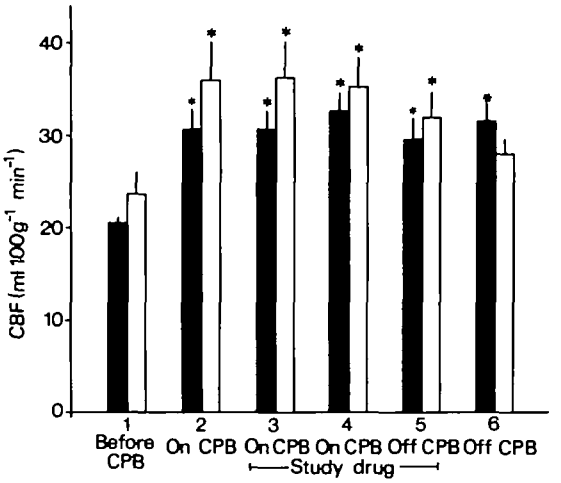

FIG. 2. Cerebral blood flow (CBF) measured before, during and after cardiopulmonary bypass (CPB) in patients treated with nimodipine (■) ($n = 18$) or placebo (□) ($n = 17$) when on CPB. *$P < 0.05$ compared with the value before CPB.

psychological testing 6 months after surgery. In the nimodipine group two died (cardiac failure, sepsis) and three declined, while in the placebo group two patients died (cardiac failure), leaving 13 in the nimodipine group (five valve replacement, eight CABG) and 15 in the placebo group (five valve replacement and 10 CABG). The first five patients were tested also within 5 days of surgery, but this was discontinued as the general physical condition of the patients influenced the test results so that it was not possible to evaluate adequately any changes.

Significant differences were found in six variables of 31 tested 6 months after surgery. Verbal fluency [15] was unchanged in the nimodipine group and decreased significantly in the placebo group. There was an improvement in the Benton visual test [16] in the nimodipine group, the results in the placebo group being unchanged. In two attention and psychomotor tests, both groups showed improvement after surgery. Two test variables for mental state were decreased after surgery, but did not show any differences between the groups.

DISCUSSION

Nimodipine 0.5 μg kg^{-1} min^{-1} did not affect CBF during or immediately after CPB in man. We have reported previously that the same dose doubled CBF in the hypoperfusion period following resuscitation from cardiac arrest in man [11]. Nimodipine has been reported also to increase CBF after regional cerebral ischaemia [10], but not in non-ischaemic areas [24, 25].

The present findings are in agreement, as there were no signs of cerebral ischaemia in our patients. The least of 975 regional values measured during hypothermic CPB was 14 ml 100 g^{-1} min^{-1}; this exceeds the values thought to be critical during hypothermic anaesthesia [26, 27].

Neuropsychological testing appears to be a sensitive index of cerebral damage. Early testing may show minor reversible changes, but such results are unreliable because of fatigue, anxiety and sleep deprivation. In the present study, the patients were tested 6 months after surgery. Those patients who underwent early postoperative testing showed reduced test scores of indeterminate cause. Performance decreased only in three of 31 tests, so we cannot conclude that there were definite signs of ischaemic damage. The separate analysis of the two groups showed a slightly better outcome for nimodipine-treated patients in terms of verbal fluency and visual retention. It may be postulated that some memory functions were preserved better in this group, but no firm conclusions can be drawn.

The values for CBF before CPB in the present study are similar to those reported by others [23, 28]. Those found during hypothermic CPB are comparable also, but the range of values is greater [29, 30]. These apparent discrepancies may be explained at least partly by variations in factors known to influence CBF, such as Pa_{CO_2}, anaesthesia, temperature, PCV and arterial pressure.

Another factor that could be important is the method used for evaluation of CBF during CPB. In earlier studies [28, 31, 32] CBF during CPB was calculated by the Height/Area (H/A) formula after injection of xenon-133 into the arterial port of the pump oxygenator. The H/A calculation requires instantaneous arrival of the tracer at the brain [33], and it is not obvious that this criterion is fulfilled when the tracer is injected in the arterial line of the pump oxygenator. The calculation of initial slope index used in the present study is independent of the input function of the tracer [21] and influenced only minimally by recirculation. The index is completed in 1 min, while the H/A measurement requires 10–15 min, and it might be difficult to keep stable all variables such as temperature, Pa_{CO_2}, PCV and cerebral perfusion pressure.

Although CBF did not change with termination of CPB, the post-CPB values were significantly greater than those before CPB, as was found by Johnsson and colleagues [29] and Feddersson and colleagues [30]. As there were no signs of ischaemia during CPB, this increase cannot be explained as post-ischaemic hyperperfusion. It seems more likely to be caused by the 15% reduction in PCV and possible changes in blood rheology.

Nimodipine 0.5 $\mu g\ kg^{-1}\ min^{-1}$ was well tolerated systemically, as there were no differences in any haemodynamic variables or in requirement for circulatory support between the nimodipine and placebo groups. Nimodipine did not affect CBF during or after CPB. Neuropsychological testing 6 months after operation suggested some benefits from treatment, but the small number of patients studied prevents firm conclusions on cerebral protective effect.

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